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Mammary-Like Tumor of the Vulva: A Case Report and Literature Review

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Abstract

The aim of this article is to present a rare case of a patient with Vulvar adnexal carcinoma, mammary type (VACMT). Following this unusual diagnosis, we wish to delineate our diagnostic and treatment course and clinical outcomes. We strongly support a multi-disciplinary approach when dealing with this rare type of vulvar cancer. In addition, the histologic findings of this rare malignancy are fully analyzed and described. A thorough literature review of previous cases described in literature was conducted according to the PRISMA guidelines. We have identified and highlighted key features and specific histological markers suggestive of this diagnosis and crucial in order to differentiate and diagnose this rare type of malignancy. Finally, we would like to share our experience with the chosen mode of treatment in this patient and encourage further research and sharing of knowledge among different specialists involved in the treatment of this fascinating rare tumor.

Introduction

Vulvar Adnexal Carcinoma, Mammary Type (VACMT), is a rare and diagnostically challenging malignancy that has received limited attention within the realm of gynecologic oncology. This rare and enigmatic tumor, histologically resembling mammary carcinoma, arises from vulvar adnexal structures and is characterized by unique clinicopathological features [1,2]. Vulvar malignancies are considered rare non-homogenous entity; As such, VACMT occupies a niche of its own, demanding a

comprehensive understanding of its clinical presentation, histological characteristics, diagnostic criteria, and optimal management strategies **[1,3]**. This article aims to shed light on this exceptionally uncommon tumor by presenting a detailed case report and reviewing existing literature. Through this combined approach, we sought to provide valuable insights into the diagnosis and management of VACMT. As clinicians and pathologists encounter such cases infrequently, a literature review is paramount in pooling collective knowledge and experience to optimize patient care. In subsequent sections, we will delve into the clinical course of a recent case of VACMT, discuss its histopathological nuances, and analyze the immunohistochemical markers that aid in its diagnosis. Furthermore, we explore the current state of knowledge regarding treatment modalities and highlight the challenges and gaps in our understanding of this rare entity.

Patient and Observation

A 69-year-old female presented to our gynecology clinic with persistent pruritus and a suspicious skin lesion in the vulvar region. The lesion, measuring approximately 1 cm in size, gradually grew over several months and was treated by a gynecologist with a local steroidal ointment. There was no associated pain, discharge, or any other significant symptom. On clinical examination, a solitary, well-defined, non-erythematous, and slightly raised lesion was noted 2 cm above the clitoris. The lesion appeared to be confined to the vulvar skin and did not involve the adjacent structures. There were no palpable inguinal lymph nodes or abnormal appearance of the overlying epidermis.

The lesion was removed under local anesthesia and sent to the pathology laboratory. Histopathological examination revealed the following findings:

- The lesion exhibited a cribriform, solid, and infiltrative growth pattern **(Figure 1A)**.
- Focal microcalcifications were observed within the lesion **(Figure 1B)**.
- Tumor cells displayed moderate nuclear atypia, with scattered mitotic figures, but they were not numerous **(Figure 1B)**.
- Residual cystic structures with an apocrine lining were identified within the tumor **(Figure 1B)**.
- Mucicarmine staining indicated intraluminal mucus secretion.
- Immunostaining with GATA-3 **(Figure 2A)** and CGDFP15 **(Figure 3)** showed strong and diffuse positivity.
- Immunostains with p-40, p-63, and S-100 were negative in tumor cells but positive around solid aggregates, highlighting a residual intraductal component.
- The overlying epidermis appeared unremarkable, with no evidence of Paget's disease **(Figure 1A)**.
- The proliferation index Ki-67 was not notably high.
- Additional immunoprofile:
- ER was positive **(Figure 2B)**, PR was positive in approximately 20% of the cells, and HER2 was negative.

Pathological Diagnosis

Based on the histopathological and immunohistochemical findings, the diagnosis was established as follows:

- Vulvar adnexal carcinoma, ductal, with an infiltrative invasive component of the mammary type with apocrine differentiation.
- Deep and side margins were involved.

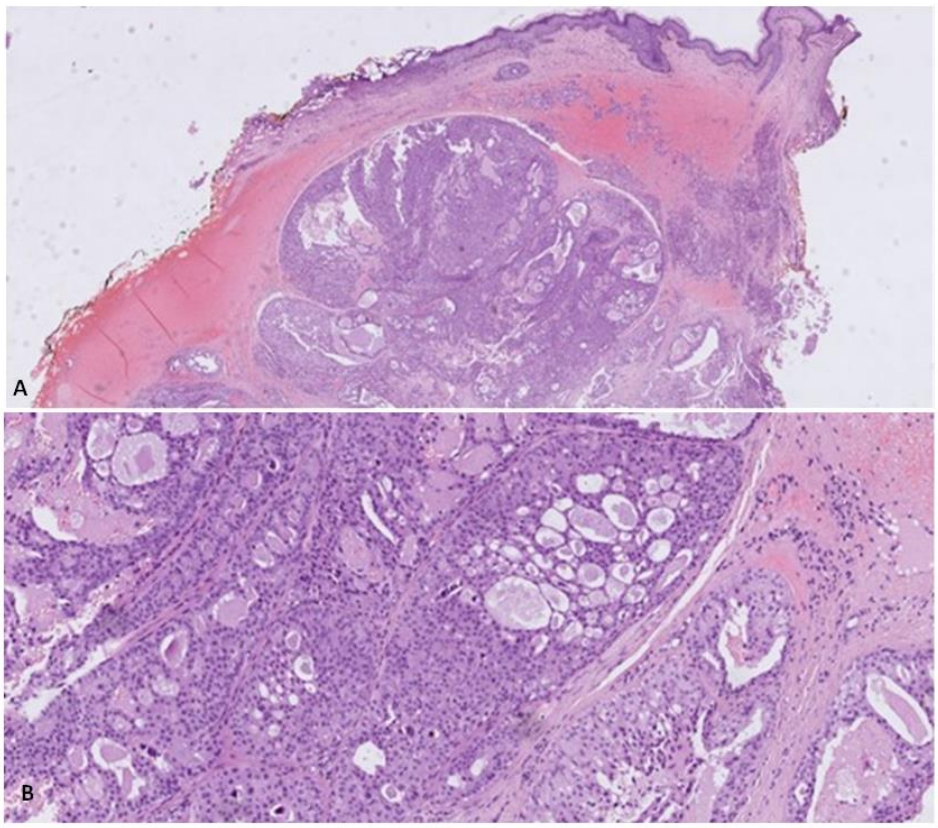

Figure 1: (A) Submucosal tumor showing a cribriform, solid, and infiltrative growth pattern. The overlying epidermis is unremarkable [Hematoxylin and Eosin (H&E), X2.5] (B) Tumor cells displayed moderate nuclear atypia, eosinophilic cytoplasm with residual cystic structures microcalcifications present. (H&E, X10).

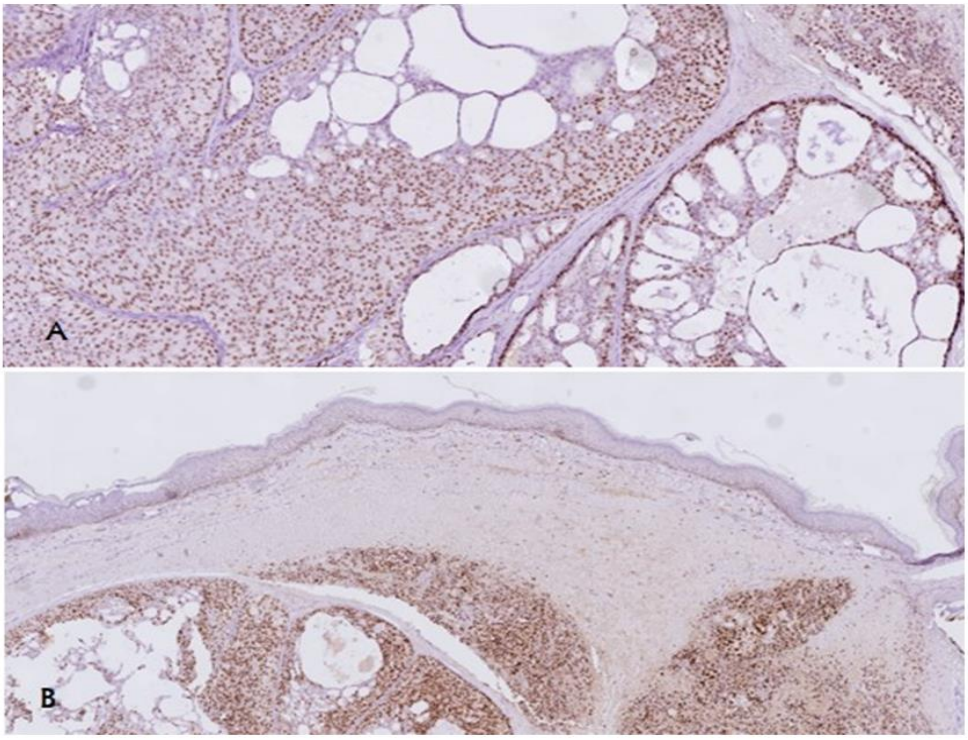

Figure 2: Immunostaind: GATA-3 (A) and ER (B) show positive nuclear staining.

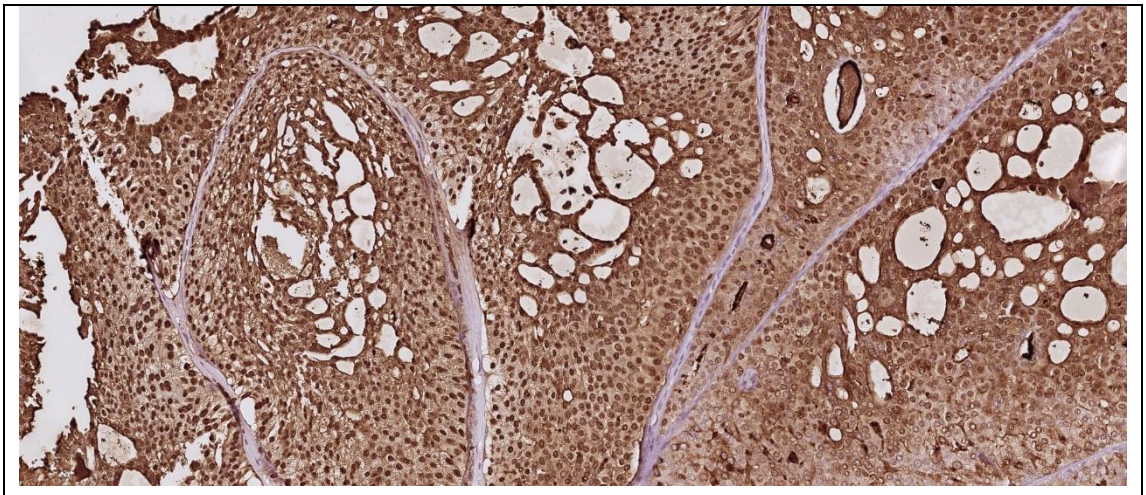

Figure 3: CDDFP15 is positive.

Management

Considering the pathological diagnosis, the patient underwent breast evaluation and was referred to a PET-CT scan, which revealed no groin or breast abnormality but showed light absorption of FDG in the uterine endometrial tissue. A biopsy of the endometrial tissue demonstrated a normal proliferative endometrium, and a clinical evaluation of the breast excluded the possibility of concomitant breast disease. Due to her Ashkenazi Jewish origin, the patient was referred for a BRCA mutation test which came back negative for all common BRCA1/2 mutations. Since the patient had been in menopause for more than 10 years, and taking into consideration the rarity of the case, a multi-disciplinary consultum

comprising of oncological gynecologists, breast surgeon, medical oncologist and pathologist, discussed the correct treatment course for the patient. It was agreed that since published cases of VACMT tend to show a poor prognosis with metastasis found on the first diagnosis a more aggressive approach should be taken. The patient underwent wide local excision of the lesion area, inguinal and pelvic sentinel lymph node resection guided by Indocyanine Green (ICG) and total laparoscopic hysterectomy with bilateral salpingo-oophorectomy. End pathology showed: no residual tumor on the local excision or in the bilateral sentinel lymph nodes taken from the groins or the external iliac arteries. The endometrial tissue was atrophic as could be expected, as opposed to the primer diagnosis from endometrial sampling. Post-operatively, the patient was closely monitored at the clinic, and had uneventful healing, with no post-operative complications.

Summary and Discussion

Carcinomas of the vulva are rare malignancies of the female genital tract and represent 3–5% of all diagnosed female genital malignancies. Most of these carcinomas are of the Squamous type, with Squamous cell carcinoma comprising 90% of these tumors, arising mostly from Bartholin's glands or extramammary Paget's disease **[1,4]**. Primary vulvar glandular neoplasms are presumed to arise from ectopic breast tissue, and mammary-like glands (anogenital sweat glands) existing in the vulvar region- are even rarer accounting for only 1% of all malignant neoplasms of the vulva **[2,5]**. Most cases are associated with extra-mammary Paget's disease and breast examination should be performed to eliminate any chance of metastasis **[1,5]**. These glands share many features with both eccrine and mammary glands and differ from normal sweat glands by positive staining for hormone receptors (estrogen, progesterone and HER2) **[6]**. 31 case reports of vulvar Paget's disease associated with primary vulvar sweat gland adenocarcinoma were described in the English literature[7]. Primary vulvar sweat gland carcinomas without associated Paget's disease are exceedingly uncommon, with only 10 cases reported in the English literature ;five of these were of eccrine differentiation, where as five were of apocrine differentiation **[2]**. The histologic patterns of vulvar sweat gland adenocarcinomas include ductal, acinar, papillary, cylindro-matous, mixed, solid, adeno-cystic (mucin secreting), microcystic, syringomatous, and clear cell **[8]**. Our case showed a case of an apocrine differentiated adeno-cystic tumor with no association to extra-mammary Paget's disease. VACMT often presents with non-specific symptoms, making early diagnosis difficult and challenging. Delayed treatment in the few cases reported to date indicates the need for aggressive treatment with a poor prognosis. A review of the literature revealed that the mean age of the patients was 60 years old. The most common symptoms are pruritus, burning pain, subcutaneous lumps and occasionally painful erosions **[9]**. The lesion is most commonly unilateral, (a bilateral occurrence has been described in one case thus far). The clitoral area is the rarest site of involvement, and the major and minor labia are the most common (two cases of clitoral site, and 21 cases of labial site were published) **[10]**. Distinguishing between these tumors and sweat gland carcinomas or adenocarcinomas of metastatic origin is particularly difficult in the absence of normal mammary-like glands and transition zones that exist between benign and tumorous areas **[9]**. Immunostaining plays a crucial role in the context of VACMT diagnosis.

Several criteria were described as sufficient for categorizing breast carcinoma of primary vulvar origin [6]: A morphologic pattern consistent with breast carcinoma, expression of estrogen receptor and/or progesterone receptor and positivity for common breast cancer markers such as EMA, CEA, and glandular keratins.

Immunostaining was used to confirm the tumor's mammary lineage, differentiate between invasive and intraductal components, characterize its features, and assess its growth potential. It helps pathologists and clinicians arrive at an accurate diagnosis, which is essential for guiding appropriate treatment strategies, such as the decision between wide local excision or radical vulvectomy or performing sentinel lymph node sampling as opposed to complete lymphadenectomy. Several of these markers were used in the present case:

- GATA-3 immunostaining helps differentiate VACMT from other vulvar malignancies and is strongly and diffusely positive in VACMT, which helps confirm its mammary origin. P-40 and P-63 immunostaining can be used to differentiate between invasive carcinoma and intraductal structures. Although these markers are typically negative in the tumor cells of VACMT, they may be positive around residual intraductal components and dictate the aggressiveness of the primary surgery.
- S-100 immunostaining is widely accepted as the marker of choice for immunohistochemical identification of malignant melanoma and cartilaginous tumors. It is generally negative in VACMT tumor cells. However, it may be positive around the solid aggregates, highlighting the residual intraductal component. This aids in characterizing the tumor features.
- Ki-67 is used as a proliferation marker, to assess the growth rate of the tumor cells and to provide insight into the tumor's growth potential and aggressiveness. Ki-67 was found to be expressed at higher levels in invasive lesions than in in-situ lesions [11].
- In the context of VACMT, the assessment of hormone receptor status (estrogen receptors/progesterone receptors)and HER2 receptors is relevant, but is typically less emphasized compared to its role in breast cancer. A positive ER and/or PR status in VACMT can provide insights into the potential responsiveness of the tumor to hormone therapy. In some cases, hormonal treatment options (e.g., Tamoxifen) have been explored in VACMT patients with positive hormone receptor status; however, the clinical benefit of such therapy in VACMT is not well established because of its rarity. The Her-2/neu over expression rate was found to be higher in patients with invasive disease (71% versus 54%) [12], and HER2-positive breast cancer may benefit from targeted therapies such as trastuzumab. However, HER2 overexpression or amplification is not common in VACMT.

It is important to note that the primary focus of VACMT diagnosis and management lies in confirming the mammary origin, assessing the tumor's invasiveness, and determining its histopathological characteristics. The rarity of VACMT and limited data on targeted therapies indicate that the role of these receptor profiles is still evolving in the context of this malignancy. Due to its rarity and similarity in clinical presentation to other vulvar malignancies, VACMT presents a significant diagnostic challenge. Although, surgery is generally considered the treatment of choice, the optimal surgical approach is unclear-Surgical excision remains the primary treatment modality, but the appropriate

location for sentinel lymph node sampling is uncertain [13], and most surgeons opt for complete lymphadenectomy only in cases of clinically apparent lymphadenopathy [14].

Adjuvant therapies, such as tamoxifen or trastuzumab, should be considered if hormonal receptors are positive. However, owing to the rarity of VACMT and the limited number of cases worldwide, standardized treatment protocols have not yet been established to guide treatment strategy. Moreover, prognostic factors, such as tumor size and lymph node involvement, may influence the outcome of these poorly prognostic malignancies [15]. However, the accuracy of any prognosis remains uncertain due to the limited data available. Collaboration and data sharing among healthcare professionals are essential to define accurate diagnostic criteria and treatment guidelines for VACMT, to ultimately improve patient care and outcomes. This article seeks to raise awareness about VACMT and guide clinicians in its diagnosis and management. Describing a rare case of clitoral VACMT, early detection and treatment might encourage physicians to be more suspicious of genital lesions, thereby improving the prognosis of these rare tumors.

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