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ORIGINAL ARTICLE

Lipomatous angiomyofibroblastoma of the vulva: diagnostic and histogenetic considerations

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Key words

Angiomyofibroblastoma • Vulva • Lipomatous variant • Differential diagnosis

Summary

We report a rare case of angiomyofibroblastoma (AMFB) of the vulva, composed predominantly of a mature fatty component, representing approximately 60% of the entire tumour. The tumour, designated as "lipomatous AMFB", should be interpreted as the morphological result of an unbalanced bidirectional differentiation of the presumptive precursor stromal cell resident in the hormonally-responsive stroma of the lower genital tract, with the adipocytic component overwhelming the fibroblastic/myofibroblastic one. The close admixture of adipocytes with spindled/epithelioid cells of the conventional AMFB resulted, focally, in a pseudo-infiltrative growth pattern and pseudo-lipoblast-like appearance, raising problems in differential diagnosis, especially with well-differentiated lipoma-like liposarcoma and spindle cell liposarcoma. Awareness of the possibility that vulvo-vaginal AMFB may contain large amount of lipomatous component is crucial to avoid confusion with other bland-looking spindle cell tumours containing infiltrating fat.

Introduction

Bland-looking mesenchymal tumours of the lower female genital tract comprise lesions which arise specifically in the vulvo-vaginal region, and soft tissue tumours that can occur at other sites of the body. Among the former lesions, at least four distinct entities can be recognised: aggressive angiomyxoma, angiomyofibroblastoma, cellular angiofibroma and myofibroblastoma [1-6]. Interestingly, overlapping morphological and immunohistochemical features have been noticed not only among these lesions [5-8], but also with spindle cell lipoma, and mammary and soft tissue myofibroblastoma [8-12]. Apart from these similarities, there is increasing evidence that spindle cell lipoma, cellular angiofibroma, mammary, soft tissue and vulvo-vaginal myofibroblastoma share the same chromosomal aberration, namely 13q14 deletion, as indicated by FISH analyses showing monoallelic deletion of *RB1* and *FOXO1* [13-16].

Angiomyofibrobastoma (AMFB) is an uncommon, benign mesenchymal tumour that usually involves the vulva and vagina, but it can also occur at other sites such as the urethra, perineum, inguinal area, fallopian tube, vagina, scrotum, spermatic cord or pararectal region in males [2 17-23]. Clinically, most AMFBs present as slowly-growing, subcutaneous painless masses which are often misdiagnosed as Bartholin's gland cyst, hydrocele of the canal of Nuck, or aggressive angiomyxoma [5 6]. Only rarely have tumours with features similar, but not identical, to AMFB been reported in unusual sites, such as the oral cavity [24]. Although mesenchymal lesions labelled as *angiomyofibroblastoma-like tumour*s have been reported in the male genital tract [25], most represent cellular angiofibroma, and not "true" AMFBs as originally described in the vulvo-vaginal region [2 5 6]. According to the original description [2], the term AMFB is referred to the two main components of the tumour: blood vessels and stromal cells. AMFB contains numerous, sometimes ectatic, small- to medium-sized blood vessels which are, at least focally, surrounded by clusters of spindled to epithelioid cells [2 5 6]. These cells are usually arranged in cords, trabeculae, or single cell files and set in a matrix that varies from myxoid to hyaline [2 5 6]. AMFB only rarely undergoes sarcomatous transformation with local recurrence [26 27]. Immunohistochemical expression, albeit variable, of desmin and less frequently α-smooth muscle actin, seems to confirm that neoplastic cells are myofibroblastic in nature [2 5 6 17-23].

Mature adipose tissue is occasionally encountered in vulvo-vaginal AMFB [5 6], but the occurrence of a prominent fatty component as an integral part of the tumour is extremely rare [19 23 28 29]; the term "*lipomatous AMF*B" has been proposed for such tumours [19 23 28 29]. We herein report a rare case of lipomatous AMFB of the vulva, emphasizing pathological features, and providing histogenetic and differential diagnostic considerations.

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Clinical history

A 56-year-old woman presented with a painless, solitary, 4.5 cm mass in the vulva that appeared to be well-circumscribed and soft in consistency on physical examination. Preoperative ultrasonography confirmed a well-circumscribed mass in the vulva. Complete surgical excision of the mass, including a rim of adjacent, grossly normal tissue, was performed. No local recurrence has been experienced 2 years after surgery.

Materials and methods

The surgical specimen was submitted for histological examination in neutral-buffered 10% formalin, dehydrated using standard techniques and embedded in paraffin; 5 micron thick sections were cut and stained with haematoxylin and eosin (H&E), Alcian blue at pH 2.5 and periodic acid-Schiff (PAS). Immunohistochemical studies were performed with the streptavidin-biotin peroxidase detection system using the Ventana automated immunostainer (Ventana Medical Systems, Tucson, AZ). The antibodies tested were vimentin (dilution 1:100); α-SMA (dilution 1:200); desmin (dilution 1:100); myogenin (dilution 1:100); S-100 protein (dilution 1:500); CD99 (dilution 1:100); CD34 (dilution 1:50); B-cell lymphoma 2 (Bcl-2) protein (dilution 1:100); CD10 (dilution 1:200); CD117 (dilution 1:400); cytokeratins (AE1/AE3 clone; dilution 1:50); epithelial membrane antigen (EMA) (dilution 1:100); anti-human melanosome (HMB45) (dilution 1:300); all from Dako, Glostrup, Denmark. Appropriate positive and negative controls were included.

Results

Grossly, the tumour consisted of a well-circumscribed, incompletely encapsulated nodular mass measuring 4.5 cm in greatest diameter. The cut surface showed a lipomatous tumour with interspersed fibrous areas. Calcifications, haemorrhage, and necrosis were absent.

Histologically, at low magnification, a well-circumscribed lesion, composed predominantly (60% of the entire tumour) of mature adipose tissue, was seen (Fig. 1). The overall appearance was that of a lipomatous tumour containing dispersed, irregularly-shaped cellular areas and thick fibrous septa (Fig. 1). The fatty component was represented by mature adipocytes lacking nuclear pleomorphism. The non-adipocytic component was represented by conventional AMFB, namely proliferation of bland-looking spindled to epithelioid cells haphazardly set in a fibrous stroma and frequently arranged around small-sized blood vessels (Figs. 2, 3). Mono- or bi-nucleated epithelioid cells, at least focally, were closely packed to form small clusters. Tumour cells had an appreciable pale to eosinophilic cytoplasm and were variably set in a loose oedematous to fibrous stroma containing thin to thick wavy collagen fibres (Fig. 3). Mitotic activity was very low (< 1 mitosis x 50 HPF). Atypical mitoses, nuclear atypia and necrosis were not observed. Mast cells

Fig. 1. Low power magnification showing a well-circumscribed lipomatous tumour containing hypocellular and moderately cellular areas, as well as interspersed thick fibrous septa (haematoxylin-eosin).

Fig. 2. Higher magnification of a cellular area showing spindled to epithelioid cells set in a fibro-oedematous stroma and arranged around small calibre blood vessels (haematoxylin-eosin).

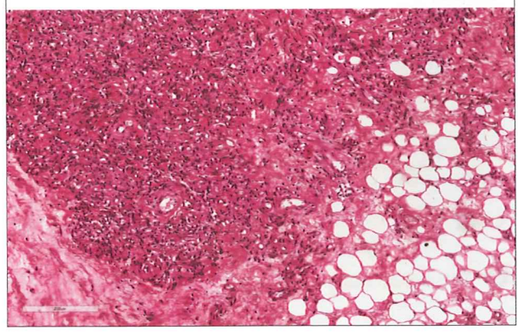
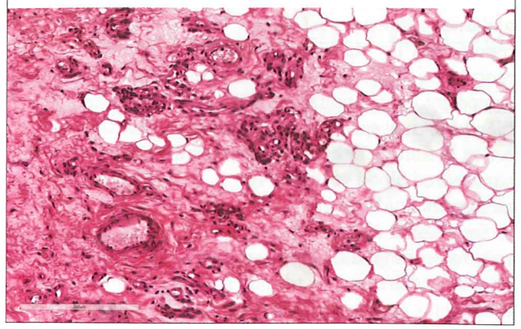


Fig. 3. Perivascular arrangement of neoplastic cells is best appreciated in this hypocellular tumour area. Thin wavy collagen fibres are interspersed throughout fibro-oedematous stroma (haematoxylin-eosin).



were readily identified in the fibrous stroma. The adipocytic and the spindled/epithelioid components were variably admixed: in some areas, the former component was represented by small islands of conventional AMFB completely surrounded by mature adipose tissue (Fig. 1), while in other areas the spindled to epithelioid cells were closely intermingling with adipocytes, resulting in a pseudo-infiltrative growth pattern of the former cells towards the latter cells (Fig. 4). In the areas that contained the juxtaposition of the two components, adipocytes focally varied in size and shape, exhibiting, at least focally, a univacuolar lipoblast-like appearance (Fig. 5). However, true lipoblasts, namely adipocytes showing hyperchromatic indented or sharply scalloped nucleus, were lacking. Neoplastic cells showing hybrid features between the two components, namely spindled/epithelioid cells with varying degrees of intracytoplasmic accumulation of lipids in the form of single large non-membrane-bound droplet or multiple small droplets, could not be identified, even after meticulous examination of the entire tumour.

Immunohistochemically, the spindled/epithelioid cells were diffusely positive for vimentin, bcl2-protein (Fig. 6) and CD99 (Fig. 7), and focally for desmin. No immunostaining was obtained with any other antibodies tested. Mature adipocytes were S-100 positive. Based on morphological and immunohistochemical findings, a diagnosis of "lipomatous AMFB" was rendered.

Fig. 5. Mature adipocytes, admixed with spindled/epithelioid cells, may acquire variable size, shape, and, at least focally, a univacuolar lipoblast-like appearance (haematoxylin-eosin).

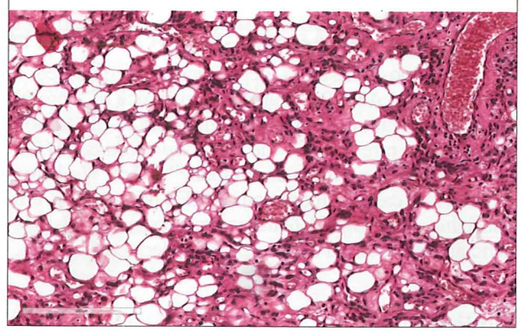


Fig. 6. The non-lipomatous component is strongly positive for bcl-2 (immunoperoxidase).

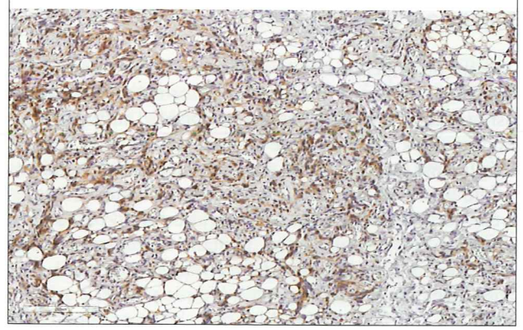


Fig. 4. Spindled to epithelioid cells are closely intermingling with mature adipocytes, resulting in a pseudo-infiltrative growth pattern (haematoxylin-eosin).

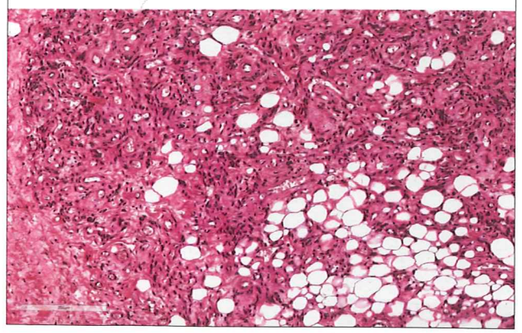
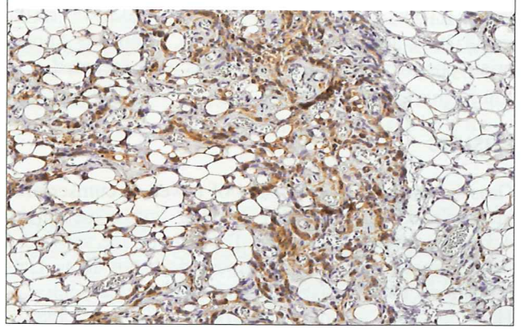


Fig. 7. The non-lipomatous component is strongly positive for CD99 (immunoperoxidase).



Discussion

Vulvar AMFB is currently included in the category of the "specific stromal tumours of the lower female genital tract", together with aggressive angiomyxoma, cellular angiofibroma and myofibroblastoma [5 6]. Although diagnosis of AMFB is usually straightforward if typical morphology is encountered [2 17-22], diagnostic problems may arise with unusual morphological variants, such as the "lipomatous variant" [19 23 28 29].

Herein, we report on a rare case of benign spindled to epithelioid cell stromal tumour of the vulva, with prominent (60% of the entire tumour) mature fatty component. Due to this morphology, the tumour was closely reminiscent of a lipomatous tumour, especially spindle cell lipoma, well-differentiated lipoma-like liposarcoma or spindle cell liposarcoma. However, morphological and immunohistochemical findings were consistent with a fibroblastic/myofibroblastic tumour that fits within the spectrum of AMFB, representing the uncommon lipomatous morphological variant, and thus the descriptive term "lipomatous *AMFB of the vulva*" seems to be most appropriate. The following morphological and immunohistochemical features, typically described in most cases of AMFB of the vulvo-vaginal region [2 5 6 17-23], support this diagnosis: i) intralesional fat was an integral component of the tumour and not the result of entrapment, as it was identified either at the periphery or in the centre of the tumour; ii) the non-lipomatous component exhibited typical morphological and immunohistochemical features of AMFB. Interestingly, we found that, apart from focal immunostaining of desmin, both bcl-2 protein and CD99 were strongly and diffusely expressed in our case. Although these molecules may be potentially exploitable for differential diagnostic purposes, we underline that these markers are not specific, and are also reported in most cases of vulvo-vaginal myofibroblastomas [8].

The origin of a large amount of adipose tissue in vulvo-vaginal AMFB is still unclear. Some authors have speculated that lipomatous AMFB may arise from a perivascular or pericytic stem cell [7], which may differentiate into a myofibroblastic and fatty lesion under unknown stimuli. We were not able to identify cells with intermediate morphological and immunohistochemical features of fibroblasts/myofibroblasts and mature adipocytes. This argues against the hypothesis that the fatty component is the result of a metaplastic process from a fully mature cell type (fibroblast/myofibroblast) into another (adipocyte). Therefore, mature adipose tissue in lipomatous AMFB seems to arise "ex novo" from precursor stromal cells. As previously postulated for "benign stromal tumours of the breast" [11 12 30-32], a category of lesions which share several morphological, immunohistochemical and cytogenetic findings with the benign stromal tumours of the lower female genital tract [8 10 16], it can be speculated that AMFB, like vulvo-vaginal myofibroblastoma [8 16], may arise from a presumptive precursor cell of hormonally responsive stroma, and capable of multidirectional mesenchymal differentiation, including fibroblastic, myofibroblastic and lipomatous differentiation. In this regard, lipomatous AMFB should be interpreted as a bimorphic tumour that reflects the plasticity of precursor cells to undergo a dual fibroblastic/myofibroblastic and lipomatous differentiation, with the former component overwhelming the latter. As most cases of AMFB may contain a small component of adipose tissue [5 6], we speculate that there is a continuous spectrum of lipomatous differentiation in this tumour, ranging from a few islands to a large amount of adipose tissue.

As lipomatous AMFB contains a prominent fatty component, the main differential diagnosis includes spindle cell lipoma, lipoma-like well-differentiated liposarcoma and spindle cell liposarcoma. Unlike lipomatous AMFB, spindle cell lipoma contains neither epithelioid cells nor abundant capillary-like blood vessels [33]. In addition, spindle cell lipoma lacks the tendency of neoplastic cells to aggregate around blood vessels and is usually a CD34-positive and desmin-negative tumour [33]. Lipoma-like well-differentiated liposarcoma contains adipocytes with hyperchromatic and atypical nuclei, as well as atypical stromal cells in the fibrous septa intersecting the adipocytic component [34]. All these features are lacking in lipomatous AMFB. In addition, the detection of lipoblasts, which however are not always present, argues against a diagnosis of AMFB. Spindle cell liposarcoma is a distinctive, relatively rare, clinico-pathological entity usually occurring in the deep and superficial soft tissues of shoulder girdle, upper limbs, groin, buttock and thigh [35 36]. Notably, the spindle cell component of spindle cell liposarcoma is fibroblastic/myofibroblastic in nature, being variably stained with desmin and CD34 [36]. However, it is distinguishable from lipomatous AMFB for the presence, even if only focally, of lipoblasts with cytological features that closely resemble the differentiation of human embryonic fat [36]. Although lipoblast-like cells can be encountered in the areas of lipomatous AMFB in which spindled/epithelioid cells closely intermingle with adipocytes, however, correct interpretation of the context, namely identification of areas with the features of conventional AMFB, is crucial for pathologists to avoid misdiagnosis of malignancy. Fibromatosis is a locally-recurring lesion that rarely occurs in the vulva [37]. Unlike lipomatous AMFB, fibromatosis exhibits infiltrating borders entrapping fat, and is composed of long sweeping cellular fascicles embedded in a variable fibrous stroma [38-40]. The three different morphological phases, namely proliferative, involutional and residual, typically coexisting concurrently in the same case of fibromatosis [38-40], are lacking in lipomatous AMFB. Immunohistochemically, fibromatosis expresses β-catenin, α-smooth muscle actin, while desmin is usually absent or only focally expressed [38-41].

In conclusion, the present case is unusual in that it was difficult to recognize as AMFB, owing to the large amount of its lipomatous component. Awareness by pathologist of the possibility that vulvo-vaginal AMFB may exhibit a dominant fatty component is crucial to avoid confusion with other benign or malignant bland-looking spindle cell tumours containing or infiltrating fat.

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