Sequential recurrences of ovarian granulosa cell tumour 10 and 11 years after initial diagnosis as haemoperitoneum and subhepatic mass: A case report and review of the literature

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Summary

Adult granulosa cell tumours (GCTs) are rare ovarian neoplasms characterised by an indolent course and a propensity for late recurrence. Due to frequent endocrine manifestations most GCTs are diagnosed at an early stage. However, clinical behaviour can not be safely predicted on the basis of conventional clinicopathologic parameters. Surgery remains the cornerstone of therapeutic management. We report on a rare case of a Stage IA GCT twice recurring ten and 11 years after initial surgical treatment. The first recurrence presented as an acute abdomen due to haemoperitoneum after tumour rupture. The second recurrence presented as a subhepatic mass. This case emphasises the need for extended, lifelong follow-up even for patients with early stage, apparently completely removed GCTs. Prognostic parameters and therapeutic options especially for patients with recurrent disease are discussed.

Key words: Granulosa cell tumour; Ovary; Recurrence; Haemoperitoneum; Subhepatic mass.

Introduction

Granulosa cell tumours (GCTs) of the ovary belong to the category of sex-cord stromal tumours which are characterised by the presence of derivatives of either or both the sex cords and the stroma [1-3]. Adult GCTs account for 1-2% of all ovarian tumours, approximately 5% of all malignant ovarian tumours and 95% of all granulosa cell tumours [1-4].They occur more often in menopausal and postmenopausal than premenopausal women, with a peak age incidence between 50 and 55 years. They are the most common ovarian tumours with estrogenic manifestations associated with the development of endometrial hyperplasia in as many as 50% of patients and endometrial carcinoma in about 5-10% of the cases [1-5].

Adult GCTs have a malignant potential, with a capacity to extend beyond the ovary or recur after apparently complete removal [1-6]. Spread is largely within the pelvis and lower abdomen; distant metastases are rare, but have been reported in many sites [1, 7, 8]. Although recurrences may appear within five years, they are commonly detected much later, occasionally three or more decades postoperatively [1-6, 9]. Therefore, even after a disease-free period of 20 years it is not possible to reassure the patient that she is fully cured with no chance of recurrence [10]. The stage at time of diagnosis is the only prognostic factor that is unequivocally related to survival [6,10-18]. Other prognostic factors have not been well defined and are controversially discussed in the literature [6, 10-18].

The cornerstone of treatment for GCT is surgical resection [4, 5]. Residual disease carries one of the most ominous prognostic signs [5, 17]. Data are limited as to whether adjuvant therapy confers any significant survival advantage [5]. Given the absence of well documented randomised clinical trials generating therapeutic guidelines, research for new treatment options is still continuing [5].

We report a case of ovarian GCT marked by sequential recurrences, the first occurring ten years after the initial operation and presenting as haemoperitoneum due to rupture, and the second one a year later as a subhepatic mass without liver invasion.

Case Report

A 50-year-old, gravida 1, para 1, white woman was initially diagnosed with GCT of the ovary in January 1994 at the age of 39 years. A tumour 3 cm at the greatest diameter and confined to the right ovary was resected with a bilateral salpingo-oophorectomy with total hysterectomy, right omentectomy and appendectomy. Pathology disclosed a moderately differentiated, Stage IA granulosa cell tumour of the ovary. The neoplasm demonstrated a mainly solid pattern of growth with areas of trabecular differentiation, moderate nuclear atypia and rare mitosis. The endometrium was of the proliferative type without

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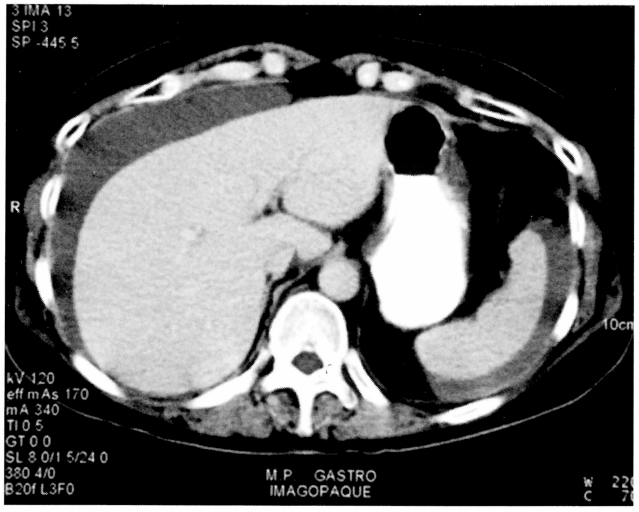

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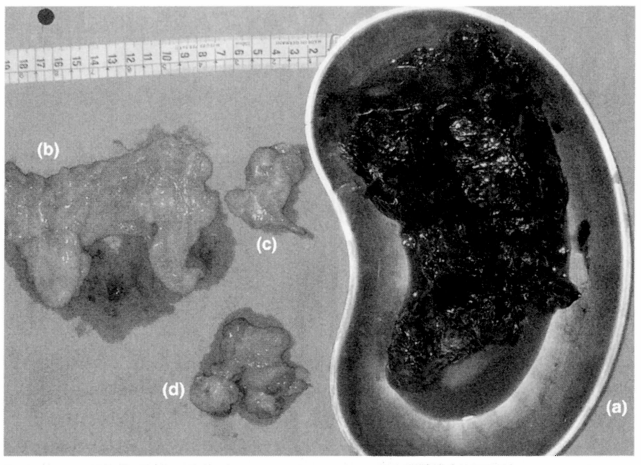

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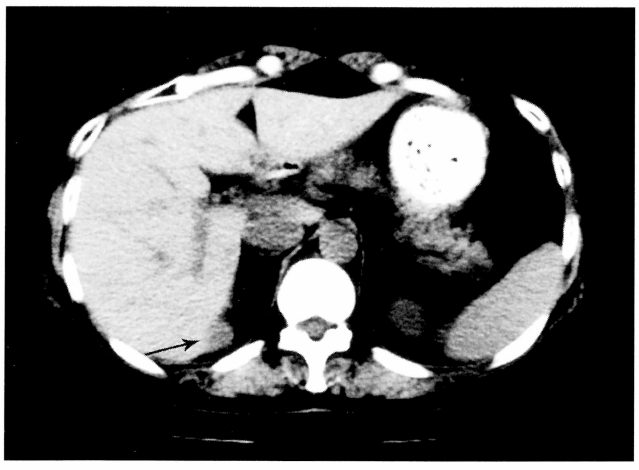

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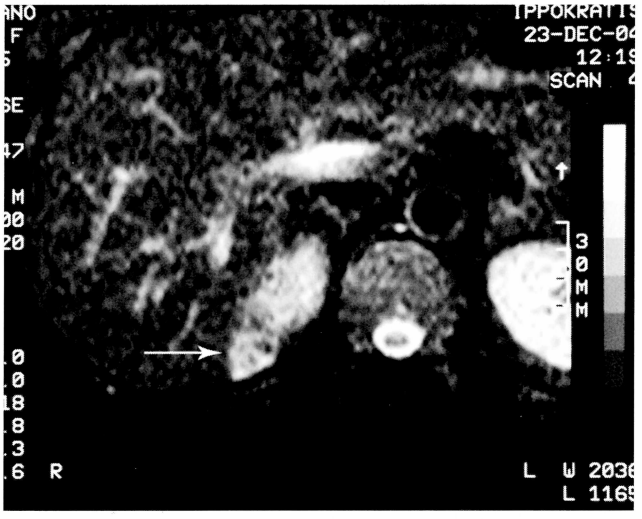

Fig. 4

Figure 1. — CT scan of the abdomen demonstrating haemoperitoneum.
Figure 2. — Macroscopic appearance of surgically removed: a) clots, b) left omentum, c) parasplenic mass, d) tumor of the left iliac fossa.
Figure 3. — CT scan demonstrating an approximately 1.2 cm subhepatic lesion.
Figure 4. — MRI revealing a rather well demarcated small subhepatic mass on the right dorsal side in close vicinity to the upper pole of the right kidney.

evidence of hyperplasia. The uterus, fallopian tubes, left ovary, omentum, appendix, peritoneal and pelvic washings showed no evidence of tumour spread. Given the early stage of the disease and the aggressive surgical treatment, no adjuvant therapy was administered. After resection follow-up consisted of annual pelvic examinations, including CT scans.

In December 2003, ten years after the initial diagnosis, the patient was admitted to the emergency department with a chief complaint of abdominal pain. Physical examination revealed an acute abdomen. Laboratory data showed haematocrit to be 26.5. Computed tomography (CT) scan demonstrated extensive fluid collection in the abdominal cavity (Figure 1). Under the impression of intraabdominal bleeding, an exploratory laparotomy was performed showing 2000 ml of haemoperitoneum, a tumour approximately 3 cm at the greatest diameter, localized into the left iliac fossa, and a solid 2.5 cm parasplenic mass (Figure 2). Haemoperitoneum was due to rupture of the tumour in the iliac fossa. At operation, blood and clots were evacuated, the peritoneal cavity was rinsed with saline solution, the two masses were resected and a complementary left omentectomy was performed. Pathology revealed recurrent GCT for both the iliac and parasplenic masses. The omentum was free of metastatic deposits.

One year later, in December 2004, the patient underwent her annual follow-up. CT scan and magnetic resonance imaging (MRI) demonstrated an approximately 1.2 cm subhepatic lesion on the right side dorsal, extending till, but not penetrating into the upper pole of the right kidney (Figures 3 and 4). Furthermore, two lymph nodes 0.6 and 1.1 cm, respectively, were seen in the mesenterium of the ascending colon. No ascites, pleural effusion or otherwise enlarged lymph nodes were found. A thorough surgery followed including excision of the subhepatic lesion in close vicinity to the upper pole of the right kidney, enlarged lymph nodes and any suspicious lesion within the abdominal cavity. Pathology disclosed recurrent GCT for the subhepatic lesion and the two mesenteric lymph nodes. The patient was referred to a specialist oncological centre for further management and received six courses of postoperative adjuvant chemotherapy with CAP regimen (cisplatin 50 mg/m^2, adriamycin 50 mg/m^2 and cyclophosphamide 500 mg/m^2, intravenously). At present, the patient is alive without evidence of recurrent disease.

Discussion

GCTs are relatively rare ovarian neoplasms with no clear pathogenesis [1]. They are derived from granulosa cells of the ovarian follicles, the proliferation of which, under normal conditions, is stimulated by the follicle-stimulating hormone (FSH) [1]. In response to FSH, granulosa cells synthesise estrogens by FSH-dependent aromatization of theca-derived androgen [19]. Fuller *et al.* attempted to identify a pathway by which activation of the FSH signaling pathway could be involved in the molecular pathogenesis of GCTs [20].

About two-thirds of patients with adult GCTs present with endocrine manifestations, leading to early diagnosis [1, 4, 5]. These manifestations are almost always related to hyperestrinism and depend on the age of the patient: postmenopausal women typically have uterine bleeding [1, 4, 5]. Women in the reproductive age group usually experience irregular, excessive uterine bleeding often preceded by a long period of amenorrhea lasting for months to years, sometimes being mistaken for menopausal amenorrhea. Rarely, androgenic changes, usually virilization or only a recent onset of hirsutism accompany adult GCTs [1, 4, 5]. Apart from endocrine manifestations most women with GCT have signs and symptoms related to a mass, usually in the form of abdominal pain or swelling; approximately 10% of patients present with acute abdominal symptoms due to rupture of the neoplasm with haemoperitoneum [1].

There is a recognised association between GCT and haemoperitoneum resulting from tumour haemorrhage or rupture of a cystic component [21-23]. Although there have been case reports describing GCTs presenting with haemoperitoneum, our case belongs to the rare ones in which haemoperitoneum consisted of the presenting symptom of the recurrent tumour ten years after the initial diagnosis. To our knowledge, a second similar case has been described by Lee *et al.* [23]. Moreover, although acute abdomen as the first presentation of recurrent ovarian tumour has been documented, it often occurs within five years after initial treatment and is often secondary to intestinal obstruction or partial intestinal obstruction [23]. If an acute abdominal attack occurs ten years later, it is probable that the possibility of a recurrent ovarian neoplasm may be overlooked [23, 24].

However, the tendency for late recurrence makes GCTs unique among malignant ovarian tumours [1, 9, 24]. It is thought that recurrent tumours arise from peritoneal seeds which begin at a point of contact between the primary tumour and a lower abdominal or pelvic structure [25]. These lesions remain after surgical excision of the primary tumour, and grow extremely slowly as discrete masses, displacing adjacent structures and organs, but only infrequently invading them [25]. This was confirmed in our case where the recurrent tumour was attached to the inferior surface of the liver without invading it.

The natural history of GCTs, as illustrated by our patient, is characterised by an indolent course and a propensity for late recurrence. The median time to relapse is four to six years after initial diagnosis although disease has recurred as late as 37 years [9, 18-25]. Hence, attempts to divide adult GCTs into benign and malignant categories are fruitless for all should be considered as being at least potentially malignant [10]. Predictors of recurrence may include advanced stage at presentation, high tumour mitotic count, bilaterality, large tumour size, tumour rupture, and lymphatic space invasion [14, 15]. However, other reports have refuted the association of these parameters with risk of relapse [26]. In a series from the Anderson Cancer Center, Houston, USA, the conclusion was that it is difficult to predict early recurrence and impossible to predict late recurrence using conventional clinical and pathological parameters [15]. Some authors hinted that Ki-67 proliferation index immunoreactivity and p53 overexpression correlate with disease stage, onset of recurrence and overall survival [27]. However, according to other histopathology reviews neither Ki-67 proliferation index nor p53 overexpression proved to be helpful in predicting the biological behaviour of GCTs [28].

The clinical utility of the gonadal peptide inhibin as a marker of tumour recurrence has generated interest recently [5]. Inhibin is produced by granulosa cells and has a negative feedback on FSH production [29]. This dimeric glycoprotein has several forms of variable molecular weight, depending on the combination of an α and β subunits [29]. Both dimeric inhibin, which is biologically active, and the free, inactive α subunit, may be found in the serum [5]. A clinical assay for inhibin was first developed in 1986, allowing the possibility of its use as a tumour marker [5]. Levels have been found to be elevated several fold in the serum of most GCT patients before surgery, as well as in selective ovarian vein sampling during surgery [5]. However, the positive predictive value and sensitivity of this peptide in routine preoperative clinical use are not known and the routine use of inhibin for all patients with a pelvic mass is not indicated [5]. What is clear about the clinical utility of this marker is that a consistently rising level in a postmenopausal woman with a history of GCT may predict recurrence and should trigger detailed clinical examination [5]. In our hospital inhibin was still unavailable, so we cannot make any comment concerning its clinical value.

The optimal treatment of a GCT in menopausal or postmenopausal women is bilateral salpingo-oophorectomy with total hysterectomy [1]. In younger women in whom the preservation of fertility is an important consideration, unilateral salpingo-oophorectomy with careful staging and endometrial biopsy – to exclude a concomitant uterine cancer – is justifiable if extraovarian spread is not evident and examination of the contralateral ovary shows no evidence of involvement [1, 4, 5]. Bilateral tumours account for 2-8% of cases [6, 12]. Two large series found no survival disadvantage for fertility-sparing surgery in premenopausal women with early stage disease [6, 30].

Sixty to 90% of adult GCTs are localised at the time of diagnosis [6, 12, 13]. When extended beyond the ovary, spread is largely within the pelvis and lower abdomen [1, 6, 12, 13]. As a result, most authors recommend surgical

staging in a manner consistent with the one performed for epithelial ovarian cancer, which includes pelvic washing for cytology, omentectomy, careful palpation and biopsy of any suspicious areas on the peritoneal surfaces or the node bearing areas [5]. Every effort should be made to resect all visible disease [5]. For recurrent tumours, operative debulking is the best procedure [16].

The place of adjuvant therapy is difficult to assess in GCTs. For those women with GCT confined to the ovary, adjuvant therapy is not generally recommended [5]. On the other hand, for those women with disease beyond the ovary or for those whose disease has recurred after primary surgical therapy, the recommended adjuvant treatment is based on level III evidence. There is a paucity of randomised clinical trials to guide decision-making. However, most authors agree with a multi-drug regimen of chemotherapy based on cisplatin [5, 31, 32]. Cisplatin in combination with doxorubicin, cyclophosmamide, bleomycin or etoposide has produced overall response rates in the range of 60-83% [31, 32]. However, toxicity is significant and the duration of response is measured in months [31]. Paclitaxel, used as a single agent, has been reported to result in partial response lasting 12 months [33]. A growing number of case reports have described hormonal treatment for recurrent disease. Hormonal therapies, such as GnRH agonists, antiestrogens and progestins demonstrate low side-effects and responses of a few months duration [34].

Overall 10-year survival figures show wide variation ranging from under 60% to over 90% while progressive declines have been documented after longer follow-up periods: the 25-year survival is only in the region of 40-60% [6, 10-18, 26, 30]. As for recurrence, the unique undisputed parameter adversely affecting overall survival is the stage at presentation [6, 10-18, 26, 30]. A 96% or 86% 10-year survival has been reported for patients with Stage I tumours compared to 26% or 49% for patients in all other stages in two large series, respectively [6, 35]. Apart from stage, other parameters reported – but not proven – to carry dismal prognostic significance include residual disease after surgery [5, 17], size greater than 5 cm [6, 35], poor (difuse) versus well (follicular or with a cylindromatous pattern) histologic differentiation [1], high nuclear atypia [35] and high mitotic activity (3 or more mitotic figures per 10 high power fields) [14, 35]. Rupture of the tumour consists of an adverse prognostic factor even within Stage I tumours [6].

In conclusion, GSTs as illustrated by the case presented here, are rare, slow growing neoplasms characterised by an indolent clinical course and a propensity for late recurrences. The long natural history of this disease highlights the importance of extended, lifelong, follow-up even for patients with early stage, completely resected GCTs. In the initial management, surgery is important for diagnosis, staging and tumour debulking. For recurrent tumours, operative debulking is the best procedure with no standard adjuvant treatment after surgery. The use of inhibin seems promising for the follow-up of GCT patients and early detection of recurrences.

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