

ATROPHIC SCIRRHOU CARCINOMA OF THE BREAST, A FORGOTTEN ENTITY? A LESSON ON THE PITFALLS OF CONFUSING SLOW GROWTH WITH TUMOR INDOLENCY.

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A hundred years ago, when screening was unknown, when breast cancer patients were diagnosed at an advanced stage, the case presented in this issue of JBH (1) would have immediately been recognized as “atrophic scirrhous” carcinoma of the breast. French authors also coined the term “squirrhe atrophique de la femme âgée” (atrophic scirrhous of old women), implying that it occurs in older patients, even though Velpeau mentioned that it was also observed in patients younger than 45 years old (2). This form of carcinoma is characterized by dense fibrotic tumor, reported to be of slow growth and associated with almost complete atrophy of the breast (3). In the terms of Velpeau, “we see frequently the atrophic scirrhous shrivel up, become hollowed out with fissures so profound, draw the integuments so strongly towards it, that all the skin of the neighbourhood is as it were deeply folded”. Its frequency was said to be 3-5% of breast cancers.

Slow growth, fibrosis and apparent shrinkage have sustained the widespread belief that the atrophic scirrhous is a favorable form of tumor. Nobel price Linus Pauling et al. commented: “... the more fortunate individual with a very slow-growing, practically noninvasive tumor encased in a dense, almost impermeable barrier of reactive scar tissue (the so-called atrophic scirrhous tumors) and with a clinical prognosis differing little from normal life expectancy... It would be a very considerable advance in cancer treatment if all tumors could be converted to the atrophic scirrhous variety.” (4).

How does the belief of fibrosis as a favorable sign hold in view of current biological studies?

Earlier on, Anastassiades and Pryce observed that fibrosis acted as an indicator of time in infiltrating breast cancer, the metastatic ratio was higher and survival poorer with the scirrhous than with the non-scirrhous tumors (5). The unfavourable effect of axillary metastases on survival was greater in the scirrhous than in the non-scirrhous tumors.

Anderson et al. showed in mathematical modeling that constrained microenvironments with limitations on space and/or growth factors gave a selective advantage to phenotypes derived from tumorigenic cell lines (6).

Van den Eynden have shown that the presence of a large fibrotic focus in the centre of a carcinoma is a surrogate marker for hypoxia and (lymph)angiogenesis in breast cancer (7). Gene expression profiling found that the presence of large fibrotic focus was associated with activation of Ras signaling and of the hypoxia-inducible factor-1alpha pathway, with overexpression of vascular endothelial growth factor A and carbonic anhydrase 9, and was correlated with a basal-like subtype, with an activated wound-healing signature, and a poor 76-gene prognostic signature (8).

Barkan et al. have shown in models of dormant cells, i.e. cells that disseminate but do not develop into clinically apparent lesions, can be induced to proliferate in a type-I collagen enriched fibrotic environment (9).

Provenzano et al. found in mice models that increased collagen in mouse mammary tissue significantly increased tumor formation three-fold and resulted in a significantly more invasive phenotype with three times more lung metastasis (10).

The paradox of slow growth and tumor aggressivity

Mutations of DNA are rare, 2.5 per 10^8 base pairs per cell generation (11), 2.2 per 10^9 base pairs per year (12), but given the genome size of 10^{10} bases and the number of cells in the human body, estimated at 10^{14} , mutations occur every minute. Ultimately when viable tumor cells are generated, they do not yet grow into invasive cancer unless stromal microenvironment resources of the host tissues are diverted to cooperate with the tumor growth. Fibroblasts are components of the microenvironment that have retained attention and are relevant for discussion of fibrosis. Liu and Hornsby showed in a xenograft model that breast cancer cell lines mixed with senescent fibroblasts displayed increased tumorigenicity, but not when the cells were implanted alone or with nonsenescent fibroblasts (13). Most recently Giannoni et al. reported that

tumor cells and cancer associated fibroblasts were reciprocally activated and stimulated epithelial-mesenchymal transition and cancer stemness (14). These new data provide an understanding of the mechanisms of tumor growth in the elderly patients. With aging, permissive microenvironment changes allows the development of low grade tumor, activating fibroblasts, which in turn enhance the tumorigenicity of the originally low grade tumor.

Slowing down of tumor growth can occur for various reasons, such as insufficient vascularization, hypoxia, tumor necrosis. But a slowing of the growth do not equate with an indolent behavior. On the contrary, hypoxia or competition of tumor cells ultimately select the most aggressive. Modern biology indicates that neither slow growth nor fibrosis should be equated with tumor indolency.

The reported case fits the pattern of increased aggressivity. The subcutaneous metastases developed over a period of 2 months and were associated with massive visceral metastases.

What is the appropriate therapy?

The patient presented with hormone receptor positivity. The question that should be asked is whether a knee-jerk reaction to give hormone therapy is justified or not.

We see very old cachectic patients with lean body mass. More likely than not these are patients who are already estrogen-depleted. What could reasonably be expected from giving an aromatase inhibitor? It is worthwhile to recall that aromatase inhibitors block the conversion of androgens to estrogens. Even though no study have shown an increase of testosterone in the serum, one may expect an increase at tissue level. In an observational study comparing 71 patients receiving in vitro fertilization combined with letrozole, versus 76 patients treated without letrozole, letrozole-treated patients showed significantly higher levels of follicular

fluid testosterone and androstenedione (80.3 vs. 43.8 pg/mL and 57.9 vs. 37.4 mg/mL, respectively) (15). Androgens have been reported to be associated with tumor response in breast cancer (16). Thus, an increase of androgens at the tumor site could be expected to be beneficial. However, this can be reversed in a situation of estrogen-depletion. Sikora et al. investigated in cell models the effect of aromatase inhibitors given in conditions of estrogen-deprivation (17). They found firstly that in the absence of estrogen, the androgens testosterone and 5alpha-dihydrotestosterone induced the growth of several cell lines. Secondly, in conditions of profound estrogen-deprivation, the cancer cells upregulated steroidogenic enzymes that can metabolize androgens to estrogen. Lastly, they found that the downstream metabolite of 5alpha-dihydrotestosterone was estrogenic in the breast cancer cells and induced growth by activation of ERalpha.

Misconceptions of old age and tumor slow growth led to overlook that the patient was in a situation of oncological emergency. Vinh-Hung et al. have reported that operable non-metastasized breast cancer patients older than 80 years with a high ratio of involved lymph nodes had a threefold increased risk of breast cancer death, that the risk of dying from breast cancer in older women with a high tumor load surpassed the risk of dying from all other causes (18). The present patient had extensive metastatic disease, her risk of dying from her cancer versus any other cause could be expected at 10 to 1. First line chemotherapy would have been a better option than hormonal manipulations.

Despite intrinsic slow growth of the primary tumor, current knowledge on the molecular biology of the tumor microenvironment indicate that the associated local desmoplastic fibrosis can adversely affect the outcome. Beyond this case report, the take home message is that elderly patients presenting with a breast cancer should not be left to evolve towards a locally untreatable tumor.

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