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Case Report

The Unusual and Potentially Fatal Growing Teratoma Syndrome

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Abstract

Growing teratoma syndrome consists of germ cell tumors that grow following chemotherapy despite complete eradication of the malignant cells and normalization of the tumor markers. They can metastasize to any site, particularly the retroperitoneum, mediastinum and cervical region. Here we report our experience with this rare syndrome and stress the need for early recognition and treatment to avoid the subsequent morbidity and mortality associated with it. We reviewed the hospital records of patients suffering from testicular tumors with retroperitoneal metastasis treated at our hospital between January 2002 and December 2006. We included those who underwent radical orchiectomy, followed by chemotherapy and retroperitoneal lymphadenectomy for persistence of post-treatment large tumor, but whose tumor markers had normalized. In this period, fourteen patients underwent retroperitoneal lymphadenectomy for persistence of tumor masses and normalization of tumor markers. Of these, the result of the anatomo-pathological examination was teratoma in six cases. Two of these patients evolved poorly and died from the disease: one because we were unable to fully remove the lesion, with subsequent renal insufficiency from bilateral ureteral obstruction and colonic obstruction with sepsis, and the other due to cachexia, because of the impossibility of removing the cervical and thoracic masses. Patients suffering from growing teratoma syndrome need to be recognized and treated surgically as soon as possible to avoid the negative consequences of morbidity and death, as occurred in two of our patients.

Keywords: Testicular Neoplasms; Teratoma; Lymphadenectomy

Introduction

Growing teratoma syndrome was first described by DiSaia in 1977,[1] in three patients with germ cell tumors of the ovary with retroperitoneal metastasis. They were submitted to adjuvant chemotherapy and subsequent lymphadenectomy for persistence of large masses. There was mature metastatic teratomatous tissue in all of them. This author suggested that a possible "chemotherapeutic retroconversion" or "in situ destruction" of the immature tissue could be the cause of this situation.

In 1982, Logothetis [2] mentioned what appeared to be similar alteration in testicular non-seminomatous germ cell tumors (NSGCT). He called it "growing teratoma syndrome". According to Amsalem et al.[3] these two descriptions probably involve the same disease.

Here we report our experience with this syndrome, calling attention to its rarity and the need to recognize and treat it surgically early to avoid subsequent morbidity and death, which occurs when it is impossible to remove the lesion completely.

Case Reports

Case 1

D.F., a 23-year-old male. Seven months before his initial visit he noted a tumor in his left testis, associated with little pain. In April 2002 he underwent scrotal ultrasound (US), which showed atrophy and

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microlithiasis of the left testis. In August 2003 atrophy of the left testicle was noted, with an irregular surface and petrous consistency. The tumor markers were normal. In September 2003 he was submitted to radical orchiectomy, whose result showed immature teratoma, endodermic sinus tumor and a malignant stromal component. In October 2003 computerized tomography (CT) of the abdomen was carried out, which indicated an extensive retroperitoneal and pelvic lymphadenomegaly (Figure-1). Four cycles of bleomycin, etoposide and cisplatin (BEP) were administered, ending in February 2004, after which imaging examinations showed that the volume of the retroperitoneal mass had not changed. In June 2004 he underwent incomplete retroperitoneal lymphadenectomy, but although we removed the abdominal lesions, the mass extended to the minor pelvis, involving the rectum and iliac vessels, and we considered it non-resectable. The diagnosis was mature and malignant teratoma, with a spindle-cell sarcomatous component. Chemotherapy was tried again, with taxol, ifosfamide and cisplatin (TIP), but without success. The patient developed acute renal failure in January 2006, when he was submitted to right nephrostomy. Soon afterward there was an important augment in abdominal and pelvic tumor, with colonic obstruction (Figure-2). He refused a colostomy and died from sepsis in April 2006.

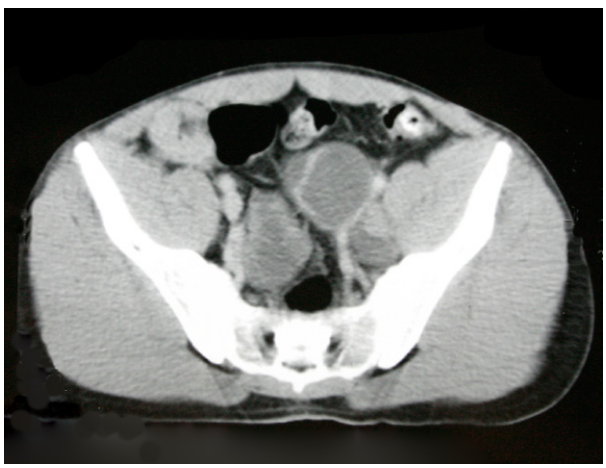

Figure 1 - CT showing multiple pelvic limphadenomegaly that was considered non-resectable

Case 2

N.J.S., a 27-year-old male. Five months before his first visit he noted a tumor in his right testicle, with gradual growth and pain. The tumor markers were only slightly elevated: lactic dehydrogenase (LDH), 514U/L (normal:240-480 U/L);human chorionic gonadotrophin (HCG), 183ng/ml (normal: < 5ng/ml) and; alfa-feto protein (AFP), 182ng/ml (normal: < 15ng/ml). One month later he was submitted to radical orchiectomy, the result of which was embrionary carcinoma. The CT showed a 9cm x 8cm retroperitoneal mass. He was given four cycles of BEP until March 2004. A new CT showed the lesion had grown slightly and tumor markers were normal. Retroperitoneal lymph node dissection was performed. The diagnosis was benign mature teratoma, with areas of necrosis. The patient evolved well.

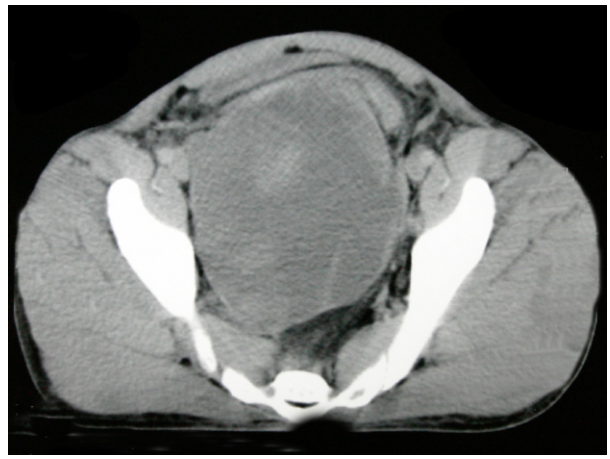

Figure 2 - CT showing enormous augments in pelvic mass that provoked ureteral and colonic obstruction

Case 3

A.A.C.A., a 32-year-old male. Two years before his first visit he noted pain in his right testicle. He underwent US of the scrotum, which showed a nodule in the left testicle. In March 2002 he was submitted to radical orchiectomy, the result of which was testicular atrophy. The image (CT) exams and tumor markers were normal. Four months before his first visit he noted a mass in his left flank. A CT in January 2004 showed a retroperitoneal adenomegaly 10cm in diameter. The oncologist who treated him in his home city thought this was a burn-out germ cell tumor and the patient was submitted to chemotherapy with three cycles of BEP. Since the voluminous mass persisted, in July 2004 he was submitted to a retroperitoneal lymphadenectomy and left nephrectomy, also in his city. The result was low-grade chondrosarcoma. During his first visit to our clinic, the original biopsy tissue was reviewed and benign mature teratoma was diagnosed. CT was also examined, which showed an oval retrocaval image 5cm in diameter,

compatible with adenomegaly. In December 2004 he was submitted to retrocaval limphadenectomy, whose result was benign mature teratoma. He is doing well.

Case 4

M.R., a 22-year-old male. One year before his first visit he noticed a left testicular node and six months later a cervical nodule. During the initial examination we noted a hardened left testicle tumor, palpable left flank mass and left supraclavicular mass. In February 2005 he was treated by the oncologist and at first submitted to biopsy of the cervical node, whose result was NSGCT, with components of immature teratoma, embrionary carcinoma and endodermic sinus tumor. The tumor markers were: LDH, 571U/L; HCG: 12.298 ng/ml and; AFP: 1210ng/ml. He underwent radical orchiectomy the same month, whose result was mixed NSGCT similar to that of the cervical biopsy. He was given three cycles of BEP until May 2005. New imaging exams showed only a discrete reduction of the volume of the abdominal mass, despite the normalization of the tumor markers. He received two cycles of TIP, but dimensions of the lesion did not reduce. Ablative chemotherapy in high doses followed by self-transplant of bone marrow was suggested. However, after evaluation of the urology section, he was submitted to an extensive retroperitoneal lymphadenectomy, with left nephrectomy and segmentary cavectomy. The result was adult cystic teratoma with necrosis and dystrophic calcification. The patient had deep venous thrombosis in the lower right leg, ascitis and respiratory insufficiency. He died in October 2006.

Case 5

M.N.B., a 29-year-old male. Eight months before his first visit he noted a large mass in the left side of his abdomen. He was submitted to laparotomy and biopsy of the lesion in May 2005. The result was undifferentiated malignant neoplasy with external necrosis and immature cartilage focus. The initial examination had indicated a palpable mass in his left flank, with 10 cm diameter, and a left testicle that was hardened, irregular and reduced in size. The tumor markers were elevated: LDH, 1191 U/L; HCG, 267ng/ml and; AFP,45.47ng/ml. In June 2006 he underwent radical left orchiectomy, whose result was immature teratoma and tumor of the endodermic sinus. The MRI showed a large retroperitoneal expansive lesion. He received four cycles of BEP, ending in October 2005. The tumor markers had normalized, but a new MRI showed partial response, with a lesion measuring 8.4cm. In March 2006 he was submitted to retroperitoneal lymphadenectomy, whose result was metastatic teratoma. His last visit was in March 2008 and he was doing well.

Case 6

W.D.B., a 28-year-old male. Nine months before his initial visit he noticed a painless increase in the size of his left testicle. After being examined in March 2005, he was submitted to radical orchiectomy at another hospital. The result was mature teratoma. Review of the slides indicated the same diagnosis. CT of the abdomen was performed, which revealed retroperitoneal metastasis, with a lesion measuring 7.0cm x 7.0cm x 7.5cm. He was given three cycles of chemotherapy with BEP. The tumor markers remained at normal levels, but a new CT showed the lesion's size had not changed. In December 2005 he was submitted to retroperitoneal lymphadenectomy, whose result was mature and immature teratoma. His last evaluation was in January 2008 and he was doing well.

Comments

By definition, teratoma is a tumor that contains more than one layer of germ cells, at various stages of differentiation. Mature teratoma resembles benign structures and immature teratoma has no differentiation of the ecto, meso and endoderm. In contrast, malignant teratoma, or teratocarcinoma, has malignant cells.[4]

This syndrome was first described by DiSaia in 1977[1] as "chemoterapeutic retroconversion" and subsequently by Logothetis as "growing teratoma syndrome." According to Amsalem et al.[3] these two phenomena are probably the same; an entity whereby germ cell tumors enlarge after chemoterapy despite complete eradication of viable malignant cells and normalization of serum tumor markers.[5]

Growing teratoma syndrome corresponds to 5% of all NSGCT. The median age at diagnosis is 23 years. Relapses occur in about 60% of all cases.[6]

There are two theories that try to explain this phenomenon: metastasis of primary teratomas or mixed gonadal tumors with teratomatous elements, or chemoterapeutic retroconvertion or in situ destruction,

with death of indiferentiated metastatic cells and later growth of a mature benign teratoma that is resistant to chemoterapy.[1-2] There is no definitive confirmation for this second theory. For the first, however, there is a study mentioning that 94% of all metastatic teratomas have the same clonal origin as primary testicular tumors.[7] These tumors have loss of heterozygosity (LOH) in 1p36, 9p21, 9q21, 13q22, 13q31, 18q21 and 18q22.[7]

In their natural history, teratomas have some biological potential. After radical orchiectomy, about 42% of the testicles removed have teratomatous elements. Of these, 67 to 81% have retroperitoneal teratoma when submitted to primary lymphadenectomy. These percentages are lower, between 28 and 41%, if the removed testicles do not have teratoma. On the other hand, 44% of patients submitted to retroperitoneal lymphadenectomy after induction chemotherapy have teratoma, while only 10 to 15% continue having viable tumor cells.[8]

The main predictors of retroperitoneum teratoma are the presence of teratoma or endodermic sinus tumors in the removed testis and alteration in the size of the mass over time.[8]

Burned-out germ cell tumors may occur in patients with metastatic disease with no evidence of a testicular tumor.[5] This condition occured in one of our cases.

The growth of retroperitoneal teratomas can be attributed to the presence of tense and expansive cysts or the occurrence of firm masses.[2] These lesions grow on average by 0.7cm to 12.9ml per month.[9]

Differential diagnosis should be performed among masses with rapid growth, especially those in the retroperitonium. The possibilities are mature residual teratoma, recurrence of germ-cell tumors, sarcomatous degeneration and, more rarely, desmoid tumors.[10] (In all cases referred from other physicians, it is important to review the original biopsy tissue because misdiagnosis is not uncommon. When there are doubts as to the correct histological diagnosis, fluorescence in situ hybridization (FISH) for isochromossome 12p should be performed. It is positive if there is a germ-cell tumor and negative if there is no germ-cell origin.[10]

The ideal treatment is resection of the entire mass, preferably all at once and as early as possible because this avoids compression, obstruction or invasion of the adjacent structures, besides preventing malignant degeneration. Retroperitoneal lymphadenectomy should be extensive, including the retrocrural area. Laparoscopic surgery can be done and has been indicated for lesions smaller than 5cm (stage IIb).[11] When persistent, the mediastinal, supraclavicular or inguinal masses should be removed. If possible, hepatic, pulmonary and cerebral resections should be performed.[4,6,12] Even total removal of the liver and transplantation has been described.[13]

In cases where removal of the mass is not possible, the use of interferon alfa-2beta and molecular target therapy with bevacizumab have been attempted, but with minimal response rates.[14-15]

Although it is uncommon, growing teratoma syndrome should be recognized and treated surgically as soon as possible to avoid subsequent deterioration, which can lead to death, as occurred in two of our patients.

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