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ORIGINAL PAPER

Pelvic Endometriosis is Rarely Associated with Ovarian Borderline Tumours, Cytologic and Architectural Atypia: A Clinicopathologic Study

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Abstract Endometriotic foci, especially ovarian ones, with epithelial cytologic atypia may be precursors of cancer. This study presents an overview of the atypical cytological and histopathological findings associated with endometriosis. Six cases of endometriosis, with atypical histological and cytological changes, were obtained from the archives of the Department of Pathology at Cleveland Clinic Foundation between year 2000 and 2003. The size of the base from which these cases were drawn was 2000 cases of endometriosis. The age range of the patients was from 29 to 52 years. The clinical presentations included infertility (three cases), pelvic pain (three cases), adenexal and pelvic masses (four cases). Stage IV endometriosis with extensive pelvic involvement was found in two patients. Intraoperatively, the endometriotic lesions involved the ovaries (all cases); Cul de sac (four cases); urinary bladder (two cases); sigmoid colon, hemidiaphragms, and uterine vessels (one case each). The endometriotic lesions were associated with uterine leiomyomas (two patients) and adenocarcinoma of the vagina (one patient). Histologically, in addition to endometrial type glands and stroma, usually found in endometriosis, we observed both cytologic and pattern atypism involving the epithelium in all cases. The features of cytologic atypia included nuclear stratification, hyperchromatism, and pleomorphism. The features of pattern atypia were complex glandular pattern, papillary formations and psammoma bodies. In two cases, these features were sufficient for diagnosis of borderline Mullerian seromucinous tumours. One patient had recurred with metastatic adenocarcinoma of the vault. She died later from disseminated metastatic disease. There is a rare association between pelvic endometriosis and borderline ovarian tumours (three cases), cytologic and pattern atypia (two cases); mesothelial hyperplasia, endosalpingiosis (two cases), and metastasis (one case). Cytologic and pattern atypia can develop in the endometriotic foci and therefore, these lesions should be thoroughly scrutinized for presence of these changes. Our findings recommend surgical excision of these foci rather than their simple cauterization.

Keywords Endometriosis · Cytologic atypia · Pattern atypia

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Introduction

Endometriosis is a common disease characterised by the presence of endometrial glands and stroma outside the uterus.

Its morphologic appearance is quite variable and usually the visual opinion at laparoscopy is not confirmed histologically [18]. Although endometriosis is a benign process, it shares some morphological and molecular features with neoplasms [15, 35]. Endometriosis is characterised by altered morphology, unrestrained growth, local invasion and distant spread, and development of malignancies morphologically identical to those arising in the eutopic endometrium [40]. Endometriosis, like cancer, is characterized by development of new blood vessels (angiogenesis) and a decrease in the number of cells undergoing apoptosis [35]. Endometriosis is therefore considered to be a possible precancerous disease. A frequency of about 1% malignant transformation has been reported in the endometriotic lesions; with 80% in the ovary and 20% in extragonadal sites being affected [38]. Pathologically, malignant transformation of endometriosis to clear cell carcinoma or endometriotic carcinoma of the ovary, via the step of atypical endometriosis was reported [30, 40].

The development of endometriosis is associated with activation of oncogenes (proto-oncogenes c-kit and K-ras) [39] and loss of tumour suppressor genes (PTEN; Phosphatase and tensin homolog deleted on chromosome Ten). Mutations in the genes that encode for metabolic and detoxification enzymes, such as GALT and GSTM, have been implicated in the pathogenesis of endometriosis and in the progression to carcinoma of the ovary. PTEN, a tumour suppressor commonly mutated (50%) in endometrial carcinoma, is found mutated in endometriod carcinoma of the ovary, but not in other forms of ovarian cancer [35, 37]. Sekizawa et al. examined K- ras mutations in the regions of normal endometriosis, atypical endometriosis, and clear cell carcinoma. They found that K- ras mutations are associated with malignant transformation of clear cell carcinoma [30]. Alterations of the tumour suppressor p53 gene and its allelic loss were identified not only in endometrial and ovarian carcinomas but also in the endometriotic tissue [1]. An increased number of Nucleolar Organiser Regions, indicative of malignant transformation, was observed in atypical endometriosis [17]. A frequent allelic loss on chromosomes 6q and 10q and chromosomal aberrations are identified in atypical ovarian endometriosis [13]. Moreover, genetic instability as evidence by alteration of the short tandem repeat (microsatellites) has been reported in atypical endometriosis [2]. Microsatellite instability may inactivate the PTEN tumour suppressor gene leading to the development of ovarian adenocarcinomas in a background of endometriosis [2].

Endometriotic cysts (endometriomas) commonly involve the ovaries. They have a variable morphologic appearance and may partially or completely replace the normal ovarian tissue [16]. About 0.7%-1% of the ovarian epithelial tumours arises from both ovarian and extra-ovarian endometriotic foci [26, 35]. Although any tumour of Mullerian origin can occur, most of them are adenocarcinomas. The typical patients are either nulliparous or premenopausal with history of pelvic irradiation and or intake of exogenous estrogens [3, 6, 36]. These tumours include clear-cell, serous, endometriod, mucinous, and squamous cell carcinomas [14, 20, 30, 40].

In this investigation, we report the spectrum of both cytologic and pattern atypia associated with pelvic endometriosis.

Materials and Methods

The cases were obtained from the archives of Cleveland Clinic foundation, Department of Pathology. These cases were seen during the years 2000–2003. Initially search of the Pathology database was performed and 2000 cases of endometriosis were examined. All tissues were routinely processed, paraffin embedded and sections were stained with haematoxylin and eosin. All available pathology slides were examined and reviewed by certified pathologists. Only six cases (6/2,000, 0.003%) had cytologic and histologic atypia and therefore were included in this study. Other cases with endometriosis but lacking evidence of atypia or associated tumors were excluded.

Results

The age range of the patients was from 29–52 years. In addition to the endometrial type glands and stroma, usually found in endometriosis, we observed both cytologic and pattern atypia involving the epithelium in six cases. The features of cytologic atypia included nuclear stratification, hyperchromatism, and atypia. The features of pattern atypia included complex pattern, papillary epithelial structures, and psammoma bodies (Table 1).

Case No. 1 A 33-year-old white female presented with a history of primary infertility. Intraoperatively, stage IV endometriosis was detected. The Cul-de sac fluid specimen contained an innumerable numbers of histiocytes. Some mesothelial cells and rare psammoma bodies were identified (Fig. 1a). These bodies were lying free and some had an attenuated envelope of epithelial cells. Additionally, the specimen contained rare aggregates of epithelial cells with relatively large nuclei and mild nuclear pleomorphism. Subsequently, surgical pathology specimen was compared to the cytology specimen and the atypical cytology (Fig. 1b) was interpreted as benign reactive changes affecting endometriosis. Endometriosis involving the bladder and peritoneum with H&E stain was shown in Fig. 1c.

Case No. 2 A 29-year-old white female presented with a history of chronic pelvic pain and a pelvic mass. Intra-

Table 1 Clinicopathologic findings associated with endometriosis

Cases	Age	Clinical findings	Intraoperative findings	Histological findings	Diagnosis
Case no. 1	30	Gravida 0, para 0 Primary infertility	Stage IV endometriosis with bilateral involvement of the ovarian fossae, cul-de-sac, anterior bladder flap and bilateral endometriomas	Endometriotic tissue with simple papillae, reactive mesothelial cells, serous epithelial cells with mild atypia and psammoma bodies	Endometriosis with mild pattern and cytologic atypia
Case no. 2	20	Gravida 1, para 0 Chronic pelvic pain Pelvic mass	Stage IV endometriosis, bilateral endometriomas, and disseminated intrapelvic endometriosis with involvement of the anterior Cul-de-sac, bowel, uterine vessels, hemidiaphragms, and the abdominal wall	Endometriotic tissue, with ovarian endometriotic cysts, lined by stratified, mildly atypical serous and mucinous epithelial cells and psammoma bodies	Endometriosis; Mullerian, seromucinous tumour, low malignant potential
Case no. 3	40	Gravida 0, para 0 Infertility Adnexal mass	Left ovary was adherent both to the pelvic sidewall and to the sigmoid colon, bulky uterus with a large Leiomyoma	Endometriotic tissue featuring mild pattern atypia, with adhesions involving ovarian surface, and tubes	Endometriosis, mild pattern atypia
Case no. 4	30	Chronic pelvic pain History of endometriosis	Bulky uterus, fibrotic peritoneum and a small endometriotic nodule on the bladder peritoneum. The posterior Cul de sac and the ovarian fossa were bilaterally scarred	Endometriotic tissue involving pelvic sidewall and bladder peritoneum Ovarian surface had papillae lined by serous cells with minimal atypia	Endometriosis associated with both cytologic and pattern atypia
Case no. 5	52	Gravida 0, vaginal mass, peritoneal implants, destroying pubic bone Death shortly from a disseminated disease	Endometriosis. Uterine leiomyoma, right ovarian cyst containing some debris; and two large left ovarian cysts in the Cul de sac filled with fluid	Endometriotic tissue. Seromucinous cystadenoma with epithelial atypia and endometriotic cyst Adenocarcinoma of the vagina	Mullerian seromucinous tumour (low malignant potential)
Case no. 6	30	Gravida 0 History of infertility Left adnexal mass	Pelvic endometriosis and chocolate cysts.	Endometriosis, left ovarian cyst lined by atypical epithelium with mild stratification, and focal papillae	Endometriosis, Mullerian mucious tumour, low malignant potential

operatively, stage IV endometriosis was detected. Laparoscopic excision of the endometriotic foci, adhesiolysis, bilateral ovarian cystectomy and ureterolysis were performed. Histological examination revealed an endometrial tissue lining the ovarian endometriotic cyst (Fig. 2a); papillae and cyst wall lined by stratified, mildly atypical serous and mucinous epithelial cells (Fig. 2b,c). These cytoarchitectural features are characteristic of seromucinous borderline tumours (Mullerian seromucinous borderline tumours of mixed serous and mucinous type). Biopsy specimen from multiple other sites, including the left ovary, revealed the presence of endometriosis but absence of any histologic atypism.

Case No. 3 A 44-year-old Caucasian female presented with adnexal mass and longstanding history of infertility. Intraoperatively, the left ovary was adherent to the pelvic sidewall and the sigmoid colon. Laparoscopic left salpingoophorectomy; adhesiolysis and myomectomy were performed. An endometrial biopsy was also performed. Histologically, the cyst was a corpus luteum cyst. The ovarian surface had fibrous tissue adhesions associated with endometriosis (Fig. 3). Additionally, the fallopian tubal serosal and muscular coats had endometriotic foci with complex hyperplasia but without cytologic atypia. The endometrium showed proliferative changes.

Case No. 4 A 38-year-old white female (single) presented with chronic pelvic pain. Intraoperatively, the uterus was bulky with normal contour; no adnexal masses were detected. Laparoscopic adhesiolysis and resection of the fibrotic peritoneum were performed. Histologically, pelvic sidewall and bladder peritoneum had atypical endometriosis (i.e. both cytologic and pattern atypism). The ovarian surface had fibrous adhesions and a serous epithelial cell proliferation characterised by simple papillae lined by

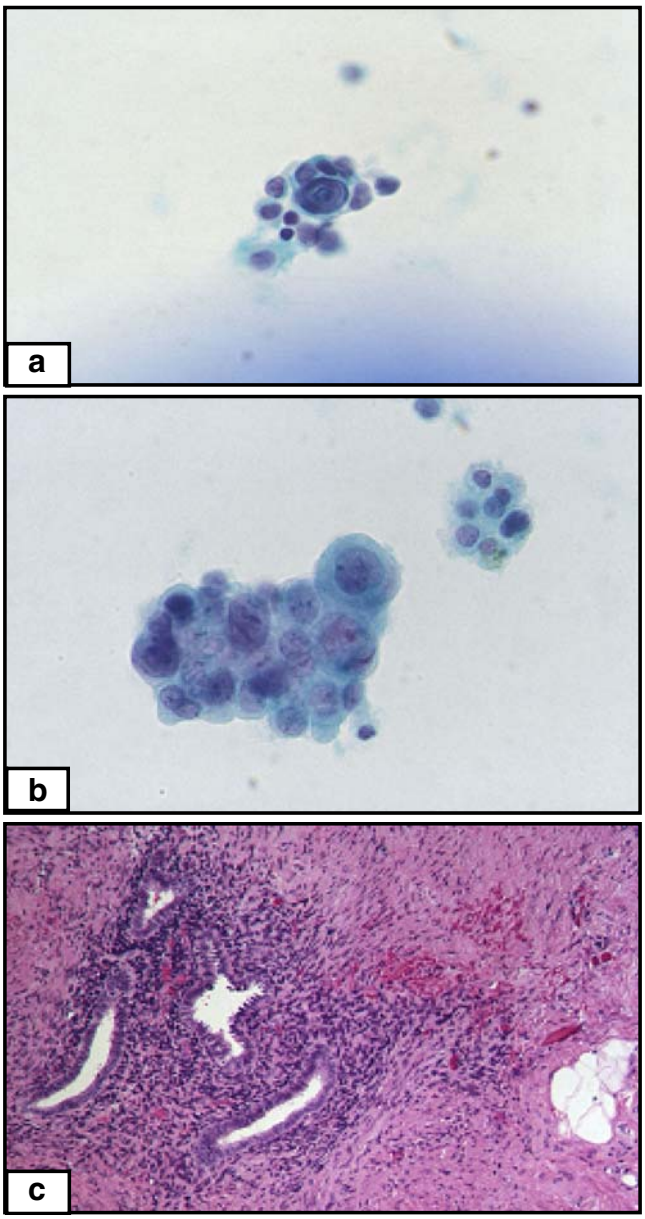

Fig. 1 **a** benign epithelial cells surrounding a psammoma body in the Cul de sac fluid cytology specimen with Papanicolaou stain, Magnification ×163; **b** Atypical epithelial cells in the Cul de sac fluid specimen with Papanicolaou stain, Magnification ×163; and **c** Endometriosis involving the bladder and the peritoneum with H&E stain, Magnification ×39.9

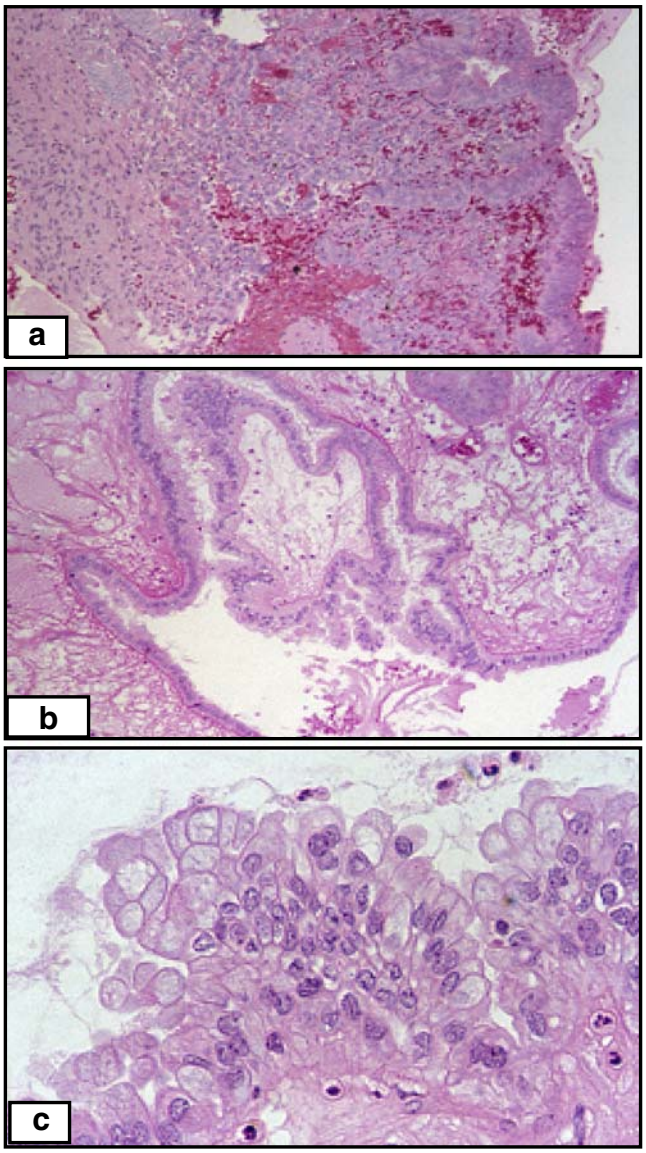

Fig. 2 **a** Endometrial tissue lining the ovarian endometriotic cyst with H&E stain, Magnification ×39.9; **b** Papillae of the seromucinous borderline tumour (Mullerian borderline tumour of mixed serous and mucinous type) arising within the endometriotic cyst with H&E stain, Magnification ×39.9.; and **c** Stratified and atypical mucinous epithelial cells of the seromucinous borderline tumour H&E stain, Magnification ×39.9

serous cells with minimal atypia (Fig. 4a). Close up examination revealed simple epithelium with bland nuclear features. Overall, the histological features were interpreted as not sufficient for the diagnosis of borderline tumour (Fig. 4a) and therefore signed out as endometriosis with complex pattern.

Case No 5 A 52-year-old white female with long standing history of endometriosis came for routine examination. Clinical examination showed a uterine leiomyoma, right ovarian cyst and two large left ovarian cysts in the Cul de sac filled with fluid. Exploratory laparotomy, total abdominal hysterectomy and bilateral salpingoophorectomy with pelvic washing were performed. Gross examination of the left oophorectomy specimen revealed collapsed cyst (8× 7 cm), with its external surface lacking any exophytic papillary growth. Its inner lining had granular tan-red slightly raised soft tissue. Examination of the right ovary revealed collapsed cyst (5×5 cm), with smooth, glistening

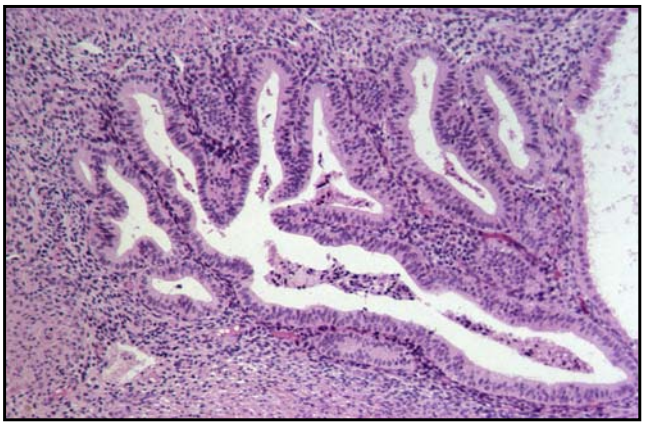

Fig. 3 Hyperplastic endometriosis within the muscular wall of the fallopian tube. The endometriosis has a mild pattern atypia H&E stain, Magnification ×79

external surface. The cyst wall was 0.2–0.45 cm thick, and had tan-brown hemorrhagic tissue lining its inner surface. Histologically, minimally stratified, mildly atypical serous and mucinous epithelial cells lined the left ovarian cyst. These cytoarchitectural features were interpreted as a seromucinous cystadenoma with epithelial atypia (Fig. 5a). The right ovarian cyst was an endometriotic cyst. Much of its wall was formed of fibrous tissue, with foci of endometrial tissue (Fig. 5b).Nine months later, the same patient presented with vaginal bleeding, chills and right back pain. A vaginal mass was found on examination. A computerized tomography examination revealed peritoneal potentially neoplastic implants, with the largest of them measuring about 5.1×3.6 cm. These implants were associated with destruction of the pubic symphysis. The subsequent vaginal vault biopsy specimen revealed poorly differentiated adenosquamous carcinoma (Fig. 5c). Right nephrostomy tube was inserted to relieve right ureteric obstruction, lysis of adhesions and distal jejunectomy with side-to-side anastomosis were performed. The patient died shortly from a disseminated disease.

Case No 6 A 31-year-old white female, presented with a history of infertility. Clinical examination showed a left adnexal mass. Left ureterolysis, left salpingoophorectomy, partial omentectomy, appendectomy, and proctoscopy with pelvic washing were performed. Gross examination of the obtained specimens revealed multiple tissue fragments ranging in size from 10.5×5.0×1.0 cm to 1.5×1.2×

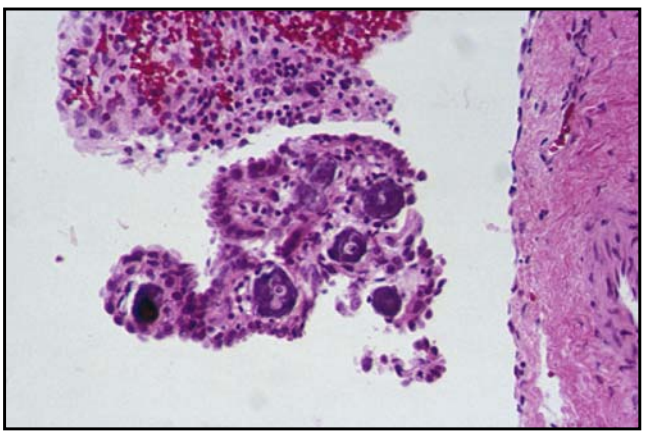

Fig. 4 **a** Serous epithelial proliferation, simple epithelium with bland nuclear features with psammoma bodies within surface ovarian adhesions H&E stain. Overall the histologic features was interpreted not sufficient for the diagnosis of borderline tumour H&E stain, Magnification ×79

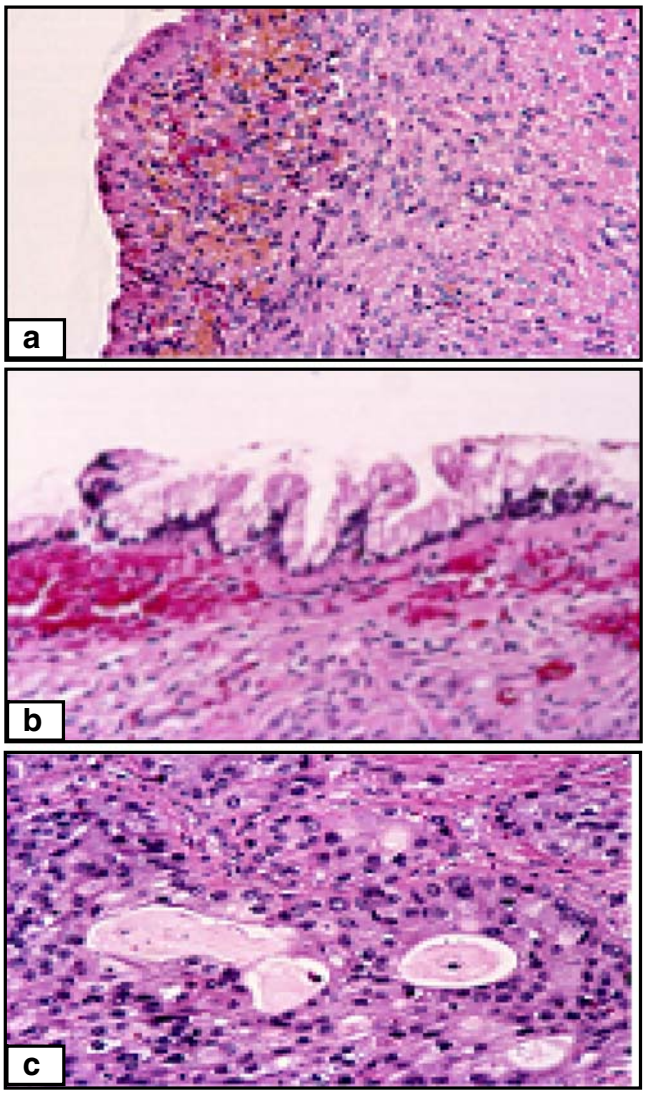

Fig. 5 **a** The ovarian endometriotic cyst has the characteristic endometrial lining (*top*) and fibrosis (*bottom*) H&E stain Magnification ×79; **b** Mullerian type mucinous columnar cells lining the right and the ovarian mucinous cystadenoma H&E stain Magnification ×79; and **c** In this field the adenosquamous carcinoma has mostly solid sheets of carcinoma cells. Glandular differentiation is evident H&E stain, Magnification ×79

1.0 cm as well as multiple irregular tan-pink soft fragments representing left oophorectomy specimen. The specimen had haemorrhagic area measuring 2.8 cm in its largest dimension. Histologically, the left ovarian cyst tissue had a variable histologic appearance. Partly, it was lined by non specific fibrous tissue while other areas had a relatively simple Mullerian lining including mucinous, serous and non specific oxyphilic cells. Much of the lining had some mild stratification and atypia. Focal papillae had been demonstrated. They were lined by Mullerian mucinous epithelium. Some of the lining epithelium had stratification and atypia sufficient for an interpretation of Mullerian mucinous borderline tumour which was intracystic (Fig. 6).

Discussion

Endometriosis is a condition characterised by the presence of tissues identical in all aspects to the endometrium, in sites distant from the uterus. The appearance of the glandular component in endometriosis can be altered by hormonal and metaplastic changes, as well as cytologic atypia and hyperplasia. The last two findings are often referred to collectively as "atypical endometriosis," and may be separately recognized as their premalignant potential likely differs. Occasional findings in endometriosis that may raise concern for a neoplasm include necrotic pseudoxanthomatous nodules, polypoid growth (polypoid endometriosis), bulky disease, and venous, lymphatic, or perineural invasion [4]. Although malignant changes may occasionally occur in endometriosis, our understanding of this issue is still incomplete. To gain more insight into the spectrum of histologic and cytologic abnormalities associated with endometriosis, we carried out the current investigation. Our study demonstrated a rare associations between pelvic endometriosis and borderline ovarian tumours (cases nos. 3, 5 and 6 respectively); cytologic and pattern atypia (cases nos. 2, 3); mesothelial hyperplasia, endosalpingiosis (cases nos. 1 and 2); and a metastatic disease (case no. 5).

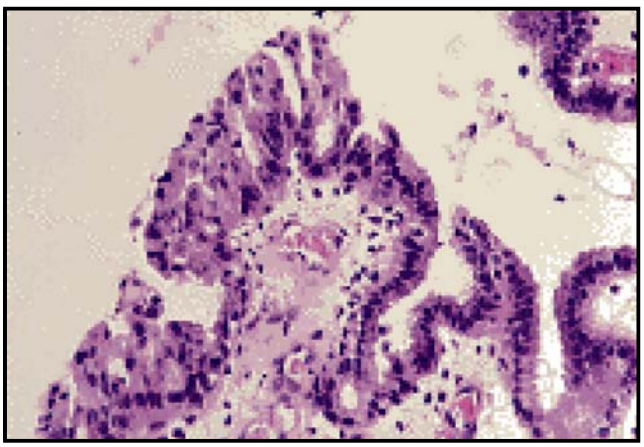

Fig. 6 Mullerian mucinous borderline tumour. The wall is lined mostly by Mullerian mucinous epithelium

Pelvic Endometriosis is Associated with Borderline Ovarian Tumours and Metastatic Disease

In our series, the association between endometriosis and borderline tumours is in agreement with the previous investigations [14, 19, 24, 25, 27]. Several studies reported a chronological association between endometriosis and tumours such as endometrioid, squamous, mucinous, and clear cell carcinomas [8, 14, 20, 30, 40]. These neoplasms were usually ovarian; however, tumours in extra-gonadal sites (tubes, bladder, pelvic peritoneum, and liver) were also reported. Jelovsek and his colleagues reported a case of liver endometrioma with foci of Mullerian adenosarcoma in a postmenopausal woman [11]. We propose that the borderline tumours, reported in our series, probably arose in the background of the associated endometriotic foci. Our proposition is supported by not only the presence of these endometriotic foci in histologic continuity with the borderline tumours, but also by the histological kinship of these lesions [32]. A hypothesis to be tested is that endometriosis and its associated ovarian cancers may represent different steps in a wide spectrum of lesions that share a common biology. At one end of this spectrum (endometriosis), the initiation stage entails aberrant immune response, excess estrogens, and unbalanced progesterone. Once the endometriotic lesions reach the stage of promotion, they acquire further genetic changes such as allelic loss at certain chromosomal regions (6q, 10q and 17 p) that promotes its neoplastic transformation [23].

Pelvic Endometriosis is Associated with Cytological and Patterns Atypia

In our series, the rare association among simple papillae, complex papillary formations with mild atypia and atypical endometriosis concurs with findings of other groups [14, 25, 33, 36, 37]. The absence of borderline malignancy in these cases may be due to the lack of genetic alterations sufficient to drive the cells towards neoplastic transformation. Further mutational analysis is mandated to verify these possibilities.

We observed three cases in which there is an association between endometriosis and psammoma bodies, endosalpingiosis, and mesothelial hyperplasia (cases nos. 1, 2 and 6). These findings not only concur with the finding of others [4, 7, 29] but also suggest that a common stimulus may be responsible for development of these conditions probably

from a multipotential pelvic mesothelium. In this regard, psammoma bodies are laminated, calcified spherules commonly associated with ovarian serous cystadenocarcinomas, and benign conditions such as endosalpingiosis. They may represent "ghosts "of dead papillae. The origin of psammoma bodies implicates matrix vesicles as the nidus for calcification [10, 21]. Alternatively, endosalpingiosis has been reported as a common association with the borderline malignancy and thus probably represent tumour implants that have undergone maturation [22].

The cytological examination of the Cul de sac fluid specimens (case no. 1) revealed aggregates of epithelial cells suspicious for malignancy. Subsequent histologic examination refuted this possibility and thus the presence of these cells was interpreted as benign reactive changes affecting endometriosis. These findings suggest that alarming cytological features may simply reflect inflammatory atypia rather than a neoplastic one. They also indicate that overinterpretation of alarming cytological features should be avoided and tissue biopsy evaluation should be thought. However, the category of "inflammatory atypia" should be maintained as it allows the cytologist to raise the possibility of malignancy in a lesion that does not meet all the criteria for malignancy [28, 31].

Pelvic Endometriosis, Ovarian Carcinomas and Hepatocyte Nuclear Factor-1beta

The transcription factor hepatocyte nuclear factor-1beta (HNF-1beta) is a widely distributed protein. It is a Pit-1, Oct-1/2, UNC-86 (POU)/homeodomain-containing transcription factor that regulates tissue-specific gene expression in several different tissue types. It plays a critical role in embryonic development of the kidney, pancreas, liver, and Mullerian duct. Thirty HNF-1beta mutations have been reported in patients with renal cysts and other renal developmental disorders, young-onset diabetes, pancreatic atrophy, abnormal liver function tests, and genital tract abnormalities [5]. HNF-1beta is a specific marker of clear cell carcinoma in both the ovary and the endometrium. Its expression seems to be associated with physiopathological cytoplasmic glycogen accumulation in these organs [43].

HNF-1beta expression was observed in atypical endometriosis, in endometriosis of a reactive nature, endometriotic cysts without a neoplasm and in clear cell tumours (strong expression) of the ovary arising in a background of endometriosis [12]. The specific expression of HNF-1beta in ovarian clear cell adenocarcinoma (but not in other ovarian carcinomas) has clinical applications in the differential cytopathological diagnosis of clear cell carcinomas from other carcinomas, as well as from mesothelial cells using cytological specimens from ovarian carcinoma patients [9]. It would be interesting to examine HNF-1beta expression in our series in the future investigations.

Here we report a rare association between endometriosis, borderline ovarian tumours, pattern and cytologic atypia. Enough tissue should be obtained from endometriotic foci and subjected for histological examination. This is justified by the fact that visual diagnosis of endometriotic lesions is usually misleading [34, 41, 42]. Moreover, a developing malignancy can overgrow the endometriotic foci, thus masking the evidence of its origin. A close scrutiny of the cytologic and pattern atypia in endometriosis as well as a careful follow-up of patients with atypical endometriosis are recommended. A complete excision of the endometriotic tissues is superior to coagulation therapy adopted by most surgeons. The concern of inviting more adhesions, due to creation of extensive raw surfaces that may jeopardise future fertility, is not warranted. This is because the reproductive outcome is equal either after treatment either with laparoscopic excision or electrocoagulation.

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