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Disseminated ovarian Growing Teratoma Syndrome: a case report highlighting surgical safety issues

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Abstract

The ovarian Growing Teratoma Syndrome (GTS) is a rare condition among patients with primary Non-Seminomatous Germ Cell Tumours (NSGCT) presenting with enlarging masses during or after appropriate chemotherapy in the context of normalized serum markers. Several modes of dissemination are suggested, with the most frequent site of metastasis being the peritoneum.
We report a case of a young patient with primary ovarian mixed NSGCT, who presented with Growing Teratoma Syndrome not only in the peritoneum but also within a trocar site after an initial surgery consisting in the laparoscopic morcellation and extraction of the ovarian neoplasm.
Beside the rarity of this clinical entity, it also demonstrates the utmost importance of the safe laparoscopic management of all complex ovarian masses.

Key words: **Growing Teratoma Syndrome, ovarian germ cell tumour, port site metastasis, iatrogenic peritoneal dissemination.**

Introduction

The Growing Teratoma Syndrome (GTS) is defined as the occurrence of a tumour mass consisting exclusively of mature teratoma, combined with normal tumour marker levels, during or after chemotherapy in patients with Non Seminomatous Germ Cell Tumours (Logothetis et al., 1982).

In 1969, Smithers (1969) published the first report of benign maturation among five patients whose primary neoplasm was of testicular origin. In this context, GTS is diagnosed in the retroperitoneum (80%) or at the thoracic level (André et al., 2000). When GTS occurs after an ovarian germ cell tumour, the peritoneal surface is the most frequent location (Djordjevic et al., 2007).

The incidence of the Growing Teratoma Syndrome is estimated to be 1,9 to 7,6% in testicular Non Seminomatous Germ Cell Tumours (Logothetis et al., 1982) and is even rarer in women.

We report the case of a Growing Teratoma Syndrome with a specific profile of concomitant peritoneal and abdominal wall distribution in a young woman with a primary ovarian mixed germ cell tumour. Initial surgery consisted in the laparoscopic morcellation and extraction of the ovarian neoplasm followed by chemotherapy.

Case report

In 2009, a 19-year-old woman undergoes investigations for abdominal and pelvic discomfort. A 20 cm large complex pelvic mass is diagnosed. Serum tumour marker study shows elevated LDH (473 IU/l range 190-390 IU/l) and a-foetoprotein (9710 ng/ml normal < 8.5 ng/ml). Human Chorionic Gonadotropin (HCG) dosage is negative. Laparoscopic evaluation confirms a tumour in the left ovary. Despite the tumour size and its heterogeneous appearance, the laparoscopic approach is

continued and necessitates the mass to be morcellated before removal. Surgical records mention a difficult extraction by increasing the left iliac port incision with 'a priori' no peritoneal contamination. The pathology report confirms a mixed ovarian yolk sac and immature teratoma tumour. Postoperative Positron Emission Tomography reveals an abnormal uptake at the level of the right ovary. Pelvic and para-aortic enlarged lymph nodes are noted. Four cycles of adjuvant chemotherapy with a triple association of bleomycin, etoposide and cisplatin (BEP) are prescribed and a complete biological and radiological response is obtained. Subsequently, the patient benefits from a 3 monthly follow-up based on clinical examination, repeated PET CT and a-foetoprotein dosage.

In April 2011, the PET demonstrates a large hypermetabolic lesion in the right iliac region associated with a left fixation above the bladder. The patient remains however asymptomatic and the tumour markers are negative.

One year later (May 2011) the patient is referred for complementary investigations and treatment. The MRI confirms a pelvic relapse with vesicular like lesions, englobing the uterus, the right ovary and the left iliac vessels region (Fig. 1). Additionally metastatic lesions are described in the posterior aspect of the left rectus abdominis muscle below the left iliac fossa incision performed at the time of surgery for the tumour extraction.

June 2011, a laparotomy is performed with extended peritonectomy, omentectomy, appendicectomy, splenectomy and right salpingo-oophorectomy (after cryopreservation). Wide excision of the transfixated abdominal wall lesions predominantly in the left iliac region necessitates an abdominal repair. Tumour burden was resected to no macroscopic residual disease. The histology report reveals multiple localizations of pluritissular mature teratoma without immature nor yolk sac elements (Fig. 2). No adjuvant treatment is recommended. The patient, followed up on a 3 monthly basis with clinical examination, radiological and biological evaluation, remains in complete remission up to July 2014.

Discussion

The observation of a growing tumour mass after/or during treatment of a malignancy is, by default, considered as a treatment failure. However in the context of regressing tumour markers after chemotherapy for Non Seminomatous Germ Cell Tumours, the clinician should also consider the likelihood of a Growing Teratoma Syndrome.

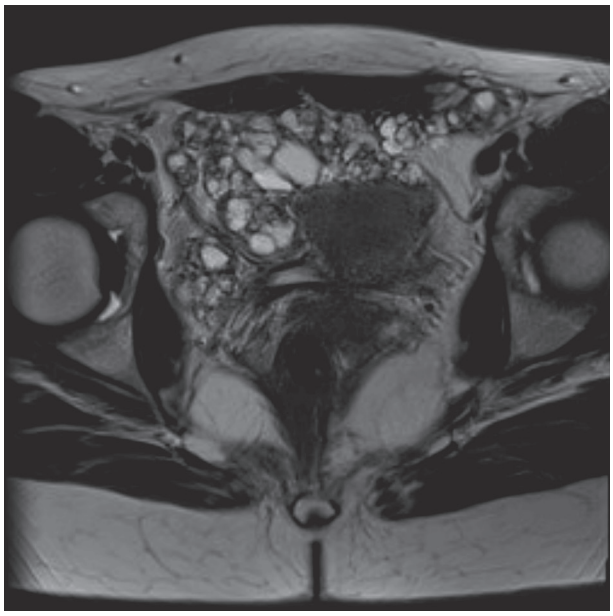

Fig. 1. — MRI abdomen pelvis, T2 axial image, important pelvic cavity invasion with vesicular like lesions, englobing the uterus, the left iliac region with involvement of the posterior fascia of the left rectus abdominis muscle.

Logothetis et al. (1982) reported 6 cases of male patients with mixed testicular NSGCT with growing isolated metastasis during chemotherapy. Complete secondary cytoreduction was achieved in all six patients. Surprisingly, the final pathology report mentioned only mature teratoma in the presumed relapse. All patients remained in long-term complete remission and it was considered that benign teratomatous tissue could mimic recurrent disease by increasing in size or persisting during chemotherapy.

DiSaia et al. (1977) characterized this event as "Chemotherapeutic Retroconversion" (CR). Others, as Djordevic B et al. (2007) stated that CR could not be considered as synonymous for GTS, because CR only refers to immature teratomas (and not to mixed Non Seminomatous Germ Cell tumours of the ovary) and to non-expanding metastatic masses.

Three criteria are mandatory to define GTS: (1) an evolving tumour mass or finding a new tumour mass during or after chemotherapy for NSGCT, (2) the regression of previously increased tumour markers (aFP, HCG or both) and (3) the presence of only mature teratoma on the final histology (Zagamé et al., 2006; Spiess et al., 2007). GTS is usually diagnosed in the twenties (Djordjevic et al., 2007) and may occur after a primary pure immature teratoma or a mixed NSGCT. There is no consensus regarding the necessary conditions underlying the development of GTS. André et al. (2000) consider that (1) the existence of mature teratoma in the first tumour, (2) insufficient dissection of the latter and (3) the absence of

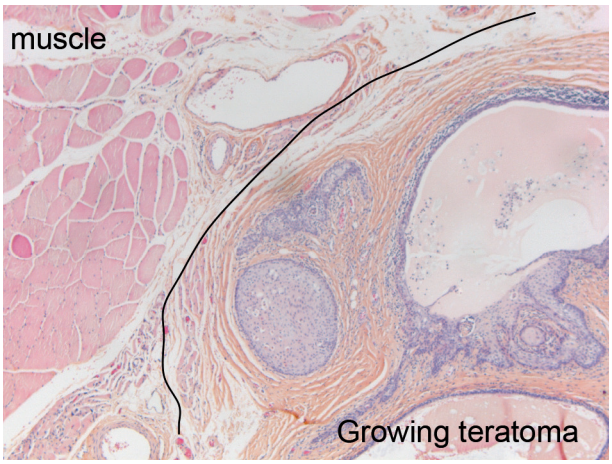

Fig. 2. — Pathologic findings of growing teratoma (right bottom) in contact with the striated muscle of the rectus abdominis muscle (HES ×50).

response of the metastasis after chemotherapy are predictors of the development of GTS. Zagamé et al. (2006) stressed the necessity of primary peritoneal involvement as well as the existence of mainly immature neuroectodermal elements in the primary neoplasm. Djordjevic et al. (2007) also mention that GTS would be unlikely to occur if the first recurrences were not within 24 months of the original presentation of an ovarian Non Seminomatous Germ cell tumour.

The aetiology of GTS remains unclear. Main hypotheses are that chemotherapy may selectively inactivate the immature elements with subsequent growth of the remaining mature tumour cells or may change the cells behaviour with immature germ cells transforming into benign teratomatous elements (André et al., 2000).

For patients with primary ovarian NSGCT and initial peritoneal extension, GTS occurs in the majority of cases in the peritoneal cavity (Tangjitgamol et al., 2006; Zagamé et al., 2006). However, in a recent single case report of GTS after FIGO stage 1C mixed ovarian germ cell tumour, three simultaneous ways of dissemination are suggested: peritoneal, lymphatic and hematogenous (Shibata et al., 2013). Distant relapses (liver, chest, mediastinum) or retroperitoneal GTS (para-aortic lymph nodes) are more common after testicular germ cell tumours (Logothetis et al., 1982; André et al., 2000). Distant GTS suggests the existence of metastatic malignant cells in these regions at the time of the initial diagnosis.

The impact of the surgical management (laparotomy versus endoscopy) and its associated risk of peroperative tumour dissemination has been questioned by Sengar and Kulkarni (2010) who report a case of GTS in the subcutaneous tissue of a patient with immature ovarian teratoma at an early FIGO stage taken in charge by laparoscopy. The present case report with laparoscopic morcellation of a 20 cm suspicious pelvic mass and subsequent abdominal port-site GTS, further supports the potential iatrogenic role of unsafe and inadequate surgery in terms of increased risk of GTS secondary to abdominal wall implants.

Surgery is the cornerstone of the management of GTS. Early diagnosis is, in this respect, crucial as late diagnosis could result in complex surgery and significant symptoms due to mechanical pressure with subsequent important morbidity and mortality (André et al., 2000; Spiess et al., 2007). Another indication for surgical excision is the known potential malignant transformation in all 3 embryologic lineages of a mature teratoma (André et al., 2000). The complete resection of GTS is mandatory, as ovarian GTS recurrence is reported with rates of 50 to 83% when incompletely resected versus 0 to 4% when complete resection is obtained (Tangjitgamol et al., 2006; Spiess et al., 2007).

Non-resectable masses of GTS may be managed with a-2 interferon but the regression is usually slow, generally partial and regrowth of the lesion is often observed after treatment discontinuation (André et al., 2000). Other medical therapies such as all-trans retinoic acid, bevacizumab and the selective cyclin-independent kinase 4/6 inhibitor PD-0,332,991 resulted in disease stabilization and clinical improvement in some case reports (Veenstra and Vaughn, 2011).

Follow-up with serum tumour markers (aFP, hCG, LDH) alone is sub-optimal accuracy and should be combined with regular morphologic imaging (MRI / CT Scan) (Hain and Maisey, 2003; Nimkin et al., 2004). While the FDG-PET can accurately identify germ cell residual masses, its utility in assessing residual mature teratoma is unclear due to the inability in distinguishing necrosis from mature teratoma (Hain and Maisey, 2003; Aide et al., 2007). As reported by Hariprasad et al. (2008) we also experienced positive FDG-PET uptake in the pelvis which eventually could be explained by a high glucose metabolism from brain tissue in mature teratoma.

Conclusion

The ovarian Growing Teratoma Syndrome is a rare entity but should be suspected when tumour masses persist or develop with normal tumour markers, during or after adjuvant chemotherapy for non-seminomatous germ cell ovarian neoplasia. The diagnosis requires histologic confirmation with presence of mature teratomatous elements

exclusively. Optimal cytoreduction with no macroscopic residual disease is essential and reported as the management of choice for GTS with subsequent favourable prognosis. Regular follow-up is recommended.

The present case report highlights the utmost importance of an optimal surgical approach for all suspicious complex adnexal masses presenting in young patients. Mass rupture, incomplete resection and tumour cells spillage must be avoided as much as possible because it worsens the patient prognosis and may result in iatrogenic GTS requiring aggressive surgical management to obtain complete cytoreduction.

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