

The growing teratoma syndrome: Current review of the literature

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ABSTRACT

Growing teratoma syndrome (GTS) is a rare condition among patients with non-seminomatous germ cell tumors who present with enlarging metastatic masses during appropriate systemic chemotherapy and in the context of normalized serum markers. This article reviews the current pertinent scientific literature on the diagnosis and management of GTS.

Key words: Enlarging metastatic mass, growing teratoma, non-seminomatous germ cell tumors

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INTRODUCTION

The term growing teratoma syndrome (GTS) was coined by Logothetis *et al.*,^[1] in 1982 to describe a rare entity among patients with non-seminomatous germ cell tumors (NSGCTs), characterized by enlarging metastatic masses despite appropriate systemic chemotherapy and normalized serum markers. Histology of those resected lesions revealed benign mature teratomatous elements with no components of viable germ cell tumor. The prevalence of GTS is only 1.9-7.6%.^[1,2] However, reports in the literature of GTS related to both testicular and ovarian carcinoma have grown in number. This may be attributed to the increased awareness of this condition, improved diagnostic imaging tools and the efficacy of our chemotherapeutic agents, which appear to potentially play a significant role in the etiology of this syndrome. The purpose of this article is to review the pertinent scientific literature that describes the diagnosis and management of GTS.

We performed an extensive MEDLINE search for articles including the term “growing teratoma syndrome” that were published from 1966 to the present. Our search revealed 26 relevant articles. Here, we report an up-to-date review on GTS based on articles found in our literature search as well as of the pertinent articles referenced in those studies.

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HISTORY

In a landmark article based on the experience at the University of Texas M. D. Anderson Cancer Center, Logothetis *et al.*,^[1] described six patients with enlarging metastases during systemic chemotherapy for primary mixed metastatic NSGCTs. All six patients had normalized serum markers after chemotherapy and remained disease-free following successful complete surgical excision of the enlarging masses. Surgical pathology consisted of benign mature teratoma with no viable germ cell element.

Although GTS was first named in 1982, the benign “transformation” or “evolution” of testicular carcinoma after chemotherapy was first noted in the early 1970s.^[3,7] The earliest report of “benign maturation” was published in 1969 by DW Smithers from the Royal Cancer Hospital of London. He described five patients who presented with primary testicular neoplasms of varying histologies, including seminoma and immature teratoma, whose metastatic sites consisted of well-differentiated teratomatous elements.^[3] In 1973, Willis and Hajdu^[5] published five case reports of patients with primary embryonal testicular carcinoma who presented between 16 months and 12 years after radiotherapy or chemotherapy with metastatic deposits composed of mature teratomatous elements. That same year, John Dees of Duke University described the finding of a benign teratoma in a patient treated for 8 years with maintenance actinomycin D for primary embryonal testicular carcinoma.^[4] In 1975, Merrin *et al.*,^[6] reported a similar phenomenon in seven patients. Hong *et al.*,^[7] in 1977, described the Memorial Sloan–Kettering Cancer Center experience with 12 patients of 600 presenting with germ cell testicular carcinoma. Finally, in 1981, Carr *et al.*,^[8] reported four more similar cases at the Wisconsin Clinical

Cancer Center. These early reports highlighted the favorable prognosis for patients after resection of these lesions and began to build the case for such a clinical entity. Of note, the above-mentioned case reports did not present tumor marker data because tumor markers did not become the standard diagnostic tool for testicular carcinoma until the 1980s.

Concurrent gynecologic literature described a similar transformation in the setting of ovarian germ cell neoplasia, a process initially named “chemotherapeutic retroconversion” by DiSaia *et al.*,^[9] Those authors defined chemotherapeutic retroconversion as conversion of a metastatic immature teratoma into a mature tumor as a result of chemotherapy. In their review of the scientific literature, Amsalem *et al.*,^[10] found “chemotherapeutic retroconversion” in ovarian germ cell tumors described by DiSaia *et al.*,^[9] and “growing teratoma syndrome” described by Logothetis *et al.*,^[11] in testicular germ cell tumors to be a synonymous phenomenon. Arguably, in GTS, not only must the mature teratoma nodules have undergone chemotherapeutic retroconversion but they also must have the ability to grow, whereas in pure definition of chemotherapeutic retroconversion, the nodules do not increase in size.^[11] Interestingly, there are also three reports of GTS after chemotherapy for primary intracranial (pineal gland) NSGCT.^[12]

DEFINITION

In general, the diagnosis of GTS is dependent on surveillance of serum tumor makers and serial imaging. In the case of testicular carcinoma, GTS should be suspected in patients with: (1) history of NSGCT, (2) increasing size of metastatic lesions on serial imaging during or after systemic chemotherapy for the treatment of testis cancer and (3) normalized serum tumor markers or a physiological explanation for the presence of abnormal tumor markers. The diagnosis is confirmed by the presence of mature teratoma and the absence of any malignant germ cells on final surgical pathology.

The etiology of GTS is unclear. The two most-quoted theories are that: (1) chemotherapy destroys only the immature malignant cells, leaving the mature benign teratomatous elements and (2) chemotherapy alters the cell kinetics toward transformation from a totipotent malignant germ cell toward a benign mature teratoma.^[6,8,9] A third hypothesis offered by Hong *et al.*,^[7] proposes an inherent and spontaneous differentiation of malignant cells into benign tissues, as suggested by the experimental murine teratocarcinoma mouse model. This hypothesis further implies that chemotherapy prolongs the course of the disease (i.e., the patients survive long enough) to permit “spontaneous evolution” to occur. Benign metastasis of unrecognized mature teratoma from the primary tumor has also been proposed.^[5]

PRESENTING HISTORY

The prevalence of GTS in metastatic NSGCT is between 1.9

and 7.6%.^[1,2] The most current series from M. D. Anderson reports a prevalence of 2.2%.^[13] GTS is most commonly observed in the retroperitoneum but has also been described in the lung, mediastinum, supraclavicular lymph nodes, inguinal lymph nodes, forearm, mesentery and liver.^[14]

The chemotherapy used before establishing a diagnosis of GTS includes a variety of single agents, such as actinomycin D or cyclophosphamide, or various combinations of adriamycin, bleomycin, etoposide, vinblastine, cyclophosphamide, chlorambucil, methotrexate, nitrogen mustard and cisplatin. Cases of GTS have been reported with current conventional systemic chemotherapy regimens [bleomycin, etoposide and cisplatin (BEP)].

DIAGNOSIS

GTS poses a diagnostic challenge for both medical oncologists and urologists because of its rarity and unusual presentation. Thus, it requires a coordinated effort among all involved physicians to make an early diagnosis. A patient’s eventual treatment and prognosis are highly dependent on the timing of diagnosis because detection of GTS in a delayed fashion results in a more extensive surgical dissection with a higher associated risk of adjacent organ injury and increasing the difficulty of the operation.^[12] Better outcomes are realized when GTS lesions are excised before they become more extensive or potentially inoperable. In an effort to avoid late diagnosis of GTS, Spiess *et al.*,^[13] recommend regular imaging in patients undergoing chemotherapy, possibly after two cycles of chemotherapy, to ensure careful monitoring of subtle changes in tumor size and appearance. Reports of the timing of presentation vary, with the earliest GTS cases diagnosed during the early courses of chemotherapy and others as late as 12 years post-chemotherapy.^[5,13]

Serum tumor markers

The hallmark feature of GTS is the normalization of tumor markers [α -feto protein (AFP), β -human chorionic gonadotropin (HCG), lactate dehydrogenase]. This element was first highlighted by Logothetis *et al.*,^[11] In cases where the tumor markers are not entirely in the normal range, it is imperative to exclude any non-malignant etiology (i.e., elevated AFP from liver dysfunction, elevated β -HCG from marijuana use or from elevated luteinizing hormone).^[15]

Radiologic imaging

Imaging is not a foolproof means of discriminating between metastatic NSGCT and GTS. However, some features on computed tomography (CT) scans, such as a better circumscribed margin, new onset or an increased number of cystic changes with elements of fat, punctuate, curvilinear calcifications or an increase in density of the masses, are commonly associated with the presence of GTS.^[16-18]

There are reports of GTS masses initially reducing in size by as much as 40% in volume in the early course of

chemotherapy and then enlarging during the latter course.^[2] No specific size or growth rate of the metastatic lesions has been defined for GTS. The reported maximal diameter of GTS lesions on CT scans is between 1.0 and 25.0 cm.^[2,13] A rapid growth rate, in the presence of normalized serum tumor markers, should raise further suspicion of GTS. The reported growth rates of GTS masses vary considerably, with findings of a median increase in circumferential diameter of 0.7 cm per month [95% confidence interval (CI), 0.1-2.4] or median volume growth of 12.9 ml/month (95% CI, 0.85-4.5).^[13]

[18F]-Fluorodeoxyglucose (FDG) positron emission tomography has been postulated to assist in identifying GTS lesions. Positive FDG imaging suggests viable tumor whereas negative uptake is likely a necrosis or a mature teratoma.^[19]

PATHOLOGY

The presence of teratomatous elements in the orchiectomy specimen should raise clinical suspicion of GTS.^[13] The occurrence of a teratomatous component in the primary tumor has been reported to be as high as 86%.^[18]

GTS can consist of cartilage, ciliated respiratory-type epithelium, enteric epithelium and neurogenic tissue with a supporting stroma of undifferentiated mesenchymal spindle cells. Both cystic and solid features may be present.^[7]

Treatment

There is no effective medical treatment for GTS. Also, GTS is unresponsive to chemotherapy or radiotherapy.^[1,9,18] Total surgical removal of mature teratomas is currently the gold standard treatment of this condition.

MEDICAL THERAPY

Some medical therapies have produced response in patients with GTS. Interferon therapy has been reported to have some role in the treatment of GTS. Rustin *et al.*,^[20] described disease stabilization with interferon in two patients. Van der Gaast *et al.*,^[21] reported a minor response to interferon. Tonkin *et al.*,^[22] described a patient with inoperable abdominal GTS whose disease was controlled for 8 years on interferon. In a promising study of biweekly 10 mg/kg dosage of the humanized monoclonal antibody bevacizumab for 6 months, Mego *et al.*,^[23] reported significant clinical improvement as well as stability of a partially resected mass on CT scans. Forty days after the treatment was stopped, disease progression occurred. Therefore, although surgery is still the recommended treatment for GTS, these medical therapies may play a role in reducing the size and alleviating surgical dissections.

SURGERY

Although GTS lesions are histologically benign, their

enveloping growth and aggressive local expansion can cause substantial morbidity and mortality. Patients in whom surgery is delayed can develop inoperable disease. Additionally, locally advancing tumors have been reported to cause severe renal, biliary, duodenal or large vessel obstruction, resulting in bowel necrosis and urinary fistula. With time, surgical excision of GTS lesions becomes more technically challenging thus potentiating serious intraoperative complications such as large vessel or ureteral injury and post-operative complications, including ileus, acute pancreatitis, chylous ascites and sepsis.^[13,21,24]

Other indications for surgery are to diminish the chances of degeneration of mature teratoma into undifferentiated testicular tumor components and to rule out secondary malignancies that can be induced by previous chemotherapy.^[21]

It is imperative to perform an adequate and total resection because GTS recurrence is impressive, with reported rates of 72-83% in patients with partial resections versus 0-4% in those who undergo complete resections.^[13,25]

Several surgical approaches, including (1) resection of mass only, (2) template-type dissection and (3) complete bilateral dissection (preferably nerve sparing) can be considered. However, we advocate a full, bilateral template (nerve sparing if possible) in most patients because of the rare chance of a residual malignant component within the residual retroperitoneal tissues in the post-chemotherapy setting.

ADJUVANT CHEMOTHERAPY OR RADIATION THERAPY

There are few reported cases in the testicular or ovarian GTS literature showing any benefit of post-resection chemotherapy or radiation therapy.^[1,9,18]

PROGNOSIS

Complete surgical resection of GTS is often curative. In the recent M. D. Anderson series, none of the nine patients with GTS developed local or distant recurrence at a median follow-up duration of 2 years.^[13] The 5-year overall survival rate of patients who undergo surgery for GTS is 89%, with mortality related to post-operative complications. None of the six patients in the early M. D. Anderson experience reported by Logothetis *et al.*,^[1] had any local or distant recurrence. These results contradict those of other case series that reported local recurrence rates between 0 and 54%.^[2,7,14] These differences in local recurrence rates may be attributable to the completeness of the resections, which would likely relate to the complexity of the presenting lesion and the surgeon's expertise.

A recent review revealed similar outcomes in patients with GTS associated with ovarian germ cell tumors, with complete resections favoring curative results, with most patients alive

at the time of the reports, with follow-up periods up to 9 years in the complete resection groups.^[18] With regard to prognosis, patients must be informed that in addition to the risk of GTS recurrence, there is always a risk of recurrent germ cell neoplasia as well as development of secondary, post-chemotherapy malignancies such as leukemia.^[15,18]

GTS IN INDIA

GTS was described in two reports from India and the treatment outcomes are comparable to those of the United States cases and the Cancer Institute of Adyar in Madras. In one report from the Tata Memorial Hospital in Mumbai, Tongaonkar *et al.*,^[16] described four patients who were all rendered disease-free after complete resections of mature teratomas. Interestingly, one patient had a retrocure recurrence of GTS after an initial post-chemotherapy resection of a mature retroperitoneal teratoma along with an embryonal carcinoma within a supraclavicular node 3 years before. The recurrent lesion encircled the aorta at the celiac axis. The patient was disease-free at 24 months post-resection. In a 1995 report from the Cancer Institute of Adyar in Madras, Ravi^[26] described favorable outcomes after complete resections of GTS tumors in three patients. In one patient, GTS was discovered 18 months after the initial retroperitoneal tumor pathology revealed necrotic tissue. The patient was disease-free at 6 months following complete GTS resection.

CONCLUSIONS

GTS is a rare clinical phenomenon. In the case of testicular carcinoma, GTS should be suspected in patients with: (1) metastatic NSGCT, (2) increasing size of metastatic lesions on serial imaging during or after systemic chemotherapy for the treatment of testis cancer and (3) normalized serum tumor markers or a physiological explanation for the presence of abnormal tumor markers. The diagnosis is confirmed by the presence of mature teratoma and the absence of any malignant germ cells on final surgical pathology. Good treatment outcomes are dependent on the following five steps: (1) awareness of this condition, (2) vigilant imaging of patients on chemotherapy for NSGCTs, (3) early recognition of the paradoxical response of disease to chemotherapy (enlarging tumors and normal serum tumor markers), (4) early diagnosis and, finally, (5) a prompt and complete surgical resection of tumors.

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