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Case Reports

Growing teratoma syndrome of the ovary presenting with liver metastasis: report of a case

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Summary

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 in the context of normalized serum markers. This is an infrequent event in the progression of testicular tumors, and is even less common in the case of ovarian germ cell tumors. The pathogenesis of GTS is not completely understood and diagnosis can only be made with certainty after complete pathologic examination. Although histologically benign, GTS may present an enveloping growth with aggressive local expansion, which can be related to substantial morbidity and mortality. Surgery is the only recommended treatment and early recognition of this syndrome is essential as it offers hope for curative resection and avoids the use of ineffective chemotherapy. The authors present a brief review of the literature, along with the case report of a 37-year-old woman presenting GTS with liver involvement who was successfully treated by debulking surgery followed by major liver resection. This report demonstrates that complete surgical resection results in excellent disease control. More importantly, it highlights that clinicians need to be aware of the possible development of GTS when monitoring their patients with non-seminomatous germ cell tumors. These patients require coordinated care between oncologist, gynecologists, and general surgeons to obtain the best possible outcomes.

Keys words: Ovary; Neoplasms, Germ cell and embryonal; Teratoma; Liver; Treatment outcome.

Introduction

The growing teratoma syndrome (GTS) was first described in 1982 by Logothetis *et al.* [1]. It is defined as an enlarging retroperitoneal or other metastatic mass that consists of mature teratoma and is detected during or after systemic chemotherapy for non-seminomatous germ cell tumors. This is an infrequent event in the progression of testicular tumors, with reported incidence ranging from 1.9% to 7.6% [2]. It is even less common in the case of germ cell tumors of the ovary. Early recognition of this syndrome is essential as it offers hope for curative resection and avoids the use of ineffective chemotherapy. The authors report the case of GTS of the ovary associated with liver invasion that was treated by radical debulking surgery and extended right hepatectomy. Ten months after surgery the patient was disease-free.

Case Report

A 37-year-old multiparous woman who originally underwent a left salpingo-oophorectomy on December 2011 at another hospital for a left ovarian cyst whose final histology showed an immature grade III teratoma according to the FIGO (International Federation of Gynecology and Obstetrics) classification. Although recommended, no complementary treatment was proposed to the patient in her original institution. Four months later, she presented with a palpable mass and a pelvic recurrence of the disease was diagnosed. Laboratory findings included an elevated α-fetoprotein (AFP) of 2,431 ng/ml, and normal levels of carcino embryonic antigen (CEA) and human chorionic gonadotropin (HCG). She was then addressed to the Department of Gynaecological Surgery of the Pitié-Salpêtrière Hospital where she underwent a first debulking of the tumor including partial abdominal wall resection, left salpingectomy, and several peritoneal lesions resection. Histology showed a mature teratoma with a 10% immature teratoma component. After surgery she received four cycles of bleomycin, etoposide, and cisplatin (BEP) at three-week intervals. Tumor markers AFP and HCG were within normal limits after the second cycle of chemotherapy.

On September 2012, during regular follow up, a multi-detector computed-tomography (MDCT) scan revealed three hepatic lesions (Figure 1), metastatic pelvic lymph nodes, right colon soft tissue mass, and multiple pelvic masses with invasion of the right ureter. She was scheduled for surgery and complete debulking of the tumor including total abdominal hysterectomy, right salpingo-

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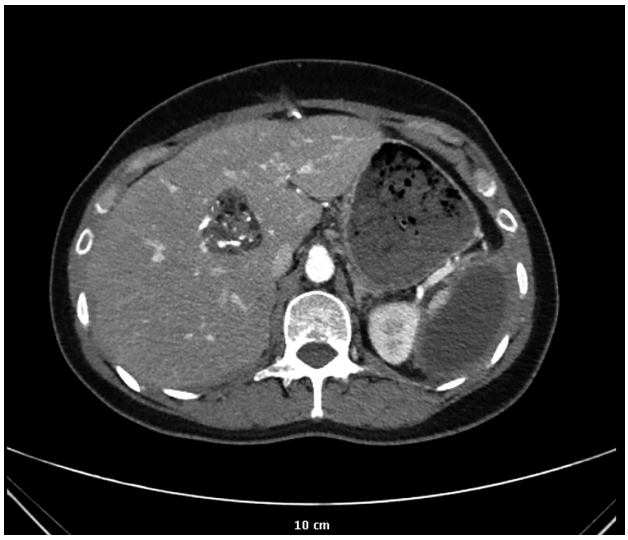

Figure 1. — Abdominal CT. Well-circumscribed lesion of liver's segment VIII presenting solid and cystic elements, and curvilinear calcifications. These findings are commonly associated to GTS.

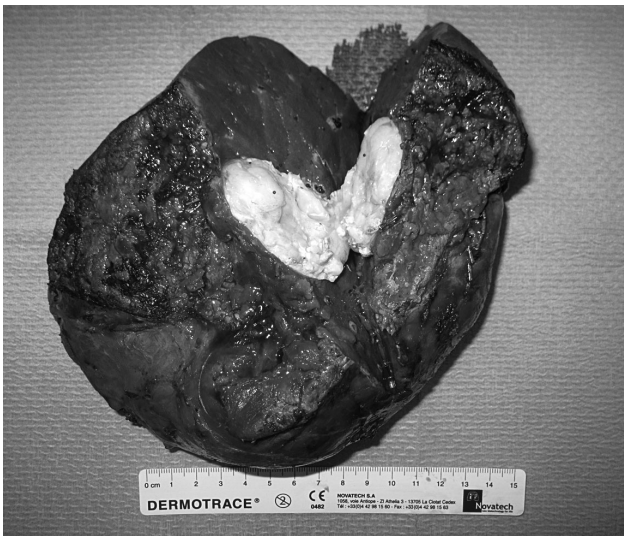

Figure 2. — Surgical specimen from extended right hepatectomy. The lesion was partially sectioned.

oophorectomy, bilateral pelvic para-aortic lymphadenectomy, two segmental small bowel resections, right nephrectomy, rectosigmoid resection, partial splenectomy, and omentectomy was performed. Histology revealed a mature teratoma without any immature component.

Before liver resection, a MDCT-volumetry was performed and showed a small left liver remnant. A right portal vein embolization was then performed to induce liver hypertrophy. Six weeks later an extended right hepatectomy was performed (Figure 2). Final histopathology revealed a five-cm mature teratoma comprising cartilage, ciliated respiratory-type epithelium, enteric epithelium and neurogenic tissue with a supporting stroma of undifferentiated mesenchymal spindle cells without any immature component confirming the diagnosis of GTS of ovary. The patient received no further treatment and regular follow up including thoraco-abdominal-pelvic CT and tumor markers did not reveal any sign of recurrence within ten months follow-up.

Discussion

Although GTS was first named in 1982, the benign transformation or evolution of germ cell carcinomas after chemotherapy was first noted in the early 1970 [3, 4]. Actually, the earliest report was published in 1969 and 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 [5]. Immature ovary teratoma represents less than 1% of all ovarian tumors. It is usually seen in women of the first two decades and contains immature neural tissues, the amount of which determines the grade of the tumor [1]. GTS is a rare complication of these malignant tumors. The hallmark feature of GTS is the normalization of tumor markers [AFP, HCG, lactate dehydrogenase]. Indeed, 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 HCG from marijuana use or from elevated luteinizing hormone) [4,6].

Three criteria have been used to precisely describe this rare entity: (1) clinical or radiologic enlargement of metastases during or after chemotherapy, (2) normalization of previously elevated serum tumor markers (AFP or HCG), and (3) metastases consisting of pure mature teratoma without malignant cells on histologic examination. [7, 8] The present case reported here presents all three criteria, with an enlargement of peritoneal lesions seen just after the end of chemotherapy associated with the complete normalization of serum tumor markers.

Some authors distinguish GTS from chemotherapeutic retroconversion (CR) [2], which was first defined in 1977 by DiSaia *et al.* [9] in the context of immature ovarian teratoma. CR is a chemotherapy mediated transformation of a metastatic immature teratoma into mature teratoma. They hypothesized that there are two possible mechanisms for this process: chemotherapy either promotes the conversion of immature teratomatous tissue into mature tissue or chemotherapy destroys only the immature component, leaving the mature tissue behind [9].

Djordjevic *et al.* [2] pointed out that CR meets only two of the three criteria for GTS. In GTS, not only must the mature teratoma nodules have undergone CR, but they also must have the ability to grow, whereas in CR the nodules do not increase in size. This is a key difference between these two phenomena; it speaks to the proliferative ability of the GTS cells despite being terminally differentiated.

GTS of the ovary can present from the age of five to 38 years, with a mean age of 20 years [2]. The primary tumor was either a pure immature teratoma or a mixed germ cell tumor of the ovary [2]. GTS nodules usually appear within the first two years from the start of chemotherapy, but at least two cases have been reported where the first GTS nodules presented at five and 11 years [2, 8, 10]. Some investigators have suggested several characteristics that could predict the subsequent development of GTS in testicular or ovarian germ cell tumors. It includes the presence of mature teratomatous elements in the primary tumor, no reduction in tumor size after chemotherapy, incomplete resection of the primary tumor, FIGO stage III disease with peritoneal involvement, and the presence of predominantly immature neuroectodermal components in the primary tumor [8, 11].

Although GTS lesions are histologically benign, their enveloping growth and aggressive local expansion can cause substantial morbidity and mortality. 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 [6,11], moreover patients in whom surgery is delayed can develop inoperable disease. The present case illustrates well this "aggressive behavior". After three months from the first debulking surgery and during chemotherapy that successfully placed tumor markers AFP and HCG values within normal limits there were hepatic, abdominal, and pelvic growths, which required an extensive debulking surgery.

Also malignant transformation of mature ovarian teratomas is a well-known phenomenon and malignancies of all three embryologic lineages can develop [2]. Usually patients who present with secondary malignancies arising from mature teratomas of the ovary are at least 15 years older than the average patient with mature cystic teratoma, and have tumors of a larger size [12, 13]. One can thus extrapolate that secondary malignancies may develop in masses of GTS of the ovary, and especially in those that have been left in the patient for many years. The chances of degeneration of mature teratoma into undifferentiated tumors or even carcinomas have been reported to be up to 3% of cases [2, 14].

Imaging is not a foolproof means of discriminating between malignant germ cell tumors and GTS. However, some features on imaging studies such as well-circumscribed lesions, 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 [15-18]. The role of [18F]-Fluorodeoxyglucose positron emission tomography has not been established but it may help in identifying GTS lesions that usually present negative uptake [19].

Unlike testicular tumors where distant metastases are common, the overwhelming majority of ovarian GTS nodules are confined to the pelvis, abdomen, or the retroperitoneum [2, 7, 8] with, to the authors' knowledge, only two reported cases of an ovarian GTS, where the GTS nodules were seen elsewhere (in the neck lymph nodes and in the lung) [16, 20]. As GTS nodules consist of mature tissue, they lack the ability to metastasize or to invade surrounding tissues [2].

Cases describing hepatic GTS lesions in the literature show that such metastasis are located at the capsule. They are characterized by a thick fibrous capsule that does not infiltrate the liver parenchyma; therefore, it gives a misleading impression of metastasis [2, 10, 20]. In the present case, although the lesion was located in the middle of segment VIII, it surprisingly did not invade liver parenchyma. Radical surgical excision is the only way to provide complete cure for these patients and in experimented centers extended liver resection or even liver transplantation have been successfully employed [21].

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]. Results are usually disappointing but significant clinical improvement as well as stability of a partially resected mass have been reported with the use of interferon, or the humanized monoclonal antibody bevacizumab [22-24]. Surgery is the only way to achieve complete disease control but these medical therapies may play a role in reducing the size and alleviating surgical dissections [4].

Conclusion

This report demonstrates that complete resection is the only way to improve survival and controlling the disease. More importantly, it highlights that clinicians need to be aware of the possible development of GTS when monitoring their patients with immature ovarian tumors. These patients require coordinated care between oncologist, gynecologists and surgeons to obtain the best possible outcomes. Immature teratomas usually present very good response with chemotherapy and recurrence is not a common event, on the other hand, the mature component may recur and long-term follow up is warranted. Surgical excision is usually technically challenging in this cases. However, it should not constitute an obstacle for the surgeon because only complete resection improves survival.

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up-to-date literature review; RML carried out the surgery (hepatectomy), performed the study, critically revised the manuscript, and is the corresponding author.

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