REVIEW ARTICLE

Growing Teratoma Syndrome: A Review Article

Richi Khandelwal[1], Sushil K Giri[2]

Abstract

It is a rare entity described among patients with non-seminomatous germ cell tumors (NSGCTs), characterized by enlarging metastatic masses despite appropriate systemic chemotherapy and normalized serum markers. The prevalence of growing teratoma syndrome (GTS) is only 1.9–7.6% after testicular NSGCT and 12% after ovarian germ cell tumor although more commonly seen is post-testicular and generally affects young adults and adolescents. The etiology remains unclear. They are mostly asymptomatic but abdominal pain/distension may be seen. Their prognosis is highly dependent on the timing of diagnosis, and early diagnosis has an excellent prognosis. There is no effective medical treatment for GTS and it is unresponsive to chemotherapy or radiotherapy. Total surgical removal of mature teratomas is currently the gold standard treatment of this condition. Hence, in this article, we have covered the complete review of this rare entity called GTS.

Keywords: Chemotherapy, Complex cyst, Growing teratoma syndrome.

Journal of South Asian Federation of Obstetrics and Gynaecology (2022): 10.5005/jp-journals-10006-1989

Introduction

Growing teratoma syndrome (GTS) is a rare entity and was first described by Logothetis et al., in patients with non-seminomatous germ cell tumors (NSGCTs).[1] The disease had peculiar characteristics in the form of enlarging metastatic masses after treatment with systemic chemotherapy and surprisingly normal serum markers. On detailed microscopic examination, these resected lesions were benign mature teratomatous elements without any components of viable germ cell tumor (GCT). Prior to the description of this unusual presentation of malignancy, any enlarging or new masses after treatment of malignancy was considered to be recurrent until it was proven otherwise but GTS is an exception to the usual clinical behavior of any malignancy.

Logothetis had established three criteria for GTS which are (1) normal level of serum tumor markers—AFP and hCG; (2) enlarging or new masses despite appropriate chemotherapy; and (3) the presence of mature teratoma in the resected specimen. Early reports indicated the relation of GTS only to testicular tumors. The prevalence of GTS reported in the literature is 1.9–7.6% after testicular NSGCT[1,2] and 12% after ovarian GCT although more commonly seen is post-testicular and generally affects young adults and adolescents. However, the etiology is unclear and various hypotheses have been published about its origin.

Pathogenesis

The most commonly cited one is the *transformation theory* which supports that chemotherapy alters the cell kinetics of a totipotent malignant germ cell toward transformation to a benign mature teratomatous component.[3]

Another hypothesis is the *retroconversion hypothesis* by DiSaia et al.,[4] which states that chemotherapy destroys only the immature malignant cells, leaving behind the mature benign teratomatous elements.

The third one is the *differentiation theory proposed* by Hong et al.,[5] in which spontaneous evolution occurs during the course of chemotherapy and the malignant cells differentiate into nonmalignant components.

[1,2]Department of Gynecologic Oncology, Acharya Harihar Post Graduate Institute of Cancer, Cuttack, Odisha, India

Corresponding Author: Richi Khandelwal, Department of Gynecologic Oncology, Acharya Harihar Post Graduate Institute of Cancer, Cuttack, Odisha, India, Phone: +91 9785077004, e-mail: richi_kh@yahoo.com

How to cite this article: Khandelwal R, Giri SK. Growing Teratoma Syndrome: A Review Article. J South Asian Feder Obst Gynae 2022;14(1): 81–83.

Source of support: Nil

Conflict of interest: None

GTS has been described as NSGCTs arising from the testes, ovaries, mediastinum, and pineal gland. They grow at the initial site of the tumor and then spread to more distant sites including the retroperitoneum, peritoneal cavity, liver, chest, lymph nodes (LNs), and mediastinum.

There are some risk factors described by Andre et al.[6] as to which teratoma is likely to develop GTS which are the presence of mature teratoma in the initial lesion—mature teratoma component initially present will less likely respond to chemotherapy and would persist and present as GTS, supported by the theory given by Di Saia et al. No decrease in size during chemotherapy also implies a risk of developing GTS and the third risk factor is the presence of teratoma in post-CT residual masses which again points that the disease which does not respond to chemotherapy initially may progress on to GTS later.

Signs and Symptoms

Patients are mostly asymptomatic but abdominal pain/distension may be seen. The median age as has been cited in the literature is 22 years. The average interval from treatment is around 8 months (although can appear during CT or as long as 12 years after treatment).

The most common site is the retroperitoneum and other sites of this peculiar disease entity may be the lung, cervical LN, and mediastinum.[7] As can be understood, it is difficult to diagnose GTS,

both for the clinician and the pathologist. As far as the prognosis goes, it is highly dependent on the timing of diagnosis; early diagnosis has an excellent prognosis. It is always better to excise GTS lesions before they become more extensive or potentially inoperable and so a vigilant follow-up is warranted, especially in cases with risk factors. It has been suggested by Spiess et al.[8] for regular imaging possibly after two cycles of chemotherapy to ensure careful monitoring of subtle changes in tumor size and appearance to potentially avoid a late diagnosis of GTS and its consequences.

Diagnosis

The hallmark is the normalization of tumor markers—α-fetoprotein and β-human chorionic gonadotropin. Although tumor markers help us in diagnosing the condition, they may not always be normal and, other causes of elevated AFP or β-HCG should be ruled out before excluding GTS.[8] A rapidly growing mass postchemotherapy may not be a recurrence especially when associated with normal serum tumor markers and should raise a further suspicion of GTS.

There exists no foolproof means of discriminating between recurrent GCT and GTS. It is a difficult and challenging task to identify this entity with imaging but MR imaging is the preferred modality. Fat saturation and gradient-echo MR imaging should be advised if this condition is suspected. CT may be an alternative to MRI.[9] The role of ultrasound is limited by its poor sensitivity. However, FDG–PET likely has a role as the viable tumor takes up FDG whereas the necrosis or a mature teratoma is negative on an FDG scan.[9,10]

The final diagnosis is by the histopathologic examination of the resected mass, and the presence of teratomatous elements raises the suspicion of GTS.[11] The frequency of the presence of a teratomatous component in the primary tumor has been reported to be as high as 86%.[12] The tumor on gross examination has both cystic and solid areas. Microscopic examination may reveal different types of tissues like cartilage, bone, ciliated respiratory-type epithelium, enteric epithelium, and neurogenic tissue with intervening stroma composed of undifferentiated mesenchymal spindle cells.[5] Malignant transformation in a GTS is extremely rare but may be seen in 3% of cases.[6]

Management

Medical management is largely not effective to people who do not respond to chemotherapy or radiotherapy as they usually are seen following such treatment.[1,9,12]

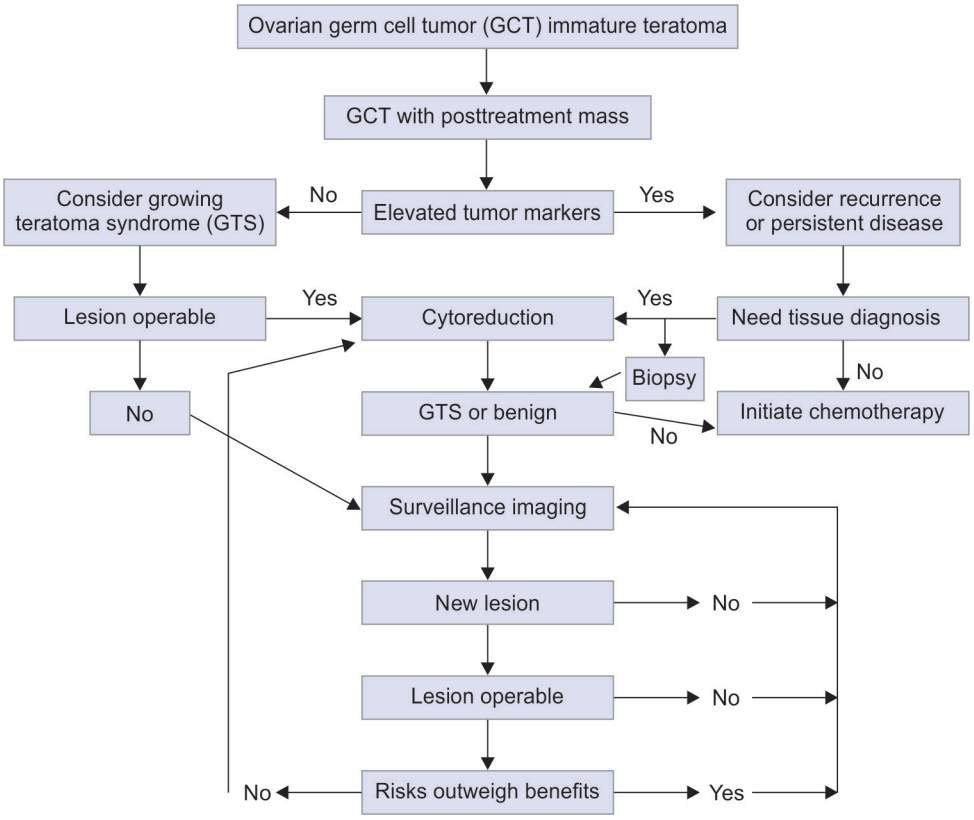
The gold standard treatment remains resection of the masses and precisely the earliest possible before they become inoperable due to their local extension to the surrounding structures. Currently, there is no standardized management protocol due to its rarity, but Byrd et al.[13] have given a comprehensive algorithm to effectively manage GTS (Flowchart 1).

The majority of patients are recognized only during follow-up as GTS usually presents without symptoms, and thus, strict follow-up of patients and vigilant attitude by the clinician are important to effectively diagnose and manage this condition.[13]

Medical Treatment

Although medical management is not the treatment of choice but newer targeted therapies have shown promising results.[14] Interferon therapy has been tried and only minor improvements have been reported in studies by Rustin et al.[15]

Flowchart 1: Comprehensive algorithm of management in a suspected case of GTS (proposed by Byrd et al.)



Bevacizumab, an VEGF inhibitor, has too been studied, and significant clinical improvements with radiological stabilization of the disease were noted by Mego et al.;[16] however, the disease progressed after stopping treatment.

Cyclin-dependent kinase inhibitors also have been depicted to have a potential role in the management of GTS.[17] Studied in a phase II trial after a median follow-up of 38 months, a median progression-free survival of 5.3 months and event-free survival of 16.2 months was noted. The role of these therapies is currently limited; however, they may be of utmost importance in surgically inoperable cases as they may help decrease the size of the lesion and make them amenable to resection. Further research into the molecular alterations leading to GTS will help understand and would open up newer treatment options for effective management and possibly prevention.

Surgical Treatment

Surgical approaches can be only resection of the mass or removal of the involved structures also if any. These lesions are locally aggressive and can generate symptoms due to their expansile nature depending on their location. Hence, a good preoperative workup is mandatory along with a surgical team with experts from different specialties according to the requirement of the case. Surgical resection remains the main treatment modality as medical management is still ineffective. Currently, it is the gold standard as they are resistant to both chemotherapy and radiotherapy. Removal of all lesions should be the goal but should be balanced at the cost of increased morbidity. It has been seen that 7% of cases needed a caval resection and nephrectomy was necessary in 31% of cases.[18] Surgery is also indicated to decrease the chances of degeneration into an undifferentiated testicular tumor component. Histopathology can reveal the development of secondary malignancies induced by previous chemotherapy.

Recurrence

Recurrence of GTS has also been reported and is more common in patients who have undergone partial resections (0–4%) compared to those who undergo complete resection (72–83%).[6,18] Laparotomy is commonly done for these cases due to the difficult-to-resect masses and previous surgery; however, laparoscopy can be used especially in the cases of questionable or limited GTS. Postsurgery, further treatment depends on the histopathologic picture, and chemotherapy is reinitiated if new malignant cells are detected in the specimen.

Prognosis

The prognosis of GTS is good and the 5-year overall survival rate of patients who undergo surgery for GTS is 89%. These lesions are locally aggressive which can cause substantial morbidity and mortality if not diagnosed or treated early. Diagnosis at the earliest helps remove the disease in toto as later it may not be excisable due to the locally aggressive nature. There have been reports of serious consequences due to their extensive spread like intestinal necrosis, renal necrosis due to vascular obstruction, and fistula formation among others.[19] There is often a significant involvement of the great vessels and/or common iliac vessels. The key is to do surgery at the earliest.[18] Also, not only consequences due to local spread are dangerous but also there is albeit a small risk of malignant transformation.

There is a risk of recurrence of GTS and also recurrence of GCTs in these patients, and hence, patients must be followed up and patient education should be imparted to maximize the quality of life and improve survival.[20]

References

1. Logothetis CJ, Samuels ML, Trindade A, et al. The growing teratoma syndrome. Cancer 1982;50:1629–1635. PubMed: 6288220.
2. Jeffery GM, Theaker JM, Lee AH, et al. The growing teratoma syndrome. Br J Urol 1991;67:195–202. PubMed: 2004236.
3. Carr BI, Gilchrist KW, Carbone PP. The variable transformation in metastases from testicular germ cell tumors: the need for selective biopsy. J Urol 1981;126:52–54. PubMed: 7253077.
4. DiSaia PJ, Saltz A, Kagan AR, et al. Chemotherapeutic re of immature teratoma of the ovary. Obstet Gynecol 1977;49:346–350. PubMed: 65751.
5. Hong WK, Wittes RE, Hajdu ST, et al. The evolution of mature teratoma from malignant testicular tumors. Cancer 1977;40:2987–2992. PubMed: 563283.
6. Andre F, Fizazi K, Culine S, et al. The growing teratoma syndrome: Results of therapy and long-term follow-up of 33 patients. Eur J Cancer 2000;36:1389–1394. PubMed: 10899652.
7. O'Callaghan AM, Katapodis O, Ellison DW, et al. The growing teratoma syndrome in a nongerminomatous germ cell tumor of the pineal gland. Cancer 1997;80:942–947. PubMed: 9307195.
8. Spiess PE, Tannir NM, Tu SM, et al. Viable germ cell tumor at postchemotherapy retroperitoneal lymph node dissection: can we predict patients at risk of disease progression? Cancer 2007;110: 2700–2708. PubMed: 17948916.
9. Aide N, Comoz F, Savin E. Enlarging residual mass after treatment of a nonseminomatous germ cell tumor: growing teratoma syndrome or cancer recurrence? J Clin Oncol 2007;25:4494–4496. PubMed: 17906212.
10. Inaoka T, Takahashi K, Yamada T, et al. The growing teratoma syndrome secondary to immature teratoma of the ovary. Eur Radiol 2003;13:2115–2118. PubMed: 12928961.
11. Tangjitgamol S, Manusirivithaya S, Leelahakorn S, et al. The growing teratoma syndrome: a case report and a review of literature. Int J Gynecol Cancer 2006;16:384–390. PubMed: 16515629.
12. Maroto P, Tabernero JM, Villavicencio H, et al. Growing teratoma syndrome: experience of a single institution. Eur Urol 1997;32: 305–309. PubMed: 9358218.
13. Byrd K, Stany MP, Herbold NC, et al. Growing teratoma syndrome: brief communication and algorithm for management. Aust N Z J Obstet Gynaecol 2013;53(3):318–321. DOI: 10.1111/ajo.12084.
14. Tonkin KS, Rustin GJS, Wignall B, et al. Successful treatment of patients in whom germ cell tumour masses enlarged on chemotherapy while their serum tumour markers decreased. Eur J Cancer Clin Oncol 1989;25:1739–1743. PubMed: 2483686.
15. Rustin GJS, Kaye SB, Williams CJ, et al. Response of differentiated but not anaplastic teratoma to interferon. Br J Cancer 1982;50:611–616. PMCID: PMC1976992.
16. Mego M, Reckova M, Sycova-Mila Z, et al. Bevacizumab in a growing teratoma syndrome. Case report. Ann Oncol 2007;18(5):962–963. PubMed: 17434900.
17. Narayan V, Hwang WT, Lal P, et al. Cyclin-dependent kinase 4/6 inhibition for the treatment of unresectable mature teratoma: long-term follow-up of a phase II study. Clin Genitourin Cancer 2016;14(6):504–510. DOI: 10.1016/j.clgc.2016.03.010.
18. Spiess PE, Kassouf W, Brown GA, et al. Surgical management of growing teratoma syndrome: the MD Anderson cancer center. Experience J Urol 2007;177:1330–1334. PubMed: 17382725.
19. Ravi R. Growing teratoma syndrome. Urol Int 1995;55:226–228. PubMed: 8588272.
20. Beck SD, Foster RS, Bihrle R, et al. Long-term outcome for patients with high volume retroperitoneal teratoma undergoing post-chemotherapy surgery. J Urol 2009;181(6):2526–2532. DOI: 10.1016/j.juro.2009.01.116.