Unusual association of diseases/symptoms

Appendiceal metastasis 10 years following 'curative' resection for low-grade primary endometrial carcinoma

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Summary

Metastasis of primary endometrial adenocarcinoma to unusual sites has been occasionally reported. However, the authors believe this to be the first case report of metastasis to the appendix. This occurred more than 10 years after curative resection, and presented as sepsis with an intra-abdominal focus.

BACKGROUND

Endometrial cancer is the fourth most common cancer in women in the UK, with incidence over 7500 per year and accounting for around 5% of all female cancers.¹ The majority of women present with stage 1 disease, which carries a projected cure rate as high as 75%.

The most common extra-pelvic sites for recurrence are lungs, peritoneum, para-aortic lymph nodes, brain, bones and liver. More rarely, recurrence has been reported in the anterior scalene, supraclavicular and inguinal lymph nodes.² To our knowledge there are no reported cases of metastasis to the bowel.

CASE PRESENTATION

A 62-year-old lady was initially admitted on 25 September 2010 under the care of the medical team with a history of fever of unknown origin for 4 weeks, anorexia and abdominal pain which, initially generalised became localised to the right flank. She denied any bowel or urinary symptoms or recent weight loss. She had a history of previous endometrial cancer, International Federation of Gynaecology and Obstetrics stage 1B (T1b, N0, M0) diagnosed in October 2000, for which she had undergone total abdominal hysterectomy, bilateral salpingo-oophorectomy and adjuvant radiotherapy. There was no evidence of metastatic or recurrent disease at her last follow-up in January 2006, after which the patient was discharged.

On examination, she was pyrexial at 39.1°C, tachycardic in atrial fibrillation, hypotensive (92/50 mm Hg), dehydrated and had mild right flank tenderness. Her inflammatory markers were raised (C reactive protein 253 mg/l, white cell count $25.1 \times 10^9/l$) and she was in acute renal failure (urea 17 mg/l, creatinine 197 $\mu\text{mol/l}$). An x-ray of the chest did not show any obvious pathology.

She responded well to aggressive rehydration and empirical intravenous co-amoxycylav. A CT scan of the thorax and abdomen revealed a large retroperitoneal collection consisting mainly of pockets of gas extending from the right subhepatic pouch into the pelvis, involving the right psoas

muscle. There was no intraperitoneal free fluid or gas. Also noted was an extensive deep vein thrombosis involving the right external iliac, common iliac veins and the distal inferior vena cava (IVC). A small pulmonary embolus in the left lower pulmonary artery was also present but there was no evidence of any other mediastinal pathology.

With the addition of therapeutic enoxaparin, she responded well to treatment for the next 3 days, before deteriorating again with fever (38.6°C), tachycardia and hypotension (89/61 mm Hg). Her abdomen became distended with marked right iliac fossa tenderness. Her inflammatory markers were significantly raised (WCC up to $47.2 \times 10^9/l$ from 14.8×10^9). Her haemoglobin dropped from 11 g/dl to 7.7 g/dl. Treatment was continued with rehydration, change of antibiotics to gentamicin and meropenem and blood transfusion. A clinical diagnosis of acute appendicitis with perforation was made. A second CT scan of the abdomen and pelvis confirmed progression of the retroperitoneal abscess, with free fluid mixed with blood (but no gas) in the pelvis, and a pseudoaneurysm in the right external iliac artery with suspected contained leak.

The patient was now transferred under the joint care of vascular and general surgeons. She was optimised in high dependency unit, had an IVC filter inserted to allow her heparin to be stopped for laparotomy but also to prevent further pulmonary emboli. She was taken to theatre with an intention to carry out an appendicectomy, ligation of the external iliac aneurysm, and a left to right femoro-femoral bypass. At laparotomy, a large, slightly purulent haematoma of about 1.5 litres was evacuated. The appendix was found to be adherent to the external iliac vessels. The external iliac vessels were seen to be encased by a fibrous inflamed mass, but there was no active bleeding or oozing. An appendicectomy was carried out, with copious lavage of the infected haematoma. The iliac artery pseudoaneurysm was left undisturbed, being subsequently stented endovascularly under continued antibiotic cover.

She went on to make a slow and uncomplicated recovery.

Figure 1 Invasive secondary endometrial cancer.

Figure 2 Immunohistochemistry section stained with CK20. (A) Positive staining of normal appendix. (B) No staining of endometrial cancer.

Figure 3 Immunohistochemistry section stained with CK7. (A) No staining of normal appendix. (B) Positive staining of secondary invasive endometrial.

Histology of the appendicectomy specimen confirmed appendicitis with peritonitis. In addition however, an invasive adenocarcinoma (figure 1) was found at the base of the appendix at diathermied margin invading the submucosa. Although initially this was thought to have arisen locally because of its apparent origin from the mucosa, careful inspection did show subtle areas of morular or squamoid differentiation. Immunohistochemistry showed positivity for CK7 and was negative for CK20 and CEA—a profile much more in keeping with a metastasis from the endometrium rather than a large bowel primary (figures 2 and 3). CDX-2 staining showed a particularly interesting pattern with nuclear positivity restricted to the morular or squamoid areas – this contrasts with the typically diffuse positivity in cases of large bowel adenocarcinoma as well as that of normal large bowel epithelium.

The patient was referred to the gynaecological oncologists for consideration of palliative radiotherapy and endocrine therapy. However, after being evaluated by the oncological team, she was thought to be unlikely to benefit from further treatment, and was offered supportive palliative care.

DISCUSSION

Histology samples taken at the time of hysterectomy showed a stage 1b, G3 adeno-squamous carcinoma (T1b, N0, M0) superficially invading the myometrium. She consented to taking part in the (A Study in the Treatment of Endometrial Cancer) trial wherein she received adjuvant external beam radiotherapy.

Most recurrences of endometrial cancer occur within 2 years of initial diagnosis. Local recurrences occur within 14

months while distant metastasis occurs within 19 months of initial treatment.³ Recurrences in patients treated with surgery alone tend to be more localised to the pelvis (40%), particularly at the vaginal cuff and present with vaginal bleeding, pain or weight loss (70%). These recurrences are usually salvageable with radiotherapy, surgical excision or both. The prognosis for these patients is better if the original diagnosis was made more than 2 years before the recurrence.⁴

In cases where recurrence occurs after treatment with surgery and radiotherapy, it is unusual for the disease to be localised and amenable to further surgical excision or radiation.⁵ In such cases if the tumour is hormone receptor-rich, it may respond to progestin or antioestrogen

therapy. Otherwise, chemotherapy can produce response rates of 20% to 30%. Multi-agent chemotherapy produces higher response rates than single-agent therapy but since many patients with recurrent disease are older, have received prior pelvic radiotherapy, or have limited haematological reserve, chemotherapeutic regimens are often limited by toxicity.⁶

The importance of the clinical history in correctly interpreting histopathology in recurrent neoplasm is well illustrated by this case. Without such knowledge, this case could easily have been reported as a primary large bowel adenocarcinoma resulting in inappropriate clinical management. The staining pattern of CDX-2 is another important feature. CDX-2 is a homeobox protein responsible for bowel differentiation and its expression was initially thought to be exclusively limited to the gastrointestinal tract, especially large bowel. However, it is now recognised that certain tumours with a morular pattern (for example,

adenocarcinomas with focally solid groups of cells with squamoid appearance but not with true squamous differentiation), in particular endometrial adenocarcinoma, may also be positive for CDX-2 in these morular areas.

Learning points

- ▶ This is a unique presentation of recurrent endometrial carcinoma presenting with fever of unknown origin and appendiceal metastasis.
- ▶ The use of adjuvant radiotherapy may have played a role in delaying recurrence but may also have been responsible for the unique site of presentation.

Competing interests None.

Patient consent Obtained.

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