picture, the non-destructive nature of many of these infections, and the resolution of cases without anti-microbial treatment.⁵ Many authors have also documented the existence of immunological abnormalities in *Brucella* arthritis, including IgG agglutinating anti-*Brucella* antibodies in synovial fluid of such patients, and point to the similarity of the condition with other "reactive" arthritides such as those following *Shigella* and *Yersinia* infection.⁴ However, isolation of organisms from the joint in such cases, improved by using appropriate media and conditions, immediately moves cases of otherwise typical "reactive" arthritis into the "infective" category. Further improvements in organism detection are likely to follow the application of molecular biological techniques to the field, such as PCR amplification of *Brucella* DNA.

The current case illustrates the lengthy delay in reaching a firm diagnosis in musculoskeletal brucellosis. The rarity of the condition, the "non-infectious" synovial fluid picture, and the difficulty in culturing the organism all militate against prompt diagnosis and treatment.⁴ These factors were compounded in this case by the absence of any of the more traditional risk factors for the illness, such as farming or abattoir work (the patient had had a number of occupations, but was a courier at the time of initial presentation). The predominant bursal location of the inflammatory process without evidence of direct articular disease which allowed normal range of movement throughout the seven year history of the lesion was also perplexing. Bursal disease is uncommon, with the three

cases described by Johnson and Weed representing the largest series to date. Bursitis and tendinitis were not separated as clinical syndromes in the series reported by Mousa *et al.*,⁷ but the combination represented only 1.2% of the 169 cases of osteoarticular brucellosis they described, and bursitis is not recorded in other large series.^{2,3} The formation of a sinus tract in this setting has also not been described before.

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Cushing's syndrome associated with recurrent endometrioid adenocarcinoma of the ovary

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Abstract

Ectopic production of adrenocorticotrophic hormone (ACTH) by malignant neoplasms is a well recognised cause of Cushing's syndrome but is extremely rare in ovarian carcinoma. A patient who underwent surgery for ovarian carcinoma followed by a course of chemotherapy is reported. The tumour was a bilateral moderately differentiated endometrioid adenocarcinoma and contained numerous chromogranin immunoreactive endocrine cells as well as small foci of ACTH immunoreactivity. She subse-

quently presented with Cushing's syndrome in association with extensive pelvic recurrence of the tumour.

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Cushing's syndrome due to ectopic adrenocorticotrophic hormone (ACTH) production has been described in a wide range of ovarian tumours including sex cord stromal tumours,¹ carcinoid tumours,^{1,3} and teratomas.⁴ However, ovarian tumours of common epithelial type are an extremely uncommon cause of

ectopic ACTH production, with only one other well documented instance.⁵

Case report

A 59 year old woman gave a one year history of lower abdominal swelling. A mass was palpable in the lower abdomen. An ultrasound scan showed that this arose from the pelvis and filled the lower abdomen. Routine biochemistry was normal. At laparotomy, bilateral ovarian tumours were found and removed and there was no macroscopic disease at the conclusion of the procedure. She was referred for further treatment a week later at which time CA 125 was 155 U/ml (upper limit of normal 35 U/ml).

She was treated with six courses of cisplatin 100 mg/m² and cyclophosphamide 750 mg/m². Her CA 125 quickly returned to

normal and she was followed up for 14 months with no evidence of recurrent tumour. During the last three months of this period she began to gain weight and complained of ankle oedema which was controlled with diuretics.

She then developed severe oedema and she was noted to be pigmented with centripetal obesity. The CA 125, which had been undetectable in the serum, reached 14 U/ml at 14 months of follow up and rose to 31 U/ml over the next six weeks. At the time of her re-presentation she had abnormal biochemistry: sodium 141 mmol/l, potassium 2.8 mmol/l, bicarbonate 33.6 mmol/l, chloride 95 mmol/l, urea 9.6 mmol/l, and creatinine 143 µmol/l. Random glucose was 7.3 mmol/l. Plasma cortisol measured at 22.15 hours was 1386 nmol/l (upper limit of normal 690 nmol/l) and after dexamethasone this fell to 1054 nmol/l. It was concluded that she had Cushing's syndrome. Her ACTH was 1380 mg/l. A mass was palpable in the lower abdomen and confirmed on ultrasound scan to be filling the lower abdomen and arising from the pelvis. A percutaneous biopsy was performed. She received treatment with aminoglutethimide increasing to 1.5 g/day and spironolactone increasing to 450 mg/day. Potassium remained low and the bicarbonate remained high. She then received chemotherapy with carboplatin in a dose calculated to give an area under the concentration time curve of 7 mg hours/litre.

Her urine output had been adequate at 2000 ml a day, but this fell sharply to 500 ml a day. The creatinine rose, although the potassium and bicarbonate remained unchanged until one week after chemotherapy when urine output stopped. She died that evening. After chemotherapy her cortisol had fallen to 810 nmol/l.

Figure 1 Histological features of the tumour at initial presentation. Glandular structures lined by pseudostratified columnar epithelial cells characteristic of endometrioid carcinoma (haematoxylin and eosin).

Figure 2 Although predominantly glandular in differentiation, both tumours contained solid foci of poorly differentiated carcinoma (haematoxylin and eosin).

Pathological findings

On microscopic examination the surgically resected ovarian masses were composed, for the most part, of tubular glandular spaces lined by stratified columnar epithelial cells showing the cytological features of malignancy (fig 1). There were also occasional small solid foci of poorly differentiated carcinoma (fig 2). The appearances were those of a bilateral moderately differentiated endometrioid adenocarcinoma of the ovary.

A percutaneous biopsy specimen taken at the time of relapse showed an undifferentiated tumour. There was insufficient material for immunocytochemical studies.

At necropsy the pelvis and lower abdomen contained nodular masses of necrotic tumour, the largest being 25 cm in diameter. Microscopically, these showed the features of an anaplastic carcinoma with extensive necrosis. There was no evidence of metastatic tumour. The pituitary gland was macroscopically and microscopically normal. The adrenals were enlarged to about three times the normal size, with nodular thickening of the cortex. Microscopic examination of the adrenals showed cortical hyperplasia. No evidence of

an adrenal neoplasm was seen and the medulla was normal. The lungs, pancreas, and gastrointestinal tract were normal.

The resected tumour contained numerous endocrine cells immunoreactive to chromogranin as well as occasional foci of ACTH immunoreactivity within small foci of poorly differentiated tumour. The necropsy specimen showed chromogranin immunoreactivity in some tumour cells, but no ACTH immunoreactivity was demonstrated.

Discussion

The special features of this case are that there was no evidence of any endocrine disturbance at the time when she presented with a large ovarian primary, even though ACTH was subsequently found immunohistochemically. The course of the illness when she relapsed was short and the tumour marker associated with ovarian cancer was not increased to the extent that it had been initially, despite having a similar bulk of tumour. On relapse there was substantial biochemical disturbance characteristic of Cushing's syndrome with increased ACTH concentration, and neurone specific enolase was increased in the serum. These findings suggest dominance of the ACTH producing clone at relapse associated with a particularly aggressive clinical course.

In a comparison of the features of ectopic and pituitary ACTH production resulting in Cushing's syndrome, Howlett *et al* noted that all 16 patients with ectopic production of ACTH presented with hypokalaemia.⁶ Most of these tumours were small cell carcinomas of the lung or carcinoid tumours; there were two pancreatic endocrine tumours, and in 10 of the 16 the tumour was occult at the time of presentation, the only manifestation being the metabolic disturbance. The histology of 18 tumours including these has subsequently been reported.⁷ Ten cases showed immunohistochemical evidence of ACTH production or production of related peptides, and 17 of the 18 showed evidence of neuroendocrine differentiation defined by the presence of neurone specific enolase.

Endocrine cells are widely distributed in the normal genital tract and well documented in the normal endometrium⁸ and its tumours.^{8,9} Endometrioid carcinomas of the ovary are microscopically very similar to tumours arising in the endometrium and likewise contain argyrophil endocrine cells.¹⁰ Ueda *et al* described argyrophil cells in 19 of 42 endometrioid adenocarcinomas of the ovary.⁹ Immunocytochemistry with a panel of antibodies to peptide hormones, including anti-ACTH, showed that one of these tumours was immunoreactive with somatostatin. None of the tumours contained immunocytochemically detectable ACTH.

In our case the pituitary gland was normal with no evidence of excess ectopic ACTH synthesis. ACTH immunoreactivity was found in the poorly differentiated areas of the surgically resected tumour before the onset of clinical Cushing's syndrome. Although no ACTH immunoreactivity was demonstrated in the post mortem tumour, no other possible source of ectopic ACTH secretion was demonstrated at necropsy. We therefore postulate that this patient's Cushing's syndrome was due to ectopic ACTH secretion by the recurrent ovarian carcinoma. The lack of ACTH immunoreactivity in the necropsy specimen could have been due to poor preservation of the tumour owing to post mortem autolysis or to cell damage consequent on recent chemotherapy.

The anaplastic nature of the recurrence suggests that the relatively well differentiated areas of the tumour associated with CA 125 production were eradicated by chemotherapy while the poorly differentiated ACTH secreting tumour cells acquired a growth advantage. Interestingly, the only other reported case of Cushing's syndrome associated with an ovarian carcinoma also occurred in an anaplastic tumour.

The development of Cushing's syndrome in association with tumour recurrence in this patient illustrates the propensity of tumours towards phenotypic variation with consequent changes in clinical behaviour.

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