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Uterine Müllerian adenosarcoma with histiocytic (xanthomatous) mesenchymal component

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Summary. We present an endometrial Müllerian adenosarcoma in which the sarcomatous component showed prominent nests of foamy cells that accounted for 50% of the neoplastic mesenchyma. Such foamy cells showed occasional cytological atypias and immunohistochemical features of histiocytic (macrophagic differentiation in the absence of changes that could substantiate the presence of an inflammatory infiltration of foamy histiocytes. These facts suggest histiocytic differentiation from neoplastic mesenchymal cells. Such differentiation has been reported in association with malignant mixed mesodermal tumor, but not in Müllerian adenosarcoma.

Key words: Adenosarcoma, Histiocytic differentiation, Uterus, Mixed müllerian tumor

Introduction

Müllerian adenosarcomas of the uterus are uncommon neoplasms characterized by an admixture of a benign glandular component and a sarcomatous mesenchymal component (Clement and Scully, 1974). They are considered a low grade variant of malignant mixed Müllerian tumors. Since their original description, the presence of isolated clusters of foamy cells in their mesenchymal portion, has occasionally been quoted such cells generally close to foci of necrosis and/or haemorrhage, and interpreted as histiocytes which form part of an inflammatory infiltration (Clement and Scully, 1974, 1978; Gloor, 1979). Only in 9 cases did such «foam cells» form a significant part of the neoplastic mesenchyma (Czernobilsky et al., 1983; Hirschfield et al., 1986; Clement and Scully, 1979), interpreted as «estrogenic» stromal cells (Czernobilsky et al., 1983), or as a sex-cord like differentiation of the stroma with the formation of nests of lipid-rich cells (Hirschfield et al., 1986; Clement and Scully, 1989), without any of these interpretations being reliably corroborated by means of electron microscopy or immunohistochemistry.

We here submit an endometrial Müllerian adenosarcoma in which the sarcomatous component showed prominent nests of fomay cells that accounted for 50% of the neoplastic mesenchyma. Such foamy cells showed occasional cytologic atypias and immunohistochemical features of histiocytic (macrophagic) differentiation. Additionally there was an absence of an inflammatory infiltration of foamy histiocytes. These facts suggest histiocytic differentiation from noeplastic mesenchymal cells. Such a differentiation has not been previously described in the literature about Müllerian adenosarcoma.

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Materials and methods

Case report

A 56-year-old white, multiparous woman, who underwent menopause at the age of 49, consulted her gynecologist in November 1971, with complaints of small, intermittent metrorrhages. Her past medical history revealed diabetes mellitus and hypertension. Small amounts of material were expelled through the vagina, consisting histologically of hematic elements and a piece of endometrium of a proliferative appearance. With a clinical diagnosis of endometrial adenocarcinoma, a scrape was carried out 12 days later, with the extraction of abundant material diagnosed as «polyps of the uterine body with inflammatory stroma», subsequently re-examined and defined as an endometrial Müllerian adenosarcoma. The patient continued to bleed sporadically for 3 years, when a uterine cervical biopsy was carried out, diagnosed in another hospital as «cervical fibrosarcoma». With such a diagnosis, in

November 1974 total hysterectomy, bilateral salpingo-oophorectomy, and resection of vaginal cuff were performed. Six years after this last operation the patient was well and showed no signs of relapse.

The material studied was fixed in alcohol at 50% (scrape) or formol at 10% (surgical specimen), and processed in the routine way, yielding from 2 (scrape) to 20 blocks of tissue. The sections of these blocks were stained with haematoxylin-eosin, Best's carmine (scrape), and, in selected cuts by the ABC method (Hsu et al., 1981), using antisera diluted 1:400 against alpha-1-antitrypsin (AAT) (Dako), alpha-1-antichimotrypsin (AACT) (Dako), lysozyme (Dako), concanavaline A (Con A) (Vector), and 3.3'-diaminobenzidine as the chromagen. As a positive control we used cultivated human histiocytes (Santamaría et al., 1988), while as a negative control the first antibody was replaced by a buffer (Tris 0.05 M) in a twin cut in each block.

Results

Macroscopy

The uterus measured 8 x 7 x 5 cm. On incision an endometrial polyp protruding through the cervical os was observed. The polyp, measuring 7.5 x 4.5 cm, was sessile, friable, and of a yellowish colour, with some areas whitish and others cystic. It had invaded and destroyed both the myometrium and the cervical wall, leaving only 5 mm of muscle wall unaffected.

The vaginal cuff measured 2 cm at maximum diameter and revealed a hard nodule of 1 cm maximum diameter.

The tubes did not present any significant macroscopic irregularity.

The ovaries were small, measuring 1.5 x 1 x 0.5 cm and 1.2 x 0.5 x 0.4 cm respectively, and of senile appearance.

Conventional microscopy

The scrape carried out in 1971 presented multiple fragments of tissue of papillary or lobulate appearance covered by a typical endometrial epithelium, and consisting of glandular formations of varying size and shape, with an epithelium similar to the previous one. The glands were scattered in a mesenchyma of an endometrial stromal sarcoma type, which furthermore revealed a great quantity of cells having an abundant, clear and foamy cytoplasm. The sarcomatous

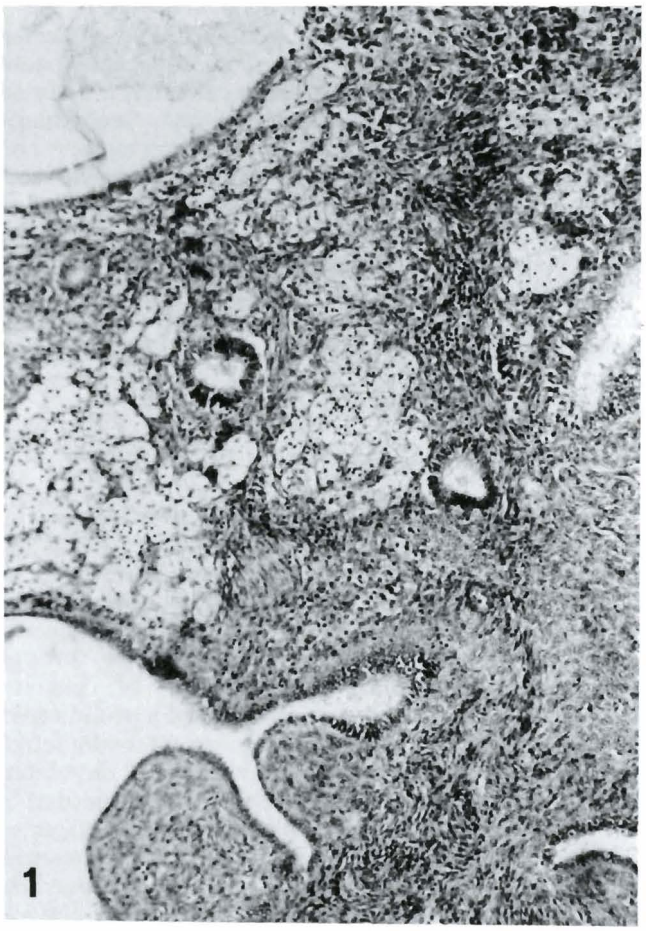

Fig. 1. Panoramic view of adenosarcoma with foci of histiocytic differentiation. H.E. × 100

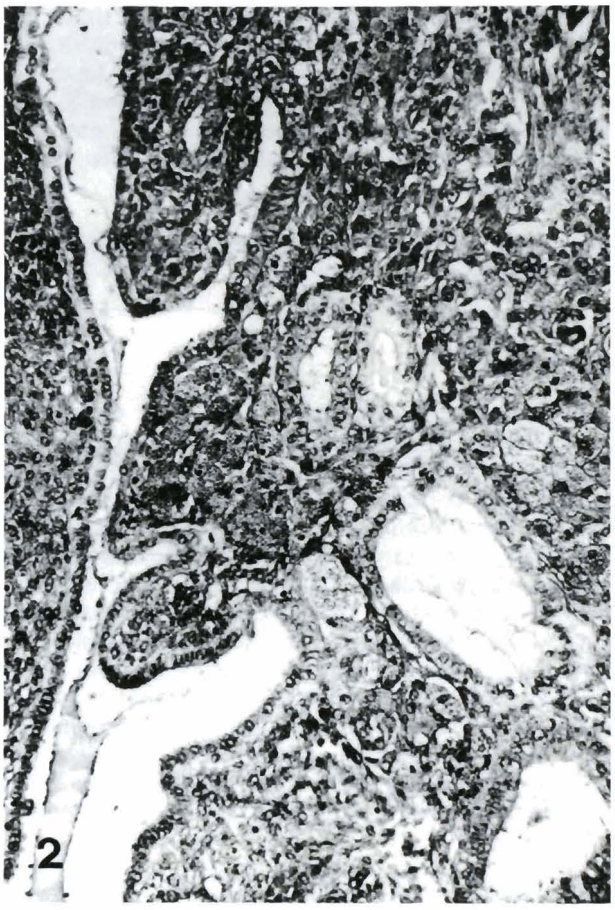

Fig. 2. Massive histiocytic differentiation which shows strong immunoreactivity to AAT/ ABC-AAT. × 250

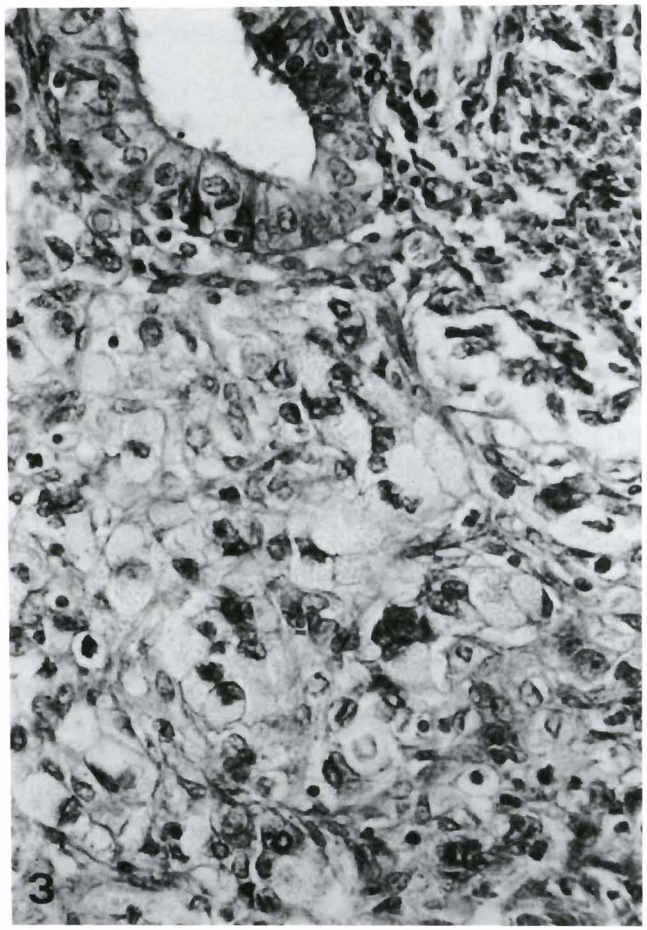

Fig. 3. High-power view of pleomorphism of histiocytic cells. H.E. × 400

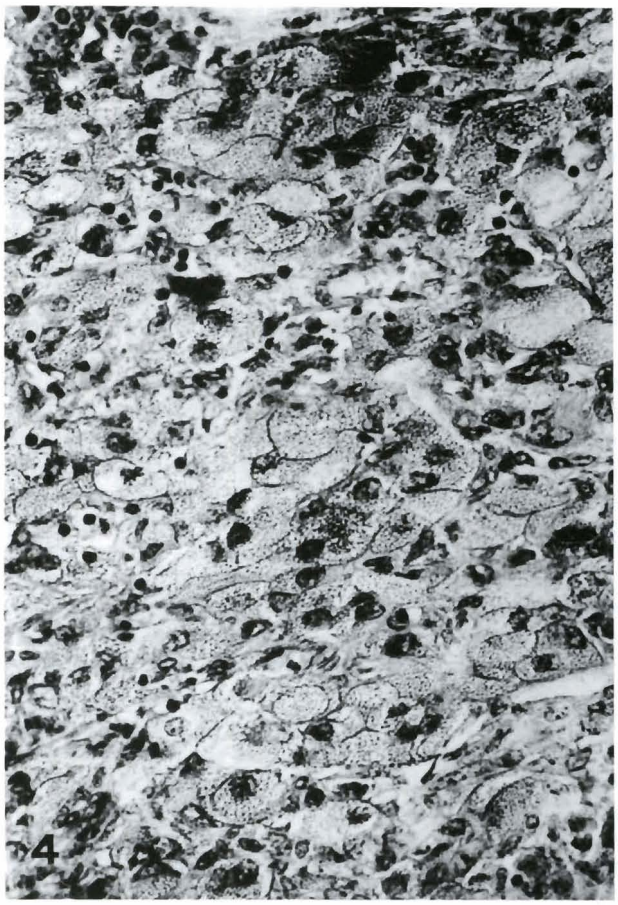

Fig. 4. Histiocytic component with extensive immunoreactivity to lysozyme. ABC-lysozyme. × 400

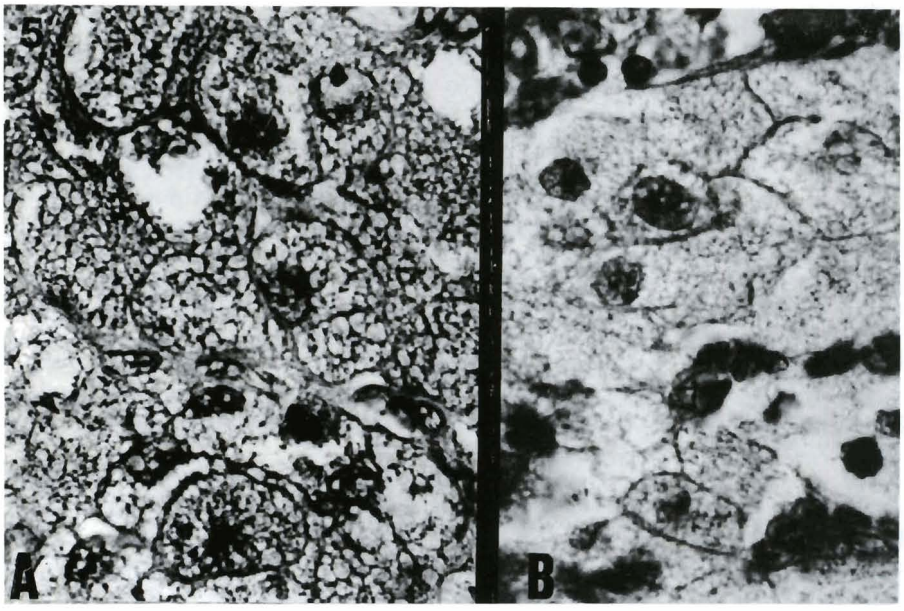

Fig. 5. High-power view of the evident cytoplasmic immunoreactivity of foam cells to AAT (A) and Con A (B). ABC-AAT (A). ABC-Con A (B). × 1,000

component presented a greater cellular density around the glandular formations, taking the form of a typical periglandular cuff, with 12 mitotic figures per 10 high power fields (MFs/10 HPFs).

The endometrial polyp found in the histerectomy specimen of 1974 was made up of an intimate admixture of a benign epithelial component and a sarcomatous mesenchymal component, which had penetrated deeply into the myometrium. The epithelial component was formed of glands of varying size and shape, generally cystic, irregularly distributed over the mesenchyma and lined by a typical proliferative endometrial epithelium (Fig. 1) with abundant stratified squamous metaplasia, histologically benign. The mesenchyma was the predominant component, arranged around the glands, forming a typical periglandular condensation, and casting thick leaflike projections towards both the gland lumina (Fig. 2), thus converting the latter into virtual cavities, and the outer surface of the tumor, thus giving it a papillary appearance. 50% of the mesenchymal component resembled a low-grade endometrial stromal sarcoma, composed of a cellular proliferation of endometrial stromal-type cells growing in a diffuse or nodular periglandular pattern, with only mild degrees of nuclear pleomorphism, and a count of 14 MFs/10 HPFs. The remaining 50% of the mesenchyma consisted of nests of benign cells of abundant clear, foamy cytoplasm (Fig. 1), except for some areas, where such cells showed obvious cytological atypias (Fig. 3), with large, hyperchromatic nuclei and occasional prominent nucleoli. Both types of mesenchyma were found to be closely intermingled.

The vaginal nodule presented a similar histopathological picture.

The ovaries showed hyperthecosis.

Immunohistochemistry

The cytoplasm of the «foam cells» showed a strong immunoreactivity to the lysozyme (Fig. 4), AAT (Fig. 5A), and Con A (Fig. 5B), while there was only a moderate response to the AACT. The cytoplasm of the endometrial stromal sarcoma cells presented a moderate immunoreactivity to the AAT.

Discussion

«Foam cells» have occasionally been described in uterine (Clement and Scully, 1974; Gloor, 1979; Czernobilsky et al., 1983; Hirschfield et al., 1986) and extrauterine (Clement and Scully, 1978) Müllerian adenosarcomas, usually in the form of small nests close to necrotic or haemorrhagic areas, and considered in such cases to be cells which form part of an inflammatory infiltration (Clement and Scully, 1974, 1978; Gloor, 1979).

However, in all the literature on the subject, there are only 9 reported adenosarcomas similar to ours, in which the foam cells formed a high percentage of the mesenchymal component of the neoplasia, occurring in multifocal form and closely intermingled with the endometrial stromal sarcoma.

Czernobilski et al. (1983) observed such cells in 3 of their 11 uterine adenosarcomas, classifying them as «estrogenic» endometrial stromal cells, but did not offer any proof to corroborate such a classification.

Hirschfield et al. (1986) studied the foam cells in a cervical adenosarcoma which also presented epithelioid differentiation of the mesenchymal component. Based on the tissues taken from paraffin blocks, they carried out an ultrastructural study of the tumor but observed no more than the presence of «lipidic vacuoles» in the cytoplasm of the foam cells, since any remaining ultrastructural features had been distorted by previous paraffin embedding. Nonetheless, the observation of an endometrial stromal sarcoma with epithelioid differentiation and lipid-rich foam cells, reminded them of the two cases of Sertoli cell tumors with lipid storage which Clement and Scully (1976) described in a series of 14 «uterine tumors resembling ovarian sex-cord tumors».

Clement and Scully (1989) have recently published a series of 8 uterine adenosarcomas with ovarian sex-cord like elements. In 5 of these cases, the presence of clear cells with foamy cytoplasm was a prominent feature of the tumoral mesenchyma. Nevertheless, as in the case described by Hirschfield et al. (1984), such cells were observed scattered in a low-grade endometrial stromal sarcoma with epithelioid differentiation, so that they were also interpreted as an ovarian sex-cord-like differentiation. Yet such an interpretation was based entirely on studies carried out by conventional microscopy, and lacked any subsequent ultrastructural or immunohistochemical confirmation.

In our case, the foam cells can only be of a neoplastic nature, because of their massive presence throughout the neoplasia, with no sign of accompanying foci of inflammation, necrosis, recent haemorrhage or quantities of haemosiderine which might have accounted for such a presence. Furthermore, these cells were found in both the first scrape and the polyp discovered 3 years after, as well as in the invading portion of the tumor and in the vaginal nodule. However, our case, in contrast to uterine adenosarcomas with sex-cord-like elements described by Hirschfield et al. (1984) and Clement and Scully (1989), did not present epitheliod differentiation from neoplastic mesenchyma. Finally, on the one hand, the foam cells presented immunoreactivity to the histiocytic markers AAT, lysozyme, Con A, and AACT (Hibi et al., 1988), while the endometrial stromal sarcoma cells presented only a moderate immunoreactivity to AAT on the other. Such findings surely offer strong evidence of the histiocytic derivation of such cells from the neoplastic mesenchyma.

Histiocytic differentiation has been suspected (Barwick and LiVolsi, 1979), and immunohistochemically suggested (Auerbach et al., 1988) in uterine malignant mixed Müllerian tumors, but has not been mentioned in Müllerian adenosarcomas.

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