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Ovarian Sertoli-Leydig cell tumour with raised serum alpha fetoprotein

A case report

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Summary. A case of ovarian Sertoli-Leydig cell tumour with a raised serum alpha fetoprotein in reported. The patient first presented at the age of 27 years with a history of 6 years' amenorrhoea followed by 3 months irregular vaginal bleeding. A ovarian tumour was found and excised and shown microscopically to be a spindle cell malignant tumour. The patient was treated with chemotherapy and had a complete response. Thirty months after first presentation there was a recurrence in the pelvis which microscopically showed the typical features of a Sertoli-Leydig cell tumour. Six months later a second recurrence had the microscopic appearance of a lipid cell tumour. A raised serum alpha fetoprotein was found at the time of the second recurrence and immunohistochemistry showed this protein in the Leydig and luteinized cells of the recurrent tumours but not in the spindle cells of the original ovarian neoplasm.

Key words: Ovarian neoplasms – Sertoli-Leydig – Alpha fetoprotein

A raised serum alpha fetoprotein (AFP) is an infrequent finding in association with ovarian sex cord-stromal tumours. In the literature there are reports of this association with granulosa cell (Donaldson et al. 1980; Mori et al. 1980) and Sertoli Leydig cell tumours (Benfield et al. 1982; Young and Scully 1983; Chumas et al. 1984; Young et al. 1984). We wish to present an example of a malignant ovarian sex cord-stromal tumour which altered its morphology under treatment, developed the typical appearance of a Sertoli Leydig cell tumour and was then found to be producing a very high level of serum alpha fetoprotein.

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Case report

A 27 year old woman, G0 P0, was admitted to hospital in August 1981 with a 3-month history of heavy, irregular vaginal bleeding following a 6-year period of secondary amenorrhoea. Her menarche was at the age of 13 and her menses had been regular (5/28) until the age of 21 when she became amenorrhoeic. She had never used any contraception.

Physical examination revealed a mildly obese female with normal secondary characteristics and no signs of virilization. On abdominal examination, a mass, compatible with a 36 weeks' pregnancy, was found. At laporotomy there was a tumour in the right ovary adherent to the pelvic peritoneum and a right oophorectomy was performed. Three weeks later a left salpingo-oophorectomy, total abdominal hysterectomy and omentectomy were performed. Eight weeks after this second operation, the serum alpha-fetoprotein (AFP) was 1,53 ng/ml. It had not been measured prior to this.

Pathology. The ovarian tumour measured 25 × 22 × 15 cm and weighed 2,225 gm. The capsular surface was smooth and showed no evidence of penetration. The cut surface showed cream coloured tissue and occasional cysts measuring up to 3 cm in diameter. Eleven blocks were taken for histology. Microscopy showed spindle cells, with a moderate amount of cytoplasm, arranged in bundles (Fig. 1). In areas these bundles were separated from each other by a loose oedematous stroma. In these areas there were occasional polygonal cells with a foamy cytoplasm. A moderate amount of necrosis was present and the cysts were due to degeneration. Silver stains demonstrated abundant reticulin around individual cells. Stains for lipid were negative but electron microscopy, performed on formalin-fixed tissue, showed some lipid droplets within the cytoplasm of the spindle cells. The necrosis and a mitotic count of 10 mitoses/mm^2 suggested a malignant tumour and a diagnosis of ovarian cortical stromal sarcoma was offered.

The uterus and cervix together measured 7 cm in length. The cervix was unremarkable. The endometrium was secretory and morphologically consistent with the 5/6th day post ovulation. The myometrium showed no abnormality. The right adnexum showed inflammation and fibrosis related to the previous surgery. The left ovary was normal and contained a cor-

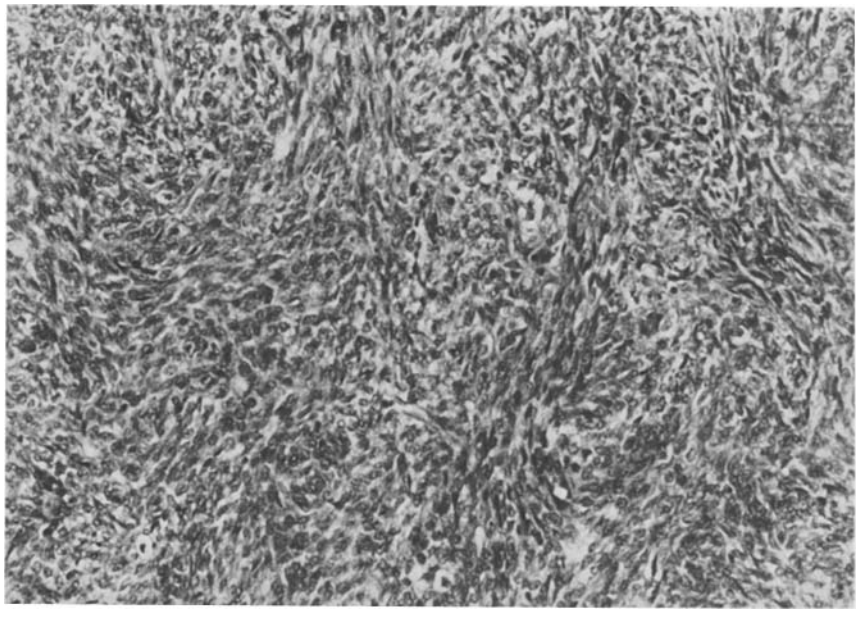

Fig. 1. The original ovarian tumour consisting of spindle cells only. H & E × 150

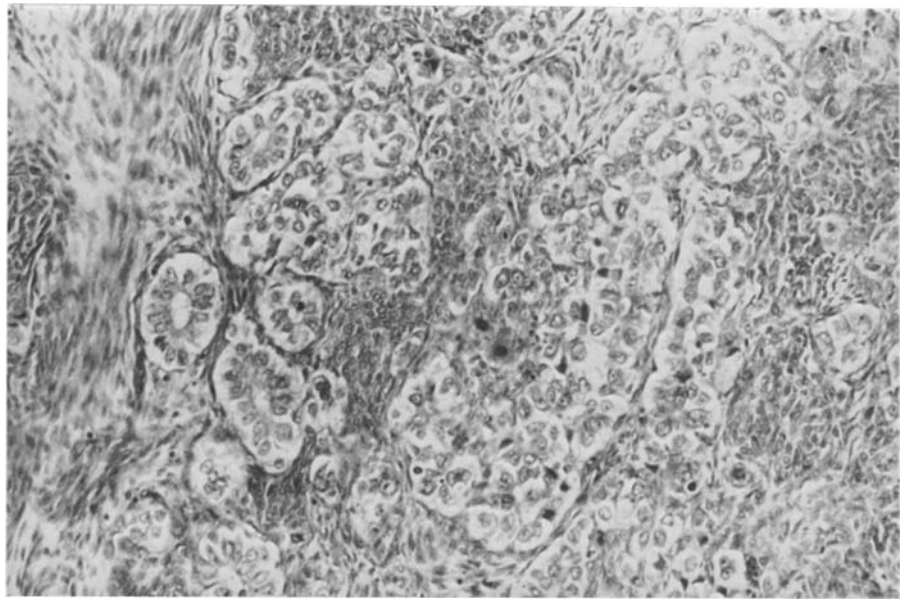

Fig. 2. The first recurrence showing tubules, spindle cells and luteinized cells. H & E × 150

pus luteum also morphologically consistent with the 5/6th post ovulatory day. The omentum contained a single small focus of metastatic tumour composed of tightly packed spindle cells.

She received 7 courses of Vinblastine, Adriamycin and Cisplatin followed by 13 courses of Actinomycin-D and Cyclophosphamide and showed complete remission. Cytology, through colpopuncture, during and immediately after chemotherapy was negative for malignant cells.

Two-and-a-half years after first presentation and 7 months after cessation of chemotherapy, she was found to have a mass in the pelvis. At laparotomy, a soft, 10 cm, vascular, solid tumour was found attached to the vaginal vault and resected. A second 5 cm solid retroperitoneal tumour, in close relationship to the aorta, adjacent to the left kidney, proved to be irresectable.

Pathology. The material examined was a well circumscribed tumour measuring 10 × 8 × 5 cm and weighing 208 gm. Twelve tissue blocks were taken for histology. Microscopy showed a mixed picture. Some areas, composed entirely of spindle cells, were identical to the previous ovarian tumour. The bulk of the lesion, however, showed the features of a Sertoli/Leydig cell tumour (SLCT) of intermediate differentiation with tubular structures mixed with spindle cells and Leydig cells (Fig. 2). After extensive searching, the occasional crystalloid could be found. In some areas the tumour had a retiform pattern. In other areas, islands of plump spindle cells, similar to those in the original ovarian neoplasm were admixed with luteinized cells and lay in a loose stroma of elongated spindle cells (Fig. 3). In places, these luteinised cells were very large with abundant eosinophilic granular cytoplasm and central vesicular nuclei

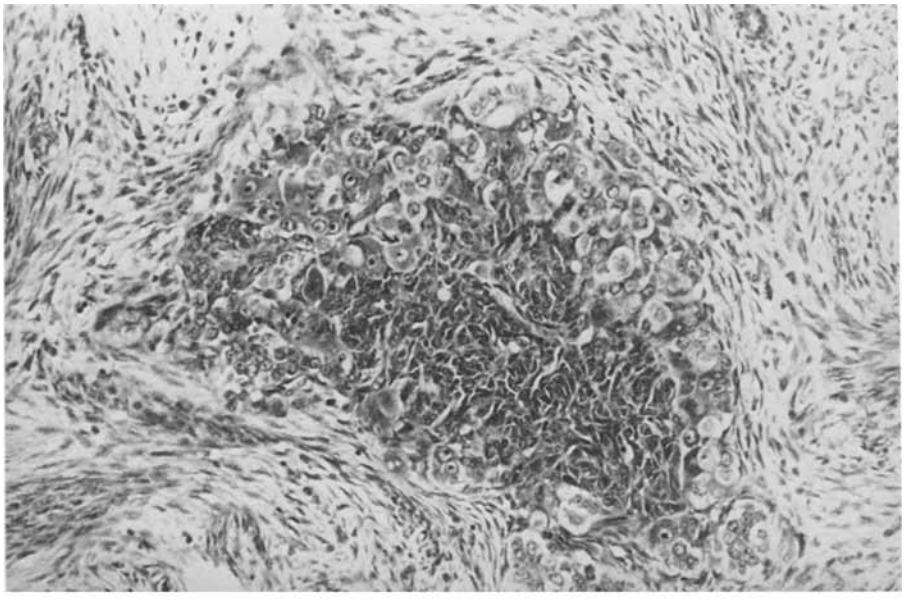

Fig. 3. The first recurrence showing nests of small spindle cells and luteinized cells. H & E × 150

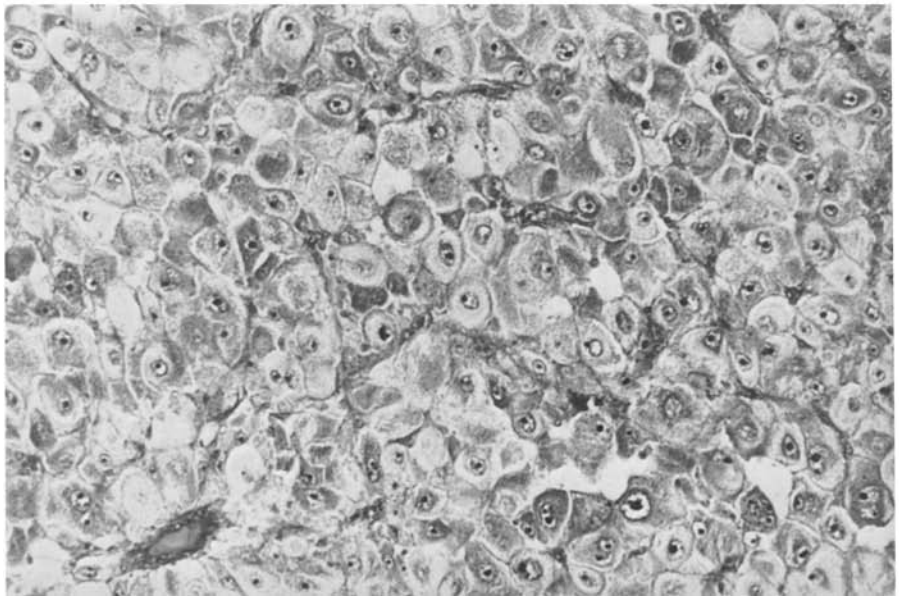

Fig. 4. The second recurrence consisting of large lipid rich cells. H & E × 150

containing very large nucleoli. Fat stains showed lipid in these cells and occasional multinucleate forms were seen. In some areas these cells were present in large sheets within which small collections of spindle cells were present.

Postoperatively, the patient received 4 courses of Vincristine, Actinomycin-D and cyclophosphamide. Six months later another pelvic mass was felt. Colpopuncture and cytology showed malignant cells. At this time, an inadvertent measurement of serum AFP showed a level of 138,300 ng/ml. At laparotomy, a 12 cm fleshy tumour was shelled out of the pelvis. The left-sided retroperitoneal mass was still present but had not enlarged. Fine-needle aspiration of this mass showed large luteinized cells with abundant cytoplasm, similar to those seen in the other tumour deposits.

Pathology. Several pieces of tissue, the largest measuring 9 cm in diameter, were received. Microscopically, the 8 sections examined showed a moderate amount of necrosis, and sheets of large cells with abundant lipid-laden eosinophilic cytoplasm and central vesicular nuclei with very large nucleoli (Fig. 4). Silver stains showed individual cells surrounded by reticulin. No crystalloids of Reinke were found. No spindle cells or tubular structures were seen. Electron microscopy performed on gluteraldehyde-fixed material showed the cytoplasm of these cells to be distended by small lipid droplets (Fig. 5).

Because of the high serum alpha feto protein (AFP) immunohistochemistry (peroxidase anti peroxidase) using antibody to AFP (Dakopatts, Copenhagen) was performed on the original tumour and the two recurrences. No positive staining could

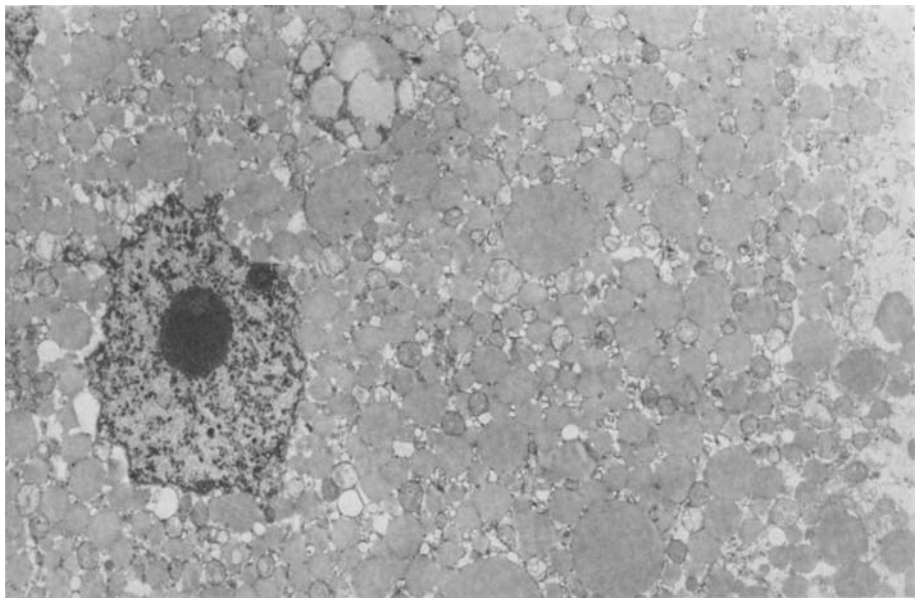

Fig. 5. The second recurrence. The cell cytoplasm contains mitochondria and numerous small lipid droplets. H & E ×3,000

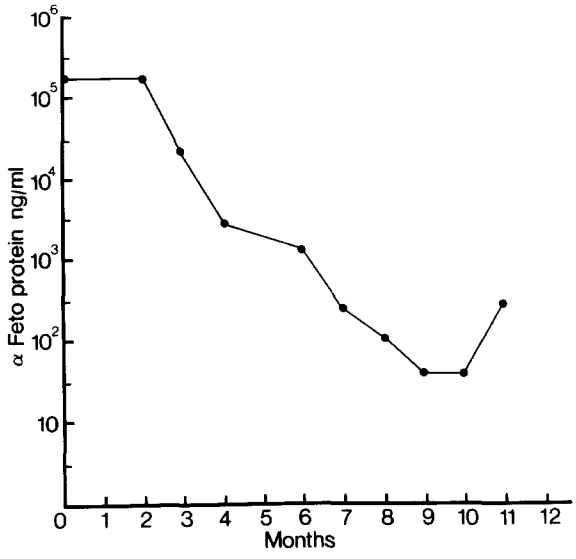

Fig. 6. Alpha feto protein levels from the time of the second recurrence showing a steady fall while on chemotherapy and a rising level shortly before demise

be found in the original ovarian tumour. Sections from the first recurrence showed positive staining in the Leydig cells and larger luteinized cells. The Sertoli cells in the tubules and retiform areas and the spindle cells were negative. The second recurrence showed strong positive staining in the large lipid rich eosinophilic cells.

Postoperatively, cytotoxics were recommenced (Etoposide, Cisplatin, Vincristine, Methotrexate and Bleomycin). The disease was monitored by serum AFP levels (Fig. 6) and when these had dropped to 50 ng/ml the administration of cytotoxics was discontinued. Three months later the AFP serum levels were again raised (130 ng/ml) and the patient died approximately 4 years after first presentation with tumour filling the abdomen. An autopsy was not performed.

Discussion

There are two features of special interest in this case – the changing microscopic morphology and the presence of a very high serum alpha feto protein in a non germ cell ovarian tumour.

Regarding the morphology, 3 different but merging microscopic appearances were seen in the 3 resections done at different times over the course of 3 years. Because the spindle cell element was admixed with the large lipid laden cells in the second resected specimen, the three are regarded as recurrences of a single tumour rather than double or multiple primary neoplasms.

The initial ovarian neoplasm showed a malignant spindle cell tumour of the sex cord stromal category which caused some difficulty in further categorization. Although poorly differentiated Sertoli-Leydig cell tumours (SLCT) are composed of spindle cells there is often a suggestion of tubule or cord formation and Leydig cell differentiation. These were not seen in any of the 11 sections examined and at that time a possible diagnosis of undifferentiated SLCT was discarded. A sarcomatous granulosa cell tumour was excluded on the presence of reticulin around individual cells and the lesion was considered to be a sarcoma of ovarian stromal origin. There are some difficulties with the terminology of malignant thecomas and fibrosarcomas and we agree with Waxman and her coworkers (1979) that the designation "stromal sarcoma" is appropriate. In retrospect, noting the subsequent morphologic development of this tumour, we believe the initial lesion was a poorly differentiated SLCT.

SLCT's often have endocrine, frequently androgenic, effects. The only suggestion of this in the present case was a 6 year history of amenorrhoea followed by a short period of menstrual irregularity. Three weeks after the removal of the ovarian tumour the endometrium and a corpus luteum in the opposite ovary were morphologically compatible with the 5/6th post ovulatory day. Assuming a 14 day pre-ovulatory phase these findings suggest an immediate return to normal ovarian function following tumour resection.

The first recurrence 2,5 years later showed some areas identical to the original tumour but most of the tissue showed the typical features of a SLCT which in areas showed the pattern that has been described as retiform (Young and Scully 1983). There was a morphologic continuum between the Leydig cells, in which occasional crystalloids were recognized, and the larger luteinized cells so that they were regarded as morphologic variants of the same cell. However, they also resembled the groups of cells which have been called by others hepatoid (Young et al. 1984). While there is a resemblance to liver cells we are reluctant to use this term as it implies a hepatic differentiation and there is no good evidence for this. The cells were not arranged in a columnar or sinusoidal pattern and there were no associated Kuppfer cells. Bile pigment could not be found and the distribution of intra-cellular lipid as small droplets was unlike that seen in the liver. Finally the occasional crystalloid could be found in these cells.

The second recurrence 6 months later was composed entirely of large lipid laden cells and in the 8 sections examined no spindle cells or tubular structures could be found. Apart from the very pleomorphic and atypical nuclear morphology, the tumour now resembled the so called lipoid cell tumour of the ovary. This category includes Leydig cell tumours and stromal luteomas. Crystalloids could not be found.

The reasons for the change in morphology between the primary and the first recurrent tumour in the pelvis are not clear. The 11 blocks of the primary tumour all showed a spindle cell sarcoma but further sampling may have shown the more typical features of a SLCT. Alternatively, the change may have been due to selective action of the chemotherapeutic drugs, allowing certain cell lines to survive and grow while inhibiting or destroying others. A further possibility, similar to that suggested for some germ cell tumours (Merrin et al. 1976), is that the chemotherapy may stimulate differentiation. The morphologic changes between the first and second recurrences include a loss of tubule formation and spindle cells. Similar mechanisms may be operative but intra cytoplasmic lipid accumulation has been shown to occur with the use of chemotherapy (Presnov 1964) and the nuclear changes present are those seen as a response to alkylating agents such as cyclophosphamide.

A raised serum alpha fetoprotein (AFP) is unusual in association with gonadal sex cord-stromal tumours. The two reports of granulosa cell tumours producing AFP (Donaldson et al. 1980; Mori et al. 1980) contain no further details and cannot be discussed. There are several well documented cases of SLCT's with a raised AFP (Benfield et al. 1982; Chumas et al. 1984; Young et al. 1984). In these reports there are differences as to the nature of the cells producing this protein. In this first reported instance, Benfield et al. (1982) suggested that it was the heterologous gastro-intestinal epithelium that was responsible. In subsequent reports where immuno-histochemistry has been performed for AFP, positive staining has been seen in cells with eosinophilic cytoplasm. Chumas et al. (19847) interpreted these cells as Leydig like whereas Young et al. (1984) referred to them as hepatoid. In the present case it was also these eosinophilic cells which stained positively for AFP. As discussed above, we believe these to be Leydig cells or luteinized stomal cells. The occasional crystalloid could be found in the haematoxylin and eosin stained sections but they could not be recognised in the immunohistochemical preparations. The large lipid laden cells in the second are similar to those in the first recurrence and were also regarded as atypical Leydig cells or luteinized stromal cells. We conclude that is these cells which are responsible for the high serum AFP levels. It is unfortunate that the serum AFP levels were not measured before the first operation as those 11 weaks later are of little significance. However, no AFP could be demonstrated in the original tumour by immunohistochemistry suggesting that the production of AFP occurred only with the emergence of Leydig or luteinized stromal cells in the tumour.

The significance of raised serum AFP in these patients relates to the observation that the majority of the reported examples of SLCT with raised serum AFP have either had heterologous elements (Benfield et al. 1982; Young et al. 1984) or have exhibit a retiform pattern (Young and Scully 1983; Young et al. 1984; Talerman and Haije 1985; and the current case). Both heterologous elements and the retiform pattern may cause diagnostic difficulties and confusion with germ cell tumours. In these circumstances the presence of a raised serum AFP

cannot be used as definitive support for a germ cell tumour.

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