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Growing teratoma syndrome after ovarian inmature teratoma: a case report and review of the literature

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Summary

Growing teratoma syndrome is an uncommon complication of malignant germ cell cancer, characterised by the development of large tumours during or after chemotherapy, despite normalisation of tumour marker levels and metastasis, which contain only mature teratoma. Given its low incidence, little is data available. The authors present the case of a 15-year-old girl with a growing teratoma and the literature review outlines the current knowledge of its pathogenesis, common sites, diagnosis, natural course, treatment, and prognosis.

Key words: Growing teratoma syndrome; Immature teratoma; Malignant germ cell tumours.

Introduction

Malignant germ cell tumours (MGCTs) represent approximately 1-2% of malignant ovarian tumours [1] These tumours are classified into two main categories: dysgerminomas and non-dysgerminomas [1, 2]. The latter group includes immature teratoma, which accounts for 35.6% of all ovarian malignant germ cell tumours [3].

Immature teratoma, a tumour that arises from pluripotent germline stem cells, is composed of organoid and embryonic structures with variable levels of differentiation [4]. Usually, it occurs most commonly in girls and young people, and grows rapidly, with early metastasis development [4]. Growing teratoma syndrome (GTS) is a rare complication of immature teratoma, defined by the presence or development of large tumours during or after chemotherapy, normalisation of tumour marker levels, and metastasis that contains only mature teratoma [5-7]. It affects 1.9-7.6% of patients after treatment for non-seminomatous testicular cancer [6, 8-10]. GTS is less common in females, and hence most data available and the management of the syndrome are based on studies on non-seminomatous testicular cancer [9].

In this paper, the authors describe the case of a 15-year-old girl with a large immature teratoma in the left ovary who underwent fertility-sparing surgery and during chemotherapy, she was found to have an increase in residual tumour tissue, as well as new tumours, despite normalisation of alpha-fetoprotein (AFP) levels.

Case Report

The authors present the case of a 15-year-old girl referred by her general practitioner for a two-week history of pain and abdominal distension. Her gynaecological and obstetric history included menarche at 12 years of age and regular periods, and she had never had sex. During abdominal examination, the authors found abdominal distension, and pain with a palpable mobile mass, extending to four fingers above the level of the umbilicus. Endorectal ultrasound revealed a tumour with a lack of clear margins and heterogeneous content (solid-cystic) that seemed to be associated with the left ovary. A computer tomography (CT) scan of the pelvis revealed an abdominal mass of 18.6 x 12 x 25 cm extending upwards to the epigastrium and downwards to the pelvis, where it lay close to the left adnexa, with calcification foci and macroscopic fat tissue, suggestive of teratoma (Figures 1a, b). In addition, the authors observed cardiophrenic lymph node involvement and subcapsular perihepatic fluid collection in the liver segment VII. Tumour marker testing found AFP levels of 679 UI/ml, cancer antigen 125 (CA125) levels of 338.7 UI/ml, carbohydrate antigen 19-9 (CA19-9) levels of 352.6 UI/ml, and normal carcinoembryonic antigen (CEA) levels.

Given these results, the authors decided to perform infraumbilical midline laparotomy and found a large (20 x 12 cm) tumour associated with the left ovary with multiple peritoneal and epiploic implants. They proceeded to carry out left adnexectomy, peritoneal lavage for cytological analysis, partial omentectomy, appendectomy, and resection of most of the implants, except for those only millimetres in diameter in the pouch of Douglas. Histopathology showed grade 3 ovarian immature teratoma in Stage III according to the International Federation of Gynecology and Obstetrics (FIGO) system, with some mature teratomatous elements and gliomatosi peritonei (Figure 2).

A CT scan performed 23 days after surgery showed residual disease in the pouch of Douglas (58 x 67 x 20 mm) and the perihepatic region (60 x 40 x 80 mm), as well as an increase in bilateral cardiophrenic lymph node involvement. Subsequently,

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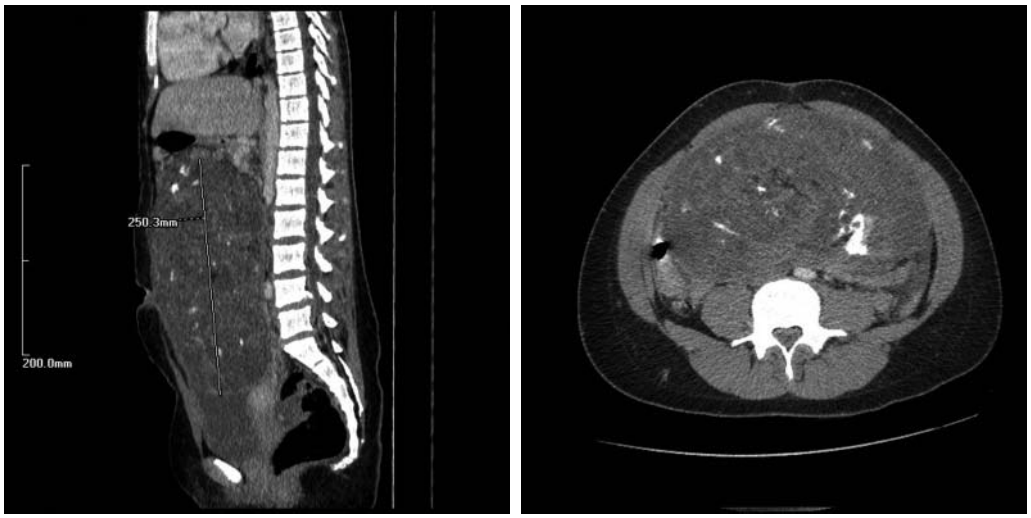

Figure 1. — Pelvic computed tomography image before first surgery, a) longitudinal and b) axial slices.

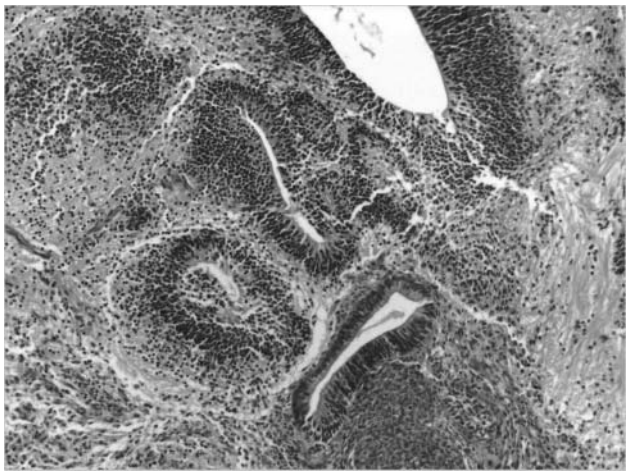

Figure 2. — Histological image of tissue sampled in the first surgery showing multiple areas of immature neuroectodermal tissue, with structures reminiscent of ependymal, surrounded by immature glial tissue, that is, immature teratoma.

chemotherapy was initiated with three cycles of bleomycin, etoposide, and cisplatin (BEP). At three months the authors detected an increase in AFP levels: from 300 UI/ml after surgery to 623 UI/ml after the first cycles, together with radiological progression on CT with growth of the peritoneal implants in the pouch of Douglas and perihepatic region, as well as enlargement of cardiophrenic lymph nodes. After these findings the treatment was changed to paclitaxel, ifosfamide, and cisplastin (TIP).

After five cycles of chemotherapy with TIP, AFP levels normalised (4.4 UI/ml). However, a positron emission tomography (PET)-CT scan revealed progressive neoplastic disease with further increase in lymph node involvement; growth of the aforementioned implants, that of the pouch of Douglas reaching 73 x 33 mm, and the perihepatic growth 120 x 80 mm; and appearance of new implants in the retropubic space and the right cardiophrenic angle (Figures 3a, b). Due to the suspicion of recurrence of immature teratoma, the authors decided to carry out rescue cytoreductive surgery, with peritoneal lavage and sample collection for cytological analysis, removal of the retrohepatic implant by peritonectomy with wide safety margins (Figures 4a, b), removal of the implant on the right kidney, opening of the right diaphragm,

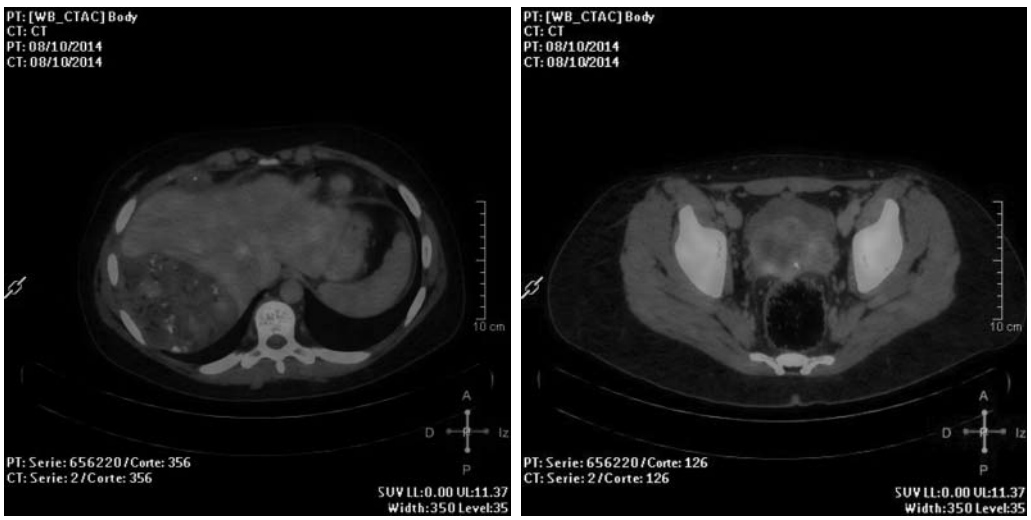

Figure 3. — Abdominal/pelvic positron emission tomography-computed tomography after chemotherapy: a) implants in perihepatic region and right cardiophrenic angle; and b) implants in the pouch of Douglas and retropubic space.

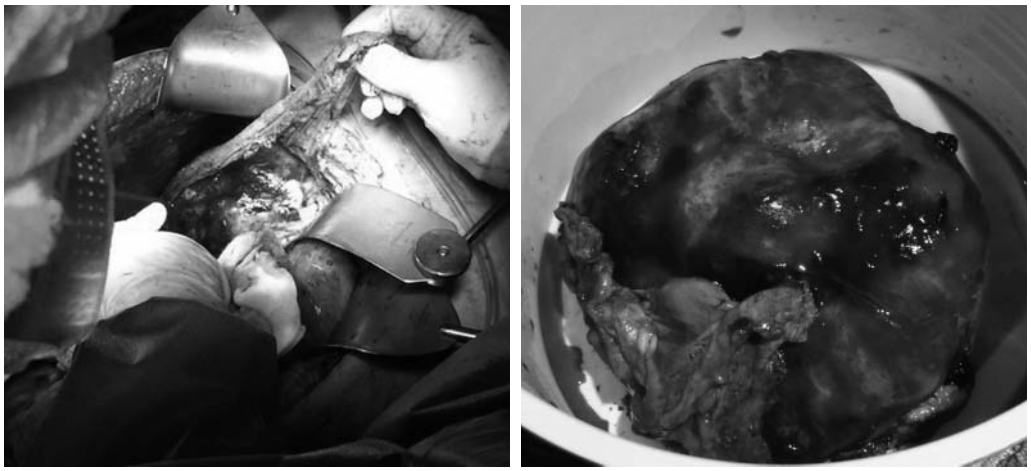

Figure 4. — (a and b): Removal of the retrohepatic implant by peritonectomy.

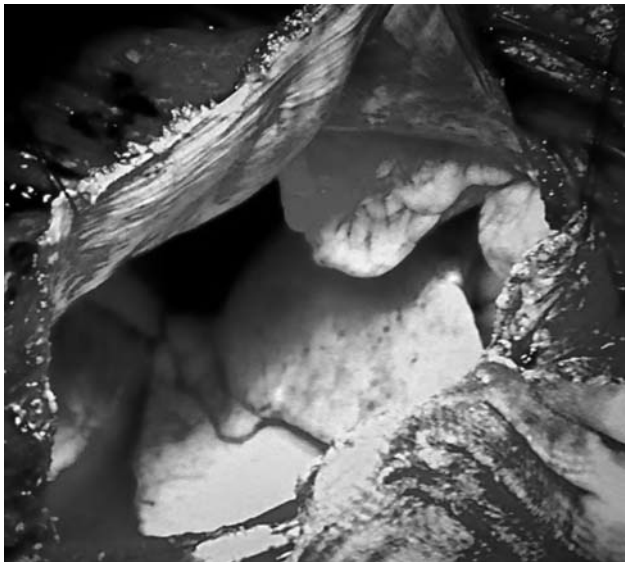

Figure 5. — Removal of the retrohepatic implant by opening of the right diaphragm.

allowing the identification and removal of two implants (Figure 5), pelvic peritonectomy with en bloc resection of the uterus, right adnexa and implant in the pouch of Douglas, after dissection from the anterior part of the rectum, resection of the implant in the retropubic space, bilateral pelvic and aortocaval lymph node dissection, infragastric dissection of the greater omentum, opening of the left diaphram allowing removal of cardiophrenic lymph nodes, and removal of the round ligament of the liver. The histopathological report, however, indicated that only mature teratoma had been found in all the samples sent for analysis (Figure 6). This clinical presentation is not attributable to a relapse of an immature teratoma, but rather chemotherapeutic retroconversion with the subsequent development of GTS.

In the immediate postoperative period, the patient was kept in the intensive care unit, and was transferred to the gynaecology ward and then discharged 14 days after surgery. At five months, the patient had no related symptoms, with no signs of disease on the follow-up CT and AFP levels of 1.1 UI/ml.

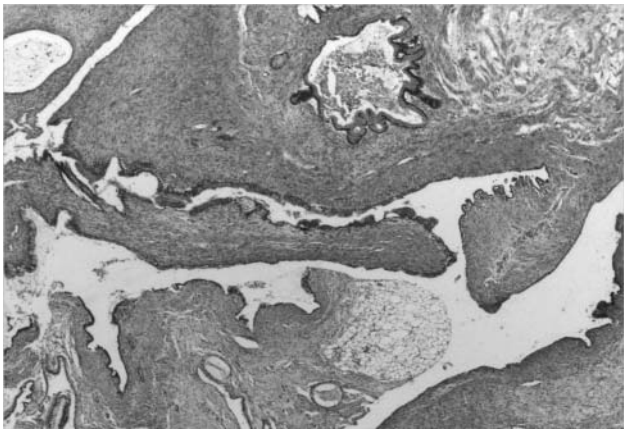

Figure 6. — Histological image of tissue sampled after chemotherapy showing glandular epithelial and mesenchymal tissue, with adipocytes, that is, mature teratoma.

Discussion

Immature ovarian teratoma

Immature teratomas are large ovarian MGCTs, between six cm and 35 cm in diameter, encapsulated, with a smooth, nodular or lobulated margins [4]. In general, they affect young women, although a case of immature teratoma and subsequent GTS has been described in a five-year-old girl. Given that they grow rapidly and to large sizes, they tend to present with pain and abdominal distension. Further, they may be associated with elevated AFP levels [1], and for this reason, it is important to measure tumour markers in all women with this type of adnexal masses.

Histologically, they are composed of elements from all three germ layers: ectoderm, mesoderm, and endoderm [4]. Immature neural tissue is the main type of tissue in immature teratoma, the proportion of this tissue type being the basis for establishing the degree of differentiation, from grade 1 (well-differentiated) to grade 3 (poorly differenti-

ated) [1, 10]. For staging, the same system is used as for ovarian epithelial carcinoma [11]. In around 30% of cases, immature teratoma have spread outside the ovary at diagnosis [4]. In fact, the present patient had grade 3 immature teratoma classed at Stage III, as it had spread beyond the pelvis, involving the peritoneum and omentum. Given that the degree of differentiation and staging are good indicators of the risk of recurrence [10], the increase in residual tissue and appearance of new growths were interpreted as suggestive of recurrence of an immature teratoma.

With regards to treatment, it is important to distinguish between mature and immature teratomas. In the former, the treatment is exclusively surgical as chemotherapy is not effective in these benign tumours [1, 8], whereas immature teratomas require both surgery and chemotherapy (except in the case of grade 1 Stage 1 tumours) [1, 12]. The surgical intervention has two goals: one diagnostic, enabling staging of the tumour, and the other therapeutic, with as much as possible of the tumour being removed. The procedure depends on the patient's age, it being uncommon to carry out total hysterectomy with bilateral adnexectomy, pelvic and para-aortic lymph node dissection, omentectomy, and appendectomy, since immature teratoma tends to affect young women. In such cases, it is more common to perform fertility-sparing surgery, performing unilateral adnexectomy, sparing the uterus and the other ovary, in combination with chemotherapy [1, 10, 12, 13]. In general, the treatment is three to four cycles of BEP [1, 10, 14], but in the present case the authors also administered five cycles of TIP with paclitaxel given that AFP levels did not normalise and there was an increase in residual tumour tissue. With this approach, they succeeded in normalising AFP levels, but failed to stop tumour progression. Histopathological analysis found that all the samples contained only mature teratoma, consistent with the clinical and pathological features of GTS.

Growing teratoma syndrome

This syndrome was first described by Logothetis *et al.* in 1982 in testicular mixed germ cell tumours [5]. Before then, in 1977, DiSaia *et al.* defined a similar phenomenon in ovarian MGCTs, which they called "chemotherapeutic retroconversion" [15]. More recently, Amsalem *et al.* concluded that these were the same phenomenon [6]. According to the original description, three criteria must be met to diagnose GTS: 1) an increase in clinical signs or radiological growth of the residual tumour or development of new tumours during or after chemotherapy for an MGCT; 2) normalisation of previously elevated levels of tumour markers (AFP, beta-human chorionic gonadotropin); and 3) histological analysis finding that metastases contain only mature teratoma [5-8, 16].

This syndrome, which is rare clinical entity, generally occurs during chemotherapy or up to two years after initiating the therapy [17], though some cases have been reported that occurred more than five years after the start of treatment [18,19].

Pathogenesis

The pathogenesis of GTS remains poorly understood, but two hypotheses have been proposed [6-8, 15]. According to the first theory, chemotherapy may induce the differentiation of malignant cells in the immature teratoma into mature teratoma; in this way, cells acquire a benign phenotype refractory to chemotherapy and grow on their own accord. The second hypothesis argues that chemotherapy may induce a selective destruction of immature elements, while mature elements, resistant to chemotherapy, persist and give rise to the syndrome. Several researchers claim that it is more likely that the underlying mechanism is the second hypothesis, given that is common to find mature teratomatous elements in primary tumours [6-8, 16].

Location

GTS tends to occur at the same sites as the primary tumour. However, cases of metastasis of the mature teratoma have also been described. The development of distant lesions of mature teratoma might be explained by the growth of small pre-existing lesions [8]. However, mature teratomas have a known tendency to metastasize, and therefore, a metastatic process cannot be ruled out. The retroperitoneum is the most common area of metastasis from testicular germ cell tumours, followed by the lung, and it is also the most common area of GTS [16, 20]. In the case of GTS arising from an ovarian MGCT, metastases tend to be confined to the pelvis, abdomen, and retroperitoneum, and distant metastasis are more rare [17]. Despite this, the present patient had metastasis in the pleural cavity and pericardium, which has not previously been described.

Diagnosis

Concerning predictors of the development of GTS, on the one hand, André *et al.* [8] described the following factors: 1) the presence of mature teratomatous elements in the primary tumour; 2) no reduction in the size of metastases during chemotherapy; and 3) the presence of mature teratoma in post-chemotherapy residual masses. This means that close monitoring by CT is warranted in high-risk patients, permitting early diagnosis of GTS and enabling complete tumour resection. Further, Moskovic *et al.* [21] described the radiological findings on CT that are suggestive of maturation and hence the development of GTS: an increased density of mass lesions, whose margins became better circumscribed in relation to adjacent tissues and the onset of internal calcification, with fatty areas of tissue and cystic changes. However, as conventional CT can underestimate tumours of less than one to two cm in diameter, in particular for those within the mesenterium and omentum, it may be useful to perform

18F-fluorodeoxyglucose (FDG) PET/CT to provide further information, to be assessed together with CT findings and tumour marker levels [22]. With GTS, there may be either positive [22] or negative [23, 24] FDG uptake. In summary, it is important to assess images and tumour marker levels together.

On the other hand, Mrabti *et al.* [25] considered gliomatosis peritonei in the initial laparotomy to be a predictive factor. Gliomatosis peritonei is a very uncommon entity defined by mature glial implants in the peritoneal cavity, omentum, and abdominal lymph nodes in patients with ovarian teratomas of any size. If implants have immature elements, however, they should not be classified as gliomatosis peritonei but rather as metastases of immature teratoma [25, 26].

Disease course

Despite the benign phenotype of GTS, two types of complications have been observed in these patients: mechanical complications and malignant transformation [7, 8, 27]. Mechanical complications are secondary to the pressure on neighbouring organs due to tumour growth: pain, intestinal obstruction, kidney failure due to ureteral compression, thrombophlebitis, and tissue necrosis. Concerning malignant transformation, Andre *et al.* [8] reported an incidence of 3% whereas Shigeta *et al.* [28] indicated a figure of 5.4%. The malignant potential of mature teratomas has been described, including their transformation to MGCTs, sarcoma, squamous cell carcinoma, adenocarcinoma, carcinoid tumours, and primitive neuroectodermal tumours [8]. There have been reports of the malignant transformation of GTS to sarcoma [29] and to carcinoid tumours [17]. This potential for malignant transformation supports complete resection of this type of tumour, given a greater risk of malignant transformation with incomplete resection [8]. Andre *et al.* [8] described that testicular MGCT developed in 50% of patients who underwent incomplete resection, compared to just 8% of those who underwent complete resection.

Treatment and prognosis

GTS, like mature teratoma, is refractory to both chemotherapy and radiotherapy; henceforth surgical treatment is the only available curative treatment. Complete surgical resection is recommended or, when this is not possible, maximal cytoreductive surgery [6, 7, 9].

In general, the long-term prognosis is good and some successful pregnancies have been described [10]. However, it is possible that further lesions appear after the treatment, especially in patients with incomplete resection [8, 22, 30, 31]. Cases of recurrence up to 19 years after the initial treatment of GTS have been described [17], and therefore it is essential to perform regular follow-up assessments for several years, using appropriate imaging techniques and measuring tumour marker levels [7, 17, 32]. Shigeta *et al.* [28] reported a 12.7% rate of recurrence, with a mean recurrence interval of 24 months. In their review of 48 cases of GTS, Kikawa *et al.* found that four out of the 48 patients who did not undergo complete resection had recurrence [22], indicating the importance of making as much effort as possible in the initial surgery. The rate of recurrence in cases of incomplete surgery is similar in GTS with a non-ovarian source, as in the series of André *et al.*, who found recurrence in 83% of the patients with incomplete surgery compared to 4% in cases of complete tumour resection [8].

The appearance of new lesions requires more surgery, and such subsequent surgical interventions are increasingly radical. For this reason, it is important to assess the operability and weigh the risks and the benefits [9].

It is difficult to predict the potential growth of GTS. Cases of long-term stabilisation have been described, but there have been no reports of spontaneous regression. Cytokines, growth factors, and steroid hormones seem to be involved in the growth potential of these tumours [8]. For this reason, though no medical treatment has been established, when surgery is not possible, treatments have been based on agents including interferon alpha (α INF), bevacizumab, and cyclin-dependent kinase (CDK) inhibitor, PD0332991. Van der Graast *et al.* [33], Kattan *et al.* [16], and Inonue *et al.* [34] have described treatment with α INF in refractory cases of GTS. This seems to be a safe and well-tolerated treatment, but, although it is believed to delay cell growth, its mechanism of action remains unknown. On the other hand, Mego *et al.* [35] published a case of a patient with inoperable GTS treated with bevacizumab. This is a humanized monoclonal antibody that inhibits angiogenesis (a vascular endothelial growth factor inhibitor). Again, in this case, tolerance to the treatment was excellent. Finally, Vaughn *et al.* [36] used PD0332991, a selective inhibitor of CDK4/6, in patients with inoperable GTS. This treatment is based on the fact that mature teratomas express high levels of retinoblastoma protein and that CDK4/6 stimulates cell growth by means of phosphorylation of this protein. These three treatments achieved tumour growth stabilisation, with some cases of slight remission. However, these treatments are long term, given that their cessation would lead to tumour progression.

Conclusions

To conclude, GTS is a rare complication of MGCTs after chemotherapy that clinicians should be aware of to avoid it being mistaken for progression or recurrence, and to enable early diagnosis and immediate complete resection; thereby, preventing malignant transformation, problems secondary to compression of neighbouring structures, and the recurrence of GTS.

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