Pitfalls in the diagnosis of endometriosis: a condition characterized by a plethora of unusual histological features

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Abstract
The histological diagnosis of endometriosis is usually straightforward. However, for a large number of reasons, there may be diagnostic difficulties. These difficulties may be related to both unusual morphological features in endometriosis and the occurrence of endometriosis at unusual sites. In this review, 10 problematic areas in the histological diagnosis of endometriosis are discussed.

Keywords diagnosis; endometriosis; female genital tract

Introduction

Endometriosis, defined as the presence of endometrial tissue in locations outside the uterine corpus, is an extremely common condition, especially in women in the reproductive years.[1] The most common locations are the ovary, fallopian tube, pouch of Douglas and pelvic peritoneum but a variety of sites may be affected. In most cases, the histological diagnosis is straightforward with endometrioid type glands and stroma often associated with pigment-laden macrophages. However, in a not insignificant number of cases, problems may occur in establishing a diagnosis and this is obviously important from a therapeutic point of view. We discuss 10 problematic areas related to the diagnosis of endometriosis. In some of the scenarios discussed, the identification of the secondary changes described is a clue to the presence of underlying endometriosis and further sampling may assist the pathologist by revealing more diagnostic foci.[2] In other cases, the presence of endometriosis may explain unusual and worrisome morphological findings, an example being florid reactive mesothelial proliferations which may occur in association with endometriosis. In this review, we do not discuss in detail malignant transformation of endometriosis but note that there is a firm association between endometriosis and the development of certain Mullerian neoplasms, especially endometrioid and clear cell carcinoma and Mullerian type mucinous borderline tumours. However, neoplastic transformation of endometriosis is uncommon and it would be wrong to consider this as a premalignant disease; rather endometriosis can be considered as a disease with the potential to develop malignancy in a small number of cases.

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Stromal endometriosis

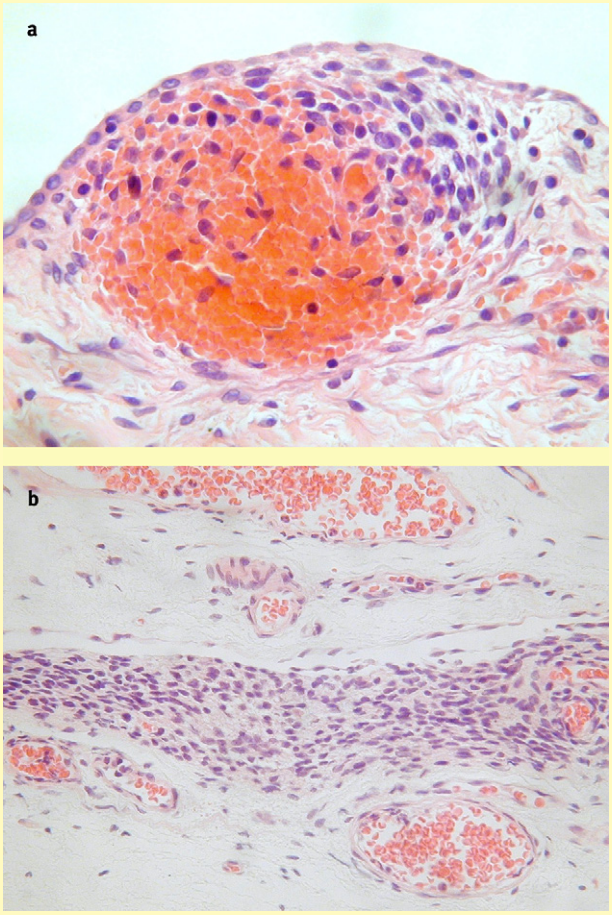
In our opinion, this is one of the commonest pitfalls associated with the diagnosis of endometriosis. Stromal endometriosis is characterized by the presence of endometrioid type stroma in the absence of glands and has been described in the peritoneum, cervix and ovary.[3–5] We have also seen this occasionally on the omentum and at other sites. Stromal endometriosis is relatively common, one study identifying it in 44.9% of peritoneal biopsies containing endometriosis, usually, but not always, in association with foci of typical endometriosis with both glands and stroma.[3] Peritoneal stromal endometriosis typically takes the form of small well-circumscribed nodules or plaques, so-called micronodular stromal endometriosis.[3,4] It is usually seen immediately beneath the mesothelial lining (or on the surface unassociated with mesothelium, presumably due to denudation of this) and may result in a small nodular protrusion on the surface of the peritoneum. Given the intimate association with mesothelium, it has been speculated that peritoneal stromal endometriosis may arise from mesothelial or submesothelial cells as a metaplastic phenomenon.[3]

The nodules or plaques of peritoneal stromal endometriosis are composed of cells with round to ovoid nuclei and usually scanty indiscernible cytoplasm (Figure 1). Typically, many small vascular channels are present around which stromal cells often appear to whorl.[3,4] In many cases, erythrocytes engorge the blood vessels or extravasate among the endometrial stromal cells. There may be stromal haemosiderin pigment and a mixed inflammatory infiltrate with lymphocytes, plasma cells and histiocytes. Sometimes there is associated mesothelial hyperplasia. If the patient has been taking exogenous hormones, decidualization of the stromal cells may occur. Stromal endometriosis may also be seen in the ovarian cortex, sometimes in association with typical endometriosis. It has been speculated that ovarian stromal endometriosis is secondary to metaplasia of the ovarian stromal cells.

It is our experience that stromal endometriosis is frequently not recognized and it may be misinterpreted as lymphoid cells or stromal cells of non-endometrioid type.

Immunohistochemistry for CD10 and oestrogen receptor (ER) may be helpful in confirming the endometrioid nature of the stromal cells,[6,7] although CD10 is a rather non-specific marker and other stromal cells in the female genital tract may be ER positive.

We have encountered occasional cases of stromal endometriosis which have been misdiagnosed as or strongly suspected to be Kaposi's sarcoma. Both stromal endometriosis and Kaposi's sarcoma are typically composed of cellular nodules of short spindle shaped cells intimately admixed with extravasated red blood cells and scattered inflammatory cells. Kaposi's sarcoma



Stromal endometriosis composed of nodules **a** or plaques **b** of endometrial stromal cells. In **a**, there is engorgement of small vessels and extravasation of erythrocytes.

Figure 1

typically has a more fasicular arrangement of cells, is more mitotically active than stromal endometriosis and may contain hyaline globules. As stated, stromal endometriosis stains positively with CD10 and ER while Kaposi's sarcoma is positive with Human Herpes Virus 8.[8]

Endometrial stromal sarcoma might also enter into the differential diagnosis and there is the potential for misinterpretation of endometrial stromal sarcoma as stromal endometriosis and vice versa. Endometrial stromal sarcoma primary in the uterus can spread to extrauterine sites and take the form of small microscopic nodules which closely resemble stromal endometriosis. Primary endometrial stromal sarcoma may also arise at extrauterine sites.[9] An awareness of the existence of stromal endometriosis, the presence of foci of typical endometriosis with glands and stroma, the absence of a tumour mass and of a history of uterine endometrial stromal sarcoma assists in diagnosing stromal endometriosis. Although small microscopic nodules identical to those of stromal endometriosis are a feature of some endometrial stromal sarcomas, there is usually an obvious tumour mass also. A past history of endometrial stromal sarcoma (or even a remote history of a uterine mesenchymal neoplasm), an obvious infiltrative pattern and vascular invasion are helpful findings in diagnosing an endometrial stromal sarcoma. Since extrauterine endometrial stromal sarcomas may arise in endometriosis, it can be difficult in some cases to determine whether small microscopic nodules of stromal cells represent tumour or pre-existing endometriosis. A further confounding factor is that endometrial stromal sarcomas may occasionally form endometrioid glands as an integral component of the neoplasm (discussed later).

Stromal metaplasias and other alterations in the stromal component of endometriosis

The stromal component of endometriosis may undergo a number of morphological alterations which if not recognized may result in underdiagnosis or in misinterpretation as an alternative pathological process. These are discussed in the next paragraphs.

Stromal elastosis is manifested by focal or total replacement of the endometrial stromal cells by fibrillary, pink to blue-grey elastic tissue which can be highlighted with an elastic stain.[2,4] It has been speculated that the elastic tissue may be of vascular origin.[4] Stromal elastosis is thought to be more common in endometriosis involving the smooth muscle of hollow viscera such as the bladder and intestine.[2,4] If there is extensive replacement of endometrial stromal cells, this may result in underdiagnosis. The diagnosis is confirmed by the presence, at least focally, of endometrial stroma and glands and these may be revealed by additional sampling. Sometimes, small nodules composed entirely of elastic tissue are present without endometriotic glands or stroma.

Smooth muscle metaplasia may occur in the stromal component of endometriosis. In one study, it was identified in 18% of cases of ovarian endometriosis.[10] Smooth muscle metaplasia can occur as isolated foci within the stroma or be extensive and is particularly common in ovarian endometriotic cysts. When extensive, it may result in the formation of a so-called uterus-like mass with endometrioid glands and stroma surrounded by a thick layer of smooth muscle.[11,12] Other examples of uterus-like masses may represent a congenital Mullerian duct anomaly, especially if associated with genitourinary malformations. Smooth muscle metaplasia usually poses no diagnostic problems unless it is so extensive as to result in total replacement of the endometrial stromal cells. It has been speculated that the smooth muscle may arise from metaplasia of endometrial stromal cells or of ovarian stromal cells.[10] Smooth muscle metaplasia should be distinguished from endometriosis involving indigenous smooth muscle, for example in pelvic ligaments and in the wall of the bowel or bladder. In such cases, the presence of endometriosis is often associated with hypertrophy of the surrounding smooth muscle.

The stromal component of endometriosis may undergo myxoid change, a finding that has been reported in endometriosis of the peritoneum, ovary and groin and in caesarean section scars.[13–15] Although usually minor in degree and resulting in little in the way of diagnostic difficulty, when the myxoid change is extensive it may result in consideration of pseudomyxoma peritonei, mucinous adenocarcinoma, adenosarcoma or a myxoid mesenchymal neoplasm.[13–15] In occasional cases, there may