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The Journal of Breast Health

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The Journal of Breast Health

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The Journal of Breast Health is the open access, scientific online-only publication organ of the Turkish Federation of Breast Diseases Societies that is published in accordance with independent, unbiased, double blind peer review principles. (The journal, which was established in 2005 under the title of Meme Sağlığı Dergisi / The Journal of Breast Health, has been published under the title of The Journal of Breast Health (J Breast Health) as an online-only publication since April 2014)

The publication language of the journal is both in Turkish and English, and it is published quarterly on January, April, July and October.

The target audience of the journal includes specialists and medical professionals in general surgery and breast diseases.

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The Journal of Breast Health

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Contents

Review

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Psychiatric Symptoms and Psychosocial Problems in Patients with Breast Cancer

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ABSTRACT

Cancer is a physical disease and also one of the leading clinical manifestations where psychosocial problems are prevalent. Psychosocial problems that these patients may have in the long run include anxiety, uneasiness, mourning, helplessness, fatigue, impairment of concentration, sleep disorders, mental and cognitive reservation, sexual dysfunction, infertility, psychological distress, and psychiatric disorders. Psychosocial problems have a nature of underpinning the emergence of psychological troubles. The prevalence of psychological disorders in patients with cancer range from 29% to 47%. Psychiatric disorders that are likely to be seen are severe stress disorder, adjustment disorder, depressive disorder, and other neurotic disorders. It is considered by the present author that in the event of breast cancer, potential psychiatric disorders may affect prognosis of the disease, adherance to and success of therapy, social and societal functioning, and survival rate. This paper aims to review the psychiatric symptoms and diseases that may develop in patients with breast cancer, which is one of the most frequent types of a globally common disease; i.e., cancer, as well as the impact of psychiatric symptoms on the treatment of disease.

Keywords: Breast cancer, psychiatric symptoms, psychosocial problems

Introduction

According to data published by the World Health Organization, the global burden of cancer has doubled within the last 30 years (1). In most countries, including ours, cancer is the second most common cause of death (2). Any diagnosis of cancer accompanies serious psychosocial problems for the patient, his/her relatives and society, as well as significant work force losses (1). It is a challenging disease that induces a crisis in the patient's psychological balance and is perceived as a disaster in the eyes of the patient and his/her family, generating huge impacts in terms of both physical and emotional aspects with the feelings of fear, hopelessness, guilt, desperation, and being abandoned (3). Behavioral factors play a part in the development of cancer, but psychiatric complications may emerge in patients with cancer due to various psychological impacts that have neurophysiologic and perceptual character. Such psychiatric complications and psychological challenges impair adjustment capabilities and quality of life of the patient, and also negatively affect the course of disease and response to treatment (4).

The prevalence of psychiatric disorders in patients with cancer reportedly ranges from 29% to 47%. The existence of depression may disturb compliance to treatment and negatively affect the course of disease, which increases the duration of hospitalization and treatment expenses (5). Recent studies found that the factors such as socioeconomic status, social support, performance capacity, recent losses, and awareness of the diagnosis of cancer might affect the rate of psychiatric disorders (6-8). In addition to its chronic and malignant nature, cancer is an important casue of emotional, mental, and behavioral reactions. In this sense, it is important to identify mental problems and underlying factors in order to understand the patient better, to facilitate his/her adjustment to the new state, and to plan a proper approach (9).

On the other hand, breast cancer is the most common cancer type among women and it has also always been the most investigated cancer type in terms of its mental and psychosocial aspects because it poses a threat to an organ that symbolizes femininity and sexuality (10, 11). In the event of breast cancer, initial reactions are usually related to pain and death, and subsequent reactions are about loss of breast, which may come into existence secondary to surgical therapies. Loss of breast, as an organ that represents motherhood, sexuality, and esthetics, is mostly perceived as a loss of attractiveness, fertility, sexuality, and femininity as a whole (12). Moreover, chemotherapy, radio-

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therapy, and surgical treatments lead to deterioration of the quality of life to a considerable extent, and to certain adverse physiological and mental effects such as anxiety, depression, body dysmorphic disorder, infections, and vomiting (13-16). The aim of this paper was to review psychiatric symptoms and illnesses that may develop in patients with breast cancer, and their potential impacts on treatment process.

Epidemiology of Breast Cancer

Examining the incidence, mortality, and prevalence of cancer for the year 2002 across the globe, it was reported that 10.9 million new cancer cases emerged, 6.7 million of which resulted in death, in addition to 24.6 million expected cases who were still alive. The most diagnosed types include lung, breast, and colorectal cancer (17). Breast cancer is the most common camcer one among women. It accounts for 33% of all cancer cases and 20% of cancer-related mortalities among women. In general terms, it is the second most common cause of cancer-related death after lung cancer (18). In Turkey, on the other hand, the incidence of breast cancer is observed to be 35% among women (19). A study on the assessment of cancer incidence and mortality across 40 European countries confirmed that the incidence of breast cancer ranked number three with a rate of 12.8% after lung and colorectal cancer cases (20). In 2006, the incidence of breast cancer was calculated to be 28.9% across Europe (21). In 2000, the rate was 24.9% for Turkey (22), reportedly tripling within last 10 years (23).

When it comes to the relationship between cancer-related mortalities among women and age groups, it is seen that leukemia ranks first in those aged 15 years and below, lung cancer comes first in the 55-74 years age bracket, colorectal cancer is the most common in those aged 74 years and above, and breast cancer ranks number one in the group aged 40-44 years (24).

Breast Cancer and Psychiatric Diseases

Cancer is a serious health problem that mostly leads to death in the absence of early diagnosis and treatment. In addition to causing death in millions of people, it brings a considerably high probability of occurrence of psychiatric disorders (25). Accompanying psychiatric disorders have a significant impacts on a patient's quality of life, self-care, adaptability to treatment, and over the course of time, the severity and prognosis of cancer as well as response to treatment (25-28). People who are told that they have cancer normally have difficulty in believing what they have heard at first place, fail to acknowledge the situation, lose their temper, and become sorrowful. After a couple of weeks, the mourning stage gives way to efforts to adjust, a desire to fight, and hope. However, in rare cases the mourning period lasts longer, turning distress and anxiety into a clinical presentation of depression (29). Features such as age, sex, personality, and variables that affect the prognosis of disease and response to treatment such as symptoms that give rise to loss of ability, location of cancer, pain, the degree to which it reduces the quality of life, life purposes, career, marriage, and family, and environmental conditions such as social support, the existence of someone who is perceived as helpful in an emotional sense, and socio-economic status have several impacts on the ability to cope with the diagnosis of cancer (28, 29). On the other hand, patients with breast cancer may suffer from significant psychological problems due to several reasons including uncertainty about treatment, physical symptoms, fear of recurrence and death, change in female identity, body image and sexuality, difficulties in daily life activities, family-related problems, and lack of emotional support (30-32). In several studies on the psychology of patients who underwent surgical procedures because of breast cancer, the psychological dysfunction rate was found to range from 30 to 47%, without any significant difference between those who underwent breast-conserving surgery (BCS) and those who underwent modified radical mastectomy (MRM). It was also observed that 20-45% of the patients continued to have a psychiatric disorder 1 year after the operation; 10% still had serious disorders 6 years after the operation (33). In a study consisting of 303 patients who underwent BCS or MRM, Kissane et al. found that 45% of the patients had various psychiatric disorders, 42% of whom had depression and anxiety, 27% had minor depression, 9.6% major depression, 8.6% solely anxiety, 6.9% phobic disorders, and 20% had 2 or more disorders (34). The diagnosis and treatment of psychiatric disorders may be helpful in increasing patients' adherence to therapy and quality of life (5). In this context, it is of high importance to identify mental problems and underlying factors in order to understand patients better, to facilitate adjustment to their new state, and to plan a proper treatment approach.

Depressive Disorder and Anxiety Disorders

Cancer involves a high probability of occurrence of psychiatric disorders, notably depression, anxiety, and adjustment disorders. The frequency of depression among patients with cancer ranges from an extremely low rate of 1% to considerably high rates such as 50%, partly due to the differences in cut-off scores suggested by varied diagnoses and scales (35). A review on this issue reported that 10-25% of patients with cancer were diagnosed with major depressive and clinically significant depressive symptoms (36). These rates imply that prevalence of major depression is 2-3 times more among patients with cancer as compared with the general population (37). Among young and middle-aged women receiving chemotherapy, levels of anxiety are usually higher (38). Patients with cancer who are diagnosed as having depression are reported to simultaneously have generalized anxiety disorders (24%), panic disorder (18%), and posttraumatic stress disorder (PTSD) (30%) (39). Patients with breast cancer cases involve a frequency of 19% according to a study conducted in our country, and of 16.7% according to a study performed abroad (40, 41). Depression in patients with cancer was confirmed to have extended the duration of hospitalization and reduced the quality of life (42). Another study found the prevalence of depression in patients with breast cancer as 9%, with an emphasis on the fact that 24% of the patients with depression had increased symptoms of depression over the course of their follow-up (43).

It is also specified that 4 in every 10 patients with breast cancer experience high levels of anxiety or depression (44). A study that assessed the patients during both the preoperative period and 3rd and 12th months within postoperative period detected that 55% of patients had anxiety and/or depression at any one or more assessment (45). In another study conducted on 503 patients with breast cancer, this rate was found as 45.3% among patients with early-stage disease and 37% in patients with advanced-stage disease (46). A study that employed the HAD scale to assess 1083 patients whose breast cancer diagnosis was received an average of 47 months previously determined anxiety and depression among 38.2% and 22.2% of the patients, respectively (47). Another study conducted on 84 women with breast cancer assessed the patients at pre-op, post-op 1-3 month, and post-op 9-12 month periods, and found anxiety rates of 33.3%, 35.7%, and 28.6%, respectively, and depression rates of 40.5%, 42.9%, and 44.0%, respectively; no statistically significant difference was observed in terms of average scores of anxiety and depression, as distributed to those three periods. The patients were found to have indicated lower scores of physical, psychological, and social relation dimensions of quality of life, as well as overall perceived quality of life, and perceived health status scores in

both early and late stages of the post-op period compared with pre-op period (48).

Another study that evaluated patients with breast cancer six times for a period of five years, from the initial diagnosis, reported that the depression rate was highest (48%) in the first year following initial diagnosis (49). Vahdadina et al. (50) found that even though average scores of anxiety and depression decreased over time, anxiety and depression rates were calculated as 38.4% and 32.3%, respectively, in the 18th month according to the cut-off score of the HAD scale (51). Hopwood et al. (52) evaluated 211 patients with advanced breast cancer using the HAD scale and confirmed an anxiety and/or depression rate of 27%. They also found that 155 patients continued to display signs of anxiety and/or depression after 1-3 months. According to another study that assessed depressive symptoms before the diagnosis of breast cancer, as well as in the post-op 1st, 3rd, 6th, and 12th months (50), the pre-diagnosis rate of depression of 40.9% decreased to 27.8% within 1 year, and depressive symptoms recovered over time (53). Burgess et al. (49) similarly indicated that the frequency of anxiety and/or depression in women with breast cancer was twice more than the general female population.

The consequence of patients with cancer developing anxiety and depression during treatment process is that their level of understanding and comprehension and skills to use coping methods deteriorate, it becomes more difficult for them to build social interactions, their adherence to treatment reduces, and their duration of hospitalization increases, which is accompanied by increased treatment costs and worsened quality of life (54-57). Psychological issues appearing in patients with cancer were reported to be associated with physical status, pain, sufficiency, emotional well-being, social relations, adjustment to disease, and relevant roles (58). Accompanying physical symptoms, cancer treatment that reduces quality of life, and a patient's disease-induced functional losses all make identification and treatment of depression more difficult (59). On the other hand, existing studies on patients with breast cancer indicate that psychiatric morbidity is associated with increased symptom load, decreased adherence to therapy, and deteriorated quality of life (40, 59, 60) (Table 1).

Table 1. Depression and Anxiety in Patients with breast cancer

Hopwood et al. (52) 1991	Depression and anxiety 27%
Ramirez et al. (45) 1995	Depression and anxiety 55%
Pasacreta (43) 1997	Depresion 9%
Gallagher et al. (44) 2002	Depression and anxiety 40%
Kissane et al. (46) 2004	45.3% (early stage) 37% (advanced stage)
Lueboonthavatchai (41) 2007	Depression 16.7%
Mehnert et al. (47) 2008	Depression 22.2% Anxiety 38.2%
Christensen et al. (51) 2009	Depression 32.3% Anxiety 38.4%
Karakoyun et al. (40) 2010	Depression 19%

Suicide

Frequency of suicide among patients with cancer is relatively higher with a relative risk of two times more than the general population (61, 62). Factors such as non-controllable pain, untreated depression, insufficient social support, substance use, history of suicide in the family, and deprivation could increase the risk of suicide (63-65). With a frequency of 8% among patients with cancer, suicide ideation may turn into actual attempt at a rate of 2-6%, particularly in the terminal stage (66, 67). Studies on this subject report that the risk of suicide considerably rises in cases accompanied by depression. Moreover, factors such as substance abuse, hopelessness, lack of social support, and advanced state of disease increase such risk (64, 65, 67). Although most patients with breast cancer are well-adjusted, single patients with advanced-stage breast cancer who have poor socioeconomic conditions have been found to have a higher suicide risk (68).

Sexual Dysfunction

The breast is a highly important organ because it symbolizes femininity and sexuality, surgical removal because of cancer poses a threat to senses of sexuality, motherhood, and attraction, and the patient's body image (3). Breast cancer involves a certain degree of malignancy, which leads to sexual dysfunction more than other cancer types because mastectomy is a common procedure (69). It is also reported that sexual life of patients with breast cancer is negatively affected by surgical intervention, radiotherapy, chemotherapy, and/or hormonal treatment through deterioration of physical well-being (70). The sexual lives of women who are diagnosed as having breast cancer are not different from those of any health individual (71). A study that investigated sexuality after breast cancer treatment underlined that the sex life was ignored following diagnosis of cancer, notably in Asian countries (72). Eighty-two percent of patients who received active treatment shared their sexual concerns with healthcare staff, the remainder stated that sexuality was the last thing on their mind during treatment (73). Radiotherapy and chemotherapy-induced fatigue decreases sexual appetite and activity of the patient (74). Other major factors that reduced sexual appetite of patients with breast cancer were reported as loss in breast tissue, hair loss, pain, body image, childbirth capacity, and changes in perception of medical status (75).

Sleep Disorders

One of the most common symptoms seen in patients with cancer is insomnia (76, 77). The prevalence of sleep disorders among patients with cancer is reported as 50%, with a higher frequency in women and more frequent occurrence among patienst with breast cancer compared with other cancers (78). When a patient has terminal cancer, sleep disorders and other symptoms increase to a considerable extent, especially in the terminal stage, which negatively impacts on quality of life (79, 80). Some other symptoms usually experienced by patients cancer include acute or chronic pain, anxiety, nausea-vomiting, depression, delirium, fatigue, infections, and high fever, which may lead to

sleep disorders. It is known that sleep disorders in patients with cancer increase mortality (81). Patients with breast cancer report higher prevalence of insomnia compared with patients with other types of cancer (from 38% to 61%) (82-85). Even though insomnia in patients with breast cancer can be associated with various factors such as psychological distress arising from the cancer diagnosis, or adverse effects of cancer therapy, patients who receive adjuvant endocrine therapy may still remain at increased risk for insomnia because of the occurrence of menopausal symptoms triggered by this therapy (86,87). A former study on the prevalence of insomnia among patients with breast cancer detected that 19% of the participants met the diagnostic criteria for an insomnia syndrome (82), and this finding was nearly identical to the clinically-significant insomnia (18.6%) reported in the present study (88). In this context, the ascertained significant risk factors for insomnia included psychological symptoms of depression and anxiety. One should not be surprised to discover a relationship between these symptoms and insomnia given the fact that psychological symptoms and insomnia are not necessarily independent of one another, and insomnia is a defining symptom of depression and generalized anxiety. It is also implied by these findings that sleep may be improved with the help of treatments devoted to rehabilitating depression and anxiety. There is another significant association found between drug use and insomnia. Higher intake of sleeping aids was significantly associated with clinical insomnia (88). A large number of women (63%) reported one or more sleep disorder types, with 37% using sleeping pills in the last 30 days. Difficulties in falling asleep were significantly linked to greater pain and symptoms of depression. Problems related with waking up at midnight were significantly associated with greater depression and less education. On the other hand, greater depressive symptoms and less social support were found to lead to the problems in waking/getting up at a significant level (89).

Psychiatric Symptoms Arising from Breast Cancer Treatment

Even though central nervous system toxicity is known to be based on chemotherapy, radiotherapy, and hormonal therapy procedures, the exact causes remain unclear. A study that compared cognitive function between patients with breast cancer who received chemotherapy and a control group indicated that cognitive functions of the patient group were more disordered than those of the control group (90). Patients who receive chemotherapy usually report changes in their cognitive functions. This state is also referred to as 'chemo-brain,' and includes the symptoms such as memory impairment, absence, and lack of concentration while doing daily life activities (91). Depending on the application of methotrexate, one of the chemotherapeutic agents, central nervous system toxicity may be seen in 3-11% of the patients on average. Toxic symptoms may manifest themselves in the form of changes in consciousness, leukoencephalopathy, seizure, cerebral infarction, paralysis, neuropathy, and ototoxicity (92). Corticosteroids, on the other hand, cause a great variety of cognitive disorders and mood changes (94). Radiotherapy may be responsible for short-term memory loss or decreases in academic success in the long term (93). Moreover, steroids and medications used in symptomatic treatment such as metoclopramide, an antiemetic drug, can lead to anxiety. Drugs that cause encephalopathy and delirium may simultaneously give rise to anxiety (94).

Psychosocial Problems in Patients with Breast Cancer

Apart from the stigmatization effect caused by breast cancer, other problems may appear associated with changes in femininity, sexuality, and fertility (95). One of the most important determinants of recovery from breast cancer is the patient's psychiatric state prior to diagnosis of cancer (96).

Diagnosis and treatment of breast cancer may induce psychological challenges such as anxiety, depression, anger, uncertainty about the future, hopelessness, desperateness, fear of recurrence of cancer, fear of separation from relatives, fear of pain, decrease in self-esteem, impairment of body image, fear of losing sexual capabilities, anxiety of not being loved or shown interest, and fear of death (97-99). A patient who experiences or displays these kinds of anxieties or symptoms may react in various ways including shock, denial, anger, depression, reflection, psychological regression, hopelessness-desperateness, weariness, and pathologic dependence (100). A study conducted on 275 patients with breast cancer reported that a statistically greater part of patients experienced psychological troubles (101). In addition to these, therapies cause several adverse effects, the most common ones were loss of energy, fatigue, pain, nausea and vomiting, hormonal changes, and sleep disorders; all of these adverse effects impair daily life functions of patients (102, 103). Physical symptoms, fatigue in particular, were reported to have a huge impact on quality of life, which gave rise to the formation of physiologic and psychological symptoms (104).

Psychosocial factors that affect the cancer can be listed as follows: personality structure, sociocultural features, psychosocial stress factors, negative feelings about the disease in the form of thinking about negative aspects such as death threat, coping methods, past experiences, lifestyle, and genetic characteristics (105, 106). Studies on chronic diseases have shown that psychiatric diseases such as depressive disorder have an environment in which they develop in an easier way in cases where social support is inadequate. It was also proven that psychosocial stress was influential in a negative way on the medical condition of those who received very little or lacked social support, and had very little or no effect on those supported by stronger systems (107). Lack of emotional and material support in patients with cancer is particularly considered to be act as a risk factor for psychiatric diseases such as anxiety and depression (108). Psychosocial stress factors reported to be prevalent in almost half of patients are more common among the patients with cancer with psychiatric disorder. The patients in this group stated that their spouses and children, who are normally sources of emotional support, could not understand them adequately, failed to be helpful at the treatment stage, and left them alone (9).

It was emphasized that support by a spouse increased patient's adherence to therapy (109). Studies also report that the patients with breast cancer have expectations of emotional support from their spouse and they adapt themselves to the treatment process more easily thanks to such support (110, 111). Uncertainty and fear often lead to an increase in a patients' need for social support. Efforts to understand patient relatives, disease, and the patient would probably change the perception of such situation as a stress factor and reduce related psychiatric problems (112, 113). The quality of life of patients and their relatives can be elevated by determining the social support perceived by the patients, planning the care to be provided, and incorporating the family into the care (114).

Impacts of Psychopharmacologic Drugs on Breast Cancer

Psychiatric treatment holds an important place in prognosis and adherence to the treatment of breast cancer. According to a study that analyzed the linkages between psychiatric comorbidity and patients with breast cancer who had started to receive psychiatric treatment, 29% of the patients were diagnosed as having a psychiatric disorder, 9% with a major depressive disorder and 6% with generalized anxiety disorder. Fifty-two percent of the patients were determined to have received psychotropic treatment over the course of disease, and 48% started psychotropic treatment without receiving any psychiatric di-

agnosis. Out of those who received treatment during cancer therapy, 80% were found to be on medication for major depressive disorder, and half were using drugs for generalized anxiety disorder (115).

The latest studies indicate that recognition of genotypes to establish metabolized activation of psychiatric drugs is considered as an effective method before starting treatment (116). Vasomotor symptoms such as hot flushes may develop as a result of anti-estrogen treatment or possible depression or anxiety. Studies on this have shown that SSRI and SNRI group psychiatric drugs reduce these symptoms in the menopausal period and in patients with breast cancer who received endocrine therapy. These are reported to be the drugs that contain active substances such as venlafaxine, escitalopram, and paroxetine, and more effective as compared with placebo. However, other studies have indicated that concomitant use of certain SSRI medications that inhibit the CYP2D6 enzyme, and anti-estrogen drugs such as tamoxifen reduces the impact of tamoxifen, and may affect the recurrence of breast cancer (117). Apart from SSRI and SNRI, antipsychotics, which are widely used in psychiatric treatment, were also found to generate some adverse effects when used in patients with breast cancer. It was considered that because patients with breast cancer had prolactin receptor overexpression, antipsychotics could trigger the activation of prolactin receptor, leading to tumorgenesis and proliferation of cancer cells in some patients (118). According to a case-controlled study conducted on the basis of the hypothesis that breast cancer could develop due to the use of antidepressants, it was found that SSRI and other antidepressants did not increase the risk of breast cancer; nevertheless, such risk might scale up due to use of tricyclic antidepressants for more than 2 years (119). A similar study concluded that exposure to tricyclic antidepressants at higher doses for more than 10 years would partly escalate the risk of getting breast cancer (120). SSRIs that affect tht CYP2D6 enzyme system such as paroxetine were also found to increase mortality risk in patients with breast cancer (121).

Conclusion

Patients with cancer may show emotional and behavioral changes during diagnosis and treatment processes. This may manifest itself both at a level of psychiatric disorder and in the form of mild emotional symptoms and behaviors. Psychiatric disorders may include anxiety, depression, adjustment disorders, and other psychiatric diagnoses that would likely be induced by medication and general medical condition. A review of the existing literature indicates that anxiety and depression are intensified during treatment, which deteriorates the quality of life. The team in charge of breast cancer treatment should have a good command of physical and psychosocial symptoms that may lead to anxiety and depression, and should be able to develop patient-specific treatment and care standards by evaluating the existing levels of depression. It is also necessary to deal with quality of life of patients with cancer and to provide them with emotional and psychosocial assistance. Each and every change in this process should be closely followed up under the supervision of specialist; all types of mental changes that affect adherence to the treatment process should be intervened in a timely manner, and social and medical support should be reconsidered.

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Original Article

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Factors that Affect Drain Indwelling Time after Breast Cancer Surgery

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ABSTRACT

Objective: The most common procedure to prevent seroma formation, a common complication after breast and axillary surgery, is to use prophylactic surgical drains. Ongoing discussions continue regarding the ideal time for removing drains after surgical procedures. In this study, we aimed to investigate factors that affect drain indwelling time (DIT).

Materials and Methods: From 2014 to 2015, a total of 91 consecutive patients with breast cancer were included in the study. The demographic characteristics of the patients, treatment methods, histopathologic features of the tumor, size of removed breast tissue (BS), tumor size (TS), number of totally removed lymph nodes (TLN), and metastatic lymph nodes (MLN), whether they had neoadjuvant chemotherapy, and the DIT were retrospectively recorded from the hospital database.

Results: The mean age of the patients was 48.9 years, and the mean DIT was 4.8 days. The mean size of breast removed was 17.3 cm and tumor size was 4.7 cm, and the mean number of metastatic lymph nodes was 3.3, and mean total number of lymph nodes was 14.1. Patients who had neoadjuvant chemotherahpy had longer DIT. There was a positive correlation between the BS, TS, TLN, MLN, length of hospital stay, and DIT. Linear regresion analysis revealed that the BS, TLN, and history of neoadjuvant chemotherahpy were independent risk factors for DIT.

Conclusion: DIT primarily depends on BS, TLN, and history of neoadjuvant chemotherahpy. A policy for the management of removing drains to prevent seroma formation should thus be individualized.

Keywords: Breast cancer, mastectomies, drainage, suction

Introduction

Drains offer a significant advantage for seroma after breast cancer surgery (1). Surgical drains are used in the immediate postoperative period because the dead space in the operation area is one of the most important factors for seroma-associated complications (1, 2). Although there are different ways to prevent seroma, including external compression, flap fixation, dead space obliteration (3) or tissue glues (1, 4), closed suction wound drainage has been accepted as the most effective technique in reducing morbidity (5-7). However, there are several disadvantages of drain insertion such as discomfort and retrograde migration of bacteria (2). According to a meta-analysis, there was no widely accepted consensus for an ideal time for drain removal following breast cancer surgery (8). Drain removal protocols vary enormously from hospital to hospital, even from department to department in the same hospital. Prolonged drainage may prolong hospital stay (9). Some patients refuse to be discharged with drains, because there are difficulties in managing them at home, which may result in wound infection. Early removal of drains has been linked with shorter length of hospital stay (LOS) (9-11). However, indiscriminate withdrawal of drains, regardless of the fluid volume of fluid drained, may be accompanied by increased seroma formation (9, 11-17). Therefore, repeated aspirations and even surgical draining may be required. Furthermore, the risk of infection, skin flap necrosis, prolonged hospital stay, and delay in the commencement of chemotherapy or radiotherapy, or both in some cases, are often increased if drains are not used (9, 11).

Drain indwelling time (DIT) has not been an issue in many centers for patients who are admitted in the early stages of cancer. However, 40% of the patients at our center are admitted with stage 3 disease and as such a common solution for this problem is still pending. There are many benefits to short-duration drains; however, early withdrawal complications and DIT are very important to know. We believe the knowledge of the factors that affect DIT is the most important step in determining the optimal time. Therefore, the need to investigate the ideal time for drain removal is warranted. The first step is to investigate factor(s) that affect DIT. Accordingly, we aimed to determine these factors in this study.

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Materials and Methods

The study was conducted from 2013 to 2014. Ninety-one consecutive patients with breast cancer were admitted to Faculty of Medicine, Department of General Surgery, and were included in the study. All procedures adhered to the ethical principles of the Helsinki Declaration. In order to identify factors that affect DIT, the demographic and tumor features of the patients management strategy, pathologic results of the tumor, the size of removed breast tissue (BS), tumor size (TS), the number of totally-removed lymph nodes (TLN) and metastatic lymph nodes (MLN), whether they had neoadjuvant chemotherapy, LOS, and DIT were retrospectively recorded from the hospital database. The greatest dimension was used for breast size and tumor size. The number of TLN and MLN was assessed using the final histopathologic report.

According to our unit protocols, all drains were removed after fifteen days regardless of the drainage volume, or when the drainage volume was less than 50 mL on two sequential days. If patients were discharged with the drain, they were seen every two days. If fluid collected after drain removal it was removed through percutaneous aspiration.

Statistical analysis

Statistical Package for the Social Sciences package program 18 (SPSS Inc.; Chicago, IL, USA) was used for statistical analysis. After preliminary analysis for factors affecting DIT, multivariate linear regression analysis was used to identify independent risk factors. $p<0.05$ was accepted as statistically significant.

Results

The study consisted of 91 women with a mean age of 48.9 years (range, 26-81 years); the mean DIT was 4.8 days (range, 0-13 days). The mean BS was 17.3±8.5 cm and TS was 4.73±2.948 cm, and the mean MLN was 3.3 (range, 0-19). The mean TLN was 14.1 (range, 2-32) and LOS was 5.93 days (range, 1-20 days). The rate of patients treated with neoadjuvant chemotherapy was 22/91 (24.18%). The mean DIT was 3.72±2.36 in the patients who had neoadjuvant chemotherapy and 8.18±2.86 in the others. The patients who had neoadjuvant chemotherapy had longer DIT ($p<0.001$).

There was a positive correlation between the BS, TS, TLN, and MLN, LOS, and DIT (Table 1). Linear regression analysis was performed for the statistically significant variable in the univariate analysis. Linear regression analysis revealed that the BS, TLN, and neoadjuvant chemotherapy used were independent risk factors for DIT (Table 2).

The effects of age, histopathologic type, hormone receptor status, concomitant disease on DIT were not statistically significant.

Discussion and Conclusion

The most common complication following breast cancer surgery is seroma, with an incidence of up to 90%. Seroma can lead to several problems including pain, delayed wound healing, skin necrosis, and infections if it remains untreated. It has been suggested that suction drainage markedly decreased the development of postsurgical seroma (10). Furthermore, it has been reported that nearly all of the total seroma formation was drained within the 48 hours of the post-operative period (1, 9). Interestingly, the levels of seroma showed wide variation between the trials. The rates were reported as 21% to 49% for early drain removal regimens, whereas 4% to 28% for late drain removal (8). Andeweg et al. (14) showed that short-term axillary drainage was related to a higher incidence of seroma. However, a similar number of aspirations were needed in the short- and long-term drainage groups with a similar volume per patient requiring aspiration.

The timing of drain removal was reported to have no influence on seroma formation (1, 11, 14, 18, 19). Moreover, no significant difference was demonstrated in the rates of infection between early and late drain removal (8, 18, 20-23). All these studies show that DIT is a very controversial issue. One reason for planning this study was that there is no consensus about DIT. We think that the consensus should begin by finding factors that affect DIT. Age, remains a controversial factor because some studies revealed apparent seroma formation, whereas others did not show a significant link, like in our study (10, 11, 24-29).

Table 1. Correlation coefficients between drain indwelling time and studied variables

		Total lymph node	Metastatic lymph node	Size of breast	Age	Tumor size	Hospital stay
Metastatic lymph node	R	0.539**	1				
	p	0.000					
Size of breast	R	0.341**	0.360**	1			
	p	0.001	0.000				
Age	R	0.102	0.064	0.064	1		
	p	0.334	0.544	0.549			
Tumor size	R	0.416**	0.359**	0.543**	-0.039	1	
	p	0.000	0.000	0.000	0.716		
Hospital stay	R	0.490**	0.280**	0.252*	0.053	0.220*	1
	p	0.000	0.007	0.016	0.615	0.036	
Drain remaining time	R	0.560**	0.244*	0.485**	0.152	0.362**	0.444**
	p	0.000	0.020	0.000	0.149	0.000	0.000

*Correlation is significant at the 0.05 level (2-tailed).
**Correlation is significant at the 0.01 level (2-tailed).

Table 2. Linear regression analysis of independent risk factors of drain indwelling time

	Unstandardized coefficients		Standardized coefficients			95% Confidence interval for B	
Model	B	Std. error	Beta	T	Sig.	Lower bound	Upper bound
(Constant)	-3.476	0.740		-4.700	0.000	-4.947	-2.006
Tumor size	-0.010	0.089	-0.010	-0.116	0.908	-0.186	0.166
Total lymph node	0.184	0.038	0.405	4.782	0.000	0.107	0.260
Metastatic lymph node	-0.040	0.060	-0.056	-0.669	0.505	-0.159	0.079
Size of breast	0.097	0.031	0.262	3.158	0.002	0.036	0.157
Neoadjuvant Chemotherapy	3.378	0.517	0.464	6.532	0.000	2.350	4.407

A. Dependent Variable: Drain Indwelling Time

In our clinical practice, we used closed suction drainage systems that are removed from skin flaps following from axilla. Dead space forming after excision is eliminated by the negative pressure applied by the drain. Thus, apposition of skin flaps is promoted and wound healing is strengthened. Negative pressure may decrease wound dehiscence, necrosis, infection and seroma formation as well (4, 10, 30, 31). Closed suction drainage systems seem to be more successful than open drainage systems (32).

First, the drain of the mastectomy skin flaps was removed. The axillary drain remained and continued to drain (1).

Various factors might affect seroma formation. Axillary dissection is related to the formation of postoperative seroma (33). The development of a seroma has been reported in 10% to 52% of cases (9, 34). If a great number of lymph nodes were dissected from the axilla, much more seromas were observed. The higher lymph node yield might be considered as an indirect measure of a more extensive axillary dissection in patients with seroma (1). The amount of drainage may project the extent of injury to the lymph vessels (13). As such, tissue ligation around the axillary vessels during dissection may decrease the amount of postoperative discharge compared with transection with a knife or diathermy (23). The number of lymph nodes remains a controversial factor because some authors declared obvious seroma formation, whereas others did not observe a significant relation (10, 11, 24-29). However, the number of lymph nodes removed during axillary dissection was found to be an independent risk factor for the duration of draining in the present study.

Sentinel lymph node biopsy (SLNB) is a minimally-invasive alternative technique to axillary dissection. SLNB has significantly lower seroma formation rates compared with axillary dissection (10, 35-37). It also prevents the damage to blood and lymphatic vessels by reducing the need for larger dissection (10). In this study, DIT was lower in patients who were SLNB negative, some of them even had no drainage performed. However, these benefits were reached only if SLNB results were benign; our patients were admitted in the later stages and benefit was limited.

Another factor is the presence of metastatic lymph nodes (9, 32, 38, 39). The number of metastatic lymph nodes remains controversial because some studies found significant seroma formation, and others showed an insignificant association, similar to our study (10, 11, 24-29).

Breast size is another important factor (9, 32, 38, 39). Wide chest wall dissection influences seroma formation (14). Breast size was not found to have a significant influence on seroma formation in some studies (40, 41). Extensive dissection causes damage to more blood and lymphatic vessels and subsequently results in larger seroma formation. More seroma is seen in modified radical mastectomy than in simple mastectomy or wide local excision plus axillary lumpectomy (7, 10, 25-27). When MRM was compared with breast-conserving surgery (BCS), although the results were mixed, MRM had an overall higher seroma formation (10, 42-45). There were correlations between removed breast size and DIT in the present study. Therefore, we found that smaller surgery corresponded with lower DIT. Studies showed that patients who underwent MRM had higher risk of developing seroma than patients who underwent BCS or completed axillary clearance (11, 19, 29). Some studies showed that tumor size had no significant influence on seroma formation (10, 40, 41). In the present study, there was a correlation between tumor size and DIT, but it was not found as an independent risk factor.

Diabetes mellitus was not found as a significant influence on seroma formation (10, 40, 41) and hypertension was significant in influencing factors for seroma formation (10, 36). In our study, neither disease had a significant effect on DIT.

Neoadjuvant chemotherapy used was an independent risk factor for DIT in our study, but other studies determined that this form of chemotherapy had no significant influence on seroma formation (10, 40, 41).

The limitations of our study include: 1. Surgical factors, including technique (surgeon A versus surgeon B), extent of dissection (total mastectomy vs. modified radical mastectomy), surgical devices used for dissection (electrocautery vs. scalpel), these were not investigated; 2. The study would have benefitted if it included patient characteristics such as body mass index and body weight.

Drain indwelling time should be individualized to prevent seroma formation. DIT primarily depends on BS, TLN, and which neoadjuvant chemotherapy is used.

Ethics Committee Approval: Ethics committee approval was received due to the retrospective nature of this study.

Informed Consent: Verbal informed consent was obtained from patients who participated in this study.

Peer-review: Externally peer-reviewed.

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Original Article

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Correlations Between Oncotype DX Recurrence Score and Classic Risk Factors in Early Breast Cancer: Results of A Prospective Multicenter Study in Turkey

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ABSTRACT

Objective: Breast cancer is the most common malignancy among Turkish women and the rate of early stage disease is increasing. The Oncotype DX 21-gene assay is predictive of distant recurrence in ER-positive, HER2-negative early breast cancer. We aimed to evaluate the correlations between Recurrence Score (RS) and routine risk factors.

Materials and Methods: Ten academic centers across Turkey participated in this prospective trial. Consecutive patients with breast cancer who had pT1-3, pN0-N1mic, ER-positive, and HER2-negative tumors were identified at tumor conferences. Both pre- and post-RS treatment decisions and physician perceptions were recorded on questionnaire forms. Correlations between RS and classic risk factors were evaluated using univariate and multivariate analyses.

Results: Ten centers enrolled a total of 165 patients. The median tumor size was 2 cm. Of the 165 patients, 57% had low RS, 35% had intermediate RS, and 8% had high RS, respectively. Multivariate analysis indicated that progesterone receptor (PR) and Ki67 scores were significantly related to RS.

Conclusion: Oncotype DX Recurrence Score does not seem to have a significant correlation with the majority of classic risk factors, but it may have a correlation with PR score and Ki67 score.

Keywords: Oncotype DX, pathology, hormone receptors, Ki67, correlation

Introduction

Invasive breast carcinoma is the most commonly seen malignancy and the leading cause of cancer-related death in Turkish women, both in premenopausal and postmenopausal age groups. Forty-five percent of all patients with breast cancer are premenopausal because of the larger young population in Turkey (1). The incidence of breast cancer has been observed to be gradually increasing in Turkey, and this has been attributed to westernized lifestyle, population growth, and aging, and most importantly, the successful implementation of nation-wide opportunistic screening programs in newly- opened cancer screening centers. The latter contributed to a higher proportion of earlier stage disease reported in recent decades (2). According to the Turkish Ministry of Health, nearly half of all breast cancer cases across the country were diagnosed at an early stage in 2011 (3). A recent analysis of 13,240 patients in the National Breast Cancer Database established within the Turkish Federation of Breast Diseases Societies showed that 50% of patients had pN0 disease, and 27% of all patients' breast cancer was diagnosed as stage I disease. Overall, 62% of patients had pathologic characteristics of luminal A- type breast cancer (1).

The prognostic features most commonly used in adjuvant treatment decisions for patients who are node-negative include patient age, menopausal status, tumor size, tumor grade, Ki67 score, HER2 status, and strength of estrogen receptor (ER)/progesterone receptor (PR)

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expression. Although the treatment decision is easier for patients with unequivocal features, it becomes challenging to personalize therapy for those with early-stage breast cancer who have less clearly defined features, especially when they are young. Occasionally, agreeing on a treatment plan may be difficult in tumor conference even for tumors with the luminal A-like phenotype, which are believed to be less responsive to chemotherapy (4, 5).

With an increasing breast cancer incidence and with nearly half of new breast cancer cases presenting as stage pN0 in Turkey, overtreatment is gaining significance as a health care and medical ethics issue facing Turkish physicians and patients, as well as the national health insurance system, which provides extensive coverage for cancer treatment and treatment-related toxicities.

There is increasing evidence that molecular tests may have a role in individualizing therapy. The Oncotype DX 21-gene assay quantifies the likelihood of distant recurrence in women with ER-positive, lymph node-negative breast cancer treated with adjuvant tamoxifen, and it has been validated to predict benefit from chemotherapy in this population (6, 7). It has been incorporated into commonly accepted guidelines including the National Comprehensive Cancer Network (NCCN) (8), the American Society of Clinical Oncology (ASCO) (9), the European Society of Medical Oncology (ESMO) (10), and St Gallen Consensus guidelines (4). The analysis of women in the lowest risk group of the recently-reported TAILORx trial (clinicaltrials.gov identifier NCT00310180) provided prospective evidence that this low-risk group (Oncotype DX Recurrence Score 0-10) may potentially be spared chemotherapy, with 5-year rates of distant relapse-free survival of 99%, invasive disease-free survival of 94%, and of overall survival of 98% with hormonal therapy alone (11). It should be noted that in the original Oncotype DX studies, the cut-off level of RS 18 or lower was indicative of lower risk with a 10-year risk of distant recurrence of 6.8% (95% confidence interval (CI):[4.0 to 9.6]), which was significantly lower than in the high-risk group (RS 31 or higher) whose 10-year distant recurrence risk was 30.5% (95%:[23.6 to 37.4]) (6). Similar data defined the current practice of using RS 18 or lower as an indicator of low risk of recurrence.

The Oncotype DX 21-gene assay is not considered feasible by many Turkish physicians owing to its cost; it is not currently reimbursed by the Turkish Social Security Administration. We designed a prospective multicenter study that aimed to assess the impact of the Oncotype DX Recurrence Score result (RS) on treatment decisions, and the physicians' perceptions regarding influence of RS results on their final treatment recommendations. We also analyzed the correlation between RS and routine pathologic risk factors used at our tumor conference discussions.

Materials and Methods

Patients and Study Design

Ten academic centers in seven Turkish cities that routinely discuss all new cases of breast cancer at weekly multidisciplinary tumor conference participated in this prospective trial. The study was approved by a central Ethics Committee, as well as by each Institutional Review Board. Consecutive patients with breast cancer who had pT1-3, pN0-N1mic, M0, ER (+), and HER2 (-) tumors were identified. Tumors with ≥1% positively-stained cells for ER and PR were considered ER- and PR-positive, respectively. "Luminal subtypes" were defined based on PR and Ki67 evaluation as follows: luminal A = PR score ≥20 and Ki-67 <20%; luminal B = PR <20% or Ki67 >20%. Adjuvant treatment decisions were made with careful consideration of clinical and pathologic information by all of the tumor conference members. This initial treatment decision (pre-RS assay decision) was recorded on a questionnaire form by site investigators, and baseline pathologic characteristics were recorded in an enrollment form. The patients identified at tumor conference were individually contacted. The pre-RS assay decision was conveyed and informed consent was obtained. Formalin-fixed paraffin-embedded (FFPE) tissue blocks were sent to the central laboratory (Genomic Health, Inc.; California, USA). Cases were discussed at tumor conference again when the RS became available and investigators filled the post-RS assay questionnaire forms with their final decision. The pre- and post-RS assay questionnaires also contained questions aimed to capture how strongly the investigator believed that the RS assay result would contribute, and did contribute to the final treatment decision, respectively.

Statistical analysis

Statistical analyses on the Oncotype-DX RS were conducted using both nominal data based on the actual RS score, and an ordinal scale with three RS categories (<18, 18-30, >30). Integrated evaluation by multivariable analysis was performed to study the association between RS (dependent variable) and all clinicopathologic risk factors (predictors) using linear regression models. The risk factors (independent variables) included in the multivariable regression analysis were age, tumor size, tumor grade, ER score, PR score, Ki67 score, and HER2 score (per immunohistochemistry). The cut-off for p value was taken as less than 0.05 for statistical significance in all analyses performed.

Results

Patient and Tumor Characteristics

In total, 165 patients were enrolled from 10 centers across Turkey. The median age was 49 years (range, 26-76 years). Table 1 outlines the patient and tumor characteristics at the time of surgery. One hundred eight (65.5%) patients had pT1 tumors and the median tumor size was 2 cm (range, 0.6-8.0 cm). Only 11 (6.7%) patients had micrometastasis in axillary lymph nodes (pN1mic). The majority of patients had modified Scarff-Bloom-Richardson grade 2 tumors (n=108, 65.5%). Overall, 76 (53.5%) patients had a Ki67 score of <20%, including 60 patients whose Ki67 scores were less than 14%. Based on PR and Ki67 scores, 90 (60.4%) patients were considered to have characteristics of luminal B molecular subtype.

Associations between RS and Clinicopathologic Features

When age groups were analyzed with three different cut-off values (age < or ≥ 40, 45 or 50 years), age was not found a significant predictor of RS in either univariate or multivariable analysis (Mantel-Haenszel test for univariate and regression model for multivariable analysis; p= 0.297, table not included). Among patients who were aged less than 40 years, 52.2% had a low RS, 30.4% had an intermediate RS, and only 17.4% had a high RS. For patients aged over 50 years, these ratios were 54.8%, 31.0%, and 12.1%, respectively.

In the univariate analysis, grade (p=0.002), Ki67 score (14% and 20% cut-offs; p<0.001 for both groups) and PR score (cut-off 20%; p<0.001) were the only risk factors that significantly correlated with RS, whereas tumor size, LN status (presence of micrometastasis), and ER score were not found significant predictors of RS (Mantel-Haenszel test; table not included). Among patients with luminal A-molecular subtype as per their PR and Ki67 scores, the vast majority

(81.4%) had a low RS and only 1.7% had a high RS. In contrast, only 41.1% of patients with luminal B tumors had a low RS and 13.3% had a high RS (Mantel-Haenszel test, p<0.001).

Multivariable analysis of all risk factors including Ki67, age, tumor size, ER score, PR score, and HER2 score (0 vs +1) showed that the combination of all these numeric variables constituted a statistically significant regression model for predicting RS (R= 0.671, R^2= 0.450, p<0.001). When each variable was examined, Ki67 and PR scores were the only variables that seemed to significantly contribute to estimating the RS (Table 2). The seven predictors included in the regression model shown in Table 2 constituted a group of variables that, in combination, could predict the Oncotype DX score, whereas when they were tested individually in the multivariate analysis, it was seen that RS decreased as Ki67 increased (Beta=0.424, p<0.001), and RS decreased as PR increased (Beta= -0.381, p<0.001), but the other variables in the model did not significantly predict RS independently.

Discussion and Conclusion

Although our results suggest correlation with some pathologic features, the RS result made a significant impact in clinical practice despite rigorous pathologic evaluation at our academic centers, as reported separately (12). The significant predictors in our multivariate analysis included the Ki67 score, which is also considered to be important in predicting luminal subtype. It should be noted that significant inter-laboratory variability is a notable concern when interpreting Ki67 score, especially in grade 2 tumors (13). Our multivariable analysis also suggests that the PR score may have a predictive value in estimating the risk group, also as reported in earlier literature (14). As in interpretation of the Ki67 score, variability in immunohistochemistry results could potentially influence physician confidence in PR score while planning treatment. The strength of PR expression may help identify those patients who could require more careful evaluation of prognostic parameters, and potentially molecular testing.

Aside from the limitations inherent in Ki67 testing in general, another main limitation of our study was the sample size, which was restricted because of the high cost of the test and the limitations of the academic grant. While providing valuable information as the largest national study within our country, reaching more patients could help us draw

Table 1. Patient and Tumor Characteristics (n=165)

		n (%)
Age	<40 years	23 (14.0)
	40-49 years	70 (42.4)
	≥50 years	72 (43.6)
Tumor size	≤1 cm	19 (11.5)
	1-2 cm	89 (53.9)
	>2 cm	57 (34.5)
LN Status	pN0	154 (93.3)
	pN1 mic	11 (6.7)
Grade	1	28 (17.0)
	2	108 (65.5)
	3	26 (15.8)
ER score	≤10%	6 (3.6)
	11-30%	4 (2.4)
	31-50%	6 (3.6)
	51-70%	14 (8.5)
	>%70	135 (81.8)
PR score	≤20%	54 (32.7)
	>%20	111 (67.3)
Ki67 score	<20%	76 (53.5)
	≥%20	66 (46.5)
Luminal Subtype (n=145)*	Luminal-A	59 (39.5)
	Luminal-B	90 (60.4)

"Luminal subtypes*" were defined based on PR and Ki67 evaluation as follows: Luminal A= PR score ≥20 and Ki-67 <20%; Luminal B= PR <20% or Ki67 >20%. Sixteen patients had missing Ki67 data and therefore a subtype could not be assigned.

ER: estrogen receptor; PR: progesterone receptor

Table 2. Correlation between RS and clinicopathologic factors, multivariate regression analysis

R	R2	Corrected R2	SE	p
0.671	0.450	0.421	7.961	<0.001
Variables	**B**	**SE**	**Beta**	**p**
Fixed	23.066	4.816		<0.001
Ki-67 score (%)	0.286	0.047	0.424	<0.001
PR score (%)	-0.111	0.019	-0.381	<0.001
Age (years)	-0.104	0.066	-0.106	0.118
Grade	1.576	1.308	0.084	0.231
HER-2 (0 or +1)	0.985	0.937	0.069	0.295
Tumor size (cm)	-0.733	0.706	-0.068	0.301
ER score (%)	-0.027	0.030	-0.059	0.374

ER: estrogen receptor; PR: progesterone receptor; RS: recurrence score

clearer conclusions that are more reflective of the Turkish population, given our ever-growing population size and the genetic/ethnic variability in our population.

Some groups have argued that results of a careful pathologic examination negate the need for Oncotype DX testing and routine pathologic parameters, or composite indexes created using these parameters can predict Oncotype DX assay results (15-18). On the other hand, despite the predictive value of a careful pathologic evaluation, breast oncologists tend to overestimate the recurrence risk in a considerable number of patients (19). The comfort level in sparing a patient from chemotherapy may be even lower in regions with less experience of using molecular testing in routine practice. Moreover, patients with equivocal pathologic features, most of whom have luminal-B subtype tumors, may be conflicted about the treatment recommendation. According to their most recent consensus report, the St Gallen Expert Panel did not believe chemotherapy should be recommended in all patients with luminal B-like disease and that it could be omitted in cases with low scores on Oncotype DX.

Oncotype DX may provide additional information to improve personalize therapy in a significant proportion of patients with early stage breast cancer. More frequent use in carefully selected patients may help spare patients from chemotherapy, and in some rare instances, it may help correctly identify high-risk patients who would otherwise be recommended hormonal therapy alone. Moreover, when used with careful consideration, it may increase confidence levels in treatment recommendations. Among pathologic parameters, Ki67 score and PR score seem to correlate with RS, which would be expected, because these parameters are included among the 16 cancer-related genes in the score.

Ethics Committee Approval: Ethics committee approval was received for this study.

Informed Consent: Informed consent was obtained from patients who participated in this study.

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Original Article

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Correlation between 18F-FDG Positron-Emission Tomography 18F-FDG Uptake Levels at Diagnosis and Histopathologic and Immunohistochemical Factors in Patients with Breast Cancer

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ABSTRACT

Objective: In this study, we aimed to determine the correlation between pretreatment-staging 18F-FDG total body positron-emission tomography/computed tomography (PET/CT) maximum standardized uptake value (SUV_{max}) levels and histopathologic and immunohistochemical predictive and prognostic factors in patients with breast cancer.

Materials and Methods: One hundred thirty-nine women with breast cancer who were treated between 2009 and 2015 at our hospital and who had pretreatment-staging PET/CT were included in the study. SUV_{max} levels and histopathologic and immunohistochemical results were compared.

Results: The median age of the women was 48 years (range, 29-79 years). The mean tumor volume was 33.4 mm (range, 0.7-120 mm). The histology was invasive ductal carcinoma in 80.6% of the patients. In the univariate analysis, SUV_{max} levels were significantly higher in patients with invasive ductal carcinoma; in patients with a maximum tumor diameter more than 2 cm; patients who were estrogen, progesterone, and combined hormone receptor-negative, triple-negative patients, and in tumors with higher grades ($p<0.05$). In HER2-positive patients, SUV_{max} levels were higher even if it was not statistically significant. There was no correlation between lymph node metastases and pathologic stage. In multivariate analysis, tumor diameter was an independent factor.

Conclusion: SUV_{max} levels are correlated with known histopathologic and immunohistochemical prognostic factors. PET/CT could be useful in preoperative evaluation of patients with breast cancer to predict biologic characteristics of tumors and prognosis.

Keywords: Breast cancer, positron-emission tomography, 18F-FDG, predictive, prognosis

Introduction

Breast cancer is the most common cancer in women in Turkey and worldwide (1). Although it can be cured when diagnosed early, it is the cause of most cancer deaths in women (2). Breast cancer is a heterogeneous disease, and it is crucial to determine its prognosis and choose an optimal treatment option (3). Traditionally, the most significant prognostic factors are patient's age, size of the tumor, histologic grade, and number of involved axillary lymph nodes (4). The patient's condition at the time of diagnosis plays a vital role in choosing the therapeutic approach. Determining the patient's prognosis preoperatively is gaining more and more importance while the number of patients that receive neoadjuvant chemotherapy and breast-conserving surgeries increase (5). The most important contributions of diagnostic imaging methods in breast cancer can be early diagnosis, more accurate and intervention-free staging, and effectiveness in monitoring treatment and determining prognosis (6).

Positron-emission tomography (PET) is a non-invasive imaging method that uses positron-emitting isotopes. In recent years, it has been used increasingly frequently in clinics, especially in oncology (7). The most commonly used radiopharmaceutical, FDG tagged with fluorine-18 (18F-FDG) is a glucose analog whose FDG involvement in tissues is in proportion to the use of glucose; it is taken up into cells like glucose but cannot be metabolized (8). The maximum standardized uptake value (SUV_{max}) is a semi-quantitative indicator of 18F-FDG's involvement by lesions and this value is related to the number of living tumor cells (9).

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18F-FDG positron-emission tomography/computed tomography (18F-FDG PET/CT) is recommended in the current treatment guidelines for conditions such as locally-advanced breast cancer and metastatic disease (10). PET/CT helps determine extra-axillary regional lymph nodes and distant metastases in patients with newly-diagnosed breast cancer and can change staging and treatment (11). In pathologically-diagnosed breast cancer, it was found that preoperative 18F-FDG PET/CT screening could give sufficient information on tumor biology, prognosis, disease-free survival, and the patient's treatment (12). Turkey's Social Security Institution covers reimbursement of PET/CT scan for breast cancer staging, restaging, and evaluating the treatment response; the examination is commonly required before surgery. In this study, we aimed to determine the correlation between maximum SUV values gathered from PET/CT scans performed for staging patients with breast cancer and histopathologic and immunohistochemical predictive and prognostic factors.

Materials and Methods

A total of 139 patients with breast cancer who underwent radiotherapy and preoperative PET/CT scan for clinical staging in our hospital between September 2009 and December 2015 were enrolled in the study. All patients were histopathologically-diagnosed as having breast cancer. Patients who underwent excisional biopsy, patients who had surgery elsewhere, patients who received neoadjuvant chemotherapy, patients who had distant metastasis, and those with no FDG involvement in tumor in their PET/CT scan were excluded from the study. Our study was carried out retrospectively, and permission was obtained from the local ethics committee and the hospital management to reach archived files. Written consent was given by all patients for PET/CT scans, surgery, and radiotherapy.

For the PET/CT scan, after at least 4-hour fasting, the patients with blood sugar value under 200 mg/dL were given intravenous 0.15 mCi/kg 18F-FDG compound and were advised to rest in a calm setting without speaking or chewing. After approximately 60 minutes, emission and transmission imaging was taken on a PET camera (Siemens Biograph TruePoint 2008A) from the skull base to the upper part of the femur for whole body images in eight bed positions, every position for three minutes. Consecutive 0.5-cm thick sections were prepared on axial, coronal, and sagittal planes of the regions within the scope of the image using the reconstruction method. Furthermore, maximum intensity projection (MIP) images were assessed. A 50 mL oral contrast agent was used for image capture. SUV_{max} was calculated as the rate of maximum activity intensity in lesion based on the dose of FDG injected per kilo. After the staging examinations were completed, the patients underwent mastectomy or breast-conserving surgery (BCS) and sentinel lymph node biopsy (SLNB) or axillary dissection. The histopathologic and immunohistochemical data were recorded from the patients' pathology reports. Histologic type, maximum tumor diameter, histologic grade, nuclear grade, estrogen receptor (ER), progesterone receptor (PR), human epidermal growth factor receptor 2 (HER2) status, number of analyzed lymph nodes, status of lymph node metastasis, and number of metastatic lymph nodes were recorded for each patient.

Statistical analysis

The descriptive analyses and numeric data are presented as mean±standard deviation. The comparison of the SUV_{max} values and histopathologic and immunohistochemical factors was performed using the Mann-Whitney U test and Kruskal-Wallis test. Multiple regression analysis test was used for multivariate analyses. P≥0.05 was considered statistically significant. Statistical analyses were completed using SPSS version 20.0 (IBM, Armonk, NY).

Results

A total of 139 patients were included in the study. The patients' clinical and pathologic characteristics are shown in Table 1. All of the patients were women. The median age was 48 years (range, 29 to 79 years). The mean values of SUV_{max} were 6.22±4.2 (range, 0.78-25.56) for the primary tumors and 4.26±2.8 (range, 1-13.6) for the lymph nodes. In the PET/CT reports, the mean tumor diameter was 24.6±11.8 mm (range, 10-100 mm). There was no FDG involvement in lymph nodes in 83 (59.7%) patients according to the PET/CT scans.

Twenty-eight patients (20.1%) underwent BCS and SLNB; 21 patients (15.1%) underwent BCS and AD; 71 patients (51.1%) mastectomy and AD; and 19 patients (13.7%) had mastectomy and SLNB. The histology was invasive ductal carcinoma for 112 patients (80.6%), 16 (11.5%) had invasive lobular carcinoma, and 11 patients (7.9%) had other histologic subtypes (medullary carcinoma in four patients (2.9%), mixed carcinoma in four patients (2.9%), papillary carcinoma in one patient (0.7%), tubular carcinoma in one patient (0.7%), and cribriform carcinoma in one patient (0.7%). The mean tumor diameter was 33.4 mm (range, 7-120 mm, SD 17.5). The mean number of mitoses in 18 and 35 patients whose number of mitoses and Ki-67 values were present in their pathology reports was 12.2 (range, 1-34) and 31% (range, 1%-80%), respectively. For T-stages, 28 patients (20.1%) had T1, 92 patients (66.2%) had T2, and 19 patients (13.7%) T3 disease. Tumor multifocality was discovered in 32 patients (23%) and multifocal tumors were found in the PET/CT scans of 12 patients (8.6%), which was evaluated using the highest SUV_{max} value. Eighty-five patients (62.2%) had pathologic lymph node metastasis. The mean number of dissected lymph nodes was 20±14 (range, 1-53, including sentinel lymph nodes). N-staging was as follows: 54 patients (38.8%) were N0, 53 patients (38.1%) were N1, 13 patients (9.4%) were N2, and 19 patients (13.7%) were N3. Micrometastasis was reported for five patients with N1 lymph node staging (N1mi: 5 patients). The mean number of metastatic lymph nodes was 7.2 (range, 1-45). Comparing FDG involvement in the lymph nodes and pathologic lymph node metastasis in the PET/CT scans, PET/CT was found false positive in 9 patients (6.5%), and false negative in 38 patients (27.3%). Histologic grades were grade 1 for 7 patients (5.0%), grade 2 for 54 patients (38.8%), and grade 3 for 78 patients (56.2%). On the other hand, nuclear grades were distributed as grade 1 for one patient (0.7%), grade 2 for 39 patients (28.1%), and grade 3 for 99 patients (71.2%). ER was positive in 106 patients (76.3%), and PR was positive in 97 patients (69.8%). When the estrogen and/or progesterone receptors were analyzed together, the hormone receptors in 109 patients (78.4%) were found positive. HER2 was positive in 47 patients (33.8%), and those whose results could not be obtained through immunohistochemical methods went through a fluorescence in situ hybridization (FISH). The results of 11 (7.9%) patients were triple-negative (ER, PR, and HER2 negative). The patients' distribution based on pathologic stage was as follows: 17 patients (12.2%) were stage IA, 2 patients (1.4%) were stage IB, 43 patients (30.9%) were stage IIA, 34 patients (24.5%) were stage IIB, 25 patients (18%) were stage IIIA, and 18 patients (12.9%) were stage IIIC.

The correlation between the PET/CT SUV_{max} values and the patients' clinical and pathologic factors is demonstrated in Table 2. For uni-

Table 1. Patient and tumor characteristics (n=165)

Characteristics	Number	%	Characteristics	Number	%
Age	Median age 48±10.2 years (range, 29-79)		Histologic grade		
Aged <45 years	51	36.7	1	7	5.0
Aged ≥45 years	88	63.3	2	54	38.8
SUV_{max} values	6.22±4.2 (range, 0.78-25.56)		3	78	56.2
PET/CT lymph node SUV_{max} values	4.26±2.8 (range, 1-13.6)		Nuclear grade		
PET/CT tumor diameter	24.63±11.8 mm (range, 10 mm-100 mm)		1	1	0.7
PET/CT lymph node involvement			2	39	28.1
Positive	56	40.3	3	99	71.2
Negative	83	59.7	Estrogen receptor		
Operation type			Negative	33	23.7
BCS+SLNB	28	20.1	Positive	106	76.3
BCS+AD	21	15.1	Progesterone receptor		
Mastectomy+SLNB	19	13.7	Negative	42	30.2
Mastectomy+AD	71	51.1	Positive	97	69.8
Histopathologic diagnosis			Hormone receptor (ER and/or PR +)		
Ductal carcinoma	112	80.6	Negative	30	21.6
Lobular carcinoma and others	27	19.4	Positive	109	78.4
Tumor diameter	33.39 mm±17.5 (7 mm-120 mm)		HER2		
T-stage			Negative	92	66.2
1	28	20.1	Positive	47	33.8
2	92	66.2	Triple-negative		
3	19	13.7	Yes	128	92.1
N-stage			No	11	7.9
0	54	38.8	Pathologic stage		
1	53	38.1	IA	17	12.2
2	13	9.4	IB	2	1.4
3	19	13.7	IIA	43	30.9
			IIB	34	24.5
			IIIA	25	18.0
			IIIC	18	12.9

SUVmax: maximum standardized uptake value; PET/CT: Positron-Emission Tomography/Computed Tomography; BCS: breast-conserving surgery; SLNB: Sentinel Lymph Node Biopsy; AD: axillary dissection; ER: estrogen receptor; PR: progesterone receptor; HER2: human epidermal growth factor receptor 2

variate analyses, the patients' age, histologic subtype, maximum tumor diameter, existence of lymph node metastasis, histologic grade, nuclear grade, ER, PR, combined hormone receptor hormone receptor, HER2 condition, triple-negative results, and pathologic stage were compared.

When the SUV_{max} values were compared based on age, the SUV_{max} values in patients aged less than 45 years were found statistically significantly high (p=0.04). The comparison based on histopathology was performed in groups as ductal carcinoma, lobular carcinoma, and others, and the SUV_{max} values in ductal carcinoma were found statistically significantly high (p=0.04). The SUV_{max} values were also statistically significantly higher in patients with tumor diameters more than 2 cm (T2, T3 tumors), compared with patients whose tumor diameters were 2 cm or less (T1 tumors) (p=0.02). There was no statistically significant difference between the SUV_{max} values of the patients with and without lymph node metastasis (p=0.24). As histologic grade and nuclear grade increased, the tumor SUV_{max} values became statistically significantly higher (p=0.001 and p=0.004, respectively). The patients with negative ER, PR, and hormone receptors had statistically significantly higher SUV_{max} values (p>0.001). Although patients with positive HER2 had higher SUV_{max} values, there was no statistically significant difference (p=0.308). The triple-negative patients had statistically significantly higher SUV_{max} values than those with negative HER2 (p= 0.05). The only finding in the multivariable analysis was that tumor diameter was an independent prognostic factor.

Table 2. Correlation between clinical and pathologic prognostic factors and SUV_{max} values

Variable	Comparison	Number	SUV_{max} (Mean±SD)	p
Age (years)	<45 years	51	6.9±0.6	0.04
	≥45 years	88	5.8±0.4	
Histopathologic diagnosis	Ductal carcinoma	112	6.6±0.4	0.04
	Lobular carcinoma and others	27	4.7±0.8	
Tumor diameter	≤2 cm (T1)	28	4.5±0.8	0.02
	>2 cm (T2-T3)	111	6.7±0.4	
Lymph node involvement	Negative	54	6.6±0.6	0.24
	Positive	85	5.9±0.5	
Histologic grade	1	7	3.3±1.5	0.001
	2	54	5.4±0.6	
	3	78	7.0±0.5	
Nuclear grade	1	1	5.7±4.2	0.004
	2	39	5.2±0.7	
	3	99	6.6±0.4	
ER	Negative	33	8.7±0.7	<0.001
	Positive	106	5.4±0.4	
PR	Negative	42	8.0±0.6	<0.001
	Positive	97	5.4±0.4	
Hormone receptor	Negative	30	8.9±0.7	<0.001
	Positive	109	5.5±0.4	
HER2	Negative	92	5.9±0.4	0.308
	Positive	47	6.8±0.6	
Triple-negative	No	128	6.1±0.4	0.05
	Yes	11	7.2±1.3	
Pathologic stage	IA	17	5.1±1.0	0.352
	IB	2	3.7±2.9	
	IIA	43	6.4±0.6	
	IIB	34	6.9±0.7	
	IIIA	25	6.1±0.8	
	IIIC	18	6.2±0.9	

SUV_{max}: maximum standardized uptake value; HER2: human epidermal growth factor receptor 2; ER: estrogen receptor; PR: progesterone receptor

Discussion and Conclusion

In the univariate analyses in our study, we found that the SUV_{max} values in young patients (aged less than 45 years) who had an invasive tumor diameter larger than 2 cm, negative hormone receptors, and triple-negative tumors were significantly higher as histologic and nuclear grades increased.

The survival rates of breast cancer are worse in young patients (aged <40 years) compared with elderly patients, and the multivariate analyses show that young age is an independent indicator of poor prognosis (13). Breast cancer at a young age progresses more aggressively; in a study with 185 premenopausal women with breast cancer, the number of those with negative ER and PR aged <35 years, the number of those with lymphatic and vascular invasion and pathologic grade 3 tumors were considerably high (14). In a retrospective evaluation with 1398 women with early-stage breast cancer, age, for those aged under 35 years, was shown as a strong and independent prognostic factor that determines relapse, distant metastasis, and mortality (15). In previous studies, there was no relationship found between age and SUV_{max} values; however, the SUV_{max} values in the young patients were higher in our study (16-18).

Similar to previous studies, 18F-FDG involvement was higher in patients with invasive ductal carcinoma (17, 19, 20). This relationship may be related to the low density of tumor cells in lobular carcinomas,

low GLUT1 (glucose transporter 1) expression, low proliferative index, and diffuse infiltrative growth pattern (16, 20-22).

Tumor diameter and axillary lymph node metastasis are the most vital clinical prognostic factors in breast cancer (4). Although a number of studies reported a positive correlation between tumor size and FDG involvement, some studies found no relationship (17, 23). In our study, we evaluated tumors in two categories as tumors with diameter of 2 cm or less, and those larger than 2 cm. FDG involvement was found higher as FDG involvement increased. In studies regarding the use of PET/CT in staging lymph nodes, it was stated that it could not be as sensitive, especially with patients with clinically-negative lymph nodes, and could not replace histopathologic examination (24-26). Zhang et al. (27) demonstrated that axillary lymph node staging was limited to 46% sensitivity in their study with 164 patients with breast cancer. There are also studies in the literature that reported a significant and positive correlation between PET/CT SUV values and lymph node metastasis (17, 23). However, there are studies that could not demonstrate a relationship between the condition of lymph node and FDG involvement (28). There was no statistically significant difference when the SUV_{max} values of the patients with and without lymph node metastasis were compared in our study, although the SUV_{max} values increased in patients with lymph node metastasis with higher N-stage. The fact that no relationship was found could be related to the high level of false negativity in PET/CT scans, late referral of patients with low grades, and the inadequacy of PET/CT scans in showing micrometastases.

Pathologic grade is one of the important predictive factors that shows tumor differentiation in breast cancer and the relationship between SUV values and histological grade is explained through high glucose metabolism in actively increasing tumors (5). The relationship between grade and PET/CT SUV values in patients with breast cancer has been reported (19). High-grade tumors were shown to have higher SUV values compared with low-grade tumors (29). In a study by Ueda et al. with 152 patients with breast cancer, the authors demonstrated that invasive tumor size, nuclear grade, and negative estrogen receptor were correlated with high SUV values in their multivariate analyses (17). In our study, we observed that the SUV values were statistically significantly higher as both histologic and nuclear grade increased. High SUV values could be an indication for high-grade and biologically-aggressive tumors.

Breast cancer is a heterogeneous disease that can be divided into histopathologic and molecular subtypes (30). According to gene-expression profiles, the first breast cancer subtypes were defined by Perou et al. (31). ER, PR, and HER2 gene expression features are significant determinants used routinely in newly-diagnosed breast tumors. Subtypes identified based on hormone receptors, HER2 status, and Ki-67 proliferative index give information on tumor biology and clinical behavior, and treatments including subtypes are recommended in guidelines (32, 33). Estrogen and progesterone receptors hold a crucial place in determining prognosis for patients with breast cancer and establishing whether they would benefit from hormonal therapy. HER2 status is an important predictive factor that determines whether the patients can start goal-directed therapy (trastuzumab) (34). Luminal A tumors (positive ER and PR, negative HER2, Ki-67 <1%) is the subtype with the best prognosis, triple-negative tumors show more biologically aggressive behavior (30, 35). In our study, negative ER and PR, positive HER2 and triple-negative patients had higher SUV_{max} values. High values of SUV have also been reported in patients with negative hormone receptors by previous researchers (17, 36). Basu et al. (37) stated that PET/CT sensitivity was 100% for patients who were triple-negative and these patients had higher FDG involvement compared with patients with positive hormone receptors, and the authors emphasized that PET/CT scanning of these tumors was important for determining tumor activity and treatment response.

Ki-67 is an indicator of the proliferation of cancer cells; however, its measurement and limit values change in different centers. In a study by Ito et al. (38) with 138 patients with invasive ductal breast cancer, the authors compared patients with Ki-67 values >14% and ≤14% and reported statistically significantly higher FDG involvement in patients with high Ki-67 values. In their comparison by number of mitosis, Ueda et al. (17) found the mean SUV values statistically significantly increased as the number of mitosis increased. In our study, no statistical comparison was performed because there was only a small number of patients whose number of mitosis and Ki67 index were reported. One of the limitations in our study is that the effects of SUV_{max} value on treatment results, local control, and survival were not investigated.

Our study demonstrates that SUV_{max} values are related to the recognized histopathologic and immunohistochemical prognostic factors in breast cancer. Predictability of predictive and prognostic factors before treatment is of importance in terms of deciding the therapeutic approach. In preoperative assessment of patients with breast cancer, PET/CT scanning is inadequate in examining axillary lymph nodes; however, it may prove beneficial in displaying the biologic characteristics and behavior of a tumor.

Ethics Committee Approval: Ethics committee approval was received for this study from local ethic committee.

Informed Consent: Written informed consent was obtained from patients who participated in this study.

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Original Article

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The Relationship between Bone Mineral Density and Estrogen Receptor Positivity in Patients with Breast Cancer

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ABSTRACT

Objective: The effect of estrogen on bone mineral density (BMD) and breast cancer has been known for a long time. The aim of this study was to compare of the BMD of patients with breast cancer and healthy individuals, and to investigate the degree of correlation of estrogen receptor (ER) with BMD.

Materials and Methods: Seventy-one patients with postmenopausal breast cancer and 79 healthy dividuals were included in the study. The patient demographics (age, menopause age, body mass index, number of children, BMD, Z scores, and estrogen status for breast cancer patients) were taken from hospital records.

Results: No significant difference was detected between the case and control groups in lumbar region Z scores (p=0.074). At the femur neck, the control group Z scores was higher than patient group (p=0.002). BMI was higher in the patients with breast cancer (p=0.001). There was no statistically significant correlation between ER positivity, BMD, and BMI in ER-positive patients (p=0.495, p=0.8, p=0.846, respectively). There was no difference between the Z scores when the patients were divided into two groups as ER positive and negative (p=0.156, p=0.335, respectively).

Conclusion: This study revealed that there is no difference in lumbar region Z scores between patients with breast cancer and heathy controls; however, the Z scores were higher in the femur neck in the control group, and the BMI was lower in the patient group. Tumor ER positivity does not positively affect BMD.

Keywords: Breast cancer, bone mineral density, estrogen receptor, body mass index

Introduction

Breast cancer is the most prevalent cancer type and the second leading cause of death in women (1). Advanced age, early menarche, first-term pregnancy at a late age, late menopause, and long-term hormone replacement treatment are among the risk factors for breast cancer (2-4). The relationship between these risk factors and breast cancer are reported to be due to the estrogen-induced increase in mitotic activity in breast tissue, which results in mutations (5).

Estrogen hormone is an important risk factor for breast cancer; however, serum levels often vary, which obstructs correlating serum estrogen levels with the risk of breast cancer (6). Serum samples are not sufficient alone to diagnose breast cancer or identify the long-term estrogen level of tissues. Bone mineral density (BMD) should be considered a good indicator of tissue levels of estrogen because BMD elevates in parallel with the increase in estrogen level (7). Estrogen lessens bone destruction while amplifying bone volume and bone mineral density. When we consider this information, we may think that there is a correlation between BMD and breast cancer. Nevertheless, studies that investigated the relationship between bone mineral density and development of breast cancer revealed contradictory results (8-11).

In patients with breast cancer, the ratio of tumor estrogen receptor (ER) positivity enhances with age. In a study carried out on Turkish women, ER was found positive in 66% of pre-menopausal women, and this rate increased to 73% in menopausal women (12). Only a few studies in the literature have shown a link of the change in ER positivity with bone density, but none were conducted in Turkey.

The objective of this study was to compare the BMD of postmenopausal women with breast cancer with that of control subjects and thus to investigate the association between tumor estrogen receptor level and bone mineral density.

This study was presented at the 13th National Breast Health Congress, 21-28 October 2015, Antalya, Turkey.

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Materials and Methods

We analyzed the data of 261 patients who presented to our clinic between January 2011 and December 2014 with breast cancer. Data including age, number of deliveries, breastfeeding duration, body mass index (BMI), pathologic stage, additional diseases, ER levels, and bone densitometry measurements prior to systemic chemotherapy were recorded. The control subjects were selected among individuals who applied to the Radiology Department of the Hospital during the same period for BMD measurement ensuring that their age was in line with that of the patients with breast cancer. Individuals with hypothyroidism and hyperthyroidism, steroid use, hormone replacement therapy, any disease that might cause of osteoporosis such as immobility, and those that took medication that may cause osteoporosis or for the treatment of osteoporosis were excluded from the study. Premenopausal patients were also not included in the study. The study was approved by the Hospital's Ethics Committee and started after the obtaining consent from the patients.

The 2nd to the 4th lumbar vertebrae and femoral neck BMD was measured using dual X-ray absorptiometry (DXA) (Hologic, Bedford, MA, USA), whose calibration is performed regularly at our clinic. The BMD of the study and control subjects were identified using the Z scores; a score ≤ 2 was regarded as osteoporosis (13).

Immunohistochemical estrogen receptor analysis was performed using a Benchmark LT (Ventana Medical Systems Inc.; California, USA) on formalin-fixed paraffin-embedded tissue sections with ab-Neomarkers-antibodies (Clone SP1) at concentration 1/100. Only nuclear staining was considered positive. The area where a number of stained cells was the highest was determined regarding the College of American Pathologists (CAP) criteria; 100 cells were counted, and the ratio of the staining was identified (14). Patients with an ER level <10% were classified as negative whereas those with an ER level ≥10% were classified as positive.

Statistical analysis

The statistical analyses were performed using SPSS version 20.0 (IBM Corp. New York, USA). The mean, standard deviation, median, minimum, maximum, frequency and ratio values were used for the descriptive statistics of the data. The distribution of variables was measured using the Kolmogorov-Smirnov test. The Mann-Whitney U test and independent sample t-test were used for the analysis of quantitative data in both groups, and Spearman's correlation analysis was used to identify correlations. The results of the study were evaluated in a 95% confidence interval considering $p<0.05$ as significant.

Results

After the exclusion criteria were assessed, 71 postmenopausal patients were included in the study group, and 79 menopausal women without breast cancer were included in the control group. Among the patients in the study group, 31% (n=22) had stage 1 breast cancer; 53.6 (n=38) had stage 2 breast cancer; 8.4% (n=6) had stage 3 breast cancer, and 7% had stage 4 breast cancer. Table 1 shows other demographic data of the patients.

The study group and control group did not differ significantly regarding the mean age of the patients, whereas BMI was found higher in the study group (Table 1). Although the mean age of menarche was different between the groups (p=0.001), no significant difference was observed when the length of the period between menarche and menopause was compared (p=0.33). There was statistically significant difference between the groups regarding the L2-4 and femoral neck Z scores (p=0.026 and p=0.002, Table 2). When the patients were classified as <25 and ≥25 kg/m² according to BMI, the group with a BMI ≥25 kg/m² had significantly lower Z-scores of the femoral neck and lumbar spine compared with the control group (Table 3.1 and 3.2).

The receptor positivity level of the patients who had positive estrogen receptor was analyzed considering the BMI and the lumbar and femoral Z-scores; no significant correlation was found between these measurements (p=0.495, p=0.8, p=0.846 respectively) (Table 4). When the patients in the study group were divided into two sub-groups as ER-positive and ER-negative; there was no statistically significant difference between these two groups regarding Z scores. Furthermore, when the ER-positive and ER-negative patients were classified as with and without osteoporosis depending on their Z scores, no statistically significant difference was identified. However, the prevalence of osteoporosis in the lumbar spine and femoral neck was lower in the ER-positive patients compared with the ER-negative patients (23% vs. 8.6%; 7.7% vs. 1.7%) (Table 5).

Table 1. Demographics of the Control and Breast Cancer Group

Patient demographics	Study Group (n=71) Mean ± SS (min-max)	Control Group (n=79) mean ± SS (min-max)	P*
Age	59.28±7.38 (45.0-81.0)	59.63±10.8	0.94
BMI	29.98±5.49 (19.10-48.20)	26.9±4.9	0.001*
Number of birth	1.90±1.00 (0-5)0-5)	1.83±1.05	0.63
Age at Menarge	13.11±1.08 (11-16)	12.54±0.97	0.001*
Breast feeding(year)	1.05±0.23 (1-2)	1.08±0.28	0.45
Age of menopause	49.6±3.9 (37-63)	49.45±4.3	0.77
Fertility time (year)	36.57±3.57	36.91±4.40	0.330

BMI: Body mass index; Min: minimum; max: maximum
*p<0.05

Table 2. Z Scores of the Control and study group in the lumbar and femur neck regions

Z score	Study Group (n=71) Mean ± SS (min-max)		Control Group (n=79) mean ± SS (min-max)		p
L2-L4 DEXA	-0.37± 1.12	-0.40 (-2.60-2.78)	0.06± 1.29	-0.30 (-2.60-2.90)	0.029*
Femur DEXA	-0.27± 0.87	-0.40 (-2.00-1.70)	0.18± 0.93	0.10 (-2.70-2.30)	0.002*

*p<0.05 was considered significant.

Table 3. 1. Clasification of the control and study group according to BMI 25

	BMI	≤25	>25
Study group	8 (11.2%)	63 (88.8%)	71 (100%)
Control group	31 (39.2%)	48 (60.8%)	79 (100%)

BMI: body mass index

Table 3. 2. Analysis of Z Scores of patients with BMI ≤25

BMD measurement region	Study Group (n=63)	Control group (n=48)	P
Femur	-0.24±0.89	0.34±0.85	0.001*
L2-4	-0.37±1.08	0.45±1.3	0.003*

*p<0.05 was considered significant.
BMD: bone mineral density

Table 4. The Level of Positive Correlation of BMI and Bone Density

Hormone receptor		BMI	L2-4 DEXA	Femoral DEXA
The rate of estrogen receptor positivity	r	-0.091	-0.034	-0.026
	p	0.495	0.800	0.846

r: rho coefficient
*p<0.05 was considered significant.
BMI: body mass index

Table 5. The comparison of the ER-negative and ER-positive patients regarding BMD

BMD		ER-negative (digit, %)	ER-positive (digit, %)	p
L2-4-DEXA	Normal	10 (76.9%)	53 (91.4%)	0.156
	Osteoporosis	3 (23.1%)	5 (8.6%)	
Femur-DEXA	Normal	12 (92.3%)	57 (98.3%)	0.335
	Osteoporosis	1 (7.7%)	1 (1.7%)	

*p<0.05 was considered significant.
BMD: bone mineral density

Discussion and Conclusion

Besides being a crucial hormone for bone metabolism, estrogen also plays a role in the etiology of breast cancer. In this regard, high BMD is considered to be associated with breast cancer (6, 16). Klift et al. (10) indicated a correlation between increased lumbar spine BMD and breast cancer; the same correlation was not observed between femoral BMD and breast cancer. In the study of Kim et al. (8) on Korean women, a similar relationship was demonstrated between breast cancer and lumbar and femoral BMD. Contrary to the studies mentioned above, Kerliowske et al. (9) claimed that lumbar and femoral BMD did not correlate with breast cancer risk. In the present study, the Z-scores of the lumbar spine and femoral neck were lower in patients with breast cancer. The conflicting results of the study may be related to the fact that various factors affect bone metabolism and play a role in the development of breast cancer. Moreover, due to polymorphisms in genes involved in the biosynthesis and metabolism of estrogen, tissues in the body may have different estrogen sensitivity (17).

On the other hand, no correlation was demonstrated in studies that analyzed the BMD-breast cancer relationship in premenopausal women (7, 18). Therefore, we did not enroll premenopausal patients in the study.

Douchi et al. (19) conducted a study on ER-positive postmenopausal women with breast cancer and showed BMD to be higher in the patients with cancer as compared with the control group. Bayraktar et al. (20) examined BMD and tumor characteristics in postmenopausal patients, no correlation was found between the ER-positive and ER-negative patients regarding BMD. Even though we also found no significant difference between ER-positive and ER-negative patients considering the Z scores, when the patients were classified as with and without osteoporosis the rate of osteoporosis was found lower in patients with positive ER. However, these results can be explained by the small number of ER-negative patients.

Obesity has been indicated to elevate the risk of breast cancer in postmenopausal women (21-23). Obesity has such an effect that ovaries no longer produce hormones in the postmenopausal period whereas fat tissue stands out as the most important source of estrogen (24). Obesity is also linked with increased bone density due to the same mechanism. Similarly, we found significantly higher BMI levels in patients with breast cancer compared with the control group. Additionally, according to the evaluation of the Z-scores in the obese postmenopausal patients who were expected to have higher serum estrogen levels, the Z scores were observed to be greater in the control group compared with patients with a BMI ≥25 kg/m^2. This result may be due to the small number of patients and control subjects or due to different impacts of the regional polymorphism in the estrogen genes on bone and breast tissue.

High bone mineral density is known to be an indicator of serum estrogen level; however, we found no significant association between estrogen receptor level of tumor tissue and bone mineral density. Also, the estrogen receptor positivity was correlated with BMD. There is a need for further larger studies to be performed with more patients to evaluate the link between bone density and ER receptor.

Ethics Committee Approval: Ethics committee approval was received for this study.

Informed Consent: Informed consent was obtained from patients who participated in this study.

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Original Article

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Diagnostic Value of Diffusion-weighted Imaging and Apparent Diffusion Coefficient Values in the Differentiation of Breast Lesions, Histpathologic Subgroups and Correlatıon with Prognostıc Factors using 3.0 Tesla MR

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ABSTRACT

Objective: The aim of this study was to evaluate the effect of the apparent diffusion coefficient (ADC) and diffusion-weighted imaging in differentiating benign from malignant breast lesions, histopathologic subtypes of breast tumors, and to find a correlation with prognostic factors using 3T MR.

Materials and Methods: A total of 165 patients aged between 16 and 78 years with 181 histopathologically-verifed breast lesions were enrolled in this study. A 3T MR system and bilateral phased array breast coil was used. Diffusion-weighted imaging was performed with spin echo ''echo planar" with ''b" values: 50, 400, and 800 seconds/mm^2. ADC values were calculated for normal fibroglandular tissue and breast lesions. ADC values of independent groups were compared using Student's t-test. ROC analysis was used to find a threshold ADC value in the differentiation of lesions.

Results: The mean ADC values were 1.35±0.16 x10^{-3} mm^2/s for normal fibroglandular tissue, 1.41±0.24 x10^{-3} mm^2/s for benign breast lesions and 0.83±0.19 x10^{-3} mm^2/s for malignant breast lesions. The AUC with ROC analysis was 0.945 and the threshold for ADC was 1.08 ×10^{-3} mm^2/s with a sensitivity and specificity of 92% and 92%, respectively. The threshold value for ADC ratio was 0.9 with 96% sensitivity and 89% specificity. The mean ADC of malignant breast lesions was statistically lower for benign lesions (p<0.01). We found no correlation between the mean ADC values and ER-PR receptor, Her2, and Ki-67 values.

Conclusion: Diffusion-weighted imaging has high diagnostic value with high sensitivity and specificity in differentiating malignant and benign breast lesions.

Keywords: Diffusion-weighted imaging, ADC, breast cancer, invasive ductal carcinoma, Ki-67, Her 2 expression

Introduction

Magnetic resonance imaging (MRI) as a method for breast exams has been used increasingly frequently during the last decade. In particular, it is preferred for selected cases as a diagnostic and problem-solving method for its high contrast resolution, multiplanar capability of examination, lack of ionizing radiation, and capacity to obtain dynamic contrast images (1, 2). Conventional MRI has disadvantages such as time-consuming screening and requirement of high-value contrast agents (3). Despite the fact that dynamic contrast-enhanced MRI is an efficient diagnostic exam with high sensitivity, but its limited specificity creates a need for new techniques (1-7). Therefore, additional sequences are sought that would increase image quality, reduce imaging time and enable differential diagnosis for lesions (4). Diffusion-weighted imaging (DWI) is one of these fast MRI sequences. By recording the free movement of water molecules in the extracellular space, DWI creates different signals in images as a result of the inhibition of this movement and therefore diffusion restriction, which occurs due to an increase in cell frequency in the presence of a malignant mass. The apparent diffusion coefficient (ADC) is a quantitative measure of the diffusion of water molecules within tissue. Using the data in various b-values obtained from DWI in MRI, ADC maps are created and ADC values of lesions can be calculated (8, 9). Recent studies showed that DWI and ADC measurements had high rates of accuracy and specificity in the differential diagnosis of malignant and benign breast lesions (10-13).

Breast cancer is a heterogeneous disease, and its natural course after diagnosis varies among patients. In the follow-up of patients with tumors of the same diameter, some experience tumor recurrence after a very short time, whereas others continue living a healthy life. Therefore, prognostic factors and molecular subgroups are used in order to determine differences between clinical and biologic behaviors of patients with breast cancer and establish the high-risk group, which demonstrates a quick disease progression (14-17). Although some of these factors (tumor diameter, axillary involvement, histologic characteristics of tumor, hormone receptors) have a well-known role in determining prognosis, there is ongoing intensive research regarding hormone receptors, tumor proliferation rate, and molecular prog-

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nostic factors. The prognostic importance of estrogen receptor (ER) and progesterone receptors (PR) was established in a group of neoplastic diseases, breast, and endometrial carcinoma in particular. ER and PR positive tumors respond to hormone therapy and provide a better prognosis (18). There are subcategories that include the prognostic values of tumor proliferation rate. Prognostic factors exist such as mitotic index, immunohistochemical proliferation markers (Cyclin A, Ki-67), S-phase reaction, thymidine labeling index, and bromodeoxyuridine (BrDu) labeling index. There are still extensive studies regarding most of these factors today (19). C-erbB-2 (Her2) oncoprotein shows protein-tyrosine kinase activity, which is structurally associated with epidermal growth factor receptor. Previous studies have shown that Her2 oncogene is a significant mediator of cell proliferation and differentiation (20). This gene is located on chromosome 17. Her2 positivity is encountered in breast cancers with high histologic grade, negative ER and PR, positive lymph node, and high proliferation rate (20, 21).

The aim of this study was to evaluate the diagnostic significance of ADC value and DWI in the differentiation of benign and malignant breast lesions and to investigate their correlation with histopathologic subtypes of breast tumors and prognostic factors such as ER, PR, Her2, and Ki-67 using 3T MR.

Metarials and Methods

The subjects in our retrospective study were chosen from patients who had undergone a preoperative MRI and were scheduled for a breast biopsy procedure in our clinic between November 2012 and November 2014. Informed consent forms were obtained from the patients as well as approval from the local ethics committee for this study.

Histopathologically diagnosed, 312 patients who had undergone ultrasound-guided tru-cut, mammography-guided stereotactic vacuum-assisted biopsy and routine breast screening were enrolled into the study. Of these patients, 56 patients with lesions smaller than 1cm and 91 patients with diagnostically inadequate quality of DWI-MRI sequences were excluded from the study. The remaining 165 patients with 181 lesions were included in the study. The patients' ages ranged between 16 and 78 years (mean age: 46.7±12.01 years), and all patients were female.

MR Imaging

All MR images were obtained using a special 16-channel 3.0 Tesla coil (Magnetom Siemens Verio, Germany) with the breast in the prone position. All the patients had routine breast MRI examinations with conventional sequences. The sequences used in the conventional MRI were as follows: TRIM axial T2-weighted (TI:230ms, TR:4000ms, TE:72 ms, 3 mm section thickness, FOV:300-340 mm) images were obtained before T1 axial IV contrast-enhanced axial dynamic 3D (TR:5.04 ms, TE:1.91 ms, fl3d1/10, 1 mm section thickness, FOV:280-300 mm Matrix 420x400) examination; 1 pre-contrast sequence and 6 post-contrast sequences were performed, and the temporal resolution was 82 seconds. Subtraction images were acquired by subtracting the post-contrast images from the first images. For the contrast images, a dose of 0.1-0.2 mmol/kg of gadolinium-containing gadobutrol and gadoterate meglumine were injected via IV with an automatic injection device over 20 seconds.

As the primary subject of our study, DWI was performed before the contrast-enhanced examination. The diffusion-weighted sequences (TR/TE: 8300/93, flip angle: 80 degrees, 4 mm section thickness, FOV:300-320, Matrix 192x192 Nex:4) were performed with single-shot spin-echo echo-planar in the axial plane with 3 different b values (b=50, 500, 800). The ADC values were automatically measured at the workstation, and ADC (b=800-b=50) map images were prepared.

Lesion Evaluation

The lesions were evaluated by a single radiologist (YA) who has one-year experience of breast radiology; the radiologist was blinded the histopathologic diagnoses. A total of 165 patients with 181 lesions were evaluated by analyzing the conventional MRI and DWI to determine whether there were breast lesions with abnormal contrast enhancement. The DWI was examined for the presence of diffusion restriction on the breast tissues connected to the lesions, and the measurement values on the ADC map were taken into account. The equivalent of the most contrasted part in the masses detected in the conventional MRI examination was found in the DWI. A standard round region of interest (ROI) with a 5 mm diameter was placed on the image of this area in the ADC map. During the measurement, the cystic and necrotic component of the lesion was left out of the measuring range. Additionally, the ADC values of normal breast tissues on the lesion-free breast were measured in every patient, and the ADC rates of lesion-normal breast tissues were calculated.

The sizes of the 181 lesions included in the study ranged between 10 mm and 64 mm (mean 18.3±8.9 mm). Small lesions sized less than 1.5 cm were measured with one ROI, and large lesions were measured with 3 different ROIs. The lowest value of three measurements was taken into account. Furthermore, the ADC value of the mass in each patient was divided by the ADC value of the opposite normal breast for a proportion measurement.

Biopsy was performed on all lesions through either ultrasound-guided tru-cut (152 cases) or stereotactic vacuum-assisted biopsy (29 cases). The histopathologic diagnoses were considered as the referral diagnosis. The postoperative histopathologic findings of the malignant cases were accepted as a reference. Surgical excision was performed on 9 patients who had been diagnosed as having atypical ductal hyperplasia after which the diagnoses for 3 of these patients were changed to ductal carcinoma in situ (DCIS).

Hormonal prognostic factors were evaluated in 3 subgroups when both ER and PR were negative, both were positive, and when only one was positive. In total, hormone receptors were analyzed in 80 of 89 malignant lesions. Hormone receptors were not analyzed in 8 cases of DCIS and 1 well-differentiated liposarcoma. The postoperative histopathologic findings were investigated for the malignant lesions.

Ki-67 value was taken into consideration while evaluating tumor proliferation. Not including 8 DCIS and 1 well-differentiated liposarcoma malignant lesions, the Ki-67 values of 80 malignant lesions were analyzed. Pearson's correlation test was used for the correlation between the Ki-67 values and ADC.

Of molecular prognostic factors, Her2 was used as a base. Excluding 8 DCIS and 1 well-differentiated liposarcoma case from 89 patients with a malignant diagnosis, 80 lesions were rated with one positive (+), two positives (++), three positives (+++) and 'no immunoexpression.' Three positives (+++) was considered a positive result, whereas results with no immunoexpression and + were considered negative. Fluorescence in situ hybridization (FISH) was used in 8 patients with two positives (++). As a result of the FISH test, 4 lesions that had no amplification were considered negative, the remaining 4 lesions, which had positive amplification, were considered positive.

Statistical analysis

The ADC values were reported with min ± standard deviation using SPSS version 15 (SPSS, Inc.; Chicago, Illinois, USA) in the statistical analysis of our study. The mean min ADC values between the independent groups were compared using Student's t-test. A p value of <0.05 was considered statistically significant. The threshold ADC values used to differentiate between benign and malignant lesions were determined using receiver operating characteristic (ROC) analysis. A post-hoc Tukey test was performed to evaluate the diagnostic difference in different subgroups. The Kruskal-Wallis H test was used to determine whether there was a statistically significant difference between the malignant and benign subgroups after which the Mann-Whitney U test was performed to determine which group had caused the difference. Pearson's correlation" test was conducted for the correlation between the Ki-67 values and ADC.

Result

Ninety-two of the 181 lesions involved in the study were diagnosed as benign and 89 were malignant. The histopathologic distribution of lesions is shown in Table 1.

The ADC values in the measurements determined from normal breast parenchyma ranged between 0.96 $x10^{-3}$ mm^2/sec and 1.94$x10^{-3}$ mm^2/sec (mean 1.35 ± 0.16$x10^{-3}$ mm^2/sec).

In the ADC measurements of the lesions, the lowest ADC lesion value was 0.51 $x10^{-3}$ mm^2/sec with invasive ductal carcinoma, and the highest ADC lesion value was 1.79 $x10^{-3}$ mm^2/sec with fibroadenoma. The lowest lesion/normal breast tissue ADC rate was (0.40) in an invasive ductal carcinoma case, whereas the highest was (1.36) in a case of fibroadenoma.

The mean size of the 92 benign lesions was 15.5±6.4 mm. The mean min ADC value was found to be 1.41±0.24 $x10^{-3}$ mm^2/sec for all the benign lesions. Among the benign lesions, the lowest ADC value belonged to an abscess with 0.57 $x10^{-3}$ mm^2/sec and the highest ADC value was 1.79$x10^{-3}$ mm^2/sec in a fibroadenoma. The mean lesion/normal breast tissue ADC rate was 1.07±0.17 in these lesions. The lowest rate among all the benign lesions was 0.4 in an abscess and the highest rate was 1.36 in a fibroadenoma.

The mean size of malignant 89 lesions was measured 20.9±9.9 mm. The mean min ADC value was 0.83±0.19$x10^{-3}$ mm^2/sec for all the malignant lesions. Among the malignant lesions, the lowest ADC value was 0.51$x10^{-3}$ mm^2/sec in an invasive ductal carcinoma, and the highest ADC value was 1.50$x10^{-3}$ mm^2/sec in an invasive mucinous carcinoma. The mean lesion/normal breast tissue ADC rate was 0.61±0.14 in these lesions. The lowest rate was 0.4 in an invasive ductal carcinoma and the highest rate was 1.15 in an invasive mucinous carcinoma among all the malignant lesions.

The difference between the mean ADC values of the malignant lesions and benign lesions was statistically significant (p=0.001). The difference between the lesion/normal breast tissue ADC values of the malignant lesions and benign lesions was statistically significant (p=0.001) (Table 2).

When the threshold value for the mean min ADC value of the lesions was considered 1.08$x10^{-3}$ mm^2/sec, in the ROC analysis the AUC was 0.95 and the sensitivity and specificity of detecting malignant lesions were 92.1% and 92.4%, respectively (Figure 1) (Table 3). With a 0.9 threshold value for the lesion/normal breast tissue ADC rates, the AUC was 0.956, and the sensitivity and specificity of the differentiation capability for benign and malignant breast lesions were 96.6% and 89.1%, respectively (Figure 2).

Table 1. The distribution of histopathologic diagnoses

		n	%
Benign Lesions		**92**	**50.8**
	Fibroadenoma	37	40.2
	Columnar Cell Hyperplasia	10	10.8
	Fibrosis	11	11.9
	Apocrine Metaplasia	7	7.6
	Sclerosing Adenosis	6	6.5
	Fibrocystic Changes	2	2.2
	Postoperative Granulation Tissue	1	1.0
	Atypia	6	6.5
	Abscess	8	8.2
	Intraductal Papilloma	4	4.1
	Total	92	100
Malignant Lesions		**89**	**49.2**
	Ductal carcinoma in situ	8	9
	Invasive ductal carcinoma	63	70.8
	Invasive lobular carcinoma	6	6.7
	Invasive mucinous carcinoma	4	4.5
	Invasive mixed carcinoma	5	5.6
	Invasive medullary carcinoma	1	1.1
	Invasive apocrine carcinoma	1	1.1
	Well-differentiated liposarcoma	1	1.1
	Total	89	100.0
Total		**181**	**100.0**

Table 2. The distribution of ADC levels and lesion/ADC rates by histopathologic result

	Benign (n=92)		**Malignant (n=89)**			
	Mn	**Sd**	**Mn**	**Sd**	**t**	**p**
Lesion ADC	1.414	2.388	0.826	0.187	18.418	<0.001
Lesion/ ADC	1.074	0.171	0.607	0.136	20.328	<0.001

ADC: Apparent Diffusion Coefficient; Mn: mean; Sd: standard deviation; t: t value; p: p value

Table 3. ADC limit values in differentiation of benign and malignant breast lesions, sensitivity and specificity levels found in different threshold values in the ROC analysis

Threshold value	Sensitivity	95% CI	Specificity	95% CI	PPV	95% CI	NPV	95% CI
≤908	79.78	69.9 - 87.6	95.65	89.2 - 98.8	94.7	86.9 - 98.5	83.0	74.5 - 89.6
≤914	80.90	71.2 - 88.5	95.65	89.2 - 98.8	94.7	87.1 - 98.5	83.8	75.3 - 90.3
≤920	82.02	72.5 - 89.4	95.65	89.2 - 98.8	94.8	87.2 - 98.6	84.6	76.2 - 90.9
≤926	83.15	73.7 - 90.2	94.57	87.8 - 98.2	93.7	85.8 - 97.9	85.3	76.9 - 91.5
≤948	84.27	75.0 - 91.1	94.57	87.8 - 98.2	93.7	86.0 - 97.9	86.1	77.8 - 92.2
≤979	85.39	76.3 - 92.0	94.57	87.8 - 98.2	93.8	86.2 - 98.0	87.0	78.8 - 92.9
≤1000	86.52	77.6 - 92.8	94.57	87.8 - 98.2	93.9	86.3 - 98.0	87.9	79.8 - 93.6
≤1026	87.64	79.0 - 93.7	94.57	87.8 - 98.2	94.0	86.5 - 98.0	88.8	80.8 - 94.3
≤1033	88.76	80.3 - 94.5	94.57	87.8 - 98.2	94.0	86.7 - 98.0	89.7	81.9 - 94.9
≤1036	88.76	80.3 - 94.5	93.48	86.3 - 97.6	92.9	85.3 - 97.4	89.6	81.7 - 94.9
≤1047	89.89	81.7 - 95.3	93.48	86.3 - 97.6	93.0	85.4 - 97.4	90.5	82.8 - 95.6
≤1065	91.01	83.1 - 96.0	93.48	86.3 - 97.6	93.1	85.6 - 97.4	91.5	83.9 - 96.3
≤1079	91.01	83.1 - 96.0	92.39	84.9 - 96.9	92.0	84.3 - 96.7	91.4	83.8 - 96.2
≤1082	92.13	84.5 - 96.8	92.39	84.9 - 96.9	92.1	84.5 - 96.8	92.4	84.9 - 96.9
≤1083	92.13	84.5 - 96.8	91.30	83.6 - 96.2	91.1	83.2 - 96.1	92.3	84.8 - 96.9
≤1089	92.13	84.5 - 96.8	90.22	82.2 - 95.4	90.1	82.1 - 95.4	92.2	84.6 - 96.8
≤1103	92.13	84.5 - 96.8	89.13	80.9 - 94.7	89.1	80.9 - 94.7	92.1	84.5 - 96.8
≤1138	92.13	84.5 - 96.8	88.04	79.6 - 93.9	88.2	79.8 - 93.9	92.0	84.3 - 96.7
≤1143	92.13	84.5 - 96.8	86.96	78.3 - 93.1	87.2	78.8 - 93.2	92.0	84.1 - 96.7
≤1146	93.26	85.9 - 97.5	86.96	78.3 - 93.1	87.4	79.0 - 93.3	93.0	85.4 - 97.4
≤1160	93.26	85.9 - 97.5	85.87	77.0 - 92.3	86.5	78.0 - 92.6	92.9	85.3 - 97.4
≤1163	94.38	87.4 - 98.2	85.87	77.0 - 92.3	86.6	78.2 - 92.7	94.0	86.7 - 98.0
≤1203	94.38	87.4 - 98.2	84.78	75.8 - 91.4	85.7	77.2 - 92.0	94.0	86.5 - 98.0
≤1213	94.38	87.4 - 98.2	83.70	74.5 - 90.6	84.8	76.2 - 91.3	93.9	86.3 - 98.0
≤1216	94.38	87.4 - 98.2	82.61	73.3 - 89.7	84.0	75.3 - 90.6	93.8	86.2 - 98.0
≤1242	94.38	87.4 - 98.2	81.52	72.1 - 88.9	83.2	74.4 - 89.9	93.7	86.0 - 97.9
≤1244	94.38	87.4 - 98.2	80.43	70.9 - 88.0	82.4	73.6 - 89.2	93.7	85.8 - 97.9
≤1246	94.38	87.4 - 98.2	79.35	69.6 - 87.1	81.6	72.7 - 88.5	93.6	85.7 - 97.9
≤1255	94.38	87.4 - 98.2	78.26	68.4 - 86.2	80.8	71.9 - 87.8	93.5	85.5 - 97.9
≤1266	94.38	87.4 - 98.2	77.17	67.2 - 85.3	80.0	71.1 - 87.2	93.4	85.3 - 97.8
≤1290	94.38	87.4 - 98.2	76.09	66.1 - 84.4	79.2	70.3 - 86.5	93.3	85.1 - 97.8
≤1292	94.38	87.4 - 98.2	75.00	64.9 - 83.4	78.5	69.5 - 85.9	93.2	84.9 - 97.8
≤1294	94.38	87.4 - 98.2	73.91	63.7 - 82.5	77.8	68.8 - 85.2	93.2	84.7 - 97.7
≤1299	95.51	88.9 - 98.8	73.91	63.7 - 82.5	78.0	69.0 - 85.4	94.4	86.4 - 98.5
≤1301	96.63	90.5 - 99.3	73.91	63.7 - 82.5	78.2	69.3 - 85.5	95.8	88.1 - 99.1
≤1305	96.63	90.5 - 99.3	72.83	62.6 - 81.6	77.5	68.6 - 84.9	95.7	88.0 - 99.1

NPD: negative predictive value; PPV: positive predictive value; CI: confidence interval

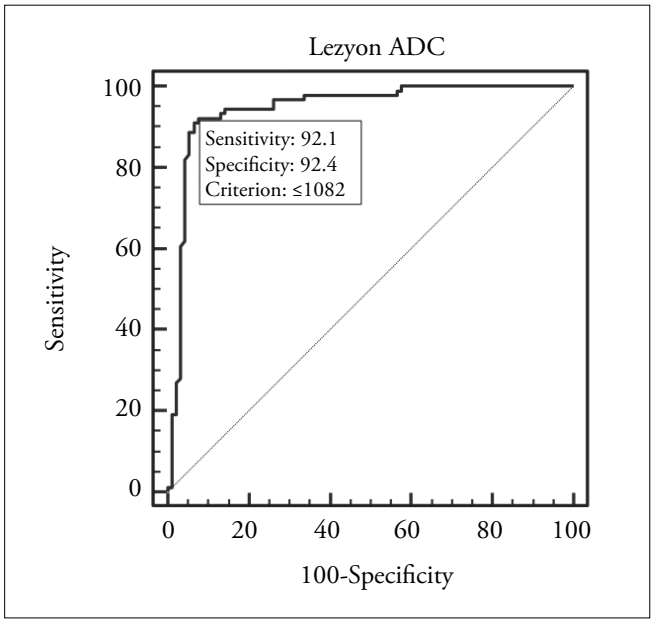

Figure 1. The differentiation curve of malignant-benign lesions for the ADC values based on the ROC analysis AUC=0.945

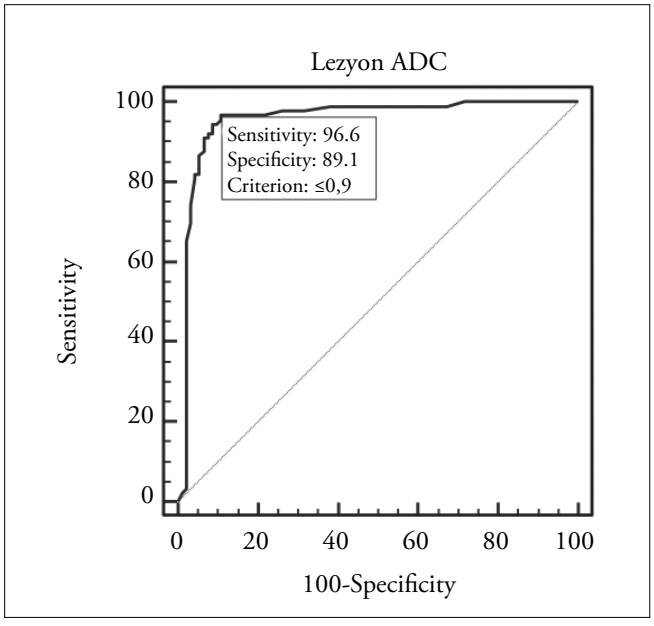

Figure 2. The differentiation curve of malignant-benign lesions for ADC lesion/normal breast tissue rates based on the ROC analysis AUC= 0.945

Of the benign lesions, 7 (7.6%) had lower ADC values than the determined threshold value 1.08 x10^{-3} mm^2/sec. Of these 7, 1 was fibroadenoma (Figure 3), 2 were atypical ductal hyperplasia, 3 were abscesses, and 1 was intraductal papilloma. Of the malignant lesions, 8 (9%) had higher ADC values than the determined threshold value 1.08 x10^{-3}. Of these 8, 3 were DCIS, 1 was invasive lobular carcinoma, 3 were invasive mucinous carcinoma, and 1 was well-differentiated liposarcoma.

Of the 89 malignant lesions, 63 (71%) were diagnosed as invasive ductal carcinoma. The mean min ADC value of the lesions diagnosed as invasive ductal carcinoma was 0.76±0.09 x10^{-3} mm^2/sec (Figure 4). The mean min ADC value of 6 lesions (6%) diagnosed as invasive

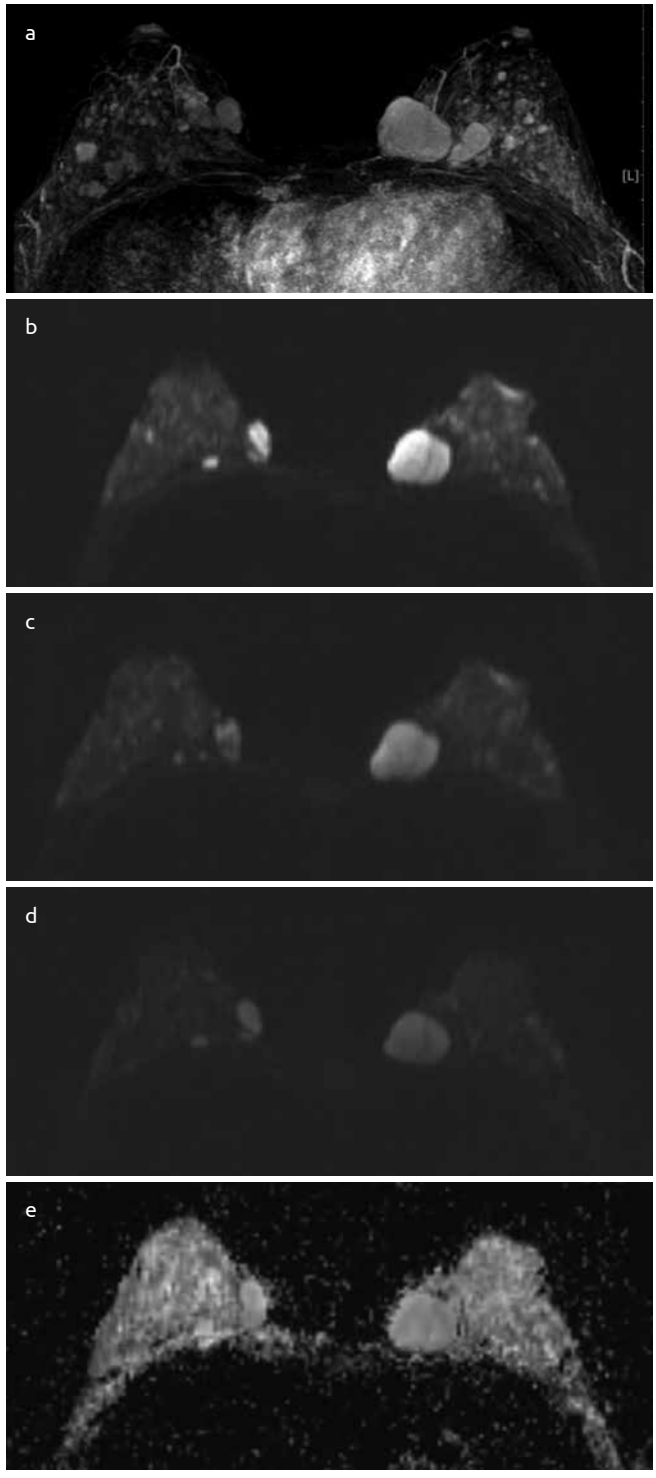

Figure 3. a-e. A woman aged 22 years. A large number of fibroadenomas were monitored in both breasts, the largest of which was located in the upper inner quadrant of the left breast with a 33 mm diameter. (a) Contrast-enhanced T1-weighted imaging (b) Diffusion-weighted Imaging (DWI) (b=50mm^2/sec) (c) DWI (b=400mm^2/sec) (d) DWI (b=800 mm^2/sec) (e) ADC value: 1587 x 10-6 mm^2/sec

lobular carcinoma was 0.94±0.14 x10^{-3} mm^2/sec. The mean min ADC value of 4 patients (4%) who were diagnosed as having invasive mucinous carcinoma was 1.21±0.15x10^{-3} mm^2/sec. The mean min ADC value of 5 patients (5%) diagnosed as having invasive mixed carcinoma was 0.73±0.10 x10^{-3} mm^2/sec. The mean min ADC value of 8 (8%) DCIS lesions was 1.06±24 x10^{-3} mm^2/sec (Figure 5). The mean

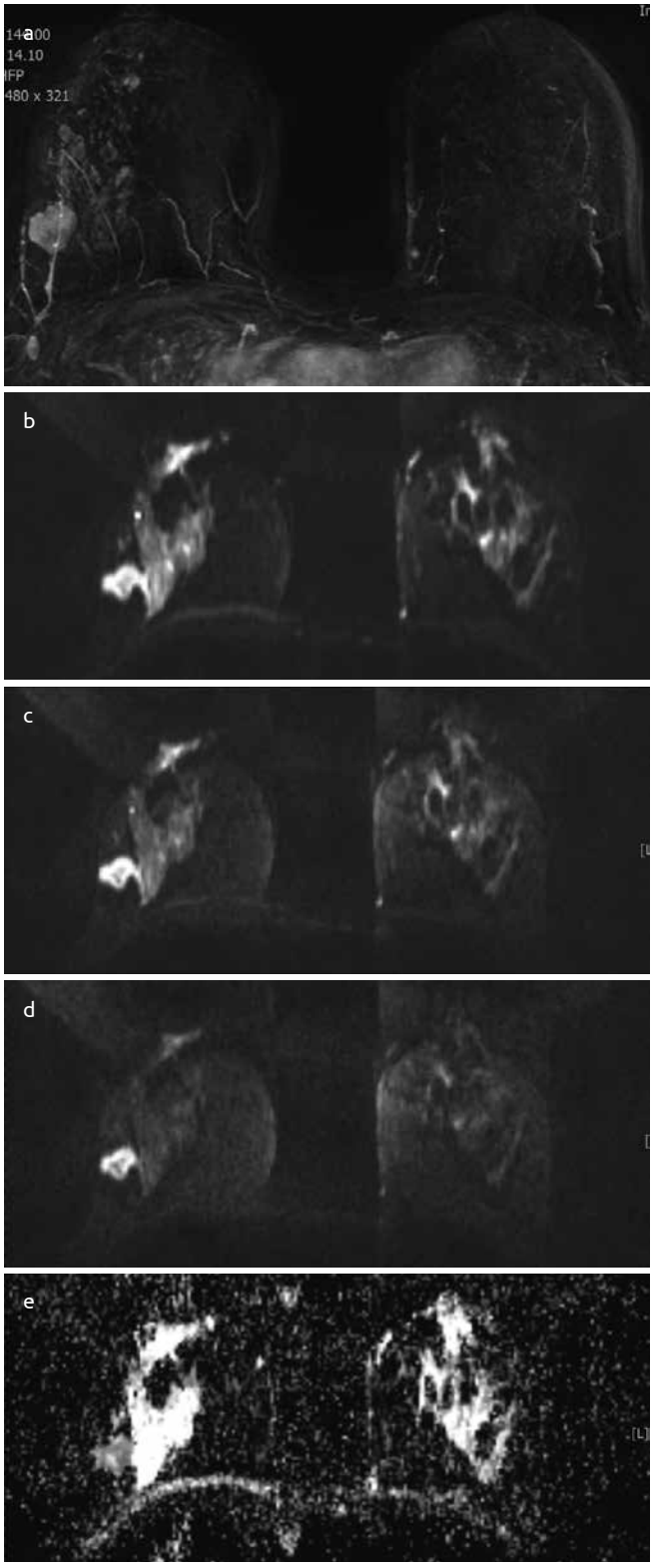

Figure 4. a-e. A woman aged 32 years. A lesion diagnosed as invasive ductal carcinoma with a 23 mm diameter located in the upper outer quadrant of the right breast. (a) Contrast-enhanced T1-weighted imaging (b) Diffusion-weighted Imaging (DWI) (b=50 mm²/sec) (c) DWI (b=400 mm²/sec) (d) DWI (b=800 mm²/sec) (e) ADC value: 809 x 10-6 mm²/sec

min ADC values within the malignant groups were found significantly different in terms of the histopathologic result variable (p<0.05). The mean min ADC values of DCIS, invasive lobular carcinoma and invasive mucinous carcinoma were significantly higher than the mean min ADC values of invasive ductal carcinoma and invasive mixed carcinoma (p<0.05). The group with the highest mean min ADC value of the malignant lesions was invasive mucinous carcinoma. Among the benign lesions, the mean min ADC value of 37 fibroadenoma lesions was 1.54±0.13 x10^{-3} mm²/sec, and the mean min ADC value of 4 intraductal papilloma lesions was 1.17±031 x10^{-3} mm²/sec. The mean min ADC value of the fibroadenoma lesions was significantly higher than that of the intraductal papilloma lesions (p<0.05). When the fibroadenoma and mucinous tumors were compared, the difference between the mean min ADC values of the invasive mucinous carcinoma and fibroadenoma lesions was statistically significant (p<0.05) (Table 4).

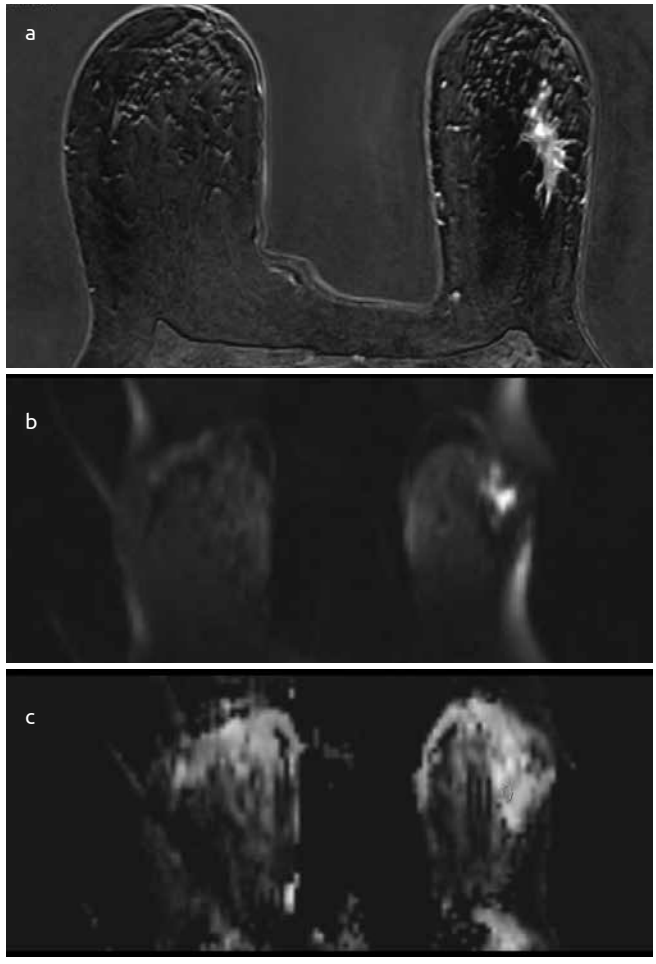

Figure 5. a-c. A woman aged 51 years. An irregular spiculated mass 28 mm in diameter with contour in the contrast-enhanced images located in the upper outer quadrant of the left breast. Histopathologic result: DCIS. (a) Contrast-enhanced T1-weighted imaging (b) Diffusion-weighted Imaging (DWI) (b=800 mm²/sec) (c) ADC value: 1299 x10-6 mm²/s

The mean min ADC value of 15 malignant lesions with negative ER and PR molecular prognostic factors was 0.77±0.11 x10^{-3} mm²/sec, whereas the mean min ADC value of 7 malignant lesions with one positive ER or PR was 0.76±0.07 x10^{-3} mm²/sec, and the mean min ADC value of 58 patients with positive ER and PR was 0.80±0.16 x10^{-3} mm²/sec. Based on these results, the group with negative ER and PR had a lower mean min ADC value than the group with positive ER and PR. However, this difference was not statistically significant (p=0.684) (Table 5).

Table 4. The mean values of ADC levels by histopathologic subgroups

		N	Mean ADC	SD	Minimum	Maximum
Benign						
	Apocrine metaplasia and columnar cell hyperplasia	37	1.469	0.176	1.187	1.783
	Fibroadenoma	37	1.543	0.133	0.926	1.791
	Atypia	6	1.194	0.270	0.720	1.448
	Abscess	8	1.188	0.397	0.570	1.597
	Intraductal Papilloma	4	1.172	0.314	0.818	1.573
Malignant	Ductal Carcinoma In Situ	8	1.056	0.242	0.747	1.356
	Invasive Ductal Carcinoma	63	0.758	0.093	0.508	1.065
	Invasive Lobular Carcinoma	6	0.944	0.144	0.785	1.163
	Invasive Mucinous Carcinoma	4	1.210	0.153	1.026	1.504
	Invasive Mixed Carcinoma	5	0.727	0.104	0.617	0.875
	Invasive Medullary Carcinoma	1	0.898	-	0.898	0.898
	Well-Differentiated Liposarcoma	1	1.499	-	1.499	1.499
	Invasive Apocrine Carcinoma	1	0.775	-	0.775	0.775
	Total	181	1.125	364.30	0.508	1.791

ADC: apparent diffusion coefficient; SD: standard deviation; N: number

Table 5. Lesion ADC levels by ER/PR

	ER and PR –(15)		ER or PR –(7)		ER and PR +(58)			
	Mn	Sd	Mn	Sd	Mn	Sd	F	p
Lesion ADC	0.771	0.114	0.762	0.065	0.803	0.160	0.382	0.684

ER: estrogen receptor; PR: progesterone receptor; ADC: apparent diffusion coefficient

Table 6. Lesion ADC levels by C-erbB-2

	c-erbB-2(-) (n=56)		c-erbB-2(+) (n=24)			
	Mn	Sd	Mn	Sd	t	p
Lesion ADC	0.807	0.164	0.766	0.089	1.43	0.157

C-erbB-2: Her2 immunoexpression
ADC: apparent diffusion coefficient; SD: standard deviation; Mn: mean value

The mean min ADC value of 56 lesions with a negative, 1+ and 2+ Her2, a molecular prognostic factor, and no amplification found in FISH was 0.81±0.16 x10^{-3} mm^2/sec, and the mean min ADC value of 24 lesions with 3+ and 2+ Her2 and amplification found in FISH was 0.77±0.09 x 10^{-3} mm^2/sec. Based on these findings, the mean min ADC value of the group with Her2-positive lesions was lower compared with the mean min ADC value of the group with Her2-negative lesions. However, the difference was not statistically significant (p=0.157) (Table 6).

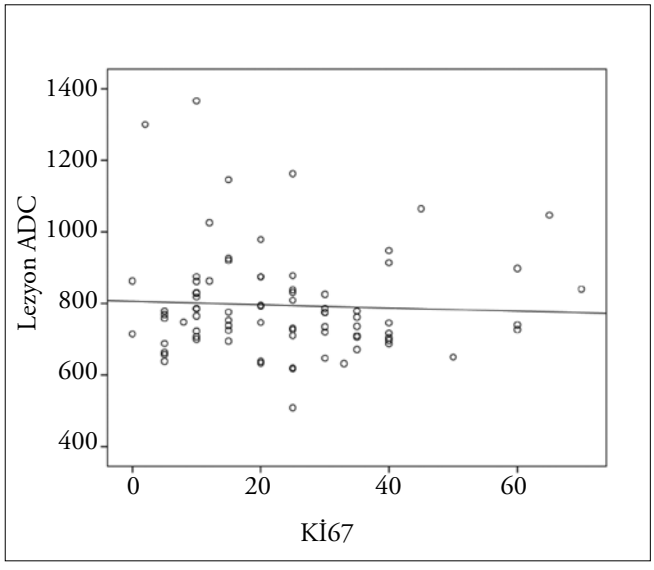

Figure 6. Pearson's correlation was performed for the correlation of the Ki-67 values and ADC values, p=0.669

When the correlation between the tumor proliferation rate indicators Ki-67 and ADC values was analyzed, there was no correlation found between the values (p= 0.669) (Figure 6).

Discussion and Conclusion

There was a statistically significant difference between the ADC values of the malignant breast lesions and benign breast lesions in our

study (p<0.01), and the diagnostic value of the test showed a very high AUC value (0.945) in the ROC analysis. This difference was caused by the decrease in the extracellular volume content of the tumors due to the increased cellular density and the fall in the ADC value due to restricted water diffusion (10). The dynamic contrast-enhanced examinations are directly related to the vascularity of the tumors and unrelated to tumor cellularity (5). In our study, fairly high sensitivity (92%) and specificity (92%) were acquired in evaluating the breast lesions with DWI. The dynamic contrast-enhanced breast MRI had a high sensitivity in detecting malignant lesions but a low specificity, which imposed limitations. There are studies stating that this specificity can be improved with DWI (22-24). However, different threshold values were reported in studies with DWI based on the station and magnetic field of the device. The reported values range between 1.02 and 1.43 $x10^{-3}$ mm^2/sec, and differed from each other. According to the ROC curve in our study, the best threshold value was 1.08 $x10^{-3}$ mm^2/sec. This value fell between the reported values in the literature; however, it was closer to the low values. The fact that the values differ greatly amongst studies raises difficulties in using DWI as a standard method. Baltzer et al. (25) determined a threshold ADC value of 1.4 in the evaluation algorithm they proposed, and created an evaluation chart accordingly. According to this chart, biopsy should not be recommended for lesions with an ADC higher than 1.4 even if the other criteria of the lesions indicate biopsy. Ours is the highest threshold value reported in the literature, and the sensitivity was 96.6% for this threshold value. However, there were cases with invasive mucinous carcinoma that did not comply with this criterion and had an ADC value higher than 1.4. The mean min ADC value of 4 lesions diagnosed as invasive mucinous carcinoma was 1.21±0.15 $x10^{-3}$ mm^2/sec, and there was a significant difference between this type of cancer and other types of cancer (p<0.05). Similarly, high values were reported in the literature for mucinous carcinoma between 1.6 $x10^{-3}$ and 2.1 $x10^{-3}$ mm^2/sec, but the mean value in our study was below these values (26-28). The most typical feature of mucinous carcinoma is the mucin content observed in the extracellular area. The mucin content makes diffusion of liquids easier, and there is less restriction compared with other malignant lesions (26-28). Mucinous carcinomas are sharply-bordered like fibroadenomas in morphologic analyses, and are seen as lesions that contain black septa in T2-weighted and contrast-enhanced examinations, and therefore may cause diagnostic errors. We found a distinctive difference between the fibroadenoma ADC values and mucinous carcinoma ADC values in our evaluation (p<0.05).

When we assessed the lesion/breast tissue ADC rates and the lesions, we found a higher AUC, going up to 0.956 from 0.945, according to the ROC analysis. When we determined a threshold value as 0.9, the sensitivity went up 96% and the specificity was 89%. Similar studies in the literature reported that measuring the ratio of ADC values for healthy breast tissues and lesions helped diagnostic accuracy, whereas an increase in sensitivity caused a decrease in specificity in our study (23, 29).

There was a significant difference between the mean ADC values of invasive ductal carcinomas and ductal carcinoma in situ in our study (p<0.005) when we evaluated the ADC values of cancers in different histopathologic groups. The ADC values of DCIS were significantly high. In a study by Choi et al. (30) with 276 cases of invasive ductal carcinoma and 59 cases of DCIS, the mean ADC value of invasive ductal carcinoma was 0.907 $x10^{-3}$ mm^2/sec, and the mean ADC value of DCIS was 1.113 $x10^{-3}$ mm^2/sec. Bickel et al. (31) reported in their study 155 patients with invasive ductal carcinoma and 21 patients with DCIS that the mean ADC value of invasive ductal carcinoma lesions was 0.900 $x10^{-3}$ mm^2/sec and the mean ADC value of DCIS was 1.240 $x10^{-3}$ mm^2/sec. In a study by Qiu Lang Hua et al. (26) the authors used two different b values, the mean ADC value of 48 invasive ductal carcinoma lesions was 1.099 $x10^{-3}$ mm^2/sec and the mean ADC value of 6 DCIS lesions was 1.305$x10^{-3}$ mm^2/sec when the b value was 1000. The reasons for this difference were that invasive ductal carcinoma is a type of cancer that is heavier with cells and it restricts water diffusion more compared with DCIS (32, 33).

Various studies have investigated the relationship between tumor prognostic factors and DWI (30-41). Some studies concluded that there was a relationship between tumor grade and ADC values. In these studies, it was argued that high-grade tumors had more diffusion restriction than low-grade tumors due to cell morphology and differences in extracellular matrix (33, 35). Therefore, we compared the ADC values particularly in terms of molecular markers that determine the prognosis of tumor. However, we found no relationship especially between the ADC values and Ki-67 values that inform about the tumor's mitotic activity. Similarly, we could not demonstrate a relationship between ER and Her2. Jeh et al. (40) reported a relationship between ER positivity and Her2 negativity and low ADC. However, they did not report a relationship between other prognostic factors, and especially Ki-67. In the study by Choi et al. (30) of 335 patients with invasive ductal carcinoma, the ADC value of ER(+) and PR(+) tumors was significantly lower than the ADC value of ER(-) and PR(-) tumors (p=0.003 and p=0.032). Aglietta et al. (41) reported a slight but significant relationship between ER and ADC. On the other hand, Park et al. (39) could not demonstrate a relationship between ER, PR, and Ki-67 in their study on 190 malignant lesions. Similarly, Kim et al. (35) could not report a distinctive relationship with ER and PR in their study. Contrary to these studies, the mean ADC values were higher with positive ER and PR in our study; however, we did not find a statistically significant result.

Her2 expression with cell proliferation occurs in more invasive tumors with poor prognosis. Therefore, a decrease in ADC values is expected after cell growth in Her2 expression. However, studies have shown low ADC values in cases with no Her2 expression (39, 41). Park et al. (39) claimed that increased angiogenesis and increased perfusion secondary to neovascularization in patients with Her2-positive suppressed the diffusion restriction the tumor creates. The effect of perfusion becomes more suppressed as the determined b value increases. However, although Park et al. (39) used a b1000 value that would effectively suppress the effect of perfusion, they included the strong perfusion that could have occurred due to Her2-positivity in their report but did not explain why the high b value did not suppress the perfusion. Additionally, regardless of the number of the statistical differences found in this study, the difference between the ADC values of Her2 0 and Her2 +++ cases was between 0.88 and 0.92 with a very small gap of 0.4. Despite the fact that the gap was similarly 0.4 units between the 0.81 mean ADC value of the Her2-negative cases and the 0.77 mean ADC value of the Her2-positive cases, there was no statistical significance found in our study. Choi et al. (30) did not report a correlation between the Her2 and ADC values in their study with 335 patients with invasive ductal carcinoma. Similarly, Kamitani et al. (36) did not report a correlation between the Her2 and ADC values in their study with 81 patients with invasive breast cancer. Although we found no statistical significance in terms of ER and PR values and Her2 values compared with the literature, the mean ADC values were much lower in patients with negative ER, PR and Her2 than in the patients with

positive ER, PR and Her2. Park et al. (39) found low ADC values in both ER-positive and PR-negative patients in their study. However, although there was a difference between the PR-positive and PR-negative patients, they did not find a statistical significance. The results of the studies reported in the literature are inconsistent. The mean ADC values with very small differences were significant in some studies but not significant in others (31-41). Therefore, we believe large series with the participation of more patients are needed in this regard.

In our study, there was no correlation between the Ki-67 and ADC values. In the study by Choi et al. (31), the threshold value for the Ki-67 value was considered as 20, when values over 20 were categorized as Ki-67(+) and values under 20 were (-), the ADC values of the tumors with high Ki-67 were significantly low. In a study by De Felice et al. (37) of 75 patients with invasive ductal carcinoma, the threshold value for Ki-67 was 30. Accordingly, there was no significant correlation found between the Ki-67 values and ADC values. There was no significant correlation found between prognostic factors such as ER-PR, Her2 and Ki-67, and ADC value in the study by Cipolla et al. (38) of 96 patients with invasive ductal carcinoma, or in the study by Kim et al. (39) in 67 patients with invasive breast cancer.

One of the limitations in our study is that it was a retrospective study and a large number of examinations were excluded because of technical errors. Therefore, objectivity may have been damaged with regard to lesions. Another limitation is the possibility of mismeasurement due to mis-locating a region of interest (ROI) (42). The ADC levels of malignant lesions with necrotic centers are expected to increase in localization of necrosis (42). In lesions with thin periferically-enhanced tumor tissues, an adjacent necrotic part, adjacent normal fibroglandular tissue and adipose tissues may enter inside the region of interest, and this may cause incorrect positive or negative results. Another limitation was that invasive ductal carcinoma was dominant in the histopathologic subgroup distribution of malignant lesions, and the number of other lesions was small in comparison. A similar inequality is present in some of the molecular subgroups (ER, PR, and Her2). Another limitation of the study was that the performance of DWI alone was analyzed without including its contribution to dynamic contrast-enhanced examination.

Consequently, DWI is a method with high sensitivity and specificity that demonstrates a high diagnostic performance in the differentiation of benign and malignant breast lesions. However, it was not deemed adequate for evaluating prognostic molecular markers such as ER, PR, Her2 and Ki-67.

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Informed Consent: Informed consent was obtained from patients who participated in this study.

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Case Report

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Periductal Stromal Tumor of the Breast: A Case Report and Review of the Literature

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ABSTRACT

We present a woman aged 50 years who underwent a Tru-cut biopsy for a BI-RADS 4 lesion on her right breast and received a histopathology diagnosis of a fibroadenoma. In her one year follow-up, the lesion had progressed and she underwent an excisional biopsy. Her final diagnosis was a periductal stromal tumor. Periductal stromal tumor is an extremely rare and different entity from phylloides tumor, which makes appropriate diagnosis difficult in Tru-cut biopsy and care should be taken. Lesion progression of should require a re-biopsy. Their tendency to recur warrants follow-up. We believe that radiologic, pathologic, and clinical correlation is key in decision-making and diagnosis of these tumors.

Keywords: Breast neoplasm, periductal stromal tumor, ultrasound, mammography

Introduction

Periductal stromal tumor (PST) is an extremely rare, low-grade neoplasm that arises from breast connective tissue. It has biphasic morphology with benign ducts and a sarcomatous stroma with no specific clinical or radiologic findings, which makes it difficult to diagnose (1-4). It was classified as a different entity by the World Health Organization (WHO) in 2002 because of lack of phylloides architecture. PST has a tendency to recur if excised incompletely and can be transformed to sarcomas, which is why surgery with safe margins is recommended (2, 3, 5). Herein, we present the radiologic features and histopathology of this case especially to emphasize the importance of diagnosis using Tru-cut biopsy with radiologic-pathologic correlation, and to discuss the differential diagnosis of periductal stromal tumor of the breast.

Case Presentation

A woman aged 50 years who has yearly mammography screening had a new mass in her mammogram. Her mammogram showed a mass of 7 mm at its widest diameter in the upper inner quadrant of the right breast, which did not exist on her prior mammograms (Figure 1a). The mass was oval with circumscribed margins and showed equal density. An ultrasound (USG) examination showed an oval mass in parallel orientation with circumscribed margins in the upper inner quadrant of the right breast. The mass was 6.8 x 6.0 mm in size (Figure 1b). The lesion was de novo and interpreted as BIRADS 4a and a biopsy was recommended. A Tru-cut biopsy was performed and interpreted as fibroadenoma with intraductal hyperplasia by an external pathology clinic. One year later, her routine screening mammogram showed indistinct margins (Figure 1c). A USG examination showed similar features to the prior examination but the size had enlarged to 9.0 x 7.5 mm (Figure 1d). Rebiopsy of the lesion was planned. Reinterpretation of her prior biopsy specimen showed a tumor with biphasic proliferation with minimal atypical spindle cells that surrounded open ducts and tubules with lack of leaf-like growth pattern. A multidisciplinary breast board recommended an excisional biopsy depending on the new interpretation and enlargement of the lesion. An excisional biopsy after guide-wire localization was performed. Excisional biopsy 13 months after the first Tru-cut biopsy showed a 70 x 60 x 30 mm specimen; by multiple sectioning, lobulated lesion that was a beige in color and 8 mm in diameter. The lesion was 5 mm distant to the nearest surgical margin.

Microscopically, for both previous Tru-cut biopsies (Figure 2a) and present excisional biopsy (Figure 2b), the tumor had biphasic proliferation and a multinodular growth pattern composed of spindle cells without significant atypia, cuff formations around open tubules without leaf-like patterns, and occasional mitoses (1 /10 HPF). Epithelial components had a double layer or hyperplastic features without atypia and leaf-like growth pattern. The resection margins were negative and the closest distance between tumor and nearest resection margin was 5 mm. In immunohistochemistry staining, ductal cells were positive for estrogen receptor (ER), progesterone receptor (PR),

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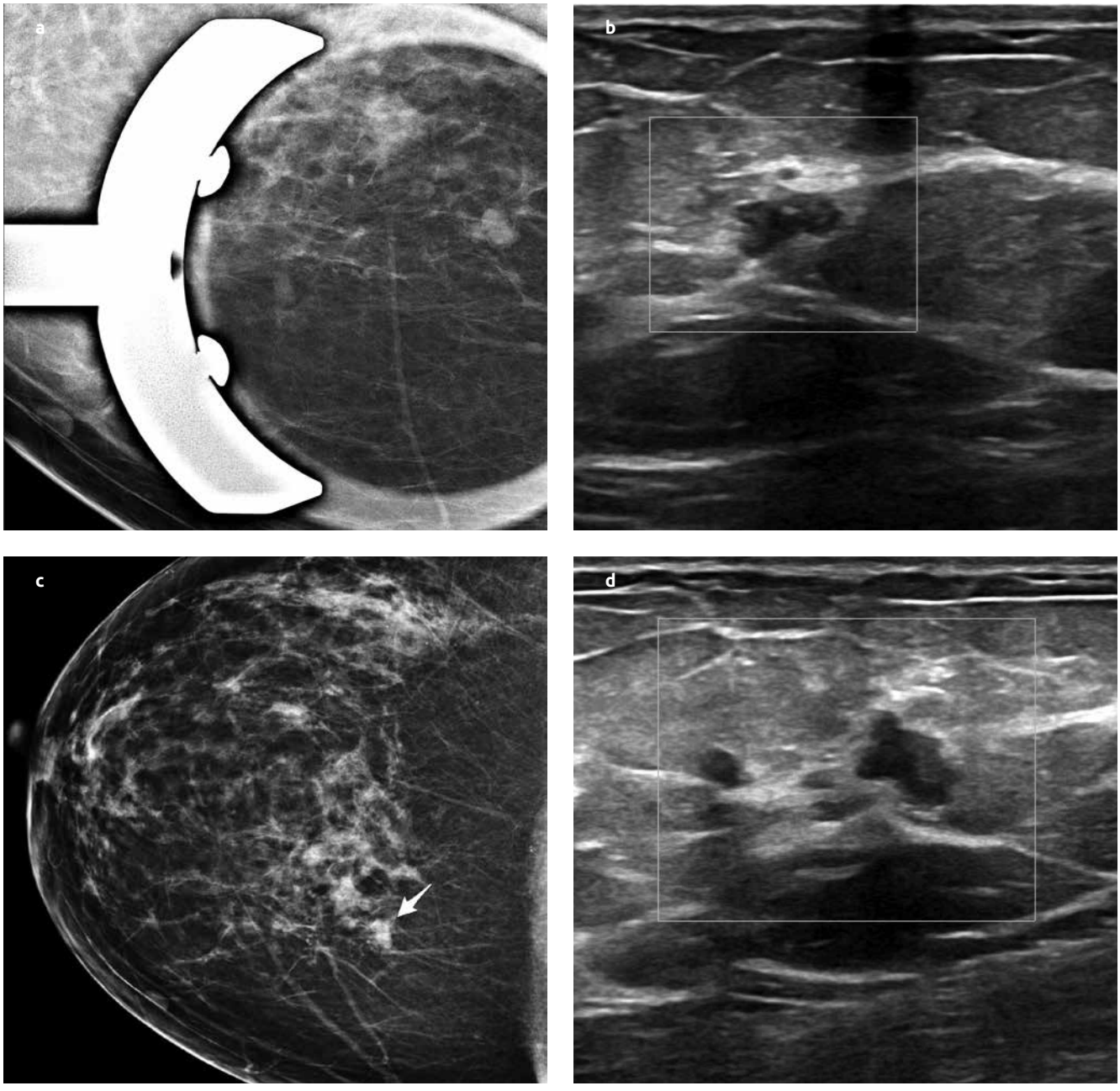

Figure 1. a-d. (a) RCC spot mammogram shows a mass of equal density with an oval shape and circumscribed margins. The margins are lobulated (b) USG image of the lesion. A parallel oriented, oval, and well-circumscribed hypoechoic mass with no posterior features is seen (c) The same mass as in Figure 1 one year later; the margins are indistinct (d) The mass has the same USG features with Figure 1b but shows significant enlargement. Lobulation of the margins is more prominent

GCDFP15, CK19 and CK14; stromal cells were only positive with CD10 and CD34 (Figure 3). Proliferation index (Ki-67) was 1%. According to the histomorphologic and immunohistochemical findings the diagnosis of low-grade periductal stromal tumor was established.

Discussion and Conclusion

Periductal stromal tumor was previously accepted as a synonym for phylloides tumor, but it was recently classified as a distinct entity by the WHO in 2002 because of lack of leaf-like growth pattern (1, 2). Unlike phylloides tumor, the incidence is higher in perimenopausal and post-menopausal women. Similar to phylloides tumor, it has a tendency for local recurrence when incompletely excised and can transform to sarcomas (2). Histologically, it has a biphasic proliferation with spindle tumor cells around open ducts, tubules, and cellular sarcomatous stroma (5, 6). The histologic criteria for PST according to the Armed Forces Institute of Pathology (AFIP) include: predominantly sarcomatous spindle cell stromal proliferation around open ducts and tubules, lack of leaf-like growth pattern, one or more nodules that can be separated by adipose tissue, mitotic activity equal to or more than 3 in 10 high power fields (HPF) and infiltration into surrounding adipose tissue (2, 3). The histologic grading depends on atypia and mitotic count ranges from low to high grade. Tumor cells are only positive with CD34, CD10, and lacks CD117, S-100, ER, and PR expression (2, 7). PST is a tumor of intermediate behavior and resection with significant margin is considered sufficient for treatment. Adjuvant chemotherapy or radiotherapy is not recommended.

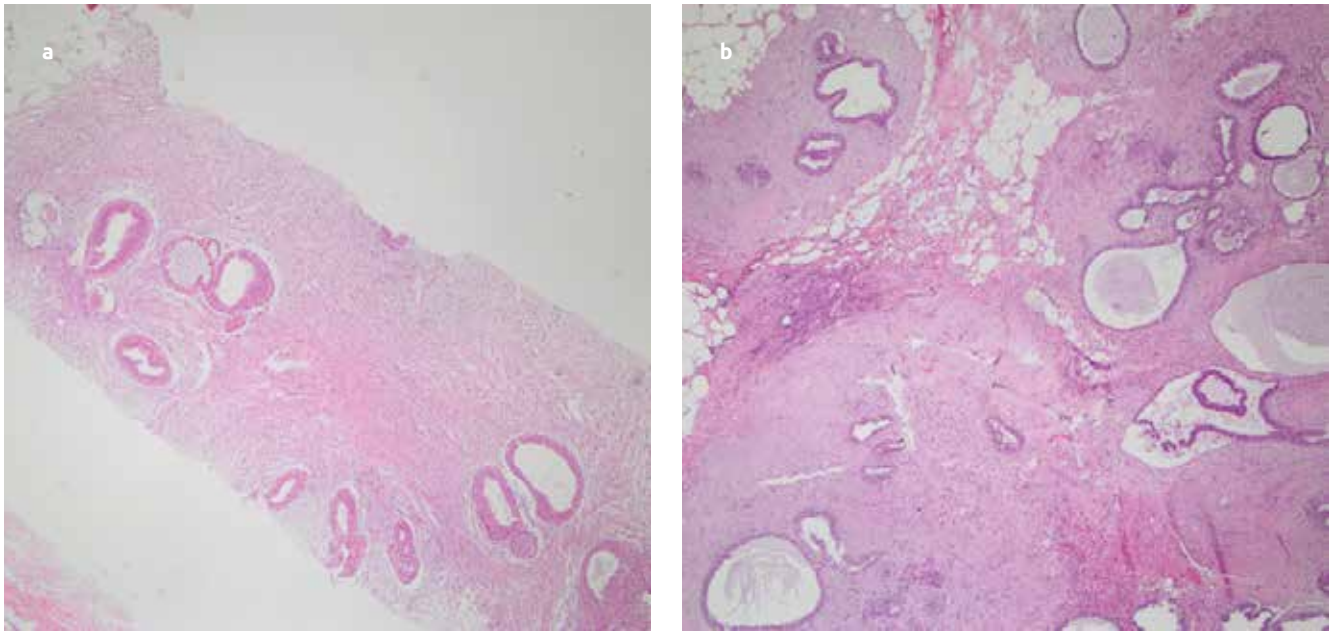

Figure 2. a, b. (a) The tumor had biphasic proliferation and a multinodular growth pattern and was composed of spindle cells without significant atypia, cuff formations around open tubules without leaf-like pattern (X40) (b) Epithelial components had a double layer or hyperplastic features without atypia and leaf-like growth pattern (X100)

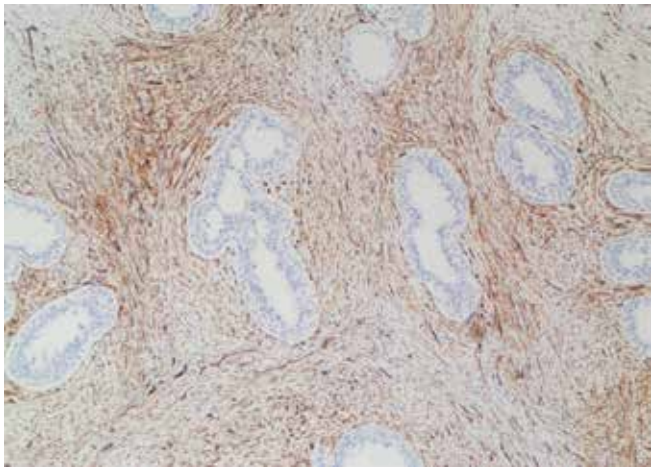

Figure 3. Stromal cells were positive with CD34 (X100)

In differential diagnosis several tumors should be thought; firstly phyllodes tumor, then spindle cell carcinoma, myoepithelial carcinoma and other breast sarcomas (1). The main difference from phyllodes tumor is the lack of leaf-like pattern in PST. The differential diagnosis of spindle cell carcinoma is important because of different targeted therapy and immunohistochemistry can also be helpful; tumor cells are positive with CK5, CK14, p63, and negative with CD34 (8-10). Breast sarcomas have highly pleomorphic nuclei, abundant mitotic figures, and positive with CD10 and Vimentin, and negative with CD34. Myoepithelial carcinomas have an infiltrative growth pattern with biphasic or glandular pattern, are highly pleomorphic, mitotically active, and positive for Vimentin, SMA, S100, p63 and CK14 (1, 10). In the present case, tumor composed of minimal atypical spindle cells surrounded open ducts and tubules without a leaf-like growth pattern. Spindle cells were only positive with CD10 and CD34, and the proliferation index was 1%, which was compatible with PST.

As a result, PST is an extremely rare entity, and shows similar symptoms with other benign and malignant breast tumors, absence of specific radiologic findings make the diagnosis difficult (2). Extensive tumor sampling and additional immunohistochemistry should be performed for appropriate diagnosis. Before making a decision, other spindle cell tumors should be taken in consideration in the differential diagnosis because of different targeted therapy.

There are few case reports published in the English literature because PST is a rare entity (3, 11-13). There is little information about the radiologic features of these lesions; the only two separate cases reported in the literature roughly describe the radiologic features without using definitive images (12, 13). Although the descriptions and images are not clear in these reports, the lesions seem to have similar radiologic features (12, 13). The radiologic features of our case were similar to a fibroadenoma. However, de novo presentation after middle age and enlargement during follow-up should raise suspicion in such cases. To our knowledge, this is the first detailed report of PST with USG and mammographic findings.

We believe that radiologic, pathologic, and clinical correlation are key in decision making and the diagnosis of these tumors.

Informed Consent: Informed consent was obtained from patients who participated in this study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - G.A., H.K.; Design - G.A., H.K., E.A.; Supervision - H.K., E.A.; Materials - G.A., H.K., G.Ak, E.A.; Data Collection - G.A., G.Ak, E.A.; Anlaysis and Interpretation - H.K., E.A.; Literature Review - G.A., G.Ak, E.A.; Writing - G.A., G.Ak; Critical Review - H.K., E.A.

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Case Report

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Transcatheter Arterial Embolization for Controlling Severe Bleeding From Recurrent Locally-Advanced Breast Cancer

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ABSTRACT

One of the rare but most challenging issues in the management of the locally-advanced breast cancer (LABC) is life-threatening bleeding from the fungating and/or ulcerating focus (foci) of these tumors. Breast surgeons may need the assistance of interventional radiologists to solve this urgent condition if surgery cannot provide sufficient benefit. Herein, we report a case of recurrent locally-advanced breast cancer that presented with sudden severe bleeding, which was stopped by an interventional radiologist via transcatheter arterial embolization (TAE). In addition, we evaluate the role of interventional radiology in patients with breast cancer who present with bleeding from the breast by reviewing the relevant literature.

Keywords: Breast cancer, embolization, hemorrhage, interventional radiology

Introduction

Breast cancers, particularly those that are locally advanced, may rarely present with acute severe bleeding. They usually appear in the form of fungating and/or ulcerating tumors. This condition can be difficult to manage through a surgical procedure. Interventional radiology has gained an increased role in coping with this problem. The most frequently used method to achieve safe and efficacious hemostasis is transcatheter arterial embolization (TAE). This method was also reported to ensure a reduction in tumor size.

Case Presentation

A woman aged 47 years who had recently undergone a toilet mastectomy plus axillary dissection for locally-advanced breast cancer, presented with sudden severe bleeding from a loco-regionally recurrent tumor that had developed rapidly. She had been diagnosed as having locally-advanced left breast cancer with axillary metastasis at the age of 46 years, which was histopathologically determined as a triple-negative breast cancer. The tumor had remained unresponsive to the neoadjuvant of chemotherapy (NACT), therefore she underwent toilet mastectomy plus axillary dissection to prevent further complications. However, in the very early postoperative period, a locoregional recurrent tumor began to develop on the chest wall and in the axillary region. Recurrent masses, especially the ones in the axilla, tended to ulcerate over the course of time. Owing to ulceration, radiotherapy (RT) was not considered as an option in the treatment. Finally, approximately three months after the operation, the patient presented with sudden severe bleeding from the recurrent breast tumor. She was admitted to our general surgery clinic for treatment of this acute bleeding. On physical examination, the patient was alert, conscious, and cooperative. She had moderate pallor. Her initial blood pressure was 100/60 mmHg, and heart rate of 90 bpm. Inspection of the chest wall showed that there was a very large loco-regionally recurrent breast tumor on the left side along the incision line; the bleeding originated from the deep part of the left axilla where many large ulcerated recurrent tumors were located. She also had an apparent upper limb edema. The results of the lab tests on admission showed a low hemoglobin level of 6 mg/dL and hematocrit of 20.9%. The platelet count was found 241 x 10^3/microliter. INR and aPTT were within normal ranges. First, a temporary control of bleeding was performed by dressing the wound with sterile gauze pads and compressing them with an elastic bandage around the chest wall. Soon after, an intravenous access was established and replacement of isotonic fluid was initiated. Three units of red cell suspension were transfused consecutively as quickly as possible. Following these resuscitative measures, her vital signs improved with a blood pressure of 120/90 mmHg, and heart rate of 76 bpm. Hemoglobin and hematocrit increased to 11.1 mg/dL and 33.7%, respectively.

An interventional radiologist's opinion was requested to aid in providing safer hemostasis and the patient was transferred to interventional radiology where a digital subtraction angiography (DSA) of the left axillary artery was performed. The images revealed a giant tumoral blush

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with many feeders including the costocervical branch and internal mammary artery (IMA) (Figure 1, 2). Through a 5F Cobra catheter, a microcatheter was advanced into all branches coming off the axillary artery and then embolized up to the occurrence of reflux with 300-micron-sized particles (Embosphere; Biosphere Medical, Rockland, Mass). A test DSA showed nearly total devascularization of the tumor (Figures 3, 4). On the first day after the procedure, the patient was well with stable vital signs. When the dressings were opened, complete hemostasis was seen to be present (Figure 5). She was discharged on the second day and scheduled for daily wound care. At one month follow-up examination, there was no obvious bleeding on the left chest Wall.

Discussion and Conclusion

A high rate of recurrence during the course of LABC is a well-known issue. Katz et al. (1) evaluated a total of 1031 patients who had been treated with mastectomy and doxorubicine-based chemotherapy without RT and found that locoregional recurrence was seen in more than 20% of patients who presented with tumors sized ≥4 cm or with at least four node involvement. In addition, they determined that patients with one to three involved nodes and large tumors, extranodal extension ≥2 mm, or inadequate axillary dissections experienced high rates of recurrence. In both situations, the authors suggested complementary RT. In another report, it was demonstrated that higher tumor stage (T4), higher nodal stage (N2N3), and locally-advanced stage were associated with higher rates of locoregional recurrence and distant metastases (2).

Our patient also had rapid locoregional recurrence that consisted of a number of masses on the left chest wall and in the left axilla. The masses were about to ulcerate, the one in the axilla had ulcerated with subsequent severe bleeding, which required urgent management. The tumor had been found intractable to NACT in the beginning. It was not suitable for hormonotherapy and RT because it was a triple-negative tumor, and ulceration on the relevant region, respectively. Both at the beginning of recurrence and during the bleeding phase of the disease, neither chemo-/hormonotherapy nor RT were considered to be able to provide any benefit.

Bleeding from breast cancer is a rare condition, except in cases of LABC; surgery is the usual treatment under appropriate circumstances. Nagasawa et al. (3), and Kijima et al. (4), reported cases of breast cancer bleeding from open cavities in breasts that had no histopathologic skin invasions. Both authors treated their patients with modified radical mastectomy. Maekawa et al. (5), reported a patient who presented with a huge bleeding breast mass. The authors found that it resulted from ruptured breast cancer vessels into an adjacent cyst due to invasion. The treatment was modified radical mastectomy.

Nevertheless, owing to the skin involvement in LABC, severe bleeding from ulcerating and/or fungating lesions, especially in case of locoregional recurrence, can be seen more often. In these cases, TAE can be chosen a very practical and safe treatment option to control the bleeding instead of surgery, at which point an interventional radiologist should be called for this purpose. Embolization is an endovascular procedure that involves occlusion of arterial or venous structures with the aim of therapeutic outcomes. Interventional radiology has gained an increasing role in this field, particularly with respect to hemostasis for many advanced cancers of the body. A number of substances have been used as embolization agents, including gelatin foam, polyvinyl alcohol particles (PVA), tris-acryl gelatin microspheres, a number of various coils, detachable sack vascular occlusion devices, detachable balloons, amplatzer vascular plugs, n-butyl-2 cyanoacrylate, ethylene vinyl alcohol copolymer, calcium alginate gel, and absolute alcohol (6).

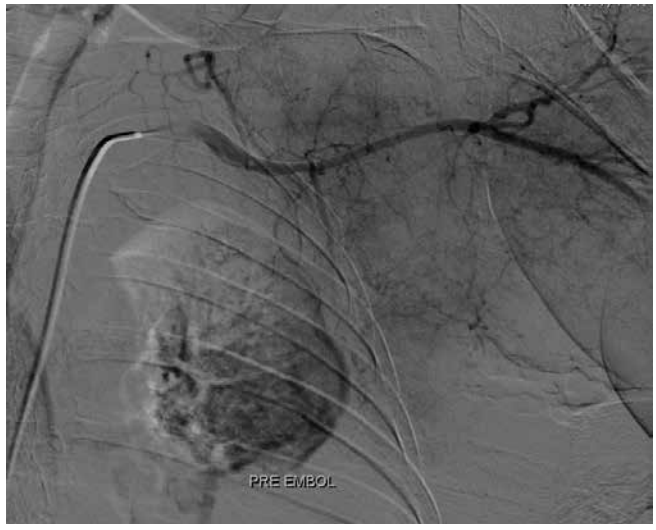

Figure 1. Preembolization DSA image acquired during left axillary artery run, giant hypervascular tumoral blush invading left upper part of thoracic wall

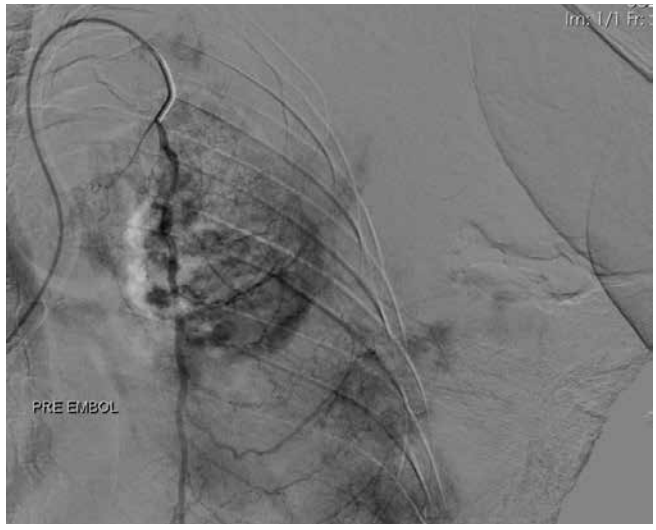

Figure 2. Preembolization DSA image acquired during internal mammary artery (IMA) run, hypervascular tumoral blush invading left anterior part of thoracic wall

Tokunaga et al. (7), reported a case of breast cancer with chest wall recurrence, which was managed with chemotherapy, TAE, and chest wall resection. The authors advocated that performance of TAE to supply arteries would provide hemostasis and promote mass reduction.

Transcatheter arterial embolization was also reported to be effective in a case of breast angiosarcoma that presented with hemorrhage and was managed using radiologic embolization using PVA, as a temporary measure before the definitive surgery. In the same patient, embolization of the main hepatic artery was also performed for multiple liver metastases (8).

Moriarty et al. (9), reported successful control of a life-threatening bleed that originated from a fungating LABC via TAE with microspheres. The authors suggested using this method with minimal risk when conventional treatment modalities fail or are too morbid to perform.

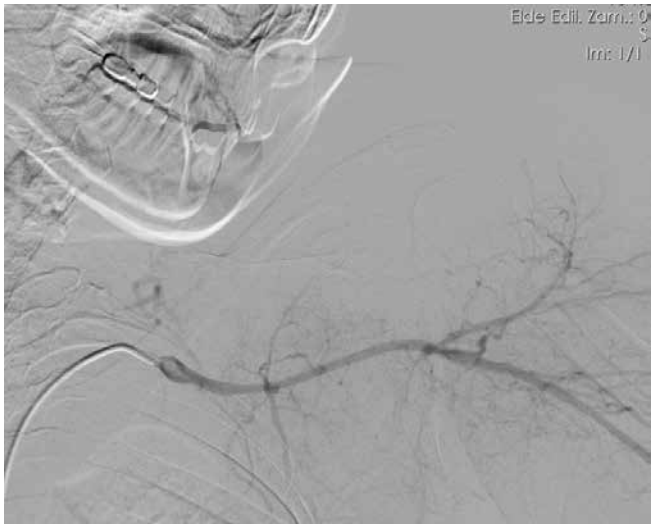

Figure 3. Postembolization DSA image of the axillary artery reflected devascularization of the tumor

Figure 4. Postembolization DSA image of the IMA reflected devascularization of the tumor

Figure 5. Complete hemostasis at the bleeding site

Another endovascular treatment method performed by interventional radiologists is the placement of a stent into vessels. Ugras et al. (10) achieved successful hemostasis in a patient with a catastrophic hemorrhage from a recurrent fungating axillary breast cancer via placement of an endovascular stent into the axillary artery. Surgical exploration was limited due to arm edema and decreased shoulder immobility in their patient. The authors later found an intimal disruption in the axillary artery under angiography as the probable origin of pseudoaneurysm, and then placed a covered stent across the defect under fluoroscopy.

The clinical pictures of the last two cases were similar to that of our case. In all, there was nothing that could be done surgically and the assistance of interventional radiology was needed.

As in the other cases, TAE was performed in the present case with an entirely palliative intent and did not ensure any benefit on overall survival for the patient; however, it saved the patient's life in a safe and practical way against a troublesome bleed. This inspired us to keep this modality in mind for use in hard times while managing of breast cancer.

In conclusion, locally-advanced breast cancer and its recurrence can rarely cause sudden severe bleeding. Many of these tumors present in the form of fungating and/or ulcerating lesions, for which the benefit of surgery can be limited. Transcatheter arterial embolization seems as an optimal option in such situations. Breast surgeons should remember to remain in close contact with interventional radiologists during the management of these patients.

Informed Consent: Informed consent was obtained from patients who participated in this study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - Ş.A., B.A., Ö.K.; Design - Ş.A., B.A., Ö.K.; Supervision - Ş.A., B.A., Ö.K., R.U.G., M.S.Ç., M.A.N., A.A.; Data Collection and/or Processing - Ş.A., B.A., Ö.K., R.U.G., M.S.Ç., M.A.N., A.A.; Analysis and/or Interpretation - Ş.A., B.A., Ö.K., R.U.G., M.S.Ç, M.A.N.; Literature Review - A.A., B.A.; Writer - B.A., A.A.; Critical Review - Ş.A., B.A., Ö.K., A.A.

Conflict of Interest: No conflict of interest was declared by the authors.

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Case Report

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Subcutaneous Oleomas Following Sunflower Oil Injection: A Novel Case and Review of Literature

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ABSTRACT

Liquid foreign material injection has been used as an early medical intervention since the end of nineteenth century for the augmentation of body shape. Nowadays, these types of procedures have been abandoned by health professionals due to late onset of serious complications. However, it is still misused by some subcultures such as bodybuilders, passive homosexuals, transsexuals, and patients with mental illness. This article discusses a male patient who injected himself with a large amount of sunflower oil, which became complicated by an inflammatory response-abscess formation and sclerosing lipogranuloma of breasts. The radiologic and pathologic signs of this entity are discussed with a review of the relevant literature. Lack of suspicion of this entity may cause a great delay in establishment of definitive diagnosis, giving rise to prominent morbidity and mortality. It is necessary to know the diagnosis and treatment of this phenomenon because illegal substances that cause factitial panniculitis are widely available on websites and threaten thousands of people, which is anecdotally referred in medical literature. Chronic or recurrent lesions of a bizarre or atypical morphology should alert the physician to this artificial phenomenon. Radiologic findings are most important criteria for diagnosis because self-injection is denied by the patient.

Keywords: Breast, panniculitis, subcutaneous injection, magnetic resonance imaging, ultrasound

Introduction

Subcutaneous injection of liquid foreign material such as mineral oil (paraffin) or vegetable oil (cotton seed and sesame oils) has been used for remodeling of body shape for more than a century. Liquid silicone injection became popular after it was shown to be well tolerated by tissues and has been used as a minor procedure to feminize the face, breasts, buttocks, hips, or calves in transsexuals (1). Liquid foreign materials induce foreign a body reaction that is known as oleoma or sclerosing lipogranuloma in subcutaneous fat. Paraffinomas have been described in the genitalia, lower extremities, male or female breasts, ureter, eyelids, lips, abdomen, and neck (2). Although subcutaneous injection of these materials is not recommended due to the late onset of serious complications, it is still misused by body builders, passive homosexuals, and transsexuals. Foreign material self-injection is a worldwide entity with thousands of users because the market is illegal and there is no legislation for the distribution of anabolic steroids and supplements (3). Diagnosis and treatment is a challenging owing to the lack of considerable medical literature and unawareness of physicians about foreign material injection.

In the current case report, we present the clinical and radiologic manifestations of breast oleoma in a male patient following sunflower oil injection, followed by a review of literature.

Case Presentation

A male smoker aged 40 years with a history of chronic alcohol and substance abuse was admitted to hospital with the symptoms of bilateral breast enlargement and remarkable weight loss. He had fistulized painful drainage in the outer quadrant of the right breast. He denied any history of trauma or self injection to the involved area. He had received anti-tuberculosis treatment for 9 months 3 years ago.

His physical examination revealed skin erythema in the right lower inner quadrant, a 3-4 cm palpable mass in the lower outer quadrant and enlarged right axillary lymph nodes. Cultures of the sero-purulent exudate and tissue biopsy material were negative for aerobic and anaerobic bacteria and acid fast micro-organisms. Gram staining revealed Gram-negative and positive bacteria and leukocytosis. Inflammation findings regressed following broad spectrum antibiotic treatment for 12 weeks. Informed consent was obtained.

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Computerized tomography (CT) of the chest was performed because of the previous history of tuberculosis. Chest CT revealed no pathologic changes in lung paranchyma, but curvilinear-reticular densities in bilateral subcutaneous tissue, which indicated that diffuse inflammation was present (Figure 1). On mammography, there was a prominent reticular pattern and asymmetric densities with central radiolucency consistent with abscess formation (Figure 2). Ultrasonography (US) showed a remarkable skin thickening and multiple anechoic cystic lesions in the skin and subcutaneous fat (Figure 3). There were also cystic lesions in the abdomen and bilateral cruris. Magnetic resonance imaging (MRI) revealed inflammatory changes and abscess formation (Figure 4). All cystic lesions detected under US showed fat signal in all MRI sequences (Figure 5). On US-guided fine needle aspiration, liquid oil material was obtained. Excisional biopsy revealed areas of adiponecrosis and lipogranuloma formations (Figure 6). During the 8th month follow-up, the patient confessed to a large amount of sunflower oil injection into bilateral breast tissue to increase muscle mass and definition (Figure 7).

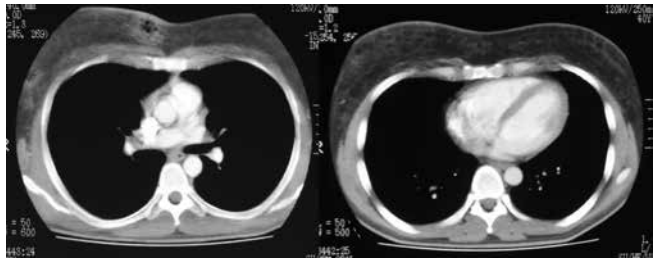

Figure 1. Contrast-enhanced axial chest CT images show curvilinear-reticular densities in bilateral subcutaneous tissue indicating diffuse inflammation and subcutaneous abscess with gas formation

CT: computerized tomography

Discussion and Conclusion

There have been many publications related to granuloma formation and other tissue reactions following mineral/oil injections; however, few are about the adverse effects of vegetable oil. The resulting tumors are defined as paraffinoma, siliconoma, or oleoma according to the injected substance. Darsow et al. (2) reported granuloma formations after intramuscular injection of sesame seed oil in body builders. In another series, a pseudotumor following injection of anabolic steroid dissolved in sesame seed oil was presented (4). To our knowledge, there are no case reports in the literature describing oleomas due to sunflower oil injection.

Figure 2. Bilateral mammography in mediolateral oblique projection shows diffuse reticular pattern consistent with subcutaneous inflammation and asymmetrical densities with central radiolucency indicating abscess. No marked parenchymal breast density is detected

Self-injection with contaminated material produces an acute suppurative panniculitis with concomitant systemic symptoms. Lesions are generally atypical and bizarre in appearance, arising on sites easily accessible to the handedness of the patients. Symmetrical distribution is not frequent. Involvement of the breast is highly suspicious for factitious disease (5). The superficial layers such as skin, dermis, and subcutaneous fat are involved. Initially, the lesions are seen as isolated or coalescent hard, brown nodules, forming typical plaques secondary to fat necrosis and suppuration. Some cases may show abscess formation, lymphangitic spread, skin sloughs, draining sinuses, contractures, and deformities. Additionally, the inflammatory process may cause granulomatous inflammation and fibrosis. Oleomas may present either as a painless mass in the breast or painful hard swellings, skin ulcerations and drainage. This presentation may be misdiagnosed as a malignant lesion. The axillary lymph nodes may be enlarged. Patients may be symptom free for 2 to 25 years. In our patient, symptoms started approximately 3 years following the injection, supporting the findings reported in literature. Darsow et al. (2) also stated that oleomas more likely occur as a consequence of subcutaneous rather than intramuscular injections. In our case, innumerable oleomas due to subcutaneous injections were detected and this finding is consistent with this report. Lesions may become life threatening due to secondary septicemia. Possible long-term complications of oil injections are regional lymphadenopathy, infiltration of adjacent soft tissues and compression of surrounding organs. Acute and chronic respiratory impairment and clinical or subclinical signs of vascular collagen disease have also been described. Recurrent small fat emboli and/or transport of olive oil by lymphatics may cause lipoid pneumonitis (6). Venous embolism in distant organs is another complication of high viscosity liquid injection. In the acute phase, even minor surgical procedures may trigger

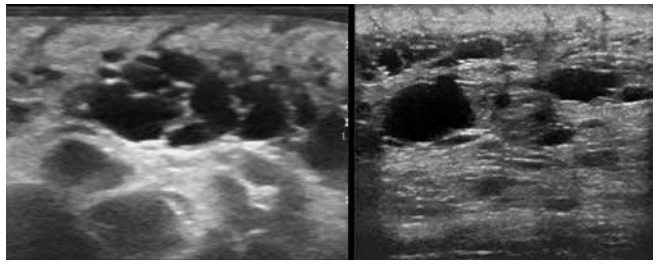

Figure 3. US shows marked skin thickening and multiple anechoic cysts that are located in subcutaneous tissue and underneath skin. Tubular anechoic areas, which indicate gland neck or hair follicle, connect the subcutaneous cysts and dermis

US: ultrasound

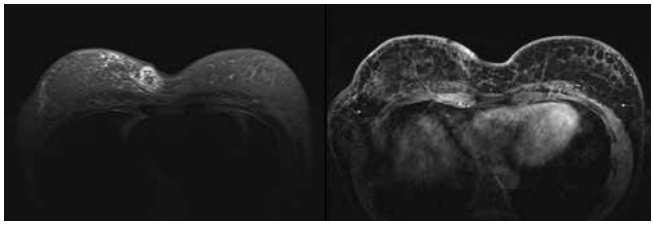

Figure 4. Axial short tau inversion recovery (STIR) and axial contrast enhanced T1-W sequence show inflammation and abscess formation with oil cysts with rim enhancement

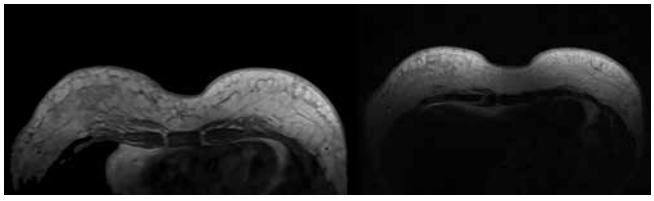

Figure 5. Axial (a) T1-W and (b) axial non-fat saturated T2-W sequences. In all sequences, the multiple cystic lesions detected on US showed fat signal on MRI

T1-W: T1-weighted; T2-W: T2-weighted; US: ultrasound; MRI: magnetic resonance imaging

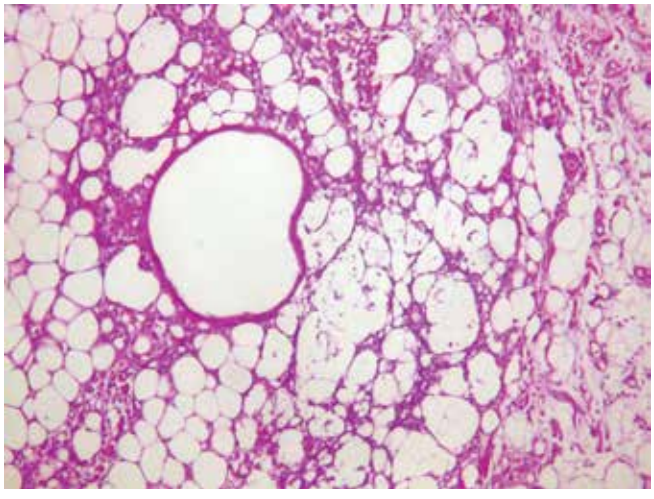

Figure 6. The histologic specimen depicts fat necrosis in subcutaneous tissue, release of fat droplets into intercellular spaces, and a granulomatous response

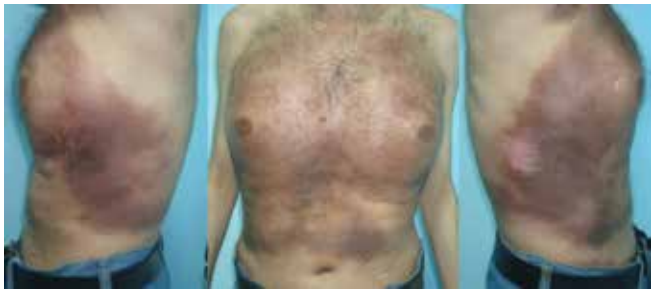

Figure 7. The physical appearance of the patient after treatment and 8 months of follow-up

the progression of the disease leading to chronic ulcerations, scarring, and secondary infections; therefore, unnecessary incisions, diagnostic biopsies, and open drainage should be avoided. In our patient, findings of inflammation regressed following antibiotherapy.

Diagnosis of factitial lesions is made largely by exclusion of other potential entities. Patients do not readily confess their self-destructive behavior, unless they admit to or are caught in the act of self-injury. Consequently, the factitial basis is usually difficult to prove conclusively. In our case, the patient persistently denied the use of any foreign substance.

On mammography, paraffinoma of the breast presents with streaky reticulated densities leading to architectural distortion. Amorphous or round calcifications may accompany. Yang et al. (7) presented 5 cases of breast paraffinomas that presented with dense fibrosis, particularly in the retroglandular area, architectural distortion, abnormal lobulated densities, and dystrophic calcifications. Darsow et al. (2) reported marked calcifications and they suggested that the presence of calcifications may be a helpful finding in the diagnosis of sesame seed oil granuloma. In our case, a prominent honeycomb pattern consistent with subcutaneous edema was present but no calcifications were detected.

Ultrasound is used to show cystic lesions, which are the main manifestations of oleomas. Georgieva et al. (8) presented a man who self-injected sesame oil and US showed cystic lesions presenting as hypoechogenic lesions with acoustic shadowing accompanied by round hyperechoic encapsulated lesions with calcifications. Yang et al. (7) showed well-defined round hypoechogenic nodules with posterior acoustic shadowing. In our case, US revealed multiple anechoic cysts underneath the skin and in subcutaneous tissue with a diffuse skin thickening. There were similar cystic lesions in the abdomen and bilateral cruris. Histopathologically, involvement of the dermis is one of the main findings of factitial panniculitis. In our case, tubular anechoic areas consistent with gland neck or hair follicle, connected subcutaneous cysts and dermis. This finding indicates that a lesion is in continuity with the dermis ultrasonographically. Therefore, we think that this US finding has important diagnostic value; we have seen no data in the literature showing this association.

Additionally, MR imaging may have an incremental value in the diagnosis of oleomas. It may help in accurate localization and extent of oleoma by enabling multiplanar imaging. The lesions are best seen on fat-suppression sequence. Khong et al. (9) reported MR imaging findings of 7 cases with paraffin oil injection for the purpose of breast augmentation. The authors detected that the main component of paraffinoma showed low to intermediate signal intensity on both T1-weighted (T1-W) and T2-weighted images (T2-W), and the round component with paraffin was hypointense on T1 and T2-W images with a remarkable suppression on fat saturation sequences. Wang et al. (10) also reported that paraffinoma was seen as low to intermediate signal on T1 and T2-W sequences. In another series, 16 women with paraffinoma was evaluated and in two cases the lesions were hypointense on T1-W, and hyperintense on T2-W and fat-suppressed sequences. It was hypothesized that the lesion turned to be semisolid during the latency period (11). As Lee et al. (12) had previously described, we detected high signal intensity in T1-W sequences and verified fatty content of the lesion in fat suppressed images. In our case, all the lesions showed fat signal in all sequences and were signal free in fat suppression sequences. MRI can be superior to mammography in patients who experience pain due to inflammatory process. As a result, we conclude that MRI may have an incremental value to reveal an artificial lesion.

In cases of foreign material self-injection history, patients often deny the action of self-harm; therefore, factitious disease is a challenging in diagnosis and treatment. In our case, the patient refused psychiatric

consultation and he did not believe that the complications were caused by self-injected material. We think that radiologic imaging is crucial in the follow-up of these patients.

In conclusion, the diagnosis of oleomas may be challenging. Involvement of the breast is very suspicious for factitious disease. Chronic or recurrent lesions of a bizarre or atypical morphology should alert the physician to this entity. Awareness of this phenomenon, obtaining an accurate history of the patient (due to denial of self-injection), and knowledge of specific radiologic manifestations may contribute to a fast and definitive diagnosis. We think that US and MRI are particularly efficacious in the determination of the extent of disease, identification of causative agent, and follow-up of the patients.

Informed Consent: Informed consent was obtained from patients who participated in this study.

Peer-review: Externally peer-reviewed.

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