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## Short Communication

# Use of novel serum markers in clinical follow-up of Sertoli-Leydig cell tumours

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## Abstract

**Background:** Sertoli-Leydig cell tumours of the ovary account for only 0.2% of malignant ovarian tumours. Two-thirds of all patients become apparent due to the tumour's hormone production.

**Methods:** A 41-year-old patient (gravida 4, para 4) presented with dyspnoea, enlarged abdominal girth and melaena. Diagnostic imaging was suspicious for an ovarian cancer. The standard tumour marker for ovarian cancer (CA 125) was elevated to 984 U/mL.

**Results:** Surgical exploration of the abdomen revealed a mouldering tumour of both adnexes extending to the level of the navel. Frozen sections showed an undifferentiated carcinoma of unknown origin. Radical surgery was performed. The final histological report described a malignant sex-cord stroma tumour, a Sertoli-Leydig cell tumour, emanating from both ovaries. Analysis of preoperative blood serum showed elevated levels of CYFRA 21-1 (10.4 ng/mL), neuron-specific enolase (36.2 ng/mL), oestradiol (485 pg/mL) and CA-125 (984 U/mL). Adjuvant chemotherapy and regional hyperthermia were performed due to the malignant potential and incomplete resection of the tumour.

**Conclusions:** Undifferentiated Sertoli-Leydig cell tumours show a poor clinical course. As only two-thirds of patients with this rare disease present with elevated hormone levels, new markers deserve further investigation to offer more specific, individualised tumour monitoring.

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**Keywords:** ovarian malignancy; Sertoli-Leydig cell tumour; serum marker; sex-cord stromal tumour.

Sertoli-Leydig cell tumours are classified as sex-cord stromal tumours. They account for only 0.2% of malignant ovarian tumours and are often found unilaterally (1). Synonyms in the literature are arrhenoblastoma, androblastoma and gonadal stromal tumour of the android type. Most of these tumours are described in young adults and less than 10% occur prior to menarche or after menopause (2). Two-thirds of all patients are diagnosed with this rare disease due to the tumour's hormone production (3).

A 41-year-old patient (IV gravida, IV para) presented with dyspnoea, enlarged abdominal girth and melaena. On physical examination, the abdomen was distended with a fluid wave. Auscultation showed decreased breath sounds over the basal lungs and dullness to percussion suspicious for pleural effusion. Gynaecological ultrasound and a computed tomography scan of the abdomen and lung revealed a more than 30-cm ovarian tumour with peritoneal carcinosis and ascites. There was bilateral pleural effusion, but no signs of pulmonary nodules or other distant metastases. The standard tumour marker for ovarian cancer (CA 125) was elevated to 984 U/mL (Table 1). Preoperative colonoscopy did not show a pathologic finding except for polyposis. Bilateral chest tubes were placed to relieve the pleural effusion. Cytological analysis of the fluid was unremarkable. Surgical exploration revealed a mouldering, extremely soft tumour of the right adnex extending to the level of the navel and a 7-cm smooth tumour of the left adnex (Figure 1). Frozen sections were compatible with a poorly differentiated carcinoma of unknown primary origin. Hysterectomy, adnexectomy, appendectomy, omentectomy, peritonectomy of the lesser pelvis and anterior resection of the sigmoid colon and rectum were performed, reducing the size of the tumour to approximately 1 cm, with a residual mass in the mesentery of the small intestine. Due to low preoperative haemoglobin (78 g/L), a need for intraoperative blood transfusions and unclear histology, a lymphonodectomy was discounted. The final histologic report based on analysis of multiple tissue samples and results for immunohistochemical stains (including keratin, inhibin, calretinin, oestrogen and progesterone receptor) led to a diagnosis of a poorly differentiated Sertoli-Leydig cell tumour involving both ovaries. The tumour infiltrated the omentum, uterus, appendix and rectum. Post-

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**Table 1** Serum markers for tumour monitoring.

Serum marker	Preoperative	9-month follow-up	Normal values
<b>Immunology</b>			
CYFRA 21-1, ng/mL	10.4	<0.5	<3.3
NSE, ng/mL	36.2	12.3	0–16.3
CA 125, U/mL	984	3.4	0.0–35.0
CA 72-4, U/mL	0.8	0.6	<7.0
CEA, ng/mL	<1.0	<0.1	<1.0
AFP, ng/mL	1.6	3.3	<15.0
<b>Endocrinology</b>			
HCG- $\beta$ , mIU/mL	<2	<2	<2
Oestradiol, pg/mL	485	18.2	<10–300
Testosterone, ng/mL	0.2	<0.8	<0.8 ng/mL

Serum markers analysed preoperatively and at clinical follow-up 9 months after primary diagnosis of the Sertoli-Leydig cell tumour. CYFRA, NSE, oestradiol and CA 125 seem to be suitable markers to monitor the clinical course of this patient's disease.

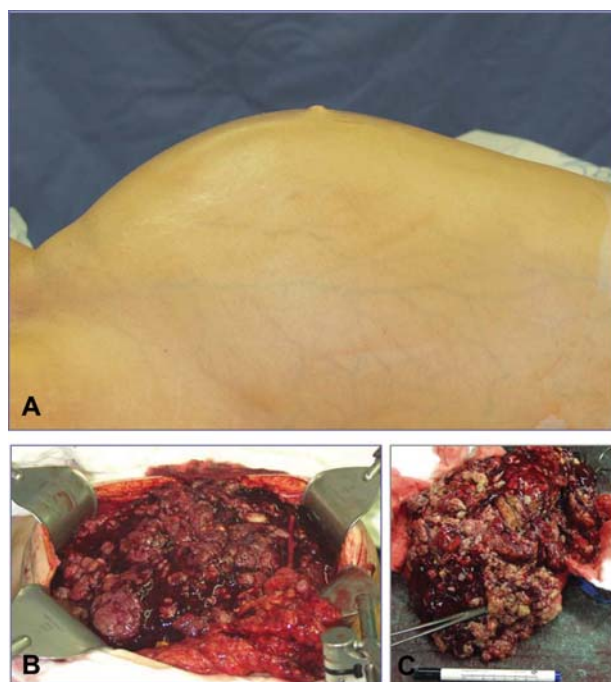
operative tumour stage was classified as pT3b, pNx, pMx, FIGO IIIB. Retrospective analysis of preoperative serum showed elevated levels of CYFRA 21-1 (10.4 ng/mL), neuron specific enolase (NSE; 36.2 ng/mL), oestradiol (485 pg/mL) and CA 125 (984 U/mL) (Table 1). Adjuvant chemotherapy with eight cycles of cisplatin 40 mg/m<sup>2</sup>/day, etoposide 100 mg/m<sup>2</sup>/day and ifosfamide 1800 mg/m<sup>2</sup>/day for days 1–4, in combination with regional hyperthermia, was chosen because of the malignant potential and incomplete resection of the tumour.

At 1-year follow-up, no recurrent abdominal mass could be identified either by physical examination or

by a computed tomography scan of the abdomen. Serum markers were analysed on a 3-monthly base, and so far show no signs of recurrence.

Sertoli-Leydig cell tumours account for 0.2% of ovarian neoplasms (1). They are classified as one of five histopathological types: well, intermediately or poorly differentiated, with a retiform component or with heterologous elements (gastrointestinal-type epithelium, hepatocytes, skeletal muscle or cartilage) (4). They consist of Sertoli and Leydig cells in varying proportions and varying differentiation. Poorly differentiated Sertoli-Leydig cell tumours are sarcomatoid in appearance (5). Sertoli and Leydig cells can stain positive for testosterone and oestradiol (6). Areas with Sertoli tumour cells are positive for vimentin and may express keratins, but are typically negative for epithelial membrane antigen (EMA), placenta-like alkaline phosphatase (PLAP), carcinoembryonic antigen (CEA), CA 19.9, CA 125 and S-100 protein (7). Leydig cells are predominantly positive for vimentin and  $\alpha$ -inhibin and stain negative for keratins (8). In our case, the tumour cells expressed keratin (C), inhibin (D) and calretinin (E), as well as oestrogen receptor (F) and progesterone receptor (G) (Figure 2).

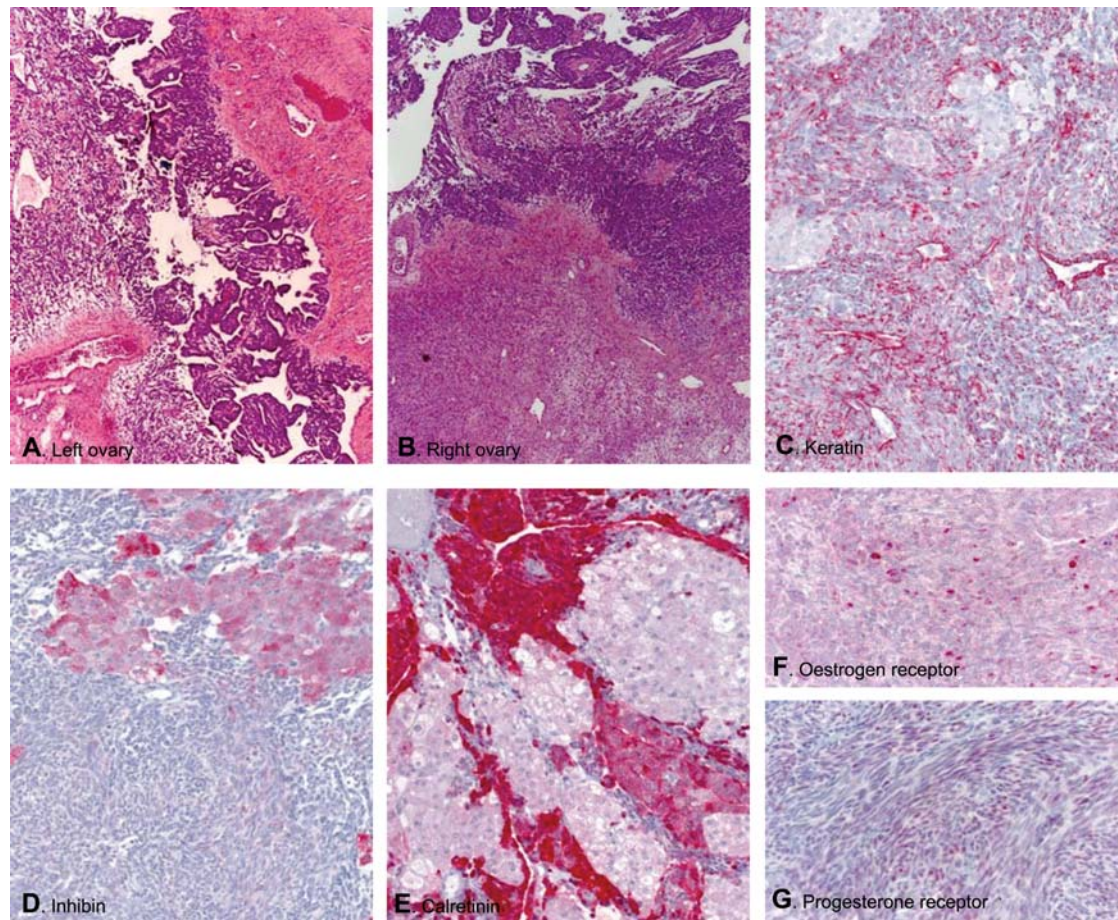
Approximately 70%–75% of Sertoli-Leydig cell tumours occur in young adults, with a mean age of 25 years at primary diagnosis (2). There are six case reports in the literature describing this rare disease in postmenopausal women (9–14). Commonly, Sertoli-Leydig cell tumours are detected at an early stage (80% stage Ia). Only less than 3% have spread beyond the ovary (15). Metastases are predominantly described in the omentum, the abdominal lymph nodes and the liver. Nonetheless, one case of a metastasis in the frontal sinus has been reported (16). Hardly ever are both ovaries involved. A review of 207 cases showed an incidence of 1.4% of bilateral Sertoli-Leydig cell tumour (17). In this review, all well-differentiated tumours proved benign (18), whereas 11% of intermediately and 58% of poorly differentiated tumours showed malignant behaviour. In the same collective, malignant behaviour was observed in 19% of patients with heterologous tumour elements (17). Moderately and undifferentiated tumours with malignant potential show a significantly poorer



**Figure 1** Clinical presentation and macroscopic tumour appearance.

(A) Preoperative photograph of the patient: the abdomen is distended compared to the cachectic body. (B) The intra-operative situs shows the abdomen filled with a mouldering tumour and bloody ascites. (C) The right adnexa consists of a more than 30-cm crumbly tumour: frozen section shows a poorly differentiated carcinoma of unknown primary origin.





**Figure 2** Tumour histology.

Low-power view of the Sertoli-Leydig cell tumour: (A) right and (B) left ovary (haematoxylin and eosin staining, original magnification  $2.5\times$ ). Immunohistochemistry reveals expression of (C) keratin, (D) inhibin (particularly in Leydig cells), (E) calretinin (particularly in the poorly differentiated Sertoli component), (F) oestrogen receptor and (G) progesterone receptor (magnification  $40\times$ ).

clinical course compared to well-differentiated tumours. Nonetheless, an analysis of 64 intermediate and poorly differentiated Sertoli-Leydig cell tumours described a 5- and 10-year survival rate of 92% (19). If recurrence occurs, it mainly appears within the first year after primary diagnosis, typically in the peritoneal space or retroperitoneal lymph nodes. A retrospective study by Chan et al. analysed prognostic factors responsible for survival in sex-cord stromal tumours. They reported that age  $<50$  years, small tumour size and absence of residual disease were important predictors of improved survival (20).

The majority of patients become apparent because of abdominal enlargement or pain caused by the enormous size of the tumour (13, 15), which is an average of 5–20 cm in diameter. Approximately two-thirds of patients present with elevated hormone levels. Typical signs of elevated oestrogen or testosterone levels are mild virilisation or irregular periods. In this context, 35% of all women show symptoms of androgen excess indicated by acne, temporal balding, progressive masculinisation of veins, deepening of the voice, disappearance of female body contours or enlargement of the clitoris (15). These patients typi-

cally have elevated testosterone levels. The endometrium can be affected by oestrogen synthesis induced by peripheral aromatase or by direct oestrogen production by the tumour.

In the case presented here, there were no obvious clinical signs of elevated hormone levels. Asked specifically, the patient mentioned period disorders (such as menorrhoea) that could be explained by the high oestrogen production by the tumour.

To detect tumour markers other than the known standard for ovarian cancer (CA 125), we performed detailed serum analysis, which revealed elevated oestrogen and normal testosterone levels, as well as elevated levels of NSE and CYFRA, which, to the best of our knowledge, have so far not been found in Sertoli-Leydig cell tumour patients. CYFRA is known to be elevated in ovarian malignancies (21). NSE is present in all neurons and is therefore recognised as a molecular marker of neuroendocrine tissue (22). In the literature, NSE has been described in the context of mature teratomas, immature teratomas, and dysgerminomas (23). These tumour markers may also be useful in our patient's clinical follow-up and offer more specific, individualised monitoring.

Treatment recommended for Sertoli-Leydig cell tumours varies with differentiation, tumour stage and patient age. Treatment modalities discussed are often controversial, as only a few studies have investigated this rare disease. Definitive operative staging should be performed in all Sertoli-Leydig cell tumours showing intermediate and low differentiation, including multiple biopsies and tissue from the omentum, as well as evaluation of the pelvic and para-aortal lymph nodes. Resection of normal lymph nodes is controversial. If the tumour is highly differentiated and if there is no sign of spread beyond the ovary involved in a young woman, unilateral adnexectomy might be justified. In our case the patient presented with a tumour of low differentiation at an advanced stage with unknown primary origin. Therefore, surgery involving hysterectomy, adnexectomy, appendectomy, omentectomy, peritonectomy of the lesser pelvis and anterior resection of the sigmoid colon and rectum was performed to reduce the tumour mass.

The benefit of adjuvant radio- or chemotherapy is not proven, but may be considered in cases of incomplete tumour resection (24). Because of the low differentiation of the tumour, the residual tumour mass and the advanced stage, chemotherapy with cisplatin, etoposide and ifosfamide combined with hyperthermia according to the MAKEI protocol was chosen for this patient. Chemotherapy regimes with cyclophosphamide in combination with either cisplatin and doxorubicin (25) or vincristine and actinomycin D (26) have also proven useful in individual cases. Hormonal manipulation has been even used as a therapeutic approach (27).

This case of a bilateral tumour in a perimenopausal woman demonstrates different rare aspects for Sertoli-Leydig cell tumours. Unlike most cases, this patient showed normal androgen but elevated oestrogen serum levels. We also found elevated serum levels of NSE and CYFRA, which, to the best of our knowledge, is a new finding in the context of Sertoli-Leydig cell tumours. As only two-thirds of patients with this rare disease present with elevated hormone levels, these two markers deserve further investigation, because they may be suitable for more specific, individualised tumour monitoring.

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