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CASE REPORT

A Rare Case Report: Primary Vulvar Adenocarcinoma of Mammary Gland Type

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Abstract: Primary vulvar adenocarcinoma of mammary gland type (AMGT) is exceedingly rare and presents significant diagnostic challenges. We report the case of a 70-year-old female with a nodular vulvar lesion, confirmed as vulvar AMGT through comprehensive histological and immunohistochemical analysis. The tumor cells were positive for SOX10, TRPS1, and E-cadherin, and negative for ER, PR, and HER-2/neu, ruling out metastatic breast carcinoma. This case underscores the importance of specific markers like TRPS1 in accurately diagnosing rare vulvar malignancies and guiding effective treatment strategies. Further studies are needed to better understand the pathogenesis and clinical characteristics of vulvar AMGT.

Keywords: vulva, adenocarcinoma, mammary gland type, differential diagnosis

Introduction

Vulvar cancer is one of the most common malignancies of the lower reproductive tract in postmenopausal women, accounting for about 4% of all female reproductive tract malignancies.[1] The tumor can originate from the skin, mucosa and accessories of the vulva, and the incidence of vulvar cancer has gradually increased.[2] The pathological subtypes of vulvar carcinoma include squamous cell carcinoma, adenocarcinoma, basal cell carcinoma, malignant melanoma, sarcoma and metastatic carcinoma.[2] The most common type is squamous cell carcinoma, with the exception for Bartholin gland carcinoma and Paget's disease, vulvar adenocarcinoma accounts for less than 0.1%, and vulvar adenocarcinoma of mammary gland type (AMGT) is exceedingly rare.[3] Fewer than 50 cases of vulvar AMGT have been documented in the literature.[4]

The vulva AGMT was characterized by a malignant tumor with histological morphology resembling that of breast homologous tumors.[5] Previously interpreted as originating from ectopic mammary gland tissue, these glands are now considered to be normal structural components of the vulva known as specialized anogenital mammary-like glands (AGMLG).[6,7] Tumors can manifest in various tissue types resembling breast cancer, including mammary ductal carcinoma, lobular carcinoma, mixed duct-lobular carcinoma, mucinous carcinoma, and adenoid cystic carcinoma.[8] Most of the tumors are highly differentiated adenocarcinoma, characterized by the secretion of whey protein and milk fat globulin, as well as the expression of estrogen receptor (ER) and progesterone receptor (PR).

Given the morphological similarities between vulvar AMGT and other types of vulvar adenocarcinomas, the utilization of immunohistochemistry is crucial for accurate differential diagnosis. The recently emerged immunohistochemical marker trichorhinophalangeal syndrome type 1 (TRPS1) has demonstrated significant value in diagnosing the triple-negative subtype of adenocarcinoma.[9] Primary vulvar adenocarcinoma can be distinguished from metastatic breast cancer based on the presence of residual normal mammary glands adjacent to the primary tumor, while no such normal mammary tissue is observed in metastatic cancer.[10] Here, we present a diagnostically challenging case of primary vulvar adenocarcinoma of mammary gland type.

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Case Presentation

Patient Information

A 70-year-old, multiparous, postmenopausal female patient was admitted to our hospital, with a slightly raised and firm nodule on the right labium majus four months earlier. Over time, the lesion exhibited progressive enlargement. The positron emission tomography-computed tomography scan (PET-CT) conducted at the external hospital revealed multiple hypermetabolic foci, raising suspicion of a malignant neoplasm. Cystoscopy at the local hospital revealed multiple masses in the trigone of the bladder and surrounding the left ureteral orifice, and pathological biopsy confirmed invasive carcinoma. The colposcopy revealed invasive carcinoma involving the cervix, vaginal wall, and clinically suggestive of cervical malignancy.

Clinical Findings

Physical examination revealed bilateral inguinal lymphadenopathy characterized by firm, non-tender, and immobile enlarged lymph nodes, predominantly on the left side, with the largest measuring approximately 2.5cm in length. An irregular, hard and fixed subcutaneous mass measuring approximately 30mm was detected in the right vulva near the symphysis pubis. Vaginal patency was observed along with stiffness of vaginal front wall and two lateral walls up to one-third of the vagina, accompanied by positive contact bleeding. No abnormalities were observed in the Bartholin, Skene, or vestibular glands. The uterus exhibited anterior positioning and atrophy. There were no evident masses or tenderness detected in the two adnexal regions, and no signs of blood staining during anal examination.

Materials and Method

The representative tissue sections obtained from the vulvar mass were fixed in 10% buffered formalin and subsequently embedded in paraffin. For routine microscopic examination, 5-μm-thick sections were subjected to hematoxylin and eosin (H&E) staining. The antibodies utilized in this study are documented in Table 1. A positive designation of "positive (+)" was assigned to cases where neoplastic cells exhibited a nuclear, cytoplasmic, and/or membranous expression in 10% or more of the cell population.

Results

Histology and Immunohistochemical Findings

The gross specimen consisted of a large elliptical piece of skin and attached subcutaneous tissue, measuring 3.4*2.4*2.0 cm in dimensions. The nodule, located beneath the epidermis, exhibited clear boundaries and measured

Table 1 List of Primary Antibodies Used in the Study

Antibody	Manufacturer	Species	Clone	Dilution
CK7	ZSGB-BIO	Mouse	UMAB161	1:200
P40	CELNOVTE	Mouse	C3B4	Predilute
P53	ZSGB-BIO	Mouse	DO-7	1:500
ER	Roche	Rabbit	SP1	Predilute
PR	Roche	Rabbit	IE2	Predilute
WT1	ZSGB-BIO	Rabbit	EP122	1:50
PAX8	CELNOVTE	Mouse	C12A32	Predilute
SOX10	ZSGB-BIO	Rabbit	EP268	Predilute
TRPS1	MXB	Rabbit	EPR16171	Predilute
TTF-1	ZSGB-BIO	Mouse	8G7G3/1	Predilute
GATA3	ZSGB-BIO	Rabbit	EP368	1:50
HMB45	ZSGB-BIO	Mouse	HMB45	Predilute
Ki67	ZSGB-BIO	Mouse	UMAB107	1:400
P120	CELNOVTE	Rabbit	EP66	Predilute
E-cad	ZSGB-BIO	Mouse	EP6	1:200

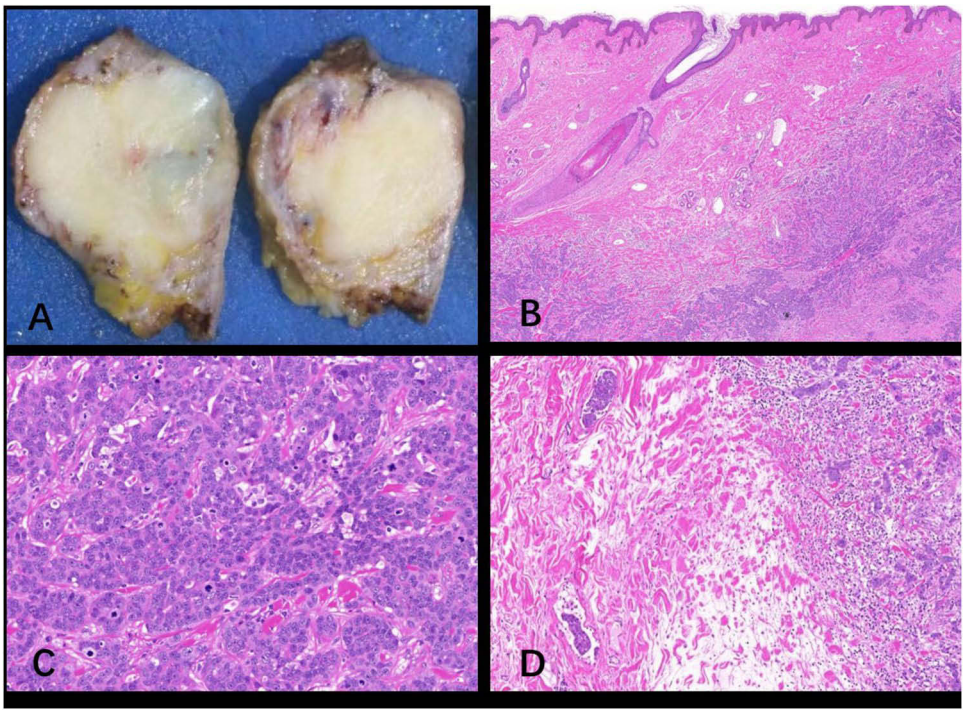

Figure 1 The Macroscopic examination and pathologic features. (**A**) Macroscopic findings revealed a well-demarcated tumor measuring 30 mm in diameter. (**B**) The tumor, located beneath the epidermis, exhibited invasiveness by infiltrating the surrounding adipose tissue (x100). (**C**) Tumor nests displayed cytologic atypia characterized by nuclear pleomorphism, an open chromatin pattern with prominent nucleoli, and abundant eosinophilic cytoplasm (x200). (**D**) Pathological mitosis and vascular tumor thrombus were prominently observed (x100).

approximately 3.0*2.0*2.0 cm in size (Figure 1A). Its texture was uniform and tough, with an irregular gray cut surface that displayed firm consistency without any evident necrosis or bleeding. The microscopic examination revealed infiltrating adenocarcinoma located in the dermis and subcutis, devoid of epidermal connections. The tumor exhibited a nest-like and cord-like arrangement, with heterogeneous tumor cells characterized by scant eosinophilic cytoplasm, round or oval nuclei, prominent pleomorphism, chromatin clumping, and large red nucleoli. The mitotic index was 15 per 10 high-power fields, with no evidence of neoplastic necrosis, and multifocal lympho-vascular invasion was observed (Figure 1B–D). All resection margins were extensively free from neoplastic involvement.

On initial immunohistochemical analysis, the tumor cells were diffusely positive for CK7, E-cadherin and P53. Conversely, the neoplastic cells demonstrated negativity for estrogen receptor (ER), progesterone receptor (PR), WT1, PAX8, Pax-2, CDX2, GATA3, CD10, P40, HMB45 and S100. The Ki67 proliferative index was determined to be 80%. The tumor was diagnosed as poorly differentiated adenocarcinoma. Additional immunohistochemistry with TRPS1, SOX10 and P120-catenin revealed the presence of positive cells in the vulva tumor, while HER-2/neu immuno-stain was negative (Figure 2).

Diagnostic Assessment

The breast physical examination, breast magnetic resonance imaging, computed tomography of the chest and upper abdominal magnetic resonance imaging yielded no significant findings. The diagnosis of vulva AMGT is supported by the precise localization of the lesion, its associated histologic characteristics combined with the immunohistochemical profile, and the absence of relevant clinical history. The histological type observed was non-special type invasive ductal carcinoma, specifically the triple-negative subtype. Considering the anatomic relationship between the vulvar tumor and adjacent organs, and the pathologically confirmed invasive behavior, it was definitively concluded that the lesions in the bladder and cervix were the result of invasion by the primary vulvar tumor.

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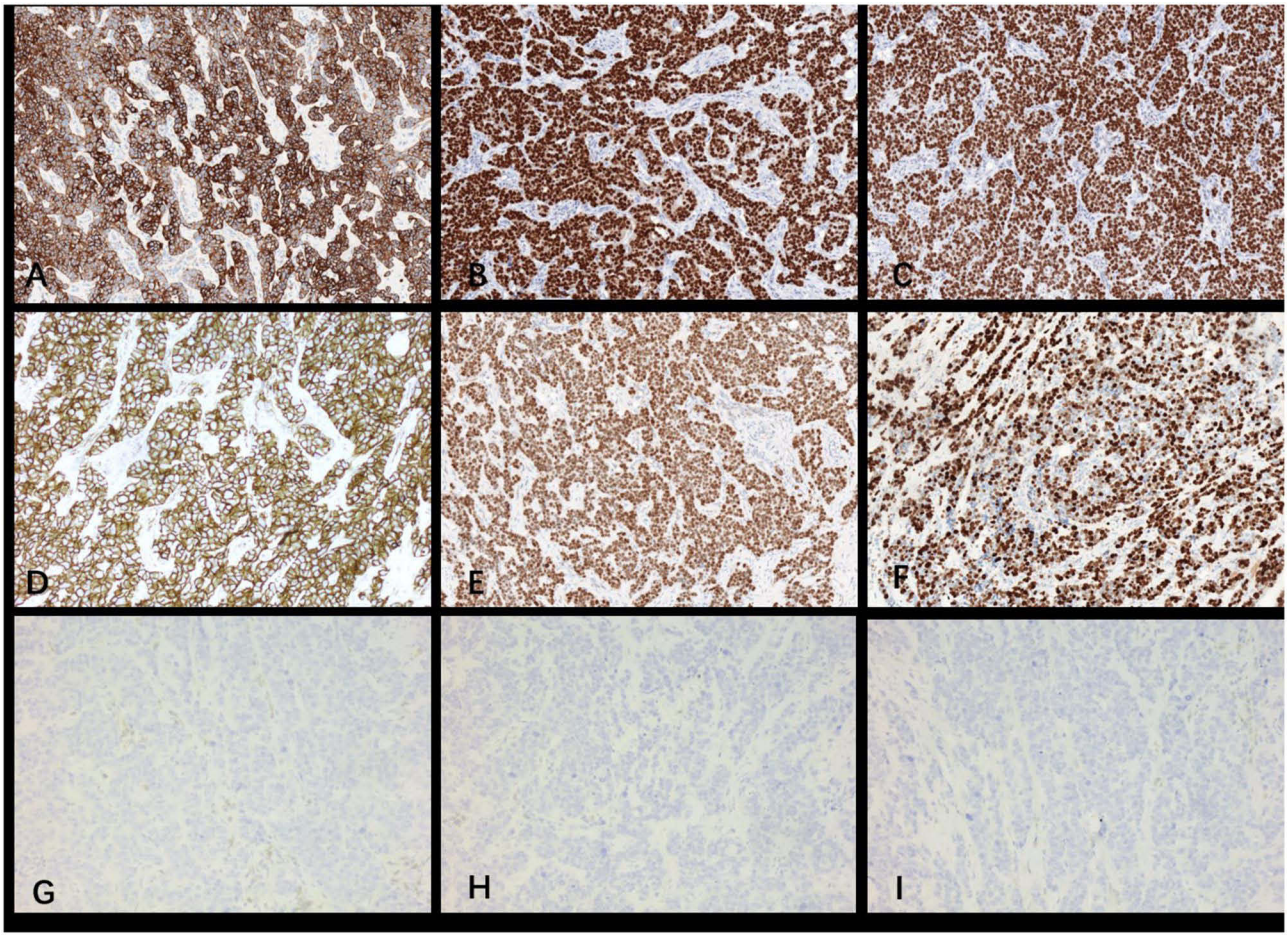

Figure 2 Representative immunohistochemical findings of vulvar tumor. Immunohistochemical staining for CK7 (**A**), SOX10 (**B**) and TRPS1 (**C**) exhibited strong and diffuse positivity in the tumor cells. The tumor cells demonstrated positive membranous staining for E-cadherin (**D**) and maintained expression of P53 (**E**). The percentage of Ki-67 expression in the area was approximately 80% (**F**). The tumor cells showed complete lack of ER (**G**), PR (**H**), HER2 (**I**) expression(x200).

Therapeutic Intervention

The patient has now reached the 10-month mark following her primary surgical resection and has completed three cycles of adjuvant chemotherapy consisting of Paclitaxel and carboplatin.

Follow-up and Outcomes

The patient demonstrated favorable postoperative outcomes within a 10-month period, and during the clinical follow-up, no complications were observed and there was no evidence of disease progression.

Discussion

The vulvar mammary-like adenocarcinoma (AMGT) is an uncommon malignancy arising from the anal genital glands of the vulva, which represents a rare entity in the field of gynecology and obstetrics. The first documented case of vulvar mammary-like adenocarcinoma was reported by Greene in 1936,[11] it has been reported that ectopic mammary gland formation can occur when the mammary crest fails to regress during human embryonic development.[12] Currently, anogenital mammary glands are considered to be a normal component of the anogenital region and exhibit numerous characteristics shared by both eccrine and mammary glands. The presence of AGMLG in anogenital specimens is often serendipitous. While normal AGMLG resembles mammary tissue, it lacks the lobular structure typically observed in mammary glands.

The reported age ranged from 45 to 90 years, with an average of 62.5 years, which exceeded the corresponding age range observed in breast cancer cases.[13] The findings from the literature review indicated that a majority (65%) of patients were primarily affected in the labia majora region, and the tumors exhibited predominantly small sizes, with an average diameter of approximately 2.5 cm.[4] In the early stage, there is no apparent vulvar skin rupture, and patients do not exhibit typical symptoms, often leading to oversight. However, as the mass gradually enlarges, it gives rise to ulcerated vulvar neoplasms and causes clinical symptoms such as pain due to invasion of surrounding tissues.[5] It is recommended that both patients and clinicians should closely monitor painless vulvar masses. In our case, the patient was a 70-year-old individual with a right labia majora lesion measuring approximately 3 cm in diameter, consistent with findings reported in the literature.

The histopathological features of mammary vulvar carcinoma include the arrangement of cells in cords, beams, clumps, glandular tubes or solid sheets. The cell boundaries are well-defined and exhibit a large volume. The cellular atypia ranges from slight to markedly polymorphic, demonstrating high heterogeneity. The cytoplasm is eosinophilic, while the nucleus appears large with a prominent nucleolus. The presence of mitotic figures can vary from absent to highly conspicuous. The tumor cells showed infiltrative growth in the stroma, characterized by desmotrophic reactive stromal hyperplasia that morphologically resembles breast cancer. The histological types of breast vulvar adenocarcinoma reported in the literature include infiltrating ductal carcinoma, lobular carcinoma, mucinous carcinoma, apocrine carcinoma and adenoid cystic carcinoma.[3] Invasive ductal carcinoma predominates as the primary histological subtype, which is also observed in this particular case.

Sometimes, solely relying on morphology can pose challenges in distinguishing cases, emphasizing the crucial role of immunohistochemical features for achieving a definitive diagnosis. Notably, established mammary markers such as GATA3, SOX10, Mammaglobin, and GCDFP15 play significant roles in this regard. However, it is worth mentioning that Mammaglobin and GCDFP15 exhibit limited expression in the majority of triple negative breast carcinoma (TNBC) cases and thus possess relatively low application value. SOX10 is a recently identified marker of mammary origin, exhibiting high sensitivity particularly in TNBC; however, its lack of specificity renders it positive in nerve and melanin tumors as well.[14] To identify more sensitive markers for breast cancer, Ai et al conducted a screening of the Cancer Genome Atlas (TCGA) database and identified TRPS1 as a specific gene associated with breast cancer.[15] Immunohistochemical analysis revealed a significantly higher expression of TRPS1 in triple-negative breast cancer (TNBC) compared to GATA3, with 86% versus 51% in non-chemotherapy-treated TNBC.[16,17] Notably, TRPS1 was found to be absent or only minimally expressed in urothelial carcinoma, lung adenocarcinoma, pancreatic cancer, colon cancer, and other tumor types.[16] Previous studies have demonstrated that vulvar AMGT exhibits similarities to breast cancer and can be classified into Luminal A, Luminal B, HER2 overexpression, and triple-negative subtypes.[5] In this particular case, GATA3, GCDFP15, ER, PR and C-erbB2 were found to be negative while TRPS1, SOX10 and E-cadherin were positive, indicating the histological subtype as triple-negative breast cancer.

In differential diagnosis, it is imperative to differentiate from other perineal tumors with similar morphology, including vulvar non-specific adenocarcinoma, apocrine adenocarcinoma, and sebaceous adenocarcinoma. This differentiation primarily relies on histopathological features and immunohistochemistry analysis. Metastasis of breast adenocarcinoma to the vulva is not uncommon, and in the absence of normal mammary glands and metastatic lesions, it is essential to conduct a comprehensive examination to exclude tumors originating from the breast or other sources. The histological morphology and immunohistochemistry of vulvar carcinoma were found to be consistent with those observed in primary breast cancer, as highlighted by Intra et al.[18] Primary vulvar breast cancer can be considered if the patient has no previous history or concurrent presence of primary breast tumor. The patient had no history of breast cancer, and a thorough breast examination revealed no discernible tumor, thereby excluding the possibility of vulvar metastatic breast cancer in our case. The limitations of our case are that despite the clinician's decision to perform a biopsy of the tumor, and the presence of an ordinary mammary-like gland of the tumor lesion was unable to be identified after thorough examination.

The vulvar AMGT is characterized by its local invasiveness, with approximately 60% of cases exhibiting regional lymph node metastasis; however, distant metastasis is uncommon.[3] According to the literature, current treatment modalities for breast vulvar adenocarcinoma primarily involve surgical resection of localized lesions, radiotherapy or

a combination thereof. Additionally, systemic diseases may be managed through cytotoxic chemotherapy, antiestrogen hormonal therapy, targeted therapy or a combination with the treatment approach employed in breast cancer.[19] In order to formulate an individualized treatment plan, several factors need to be taken into consideration, including tumor stage, grade, estrogen receptor (ER) and progesterone receptor (PR) levels, human epidermal growth factor receptor 2 (HER2) status, as well as patient age.[20] Among these factors, the diagnostic potential for targeted therapy of such tumors lies in the ER and PR levels and HER2 status.

Conclusion

Vulvar AMGT is a malignancy originating from AGMLG and exhibits histological features resembling those of breast cancer. The diagnosis of this tumor relies on histological characteristics and immunophenotype, TRPS1 exhibits high clinical utility in the diagnosis of triple-negative subtype particularly, while necessitating the exclusion of metastatic breast cancer prior to definitive diagnosis. Considering the therapeutic implications of molecular subtyping in breast cancer and detection of HER2 gene amplification, guiding targeted therapy for vulvar AMGT holds significant clinical relevance.

Data Sharing Statement

All available information is included in the manuscript.

Ethical Approval

The Ministry of Health does not require ethical approval for case reports or case series. Written informed consent was obtained from the patient for publication of this case report and any accompanying images. This research project has been approved by the Medical Ethics Committee of the Zhejiang Hospital, Zhejiang Province, People's Republic of China (approval 2024-CA-26). The publication of the case details has been approved by the Zhejiang Hospital.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Disclosure

The authors declare that they have no conflicts of interest.

References

1. Woelber L, Kock L, Gieseking F, et al. Clinical management of primary vulvar cancer. *European J Cancer*. 2011;47(15):2315–2321. doi:10.1016/j.ejca.2011.06.007
2. De Hullu JA, Oonk MH, Gj VD. Modern management of vulvar cancer. *Curr Opin Obstetrics Gynecol*. 2004;16(1):65–72. doi:10.1097/00001703-200402000-00012
3. Tseung J, Russell PJ. 'Breast-like' lesions in the vulva: histology, origin and significance. *Pathology*. 2008;40(3):321–326. doi:10.1080/00313020701813628
4. Abbott JJ, Ahmed I. Adenocarcinoma of mammary-like glands of the vulva: report of a case and review of the literature. *Am J Dermatopathol*. 2006;28(2):127. doi:10.1097/01.dad.0000171601.25315.2b
5. Konstantinova AM, Vanecek T, Martinek P, et al. Molecular alterations in lesions of anogenital mammary-like glands and their mammary counterparts including hidradenoma papilliferum, intraductal papilloma, fibroadenoma and phyllodes tumor. *Ann Diagnostic Pathol*. 2017;28:12–18. doi:10.1016/j.anndiagpath.2017.02.004
6. Fracchioli S, Puopolo M, Iardl L, Scozzafava M, Katsaros D. Primary "breast-like" cancer of the vulva: a case report and critical review of the literature. *Int J Gynecol Cancer*. 2006;16(Suppl 1):423–428. doi:10.1111/j.1525-1438.2006.00364.x

7. Konstantinova AM, Shelekhova KV, Imyanitov EN, et al. Study of selected BRCA1, BRCA2, and PIK3CA mutations in benign and malignant lesions of anogenital mammary–like glands. *Am J Dermatopathol*. 2017;39(5):1.
8. Mcmaster J, Dua A, Dowdy SC. Primary breast adenocarcinoma in ectopic breast tissue in the vulva. *Case Reports in Obstetrics and Gynecology*. 2013;2013:721696. doi:10.1155/2013/721696
9. Kong C, Yu B, Bi R, et al. TRPS1, a sensitive marker for different histological and molecular types of breast cancer. *Diagnostic Pathol*. 2024;19 (1):121.
10. Baykal C, Dünder I, Turkmen IC, Ozyar E. An unusual case of mammary gland-like carcinoma of vulva: case report and review of literature. *European Journal of Gynaecological Oncology*. 2015;36(3):333–334.
11. Greene H. Gynecology: adenocarcinoma of supernumerary breasts of the labia majora in a case of epidermoid carcinoma of the vulva. *Am J Obstetrics Gynecol*. 1936;31(4):660–663.
12. Kazakov D, Hoang M. Lesions of anogenital mammary-like glands, adnexal neoplasms, and metastases. *Vulvar Pathol*. 2015:327–354.
13. Ananthula A, Lockwood B, Savage J, Malak S, Pennisi A. Primary breast carcinoma of the vulva metastatic to lymph nodes and bones: a case report and literature review. *Permanente J*. 2020;24. doi:10.7812/TPP/19.084
14. Feng W, Liu S, Zhu R, et al. SOX10 induced Nestin expression regulates cancer stem cell properties of TNBC cells. *Biochem Biophys Res Commun*. 2017;485(2):522–528. doi:10.1016/j.bbrc.2017.02.014
15. Ai D, Yao J, Yang F, et al. TRPS1: a highly sensitive and specific marker for breast carcinoma, especially for triple-negative breast cancer. *Mod Pathol*. 2021;34(4):710–719. doi:10.1038/s41379-020-00692-8
16. Parkinson B, Chen W, Shen T, Parwani AV, Li Z. TRPS1 expression in breast carcinomas focusing on metaplastic breast carcinomas. *Am J Surgical Pathol*. 2022;46(3):415–423.
17. Yoon EC, Wang G, Parkinson B, et al. TRPS1, GATA3, and SOX10 expression in triple-negative breast carcinoma. *Human Pathology*. 2022;125:97–107. doi:10.1016/j.humpath.2022.04.006
18. Intra M, Maggioni A, Sonzogni A, De Cicco C. A rare association of synchronous intraductal carcinoma of the breast and invasive carcinoma of ectopic breast tissue of the vulva: case report and literature review. *Int J Gynecologic Cancer*. 2006;16(S1):428–433. doi:10.1136/ijgc-00009577-200602001-00080
19. Chow CY, Namuduri R, Yeo Y, Mihir G: The diagnostic challenge of primary adenocarcinoma of the vulva: a case report. 2020, 29:50–54.
20. Shah V, McCluggage WG, Asleh-Aburaya K, Tinker A. Molecular subtyping of mammary-like adenocarcinoma of the vulva shows molecular similarity to breast carcinomas. *Histopathology*. 2017:71(3):446–452.