Case Report

Growing Teratoma Syndrome: First Case Report in a 4-Year-Old Girl

Paul Daher MD, PhD¹, Edward Riachy MD¹*, Antoine Khoury MD¹, Lara Raffoul MD¹, Claude Ghorra MD², Caline Rehayem MD²

¹ Department of Pediatric Surgery, Hotel-Dieu de France University Hospital, Beirut, Lebanon
² Department of Pathology, Hotel-Dieu de France University Hospital, Beirut, Lebanon

Abstract

Growing teratoma syndrome (GTS) consists of germ cell tumors that grow following chemotherapy despite complete eradication of the malignant cells. They can metastasize to any site, particularly the retroperitoneum, mediastinum and cervical region. It typically affects young adults and adolescents. Here we describe the youngest case reported in a 4-year-old girl with an ovarian mixed germ cell tumor who underwent an oophorectomy. Her tumor markers normalized by the end of her chemotherapeutic treatment; however, she developed a retroperitoneal mass that was subsequently resected. Histopathology revealed a mature teratoma, consisting of a GTS. We stress the need for early recognition and treatment of GTS to avoid the subsequent morbidity and mortality associated with it. Although GTS has an excellent prognosis when completely resected, it is essential that the patient be regularly followed-up with serum tumor markers and imaging.

Key Words: GTS, CT Scan, Outdoor Mass

Introduction

In 1977, DiSaia was the first to publish 3 cases of "chemotherapeutic retroconversion" in which benign distal metastasis appeared following adjuvant chemotherapy for immature teratoma of the ovary. However, the term "growing teratoma syndrome" (GTS) was first coined by Logothetis in 1982 when he described 6 patients with non-seminomatous germ cell tumors who subsequently presented with enlarging metastatic masses despite appropriate systemic chemotherapy and normalized serum markers. Their histopathology consisted of benign mature teratoma with no viable germ cell elements. These 2 phenomena are in fact the same entity, in which germ cell tumors enlarge after chemotherapy despite complete eradication of viable malignant cells and normalization of serum tumor markers. Because mature teratoma is resistant to both chemotherapy and radiotherapy, a complete resection is warranted in order to prevent progression and offer a better prognosis. We herein report the youngest case described, in a 4-year-old girl presenting with GTS.

Case

A 4-year-old girl presented with a 1-month history of vomiting along with gradually increasing abdominal girth. Her physical examination was positive for a firm, distended abdomen with a large palpable pelvic mass. Laboratory tests were normal, except for elevated alpha-fetoprotein (AFP) and human chorionic gonadotrophin (ß-hCG). Abdominal ultrasonography identified the mass in the lower abdomen and pelvis. A following abdominal CT scan revealed the mass to be retro-peritoneal, but could not determine its origin (Fig. 1). At exploratory laparotomy, a left ovarian multiloculated mass of cystic and solid nature measuring 17 × 12 × 7 cm was completely resected, along with several suspicious nodules resected within the omentum. The liver, contralateral ovary, retro-peritoneal, and pelvic lymph nodes were inspected and no suspicious lesions were found nor biopsied. The final pathologic diagnosis was grade III malignant germ-cell tumor composed of yolk-sac tumor mixed with dysgerminoma and teratomatous elements.

Tumor markers level normalized in the following month. Four months later, the patient reported lower abdominal discomfort with radiological recurrence of the abdominal mass. Tumor markers were again elevated, so she was started on a chemotherapy regime based on etoposide, ifosfamide, and cisplatin. The patient...

Fig. 1. Abdominal CT scan. *, an extra-peritoneal mass of unknown origin.
remained asymptomatic during the first month, with normal serum tumor markers. However, a CT scan identified a new perihepatic mass on the right side of the liver with extension throughout the inferior vena cava. Three months later, at the completion of her chemotherapy, a control CT scan showed a right sub-phrenic mass, along with supra-umbilical left para-median mass with possible peritoneal involvement. Serum tumor markers were still normal. A second exploratory laparotomy showed multiple implants studding the right subdiaphragmatic space, the omentum, the appendix, the broad ligament and the abdominal wall. The lesions were all removed and sampled for pathologic examination. Histopathology demonstrated mature teratoma of the ovary without a malignant component. The patient was discharged home and continued to do well. She was followed with serum tumor markers which remained normal, along with surveillance abdominal ultrasonography. Seven months later, she complained of vague abdominal pain. Physical examination was non-significant and serum tumor markers were normal. Abdominal ultrasonography showed an echogenic and cystic abdominal mass in the right upper quadrant, while the abdominal CT scan revealed multiple new masses containing cystic and necrotic elements surrounding the liver and extending throughout internal inguinal orifice (Fig. 2). Tumor markers were still normal. A third laparotomy was therefore performed with resection and sampling of the lesions; mature teratoma was confirmed on histopathology. She was followed up regularly with CT scans and serum tumor markers. Five months later, and at 1 year and 8 months from the time of her initial presentation, she underwent a fourth laparotomy for similar radiological recurrent abdominal masses and a new cystic pelvic lesion. Resection and sampling of the implants and pelvic mass again revealed mature teratoma without malignant elements. Serum markers remained normal. At the time of this report, the patient is a healthy 5-year-old girl who is regularly monitored with abdominal ultrasonography and serum tumor markers.

Fig. 2. CT scan revealing multiple new masses containing cystic and necrotic elements surrounding the liver.

Summary

GTS is a rare clinical phenomenon characterized by (a) a history of a nonseminomatous gonadal neoplasm with a teratomatous component in the primary specimen, (b) elevated serum levels of AFP, β-hCG and/or LDH with radiologic evidence of metastatic disease, (c) normalization of biomarkers after chemotherapy, (d) enlargement of the metastatic masses despite normal tumor markers during or after chemotherapy, and (e) a mature teratoma in the resected metastatic specimen. The mechanism of progression from malignant teratoma to GTS is still uncertain. An intriguing question is whether differentiation is induced by chemotherapy or whether chemotherapy eradicates undifferentiated elements leaving behind pre-existing resistant benign structures.

While GTS of the gonads has been reported in over 50 males, it is much less common in females. To the best of our knowledge, only 16 cases have been previously described in the ovary. Most women were either young adults or adolescents, but only 2 were 5 years of age, making our case the youngest case to be reported.

The presence of an enlarging new mass after chemotherapy for malignant teratoma usually indicates recurrence or progression of malignancy, but this is not always the case. GTS should also be considered in such presentation, particularly if associated with normal serum tumor markers during or after chemotherapy. The GTS nodules can appear at any time after the commencement of chemotherapy, and in some cases are delayed up to 8 years, with an average interval of 8 months. It occurs most commonly in the retroperitoneum, followed by the lung, cervical lymph nodes, and mediastinum.

Although those lesions are histologically benign, their invasive growth and aggressive local expansion can cause substantial morbidity and mortality if not surgically resected in a timely manner. Other indications for resection are to diminish the chances of degeneration of mature teratoma into undifferentiated tumor components and to rule out secondary malignancies that can be induced by previous chemotherapy. In some cases, multiple operations may be necessary. Our patient needed 3 separate interventions in addition to her first surgery. It is imperative to perform an adequate and total resection because GTS can have a high recurrence rate of 72%-83% in patients with partial resections versus 0%-4% in those who undergo complete resections. With a 5-year overall survival rate of 89% in patients who undergo surgery, GTS has an overall good prognosis.

Some medical therapies may play a role in reducing the size and alleviating surgical dissections. Interferonα has been successfully used in unresectable tumors to stop their growth for a prolonged period of time. The administration of the humanized monoclonal antibody, Bevacizumab, also provided significant clinical improvement as well as growth stability of a partially resected mass. In a promising phase I trial with Palbociclib (PD-0332991, Pfizer, Andover, MA), an oral and selective inhibitor of cyclin dependent kinases (CDK) 4 and 6, the disease was stabilized in 3 men not amenable to further surgery.
Regular follow-up imaging of patients with GTS is essential. MR imaging and CT are the preferred modalities. CT scan may show a low-density cystic lesion or an increase in the cystic component of the mass suggestive of teratomatous element. Ultrasonographic surveillance is made difficult by the variable appearance of these lesions and it is also less sensitive for fat than other modalities; but it is non-irradiating and more practical in experienced hands. More recently, 3D ultrasonography has been shown to be sensitive as CT scan for the differential diagnosis, especially when combined with color flow Doppler scanning. In all cases, a rapid growth rate in the presence of normalized serum tumor markers should raise suspicion of GTS.

Conclusion

Clinicians and radiologists should be aware of the potential occurrence of GTS during or after successful chemotherapeutic treatment of germ cell tumors. GTS tumors do not respond to either chemotherapy or radiotherapy. Histological analysis of the specimen usually detects only mature teratoma, without active tumor evidence. Surgical exploration and complete resection is the only curative treatment. Although GTS has an excellent prognosis, regular follow-up with serum tumor markers as well as imaging is critical as very late malignant masses do occur in some patients.

References

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