Short reports

An unusually aggressive case of endometriosis showing p53 expression

S M Ismail, S Vandeginste, R W Shaw

Abstract
A 43 year old woman who underwent a hysterectomy and bilateral salpingo-oophorectomy for secondary dysmenorrhoea was found to have bilateral ovarian endometriosis. During the following four years she developed a series of tumour-like vaginal masses, which were locally excised, a pelvic mass causing acute large bowel obstruction, which necessitated an emergency Hartmann’s procedure, and a further pelvic mass causing hydronephrosis with a non-functioning kidney. Pathological examination of all the resected specimens showed endometriosis with abundant stromal and glandular elements. Immunoreactivity for p53 protein was detected within endometriotic foci from the initial oophorectomy as well as the latest resection specimens. Immunostaining for p53 may help identify potentially aggressive cases of endometriosis for proactive treatment.

Case report

CLINICAL HISTORY
The patient is a 49 year old woman. She first presented to another hospital in 1993 with secondary dysmenorrhoea. Diagnostic laparoscopy showed a cystic 8 cm left ovarian mass and periovian adhesions. A total abdominal hysterectomy and bilateral salpingo-oophorectomy was carried out and an oestradiol implant was inserted on closure of the abdominal wall. Histological examination showed bilateral ovarian endometriotic cysts.

During the subsequent 12 months she developed vaginal endometriosis, which recurred repeatedly despite local resection and cauterisation. She received a six month course of danazol, but a few months later developed acute large bowel obstruction necessitating an emergency Hartmann’s procedure. The obstruction was caused by a mass involving the upper rectum and distal sigmoid, with infiltration of the pelvic side wall, vagina, and ureters. The mass was resected and confirmed on histological examination as colonic endometriosis. She was treated with a two month course of nafarelin, but developed a further vaginal recurrence. She therefore received a course of pelvic radiotherapy to ablate any ovarian tissue which might have been inadvertently left behind during the initial operation.

One year later, she was referred to our institution with further vaginal recurrences and a nodule within her abdominal scar. Despite the previous bilateral oophorectomy and subsequent pelvic irradiation, serial gonadotrophin and oestradiol measurements at this time were within the premenopausal range. A laparotomy revealed a fibrotic pelvic mass encircling the right ureter. The abdominal nodule and vaginal masses were excised and the pelvic mass was biopsied. Pathological examination confirmed the pelvic mass, abdominal nodule, and vaginal masses as endometriosis. Nafarelin was restarted and her serum oestradiol dropped to postmenopausal values. Subsequent radiological investigations showed no evidence of malignancy. Immunocytochemistry for p53, carried out because the behaviour of the endometriotic lesions was reminiscent of a tumour of low grade malignancy, proved positive in both stromal and epithelial cells.
non-functioning hydronephrotic right kidney with complete ureteric obstruction. A final operation was carried out during which she had a right nephrectomy, resection of a 60 cm segment of small bowel involved by endometriosis, and resection of a further vaginal recurrence and of an involved area of the bladder wall. The pelvic mass was adherent to the right iliac vessels and could only be partially removed. A search was made for any residual ovarian tissue, but none was identified either during surgery or on subsequent pathological examination of the resection specimens. Her postoperative recovery was complicated by right iliac and femoral vein thrombosis treated with anticoagulants. She was discharged home on warfarin and nafarelin. Eighteen months after surgery she remains well and asymptomatic with gonadotrophin and oestradiol values within the postmenopausal range.

PATHOLOGICAL FINDINGS
Review of all the histological sections from the referring hospital by one of the authors (SMI) confirmed the presence of endometrial type glands and stroma in the ovaries (fig 1A), vaginal vault recurrences, and the large bowel resection. Proliferative activity was seen in both components of the lesions but there was no evidence of stromal or epithelial overgrowth. The diagnosis of endometriosis was therefore confirmed on review.

Endometriosis was also seen in subsequently resected vaginal masses, abdominal scar, ureteric wall, small bowel, and pelvic mass. Proliferative activity persisted in both components of the lesions. The sections from the resected pelvic mass showed relative prominence of glandular elements in some areas. This was considered to amount to mild epithelial hyperplasia, but no evidence of sarcomatous overgrowth or epithelial malignancy was seen.

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Sections (5 µm thick) were cut off selected blocks from an ovarian endometriotic cyst removed in 1993 during the initial operation and the pelvic mass removed during the final laparotomy. The sections were dewaxed and rehydrated. Endogenous peroxidase activity was blocked. The sections were then immersed in 0.01 M EDTA solution (pH 8.0) and microwaved at 750 W for 25 minutes, followed by five minutes standing time. After washing in tap water the sections were transferred to a Biogenex “Optimax Plus” automated staining machine and incubated with a monoclonal antibody to human p53 (Clone DO-7, Dako code no M7001) at a dilution of 1/100 for one hour. After washes in phosphate buffered saline the detection system Biogenex “Stravigen Multilink TM” kit was applied. The reaction was developed using the chromogen Biogenex “Liquid DAB”. The sections were counterstained with Mayer’s haematoxylin. As a positive control we used sections from a colonic carcinoma. Slides from each block that were processed in an identical way but omitting incubation with the primary antibody were used as negative controls.

Positive immunostaining for p53 protein was denoted by brown intranuclear staining whereas negative nuclei stained pale blue. Sections from both the initial ovarian endometriotic cyst and the subsequent pelvic mass showed focal immunostaining for p53 protein both in epithelial and stromal cells (fig 1B).

Discussion
A careful review of all the resected endometriotic lesions showed appearances of endometriosis with no evidence of a malignant epithelial or stromal neoplasm. We postulate that the unusually aggressive behaviour of this patient’s endometriosis was caused by a combination of sustained oestrogenic stimulation and derangement of p53 protein function.

Endometriosis is an oestrogen driven disease. Therapeutic strategies aim to remove endometriotic masses and prevent development of further endometriotic foci by eliminating the oestrogen drive, either surgically or pharmacologically. Accordingly, our patient underwent total abdominal hysterectomy and bilateral salpingo-oophorectomy. The postoperative oestriadiol implant might have contributed to her early recurrences, but the persistence of premenopausal gonadotrophin and oestrogen values three years after surgery indicates that not all functioning ovarian tissue was removed during her initial operation. Although no ovarian tissue was identified during subsequent operations, later recurrences were probably contributed to by oestrogen derived from residual functioning ovary. Oestrogenic stimulation, although necessary for

Figure 1 (A) Low power view of the endometriotic ovarian cyst from the first operation. (B) High power view of the endometriotic ovarian cyst showing immunostaining for p53 protein within epithelial and stromal cell nuclei.
the growth of endometriotic foci, cannot by itself account for the exceptionally aggressive behaviour of our patient’s endometriosis. The immunocytochemical detection of p53 protein within endometriotic foci is of great interest in this context.

The nuclear protein p53 plays a central role in many crucial cellular processes such as cell cycle regulation, DNA repair, cellular differentiation, and apoptosis. Disturbance of p53 function is common in malignant neoplasms. In most human cancers p53 protein is functionally inactivated by p53 gene mutations, interaction with viral products, and other mechanisms. Wild-type p53 protein has a short half life and, in normal circumstances, occurs at low concentrations that cannot be detected by immunocytochemistry. Immunoreactivity to p53 may result from the accumulation of mutant p53 protein, which is resistant to degradation, or the expression of high levels of wild-type p53 protein by normal cells that have been exposed to DNA damaging agents. Overexpression of p53 protein is also seen in some neoplasms in the absence of p53 gene mutations.

Mutational analysis was not carried out in this case and the molecular basis of the p53 immunoreactivity seen within the endometriotic foci remains uncertain. Although the patient received pelvic radiotherapy in an attempt to ablate any residual ovarian tissue, p53 overexpression was seen in endometriotic lesions removed before radiotherapy and appears to have been an inherent property of this patient’s disease at presentation.

Little information is available on the role of p53 in endometriosis. No evidence of p53 immunoreactivity was seen within endometriotic foci in a small series of 16 patients with endometriosis. However, this study does not provide any information about disease severity or inclusion criteria. Vercellini et al found no evidence of p53 gene mutations in ovarian endometriotic lesions from 10 women with severe endometriosis, but another study reported a p53 gene mutation in one case of endometriosis adjacent to a carcinoma.

Further work is therefore needed to elucidate the role of p53 in severe endometriosis. Nevertheless, our findings suggest that immunocytochemistry for p53 may help identify potentially aggressive cases of endometriosis.

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