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Diagnosis and management of primary vulvar adenocarcinoma of mammary gland type: report of two distinct cases

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SUMMARY

Adenocarcinoma of mammary gland type (AMGT) of the vulva is extremely rare and its aetiopathogenesis is not fully understood. Low incidence is partly responsible for the lack of guidelines for patient management. Here, two cases of postmenopausal patients diagnosed with AMGT with different therapeutical approaches are reported. Histopathological patterns are considered essential for diagnosis. The triple-negative immunohistochemical (IHC) profile of one of the cases represented a diagnostic challenge. Interestingly, it presented an immunophenotypical profile similar to triple-negative breast cancers, supporting the molecular similarities between vulvar AMGT and breast carcinomas. Surgical procedures include radical vulvectomy or radical local excision. Lymphatic involvement may be assessed by sentinel lymph node biopsy or lymphadenectomy. Adjuvant treatment was dependent on the IHC profile and disease staging. Although both cases had similar features on clinical examination, pathological and molecular characteristics and treatment approach were distinct. That illustrates the diagnostic and therapeutical challenge of this rare entity.

BACKGROUND

Squamous cell carcinomas represent ~90% of vulvar neoplasms, while less common histological types include adenocarcinomas, either primary or metastatic to the vulva, Paget's disease, melanomas, basal cell carcinomas and sarcomas.[1 2]

A rare form of primary vulvar adenocarcinoma arises from mammary-like vulvar glands, whose origin remains controversial.

These glands have been described to respond to hormonal stimuli and undergo physiological and pathological changes similar to breast tissue.[3–6] Their malignant transformation is extremely rare.[6] In 1936, Greene reported the first case of a mammary-type carcinoma in the vulva.[7–9] Until 2017, about 36 cases of adenocarcinoma of mammary gland type (AMGT) of the vulva have been described.[8]

The low incidence could explain the lack of specific guidelines for patient management,[4] and since the aetiopathogenesis of these tumours is not fully understood, there is no consensus about their classification, surgical approach and adjuvant treatment.[9]

Here, we discuss the approach of two different cases of postmenopausal patients diagnosed with AMGT of the vulva.

Patients' consent was obtained. Confidentiality was ensured and no ethical issues were raised.

CASE PRESENTATION AND INVESTIGATIONS

Case report number 1

A female patient in her 60s, multiparous, Eastern Cooperative Oncology Group-performance status (ECOG-PS) grade 0, without relevant personal or family history of cancer disease, presented with a vulvar mass on the left labium minus that measured approximately 20 mm. She was submitted to excisional biopsy of the lesion and was referred with a diagnosis of vulvar adenocarcinoma.

Pathological review (see figure 1) reported a nodule of 32 mm, with cribriform and papillary architecture, with some solid areas. The cytological atypia was moderate and the mitotic index was 31 mitoses per 10 high power fields (HPF). No images of lymphovascular and perineural invasion were observed. The tumour distance to deep and lateral surgical margins was 0.3 mm and 0.9 mm, respectively.

The immunohistochemistry (IHC) study demonstrated positivity for oestrogen receptors (ER) (90%–100%), cytokeratin (CK) 7, CAM5.2 and GATA3. The tumour was negative for progesterone receptors (PR), GCDDP-15, SOX10, p63 and CK20. HER-2 was classified as equivocal (2+) and fluorescence in situ hybridization (FISH) analysis of HER-2 gene amplification was negative (see figure 2).

Morphological aspects combined with the IHC profile support the diagnosis of AMGT of the vulva. The histological type was invasive ductal carcinoma, of no special type.

Clinical examination, breast ultrasound and mammography did not reveal signs of primary breast tumour. Chest CT showed no changes. The study of the gastrointestinal tract was normal.

Whole-body positron emission tomography (PET) with 18F-FDG revealed no additional hypermetabolic lesions, besides the one detected in the left vulvar region.

Case report number 2

The patient was a multiparous woman, in her 70s, ECOG-PS grade 2, with a personal history of type 2 diabetes mellitus, hypertension and obstructive sleep apnoea syndrome. In her 40s, she was submitted to total hysterectomy for benign pathology. Her father died with cutaneous melanoma and her mother had colon cancer.

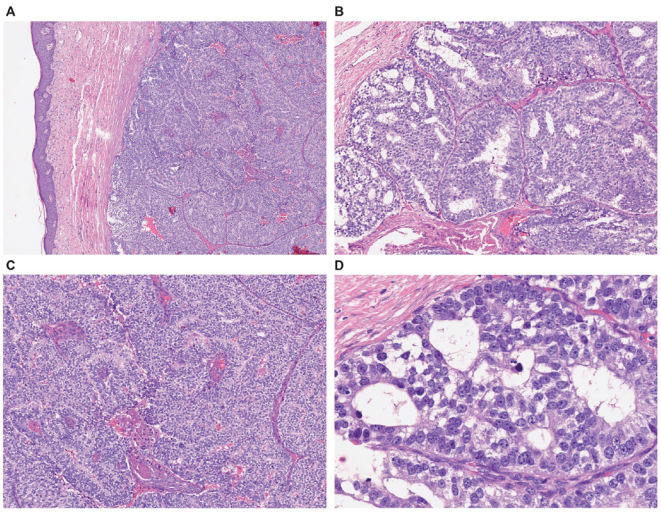

Figure 1 Histological features of case number 1. (A–D) Tumour mass presented a nodular configuration, with expansile growth, with a cribiform and papillary architecture, occasionally with solid areas. Neoplastic cells presented enlarged hyperchromatic nuclei, with vesicular chromatin (H&E, A—40×; B and C—100×; D—400×).

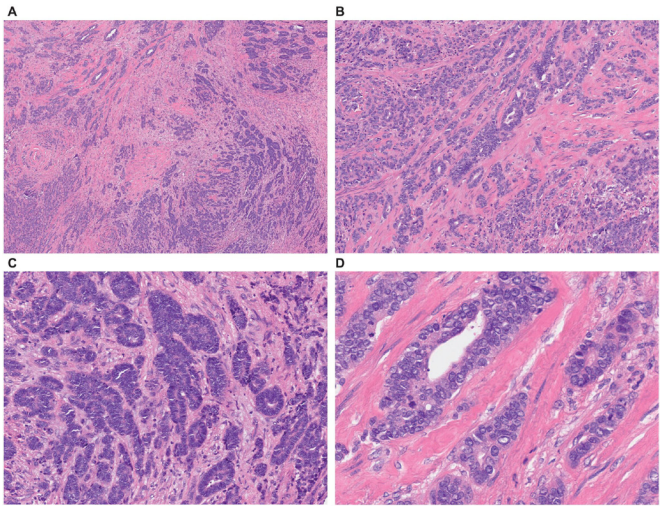

Figure 3 Histological features of case number 2. (A–D) Tumour mass presented an infiltrative growth, being arranged in a ductular and glandular architecture or in small nests and cords. Neoplastic cells presented an increased N:C ratio, with enlarged hyperchromatic nuclei and vesicular chromatin (H&E, A—40×; B—100×; C—200×; D—400×).

The patient noticed a 30 mm vulvar mass on the inner side of right labium majus. She underwent excisional biopsy of the lesion and was referred with a diagnosis of vulvar adenocarcinoma.

Pathological review (see figure 3) described a neoplasm of ductal architecture, organised in nests and cords, with an infiltrative growth pattern. Nuclear atypia was moderate to high and the mitotic index was 20 mitoses per 10 HPF. Lymphovascular and perineural invasion was observed. Margins intercepted the tumour.

IHC study demonstrated positivity for CK7, SOX10, p53 and E-cadherin. The tumour was negative for ER, PR, HER-2, GCDDP-15, GATA-3, TTF1, p63, PAX-8 and CK20 (see figure 4).

The aspects described, although unspecific, were compatible with the diagnosis of AMGT of the vulva. The histological type was invasive ductal carcinoma, of no special type.

Abdominal and pelvic MRI revealed a 12 mm right inguinal heterogeneous adenopathy. Breast examination and mammary imaging did not reveal primary breast tumour. The study of the gastrointestinal tract was normal. Chest CT showed no changes. The carcinoembryonic antigen was increased: 12.2 ng/mL. Cancer antigen (CA) 125, CA 15.3 and CA 19.19 were normal.

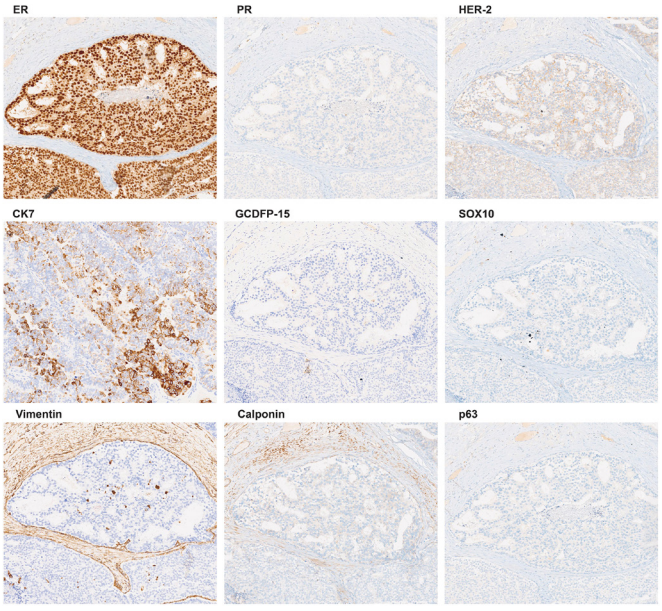

Figure 2 Immunohistochemistry profile of case number 1. Staining demonstrating positivity for ER, CK7, and negativity for PR, GCDDP-15, SOX10, p63, calponin and vimentin. HER-2 staining was classified as equivocal (2+) (10×). ER, oestrogen receptors; PR, progesterone receptors.

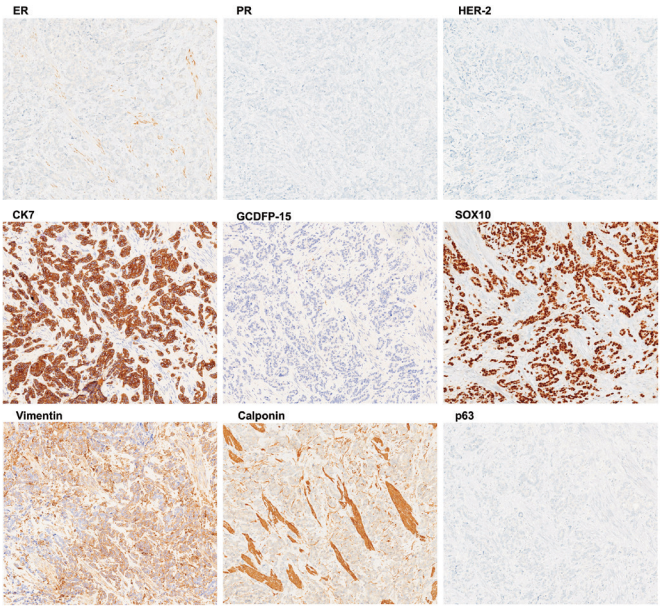

Figure 4 Immunohistochemistry profile of case number 2. Staining demonstrating positivity for CK7, SOX10 and vimentin, and negativity for ER, PR, GCDDP-15, p63 and calponin. HER-2 staining was classified as negative (0) (10×). ER, oestrogen receptors; PR, progesterone receptors.

The biopsy of the inguinal adenopathy revealed a metastasis of the vulvar neoplasia previously described.

Gynaecological examination revealed a painful scarring area, strongly adherent to the pubic bone. PET revealed hypermetabolic lesions in right inguinal and external iliac regions, in probable relationship with metastasis.

DIFFERENTIAL DIAGNOSIS

Before the histological result, several diagnoses for vulvar mass were considered. Benign tumours, adenocarcinoma arising from Bartholin glands, extramammary Paget disease, sweat gland carcinoma, and adenocarcinomas of metastatic origin were and should be considered as differential diagnoses.[8 10] However, when a vulvar mass is present, the diagnosis of AMGT should be suspected, especially if a history of breast malignancy or breast tissue morphology is present in histological examination.

TREATMENT

Case report number 1

After diagnosis of a mammary gland adenocarcinoma in the vulva, without apparent distant metastatic involvement, a multidisciplinary tumour board decided to offer a radical scar tissue excision with preservation of the clitoris and left inguinal lymphadenectomy, in order to widen margins and stage the disease. The postoperative period was uneventful and the patient was discharged on the 13th day of hospitalisation. The pathology examination showed scar tissue without involvement by the previously diagnosed neoplasia and absence of metastasis in the seven excised lymph nodes. Thus, the multidisciplinary team decided to start hormone therapy (HT) with an aromatase inhibitor.

Case report number 2

A multidisciplinary tumour board considered that the patient did not have conditions for upfront surgical approach, and thus was offered neoadjuvant chemotherapy. She completed four cycles of carboplatin and paclitaxel.

A new PET supported tumour regression showing lower FDG uptake in right inguinal metastasis and absence of uptake in the right external iliac region.

Subsequently, the patient underwent radical excision of the scar tissue and right inguinal lymphadenectomy. Pathological examination showed residual neoplasia, with 9 mm of greatest dimension, infiltrating borders and histology similar to the first excision sample, presenting signs of extensive lymphovascular invasion and positive resection margins. Two metastatic lymph nodes were isolated, the largest metastasis measuring 12 mm.

Postoperatively, she presented dehiscence of the vulvar surgical wound.

The patient underwent surgery to widen the margins of the vulvar region.

Pathology examination showed persistence of tumour intercepted by surgical margins.

A new PET showed a hyperuptake in the right external iliac ganglion and some areas of hypermetabolism in the right side of the vulva.

After new multidisciplinary discussion, the patient was offered external radiotherapy (ERT) with palliative purpose. She performed a total dose of 30 Gy in the vulva and perineum, 3 Gy per day, 5 times a week, using the Volumetric Modulated Arc Therapy technique, with good tolerance.

OUTCOME AND FOLLOW-UP

Both patients are alive and have been in regular follow-up. The first case has a short follow-up period of 6 months. The second case has already 15 months of surveillance. During the clinical follow-up, patients did not develop complications and remain with no disease progression.

DISCUSSION

Vulvar adenocarcinomas are uncommon and those originating from vulvar mammary-like tissue are even rarer. Different hypotheses about its aetiopathogenesis are mentioned in the literature. Previously, they were believed to originate from ectopic mammary tissue, which resulted from incomplete involution of the mammary ridges.[9 11] In embryogenesis, the mammary ridges develop from the fourth week after conception[4] and usually regress, except in the thoracic region where the mammary glands complete their development. This hypothesis was based on studies with mammals demonstrating the existence of a primitive 'milk lines' extending from the axilla to the groin. However, more recent embryological studies of human development have shown that human mammary ridges only develop in the axillary-pectoral area.[12 13] Thus, van der Putte and van Gorp suggest that these tumours are derived from anogenital mammary-like glands located in the interlabial folds, with subtle histological and ultrastructural differences from breast tissue, which are considered a normal constituent of the anogenital region.[14]

Regardless of either hypotheses, this tissue is hormone sensitive and has the capacity to undergo benign or malignant changes similar to orthotopic breast tissue.[1 3 9] Patients may remain asymptomatic or become symptomatic due to the physiological changes typical of menarche, pregnancy or lactation.

In 1872, Hartung described for the first time the presence of a fully formed mammary gland in the left labium majus, in an old woman in her 30s,[5 8] while Greene published the first case of a mammary-like tumour of the vulva in 1936.[7]

The mean age of patients with vulvar mammary-like adenocarcinomas is 62.5 years.[8] Here, the presented cases were slightly older than the average.

Overall, vulvar lesion is described as an asymptomatic solitary nodule, mostly located on the labia majora. This description is globally coincident with our cases, except in the second case where the tumour location was in the labium minus. In both cases, excisional biopsies were performed because there was no suspicion of malignancy at first sight and the aim was to remove the entire lesion in a single procedure.

The histological types in the vulva appear to be similar to those described for the breast, such as ductal lobular, mixed and mucinous carcinomas.[15] The most frequent histological type is invasive ductal carcinoma. Lobular carcinomas appear to be more aggressive and are often associated with lymphatic metastases.[16] Both cases were classified as invasive ductal carcinoma, thus supporting the higher frequency reported for this subtype.

Adenocarcinoma arising from Bartholin glands, extramammary Paget disease, sweat gland carcinoma and adenocarcinomas of metastatic origin should be considered as differential diagnoses.[8 10] However, when a vulvar mass is present, the diagnosis of AMGT should always be considered, especially if a history of breast malignancy or breast tissue morphology is present in histological examination.

For the diagnosis of vulvar carcinoma of mammary gland type, histopathological patterns are essential.[4 8 17] Diagnostic criteria include: (1) morphology consistent with breast carcinoma, (2) positive ER and/or PR, (3) positivity for typical immunohistochemical breast markers and (4) the presence of carcinoma in situ or non-neoplastic breast tissue, adjacent to the tumour.[3 10 11] Furthermore, it is necessary to exclude metastasis disease from

orthotopic breast carcinoma or other organs.[8 9 11] In both of the presented cases, a metastatic origin was excluded.

In both cases, there was no carcinoma in situ or non-neoplastic breast tissue present in adjacent areas. The first case meets three out of four criteria mentioned above and the second one meets one out of four, due to the absence of positive ER and/or PR and absence of typical immunohistochemical breast markers. The disparity in diagnostic criteria between both cases is one of the most interesting aspects of our article, illustrating the molecular variability within the histological subtypes, which could have implications for therapeutical orientation and outcome.

Although ER and PR expression is considered a diagnostic criterion for these neoplasms, here we report a case of an AMGT with a triple-negative profile, mimicking its breast counterpart.

Interestingly, the triple-negative AMGT expressed SOX10, a transcription factor that mediates differentiation of neural crest-derived cells, recently identified as a possible diagnostic marker for triple-negative breast carcinomas.[18] Additionally, it also expressed vimentin, a protein primarily expressed by mesenchymal cells, suggesting tumour dedifferentiation with epithelial–mesenchymal transition, which has been associated with poor prognosis and metastatic potential of some cancers.[19] These findings suggest a utility for these markers in the diagnosis and outcome of vulvar neoplasms, specifically in the differential diagnosis of hormone receptor-negative vulvar cancers with breast tumour-like morphology.

Altogether, these findings further support the existence of molecular similarities between vulvar AMGT and breast carcinomas, across different subtypes. Indeed, gene expression profiling of AMGT confirmed overlapping molecular characteristics with breast carcinoma,[20] with recent studies suggesting that molecular subtyping similar to breast carcinoma can be performed in vulvar AMGT and should be considered for the development of treatment algorithms.[21]

However, owing to their rarity, it is difficult to draw strong conclusions about the natural history and prognosis of these carcinomas, as well as develop well-established guidelines for the treatment of AMGT with primary manifestation in the vulva.[8–10]

Due to their resemblance, treatments are often extrapolated from guidelines for orthotopic breast cancers,[9 10] however optimal surgical margins and lymph node staging remain a debatable subject.

Surgical procedures usually include radical vulvectomy or radical local excision. Lymphatic involvement may be assessed by sentinel lymph node biopsy (SLNB) or homo/bilateral lymphadenectomy.[6 10 11] SLNB in the vulva is an approach used in more recent cases described in the literature.[14 22] SLNB, when performed by experienced professionals, is a good method of lymph node evaluation in patients with early-stage vulvar carcinoma.[16] In 2017, Ishigaki *et al* reported the first case of a non-recurring adenocarcinoma mammary-like of the vulva, in which SLNB was performed.[11] In our centre, there is still no experience to perform the SLNB, so lymphadenectomy was executed.

Adjuvant treatment with ERT, chemotherapy or HT varies according to the IHC study and disease staging.[3 5 15]

According to the guidelines for breast cancer, in an invasive ductal tumour with ER positive, HER-2 negative and apparently without lymphadenopathy, surgical treatment and lymph node staging are recommended. After complete excision with appropriate margins and negative lymph node involvement, adjuvant endocrine therapy is proposed. This is what was done in case number 1, following the same recommendations in the vulva. Due to the presence of positive ER and the proven benefit in the treatment of orthotopic breast cancer, HT was introduced with an aromatase inhibitor.

It was decided not to perform adjuvant ERT, considering it would increase morbidity and lower limb lymphoedema.

In the second case, due to lymph node metastasis and positive margins in the initial excision, we opted to perform chemotherapy with carboplatin and paclitaxel, the same approach as a patient with primary breast cancer in a similar stage. Due to disease persistence after several surgical interventions, lymph node metastasis in unilateral lymphadenectomy and ER negativity, the weighted option of performing ERT for palliative purposes was taken.

By reporting these clinical cases, we intend to increase the knowledge about the pathogenesis of these rare lesions, through histological and IHC analysis, as well as debate their clinical management and outcome. AMGT is a rare condition and specific guidelines are not yet available. However, taking into account the similarities and biological behaviour of both diseases, together with the low number of reported cases and lack of targeted clinical trials, we believe management and follow-up should be the same as for orthotopic breast cancer of a similar stage.

Learning points

- In the literature, there are different theories about the aetiopathogenesis of adenocarcinoma of mammary gland type (AMGT) of the vulva. Nowadays, it is thought that these tumours are derived from anogenital mammary glands which are a normal component of anogenital tissue.
- Although vulvar mammary-like tissue responds to the same physiological and pathological changes as the breast, the development of a mammary gland carcinoma is extremely rare and few cases of AMGT of the vulva have been reported in the literature.
- AMGT of the vulva presents molecular similarities with breast carcinomas, which could be considered for developing diagnostic and therapeutic schemes. Here, similarly to triple-negative breast cancers, SOX10 was expressed in a triple-negative AMGT of the vulva.
- Treatment remains controversial, however it appears that the same approach used for orthotopic breast cancer of a similar stage could be used.
- By reporting these cases, we intend to increase the knowledge about the pathogenesis and clinical management of these lesions. Both cases presented similar features on clinical examination, however pathological and molecular characteristics were distinct, which prompted different treatment approaches, thus illustrating the challenges in the management of these patients.

Contributors MM did the bibliographical research and wrote the main article, namely the background, description of the clinical cases and their orientation from the gynaecological point of view and the discussion. MM was responsible for submission. JVS was responsible for writing the part related to the anatomopathological study as well as the treatment of the images included in the article. JVS corrected the English language. MVT selected the patients and was responsible for the surgeries that they underwent. MVT was also responsible for supervising the article, writing the abstract and the learning points. MM was responsible for obtaining the consent of patients. MM and JVS revised the article following the suggestions proposed by the reviewer. MM was responsible for resubmitting the article.

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Case reports provide a valuable learning resource for the scientific community and can indicate areas of interest for future research. They should not be used in isolation to guide treatment choices or public health policy.

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