Case Study: Epithelioid sarcoma of the vulva

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Abstract
Vulval epithelioid sarcoma is a rare, locally-aggressive malignant soft tissue tumour, which may present diagnostic difficulties, both clinically and pathologically. This can result in a delay in appropriate treatment, which consists primarily of radical wide local excision of the tumour. We report a case of a recurrent epithelioid sarcoma of the vulva, with a discussion of the pathological features and management.

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Introduction

Epithelioid sarcomas are rare and aggressive malignant soft tissue tumours which were first described by Enzinger in 1970.[1] They are divided into a 'distal type', which occurs on the upper and lower limbs, and a 'proximal type', which arises on the trunk, usually of young adults.[2] Epithelioid sarcomas of the vulva fall into the latter category, and only 22 cases have been reported in the English-language literature.[3,4] As these tumours are so rare, it has been difficult to establish their optimal treatment. We report a case of a recurrent epithelioid sarcoma of the vulva.

Case report

A 30-year-old woman, gravida one para one, presented to our gynaecology outpatient department in January 2008 with a painful right-sided vulval ulcer. This was initially thought to be infective, so she was treated with acyclovir and antibiotics, which brought some relief of her symptoms, although tests for HIV, syphilis and tuberculosis were all negative. She was taken to theatre for debridement and biopsy of the ulcer, and the histology showed heavily inflamed granulation tissue and degenerate and regenerate squamous epithelium.

She was seen three months later in the Vulval Clinic complaining of vulval pain, and was found to have a persistent ulcerated lesion of the right labia. A wide local excision of the lesion was performed, and the histology of this specimen was reported as a poorly-differentiated squamous carcinoma of the vulva, with a positive deep excision margin. All other investigations and metastatic work-up were negative, and a repeat wide local excision and bilateral inguinal node dissection was performed.

The histology of the repeat specimen showed a proximal epithelioid sarcoma, with clear margins and negative lymph nodes. The patient was followed up regularly and remained asymptomatic until 18 months later, when she again was found to have a mobile 2 x 2 cm subcutaneous nodule on the right side of the mons pubis. A fine needle aspiration biopsy of this nodule revealed a recurrent epithelioid sarcoma and, as metastatic work-up was again negative, a further wide local excision was performed. Histology confirmed a recurrence, with 11 mitoses/10 high-power fields, and with deep margins involved with tumour. She was counselled about further treatment options, namely re-excision or radiotherapy, but elected to have close follow-up and early re-excision should the tumour recur.

Histology

A review of the initial wide local excision and the subsequent re-excisions showed an epithelioid sarcoma, of the proximal type, in all the specimens. The tumour was located in the dermis and subcutis, with ulceration in the initial wide local excision. It was composed of nodules of polygonal epithelioid cells with a tendency to undergo coagulative necrosis in the centre of the tumour nodules. The tumour cells had large eccentric nuclei, vesicular chromatin, prominent nucleoli, and abundant eosinophilic cytoplasm that occasionally contained a hyaline inclusion. In the re-excision specimens the tumour cells also showed a spindled morphology in areas with elongated, tapered cytoplasm.

The mitotic count ranged up to 11 mitotic figures/10 high-power fields. Vascular invasion was not seen. A chronic inflammatory infiltrate was present at the periphery. The

overlying epidermis did not show any evidence of human papillomavirus infection or vulval intraepithelial neoplasia.

Immunohistochemical studies showed that the tumour cells strongly and diffusely expressed vimentin, AE1/AE3 (pancytokeratin marker) and CD34. In addition, the tumour cells were negative for desmin.

The morphological and immunohistochemical profiles were consistent with an epithelioid sarcoma, proximal type.

Figure 1: Proximal epithelioid sarcoma showing large polygonal cells with prominent nucleoli, paranuclear hyaline inclusions (arrows) and mitotic activity (arrow head)

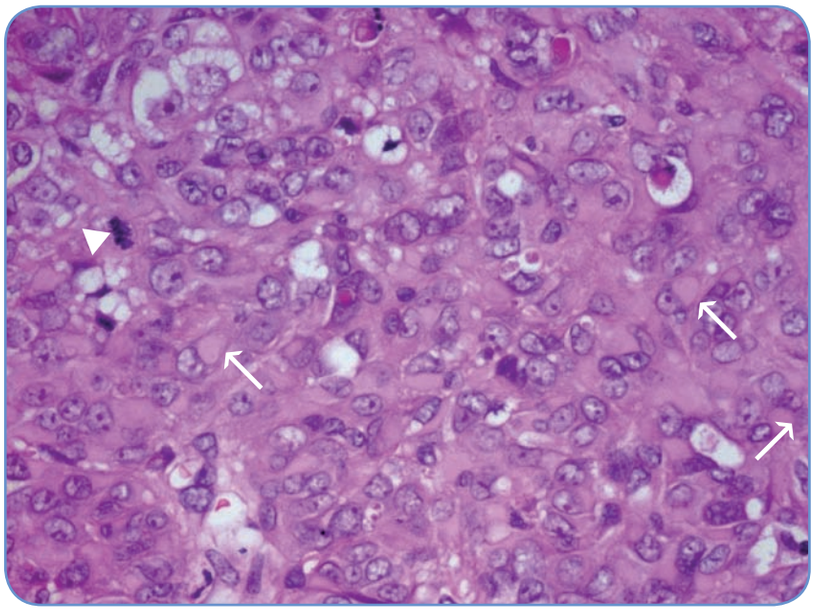
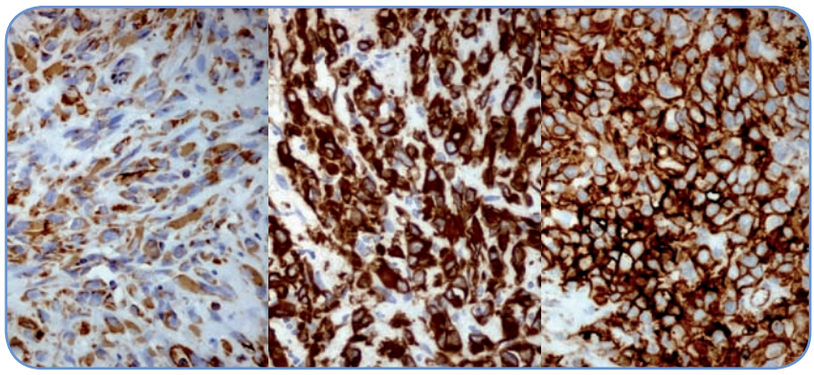


Figure 2: Epithelioid sarcoma showing positivity for vimentin, AE1/AE3, and CD34 respectively



Discussion of pathology

Epithelioid sarcoma is a rare, malignant, soft tissue neoplasm that has been confused with a variety of conditions, especially granulomas, synovial sarcomas and ulcerating squamous cell carcinomas. It affects mainly young adults 10 to 35 years of age.

There are two types of epithelioid sarcomas. The classic or "distal" type is the commonest and affects mainly the distal extremities, particularly the hands and wrist (47% in a review of 215 cases).[5] The proximal type was described in 1997 by Guillou et al[2] and tends to arise in axial locations, such as the pelvis, perineum and genital tract. It differs from the classic type by its location, more aggressive behaviour, and the predominance of large epithelioid cells, which often have a rhabdoid appearance with intracytoplasmic paranuclear hyaline inclusions. However, the proximal type shares a similar immunophenotype with the classic type, that is: positivity for cytokeratin (> 90%), vimentin (~100%), CD34 (up to 60%), and EMA (approximately 85% and usually membranous staining).[6,7] Other markers that may be positive include CD99 (25%), S100 (30%), synaptophysin (20%) and desmin (10%).[7] HMB45 may be uncommonly positive (0 to 23%).[2,7] CD31, myogenin and chromogranin A are negative.[7]

The differential diagnosis includes squamous cell carcinoma, malignant extrarenal rhabdoid tumour and malignant melanoma. Squamous carcinoma can be differentiated from epithelioid sarcoma by the presence of keratin production, intercellular bridges and overlying dysplasia. Squamous cell carcinomas are also CD34 negative.

Rhabdoid tumours are characterised by the deletion of the *hSNF5/INI1 (SMARCB1)* gene on chromosome 22q. They occur mainly in infancy and childhood, particularly in the kidney and the central nervous system, although malignant extrarenal rhabdoid tumours have also been described. Rhabdoid tumours are negative for CD34.[6] However, there may be a pathogenetic link between rhabdoid tumours and epithelioid sarcomas, as a high proportion of proximal-type epithelioid sarcomas also show inactivation of INI1,[8] which is a rare finding in other tumours. On reviewing epithelioid sarcomas, Fisher notes that many tumours previously diagnosed as rhabdoid tumours have been reclassified as proximal-type epithelioid sarcomas. He believes that rhabdoid cells represent a morphologic pattern rather than an actual rhabdoid tumour in most cases, and that many cases of malignant extrarenal rhabdoid tumours can be better classified as other types of tumours with rhabdoid cells.[9]

Malignant melanomas often demonstrate the production of melanin, are negative for keratin, and are positive for S100,

HMB45 and Melan-A, all of which are usually negative in epithelioid sarcomas.

Discussion of management

Epithelioid sarcomas usually present as rapidly-growing but painless subcutaneous nodules, which may have an ulcerated surface. As these features are non-specific, they are often mistaken for benign conditions such as granulomas, Bartholin cysts, fibromas, lipomas or teratomas.[3] As with our patient, these misdiagnoses can lead to treatment inadequacy and delays.

The primary treatment of epithelioid sarcoma of the vulva consists of wide local excision of the lesion. As with vulval carcinomas, and extrapolating data from epithelioid sarcomas that occur in extragenital sites, it is recommended that one aims for a 2 cm margin.[3]

Inguinal lymph nodes should be resected if they are suspicious or enlarged on either physical examination or imaging, although there is no evidence that this has any beneficial effect on local or distant recurrence rates.[3]

The role of postoperative radiotherapy in vulval epithelioid sarcoma is controversial. One report quotes a recurrence rate of 14% for patients who received adjuvant radiotherapy, compared to 71% for those who did not ($p = 0.01$), although there was not a statistically significant reduction in mortality from the disease.[4] Another paper recommends adjuvant radiotherapy for high-grade tumours and those with inadequate margins.[7]

The role of chemotherapy in this condition has not been defined adequately. A variety of chemotherapy regimens have been employed as initial treatments in seven patients, of whom three were free of disease at eight, 11 and 21 months; the other four died of the disease within eight months of diagnosis.[4] Chemotherapy for the treatment of recurrences has been even less effective, with only one patient surviving more than a year from the initiation of treatment.[4]

When these tumours were originally described, Enzinger stated that they had a slow, relentless clinical course, with frequent recurrence (87%) and late metastasis (30%).[1] Overall five-year survival rates for distal type epithelioid sarcoma have been reported to be between 50 and 80%,[5,7] with a worse prognosis for proximal-type tumours in some reports,[1,4,5] but not in others.[10,11] Other reported indicators of a poor prognosis include vascular invasion, tumour size of more than 5 cm, more than 30% necrosis, presence of local recurrence, and advanced stage at presentation.[10,11,12] Local recurrences are common and may develop after many years, despite adequate and negative resection margins. The high local recurrence rate is due to the infiltrative growth of the tumour along fascial planes and neurovascular structures, with the development of satellite nodules. Distant metastases eventually occur in up to 60% of cases.[7]

Conclusion

Epithelioid sarcomas are rare tumours which have been described as having an 'indolent yet persistent nature'.[7] In view of their locally aggressive behaviour when they occur on the vulva, it is important to increase awareness of this condition in order to facilitate early diagnosis and curative treatment. Excision with wide surgical margins is the most effective form of primary treatment, although the potential for psychosexual morbidity as a result of radical resection of the vulva is of great concern, particularly as these tumours occur most commonly in young women. Surgery is also advocated as therapy for local recurrences, and radiotherapy can be utilised to decrease local recurrence rates, or in cases of close surgical margins or high-grade histology. The role of adjuvant chemotherapy has not been explored adequately in the literature, and chemotherapy appears to be only minimally effective when used to treat metastatic disease.

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