CASE REPORT

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Primary Merkel Cell Carcinoma of the Breast - A Report of an Extremely Rare Case

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ABSTRACT

Neuroendocrine carcinoma of the breast is a very rare malignancy, and when it presents with characteristics similar to Merkel cell carcinoma (MCC), it is even more uncommon. This report discusses a case of small cell carcinoma exhibiting Merkel cell-like features in an 80-year-old woman who had a history of rheumatoid arthritis under treatment with immunosuppressive drugs. Microscopic analysis showed tissue fragments with areas of necrosis, as well as focal regions containing neoplastic cells. These cells were small to medium in size, with poorly defined borders, scant cytoplasm, and hyperchromatic, atypical nuclei. Immunohistochemical staining revealed perinuclear (dot-like) positivity for cytokeratin 18/8 and strong positivity for cytokeratin 20 and cluster of differentiation 56. The cell proliferation marker Ki-67 was positive in over 80% of the cells. What is extremely rare in this case is the presentation of MCC of the breast as a retro areolar lesion, located behind the areola and associated with nipple discharge, without evidence of a primary cutaneous lesion.

Keywords: Avelumab; CD56 marker, CK20 positivity; HER2 negative, Ki-67; merkel cell carcinoma; merkel cell carcinoma of the breast; neuroendocrine carcinoma of the breast

KEY POINTS

- Merkel cell carcinoma of the breast is extremely rare.
- Diagnosis is challenging due to its similarity to other neuroendocrine tumors.
- Early recognition and multidisciplinary approach are crucial for optimal management.

Introduction

Merkel cells are found in the epidermis and function as touch receptors. They help transmit sensory information related to touch, including texture and pressure, to the brain. These cells also produce certain hormones, which is why they are sometimes considered neuroendocrine cells (1). Merkel cell carcinoma (MCC) is an unusual primary neuroendocrine carcinoma that mainly appears on the skin (2). Primary neuroendocrine carcinoma of the breast (NECB) is extremely uncommon, accounting for less than 0.1% of all breast cancers (3). MCC is an even rarer and more aggressive subtype of NECB, often seen in immunocompromised

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and elderly patients (4). Here, we present a case of MCC of the breast (MCCB). Written informed consent was obtained from the patient for the publication of this case report and any accompanying images.

Case Presentation

An 80-year-old female with no personal or family history of breast cancer presented with a palpable mass in the right breast without any other significant findings in the breast morphology. The patient was given antibiotic treatment due to a diagnosis of possible mastitis after visiting another breast center with no symptom resolution. This patient has a history of rheumatoid arthritis, under treatment with immunosuppressive drugs, and liver cirrhosis. After visiting our clinical center physical examination of the right breast revealed a retro areolar mass in the right breast, with lymph nodes in the corresponding axillary region without any significant edema of the nipple of the right breast. A breast ultrasound was performed, which revealed, as the initial evaluation, a right peri areolar isoechoic lesion at the 6 o'clock position with increased vascularity and dimensions of 2.37x1.5 cm, displacing but not invading adjacent structures and associated with mild subcutaneous edema. After that visit to our center, the patient decided to abstain for a period of two months without any other visits in the interim. After those two months, the patient reappeared with a worsening of her clinical condition, a worsening of the alteration in the morphology of the nipple, initial ulceration, and a discharge from the nipple.

At this stage, after visiting our unit, the patient underwent digital mammography, which revealed a large, radiodense, retro areolar mass of the right breast causing skin and interstitial thickening with a diameter of 5.5 mm and partial obscuration of its borders, and a recommendation was made for further evaluation with a biopsy. The imaging was evaluated according to Breast Imaging Reporting and Data System (BI-RADS) and was categorized as BI-RADS 5 (Figures 1, 2).

From the magnetic resonance imaging (MRI) of the breast, a large, ovoid-oval, space-occupying lesion was detected in the retro areolar region of the right breast with maximum transverse, anteroposterior, and craniocaudal diameters of 41.2 mm, 39.1 mm, and 59.9 mm, respectively. The imaging findings were highly suggestive of malignancy. A second lesion of smaller dimensions, with a maximum diameter of 36.7 mm, was detected on the posterior surface of the central region of the same breast, 12.7 cm from the nipple. Based on its identical morphological and kinetic enhancement characteristics compared to the retro areolar mass, this posterior lesion was interpreted as a second malignant focus within the same breast, consistent with multifocal disease rather than artifact. Simultaneously, the right breast showed diffuse skin thickening and diffuse interstitial edema (Figures 3, 4).

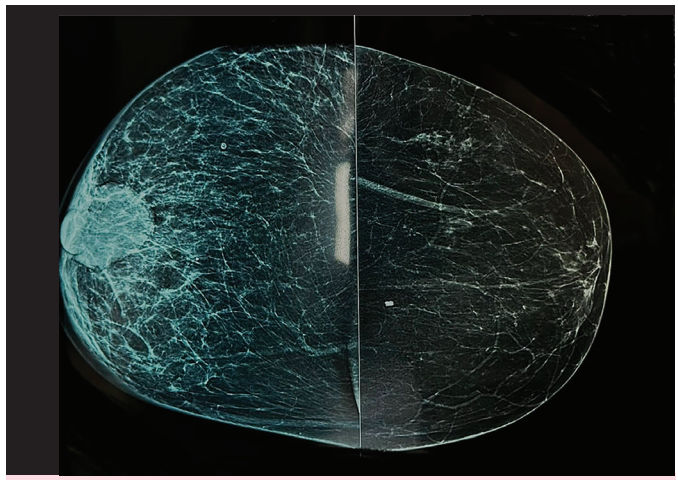

Figure 1. Digital mammography of the right breast revealing a retroareolar, radiodense mass with partially obscured borders and associated skin and interstitial thickening. The lesion measures approximately 5.5 cm in greatest dimension and was classified as Breast Imaging Reporting and Data System 5, indicating high suspicion for malignancy. A posterior density with similar morphology is also visible in the right breast, corresponding to a second malignant focus on magnetic resonance imaging (multifocal disease). Dense artifacts are visible only in the caudal subcutaneous area of the left breast mediolateral oblique projection, related to acquisition technique, without affecting diagnostic interpretation

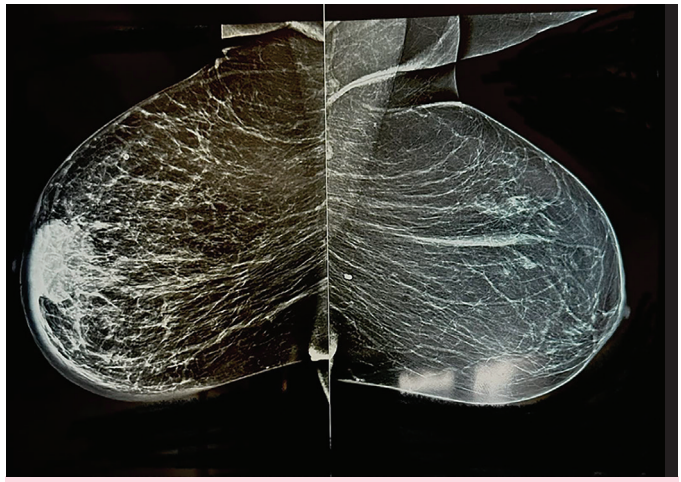

Figure 2. Mediolateral oblique view from digital mammography of the right breast, showing a dense retroareolar mass with architectural distortion and skin thickening. The lesion is radiodense with irregular borders, compatible with a Breast Imaging Reporting and Data System 5 classification. Dense artifacts are visible in the caudal subcutaneous area of the left breast, attributable to compression folds during acquisition, and do not interfere with interpretation

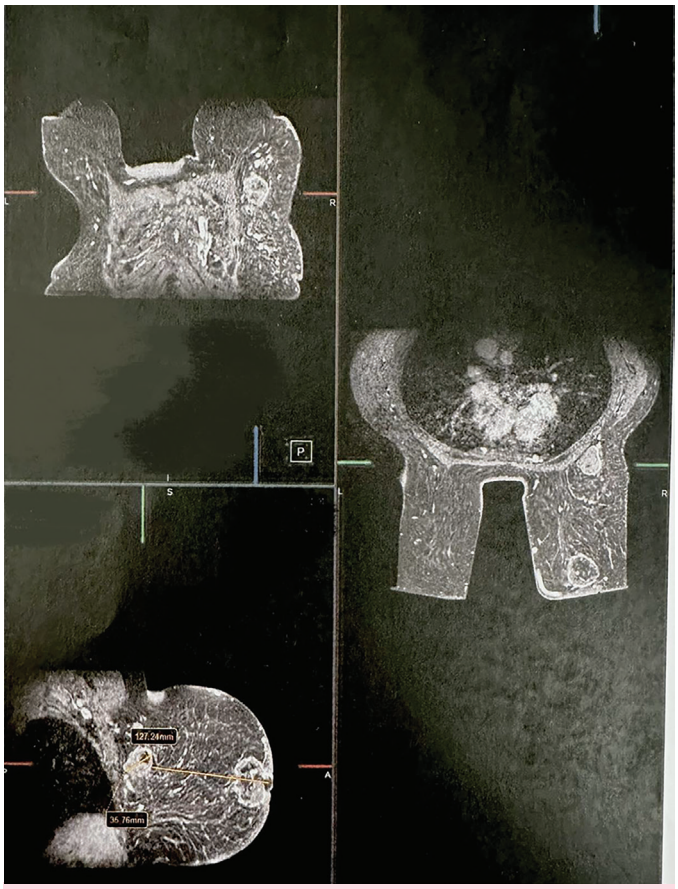

Figure 3. Contrast-enhanced breast magnetic resonance imaging (multiplanar views) showing a large ovoid-oval retroareolar mass with heterogeneous enhancement. A second lesion is visible posteriorly, located 12.7 cm from the nipple. Diffuse skin thickening and interstitial edema are also evident

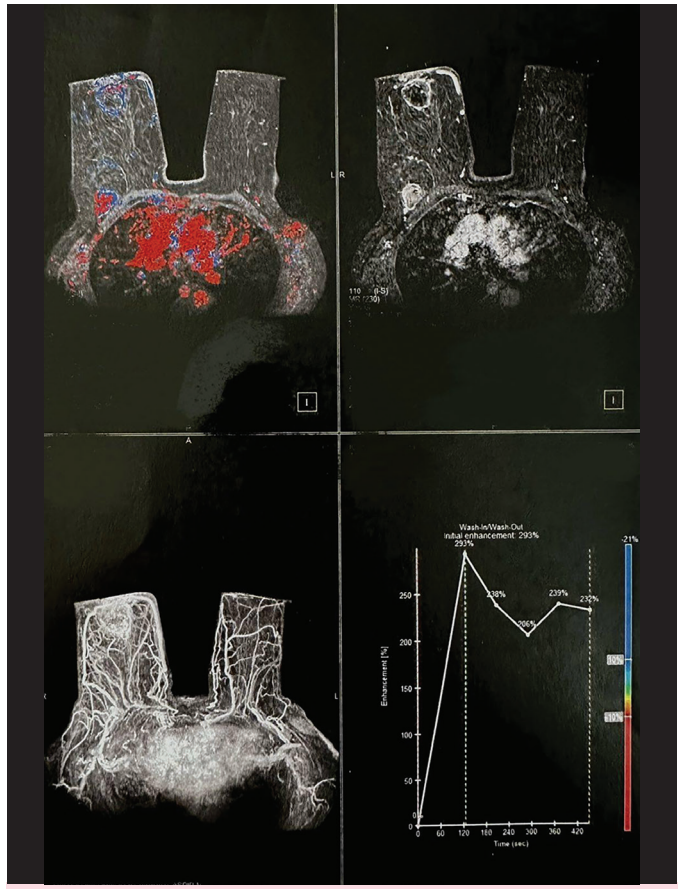

Figure 4. Dynamic contrast-enhanced magnetic resonance imaging of the right breast demonstrating a type III kinetic curve, characterized by rapid initial enhancement, subsequent washout, and a late plateau phase. This enhancement pattern supports the diagnosis of an aggressive malignancy

After the above imaging exams, the patient underwent a percutaneous breast biopsy under ultrasound guidance, and the sample was sent for histopathological examination.

During the microscopic examination, fragments with areas of necrosis were evident, along with focal presence of neoplastic tissue consisting of small and medium-sized cells with indistinct cell borders, minimal cytoplasm, and hyperchromatic nuclei with atypia (Figures 5-8).

The immunohistochemical investigation revealed features, including perinuclear (dot-like) positivity on immunostaining for cytokeratin 18/8 and strong positivity on immunostaining for cytokeratin 20 (CK20) (Figure 9) and cluster of differentiation 56 (CD56) (Figure 10). The cell proliferation marker Ki-67 was positive in more than 80% of the cells (Figure 11). The immunostaining for GATA binding protein 3, estrogen receptor (ER), progesterone receptor, human epidermal growth factor receptor 2 (HER2), and E-cadherin were negative.

The conclusion of the Histological Examination was reported as: "Morphological and immunohistochemical features are consistent with the presence of a high-grade carcinoma, primarily of small cell morphology with neuroendocrine characteristics.

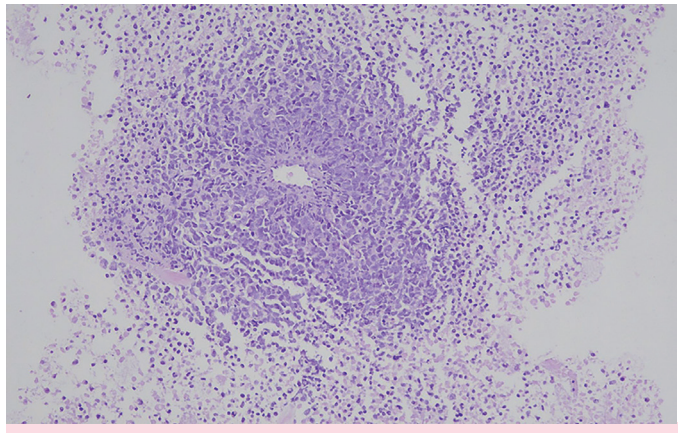

Figure 5. Hematoxylin and eosin stain x200, high-grade nuclear features

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Based on the immunophenotype, with CK20 perinuclear dot-like positivity, CD56 expression, and a high Ki-67 proliferation index (>80%), the findings are diagnostic of MCC of the breast".

To further clarify the diagnosis, the paraffin-embedded tumor tissue was sent to an external certified molecular diagnostic laboratory. Virological analysis was performed using real-time polymerase chain reaction (RT-PCR, TaqMan method) targeting the Large T Antigen region of the Merkel cell polyomavirus (MCV) genome. Total DNA was extracted from the sample, quality-checked spectrophotometrically, and amplified in the presence of positive and negative controls, as well as an internal amplification control to exclude PCR inhibition. The RT-PCR

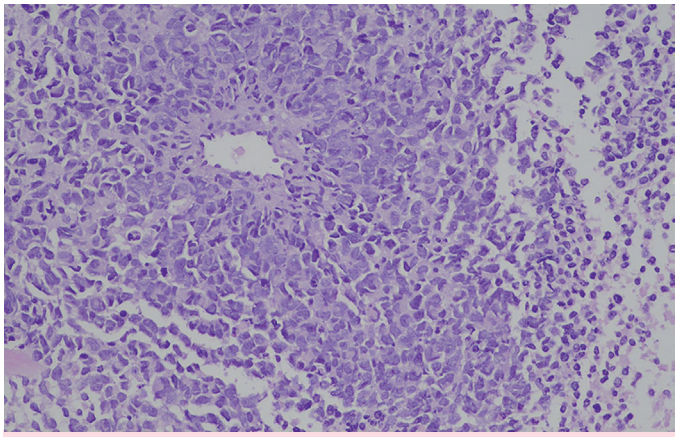

Figure 6. Hematoxylin and eosin stain x400, high-grade nuclear features

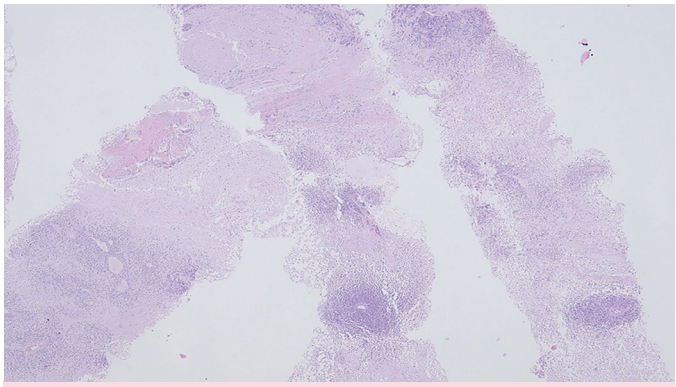

Figure 7. Hematoxylin and eosin stain showing extensive necrosis

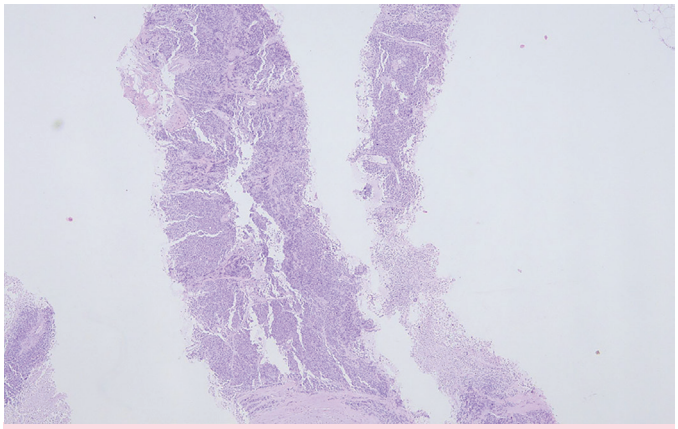

Figure 8. Hematoxylin and eosin stain x40

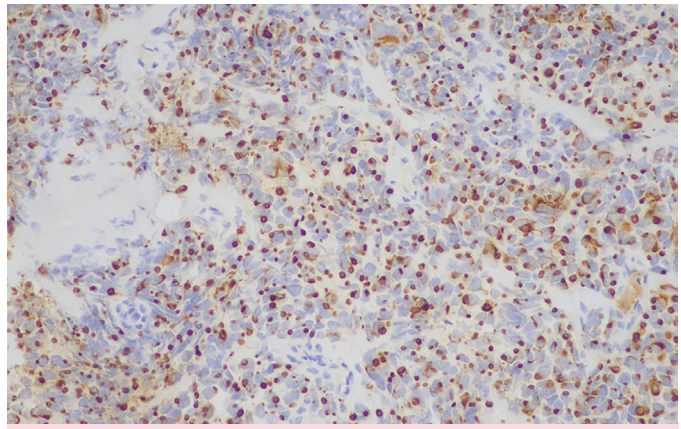

Figure 9. Cytokeratin 20 dot-like immunohistochemical positivity

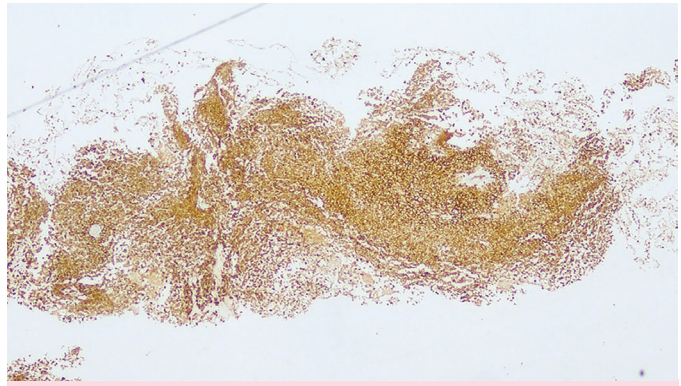

Figure 10. Cluster of differentiation 56 immunohistochemical positivity

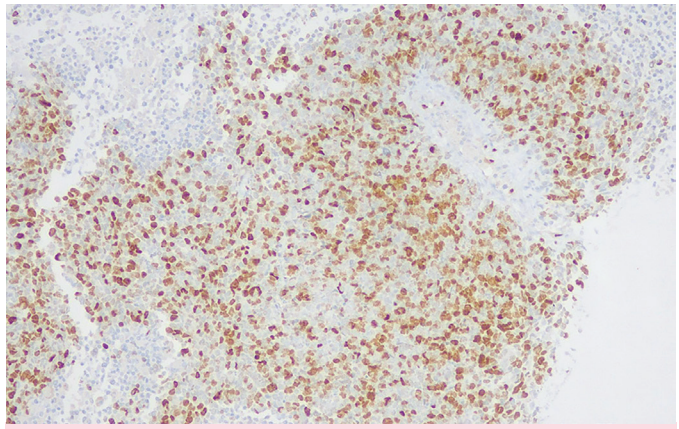

Figure 11. Ki-67 immunohistochemical positivity

result was positive (+) for MCV DNA, confirming viral detection in the tumor tissue. The assay's analytical sensitivity was 50 viral copies per reaction.

The patient, following the diagnosis, was placed on a therapeutic regimen with Avelumab 800 mg Q2W with clinical improvement in the appearance of nipple deformity, after consultation with a specialist oncologist.

Discussion and Conclusion

NECB with Merkel cell characteristics is a rare variant, representing less than 0.1% of all breast cancer cases, with few reports published. The limited literature suggests that this neoplasm primarily affects patients between 60 and 70 years old and does not present with specific clinical features (4-6). It is important to note that the patient was under long-term immunosuppressive treatment for rheumatoid arthritis, which has been recognized, among others, as a risk factor for the development of MCC (5).

On imaging, the lesions of this type of carcinoma are predominantly oval or irregular in shape on mammography, ultrasound, and MRI (7). When the presented case underwent MRI of the breast, a large, ovoid-oval, space-occupying lesion was reported. However, a second posterior lesion was identified on breast MRI. The posterior lesion demonstrated the same imaging morphology and enhancement kinetics as the primary retro areolar tumor, strongly suggesting that it represented a second malignant focus within the same breast. These findings support the diagnosis of multifocal MCCB, rather than artifact or a separate primary tumor. In the present case, the overlying breast skin was intact at initial clinical presentation, and the only finding was a palpable retro areolar mass. The skin and nipple changes observed later on MRI were most consistent with secondary tumor-associated edema and outward extension from the underlying breast parenchyma, rather than primary cutaneous involvement. Histological correlation was not available, and therefore the absence of ductal carcinoma *in situ* in the surrounding tissue could not be confirmed. The posterior lesion was not visible on mammography or during the initial ultrasound examination. It was first identified by MRI of the breast, which highlighted its similar morphological and kinetic features to the primary, retro areolar lesion.

The differential diagnosis includes mainly: i) invasive ductal carcinoma; or ii) malignant phyllodes tumor. Patients with MCCB generally present with larger tumors and are more likely to have positive lymph nodes when compared to other types of invasive breast cancer (4). This contrasts with our case, in which axillary lymph nodes were palpable on clinical examination but imaging studies showed no radiological evidence or pathological lymph node involvement.

The diffuse interstitial changes and skin thickening observed on MRI were most consistent with tumor-associated edema, in line with the dermal involvement of the retro areolar mass. Although lymphangiosis carcinomatosa cannot be entirely ruled out, no evidence of posterior lymph node obstruction was found.

Immunohistochemical analysis is essential for identifying the expression of neuroendocrine markers in tumor cells. The most sensitive and specific markers include chromogranin A, chromogranin B, and synaptophysin. Hormone receptor expression in neuroendocrine breast cancer varies, with reports showing ER positivity in the range 54-90%. The ER immunostaining was negative in the presented case. MCCs typically display a distinctive dot-like immunoreactivity around the nucleus for CK20, which represents the clustering of CK20 intermediate filaments (8). Perinuclear positivity for CK20 immunostaining was also observed in our case. NECB is often positive for hormone receptors, whereas HER2 is almost always negative, although there are also reports of HER2-positive NECB (9). HER2-positive breast carcinomas tend to have a more aggressive behavior and show higher cytological and histological grade compared to HER2-negative breast carcinomas (10). The HER-2 immunostaining was negative in our case.

CK20 is a low-molecular-weight keratin (CK) that is predominantly expressed in the gastrointestinal epithelium, urothelium, and Merkel cells. In a study, 34 individuals with MCC were investigated, and 33 were positive for CK20. That strongly suggests that CK20 positivity in a small cell carcinoma of unknown origin indicates MCC when most tumor cells are positive. A negative CK20 result can effectively exclude the diagnosis of MCC as long as proper antigen retrieval methods are employed and satisfactory staining is achieved with other cytokeratin antibodies (11).

Although our case initially demonstrated the characteristic CK20 perinuclear dot-like positivity, further molecular testing was performed to clarify the diagnosis. The patient's paraffin-embedded tumor block was sent for virological analysis using RT-PCR targeting the *Large T Antigen* region of the MCV genome. The analysis confirmed the presence of MCV DNA within the tumor tissue, providing molecular confirmation of MCCB. Therefore, the final diagnosis was established based on the combined morphologic, immunohistochemical, and molecular findings, definitively identifying this tumor as a MCCB.

Avelumab is a monoclonal antibody and immune checkpoint inhibitor that targets the programmed death-ligand 1 (PD-L1) receptor on tumor cells. By blocking the interaction between PD-L1 and PD-1, Avelumab reactivates T-cell–mediated immune responses against the tumor. It has been approved in several countries for the treatment of metastatic or advanced MCC and has shown significant clinical benefit in this patient population.

To summarize, MCCB is an exceptionally rare and more aggressive form of neuroendocrine carcinoma, sharing clinical and imaging characteristics with other, more common breast cancers. To accurately diagnose MCC and distinguish it from other NECBs, obtaining tissue samples and performing immunohistochemical staining, particularly for CK8/18 and CK20, is essential. Correctly identifying MCC is crucial, as it is often associated with a poorer prognosis for the patient. In the present case, the diagnosis was further confirmed by molecular testing confirming the presence of MCV DNA in the tumor tissue. This molecular confirmation strengthens the diagnosis of MCCB and highlights the importance of incorporating molecular virological analysis in diagnostically challenging and exceptionally rare cases. What was extremely rare and important to highlight in this case report was that the MCCB did not appear on the skin of the breast at initial presentation. On the contrary, it was located behind the areola and was associated with nipple discharge, which has not been mentioned in other case reports referring to this very rare and unusual tumor.

Ethics

Informed Consent: Written informed consent was obtained from the patient for the publication of this case report and any accompanying images.

Footnotes

Authorship Contributions

Surgical and Medical Practices: A.S., A.Bou., I.G.; Concept: A.S., I.G.; Design: A.Si., T.A.T.; Data Collection or Processing: A.Si.; Analysis or Interpretation: A.Si.; Literature Search: A.Si., T.A.T.; Writing: A.Si.

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

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