

REVIEW/DERLEME

**A rare case of Growing Teratoma Syndrome ; third recurrence after 13 years with liver metastases ; a case report and review of the literature**

**Nadir bir Growing Teratom Sendromu olgusu; 13 yıl sonra karaciğer metastazı ile üçüncü nüksü; bir olgu sunumu ve literatürün gözden geçirilmesi**

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**ABSTRACT**

**Objective:** The growing teratoma syndrome (GTS) defined as the growth of a benign tumor after removal of a germ cell tumor or after chemotherapy. There is no reached consensus managing GTS.

**Case:** A patient had undergone surgery for an adnexial mass at the age of 14 and diagnosed with immature teratoma. 13 years after the last operation she underwent a fourth time tumor free fertility sparing operation with partial resection of the right liver lobe, partial resection of the peritoneum of diaphragm and cyst removal from right ovary. Pathology result was compatible with mature teratoma having no immature characteristics. To our knowledge, this is the first case reported in the literature that reoccured such a long time after the last GTS surgery such as 13 years and having benign features on histopathological examination.

**Conclusion:** GTS has an unpredictable behavior and could reoccur even after a very long time and several surgeries.

**Keywords:** Immature Teratoma, Growing Teratoma Syndrome, Germ Cell Tumor, Delbulking Surgery, Fertility Sparing Surgery

**ÖZ**

**Amaç:** Büyüyen teratom sendromu (BTS) germ hücreli tümör için gerçekleştirilen ameliyat ya da kemoterapi sonrasında benign karakterde tümöral büyüme olarak tanımlanmıştır. BTS tedavisi için bir uzlaşma bulunmamaktadır.

**Vaka:** 14 yaşında kız hasta adneksiyel kitle nedeni ile opere olup immatür teratom tanısı almıştır. Bu operasyondan 13 yıl sonra gerçekleşen dördüncü operasyonda hastaya batında tümör bırakılmadan sağ karaciğer lobunun parsiyel rezeksiyonu, diafram peritonunun parsiyel rezeksiyonu ve sağ over kist eksizeyonu fertilitate koruyucu yaklaşımla gerçekleştirilmiştir. Patoloji sonucu immatür karakterde tümör içermeyen matür teratom olarak gelmiştir. İlk operasyondan 13 yıl sonra ve benign natürde nüks eden hasta, literatürde bu denli uzun süre sonra iyi huylu olarak nüks gerçekleşen ilk BTS hastası niteliğindedir.

**Sonuç:** BTS prognozunu öngörmek oldukça zordur, uzun zaman ve tekrarlayan cerrahiler sonrasında dahi nüksler görülebilir.

**Anahtar Kelimeler:** İmmatür Teratom, Büyüyen Teratom Sendromu, Germ Hücreli Tümör, Sitoredüktif Cerrahi

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## INTRODUCTION

Ovarian germ cell tumors are seen seldomly. They compose 5 percent of all ovarian malignant tumors and affects girls and young women (1). Pure immature teratomas are a subgroup of ovarian germ cell tumors and accounts for less than %1 of all germ cell tumors. Although pure immature teratoma is a rare entity; under the age of 20 it represents %15-20 of all ovarian malignancies and causes 30 percent of ovarian cancer mortality in this age group (2-4). Debulking surgery followed by chemotherapy is the mainstay of the treatment (5).

The growing teratoma syndrome (GTS) is defined by Logothetis et al in 1982 as the growth of a benign tumor after removal of a germ cell tumor or after chemotherapy (6). The incidence of GTS is reported to be around %1.9 - %7.6 after testicular and %12 after ovarian nonseminomatous germ cell tumors (7). The diagnostic criteria according to Logothetis definition include: 1) normalization of tumor markers (AFP and hCG ) after chemotherapy or surgery; 2) enlarging of new masses despite appropriate chemotherapy for nonseminomatous germ cell tumors; 3) the exclusive presence of mature teratoma in the resected specimen (6). The most commonly agreed theory which explains the pathophysiology of the disease is the disappearance of immature malignant components after chemotherapy and sparing of the benign (mature) parts of the tumor (4).

Up to date, case series and case reports including a total number of more than 100 GTS patients have been published (8). As it is a very rare entity and the data is lacking,

the course of GTS is unclear. Although some algorithms have been proposed, no consensus or guideline exists on the management of GTS (9). Another important aspect of GTS is the sparing of fertility perioperatively and the postoperative availability of fertility preservation options such as oocyte cryopreservation. Two pregnancies, both of which happened with the help of assisted reproductive technologies, have been reported in the literature after GTS diagnosis (10, 11).

## CASE REPORT

A 14 year old Turkish girl, with no chronic illness, presented at a tertiary care hospital in Istanbul with lower abdominal pain and bloating symptoms in January 2003. Transabdominal ultrasonography revealed a left adnexial mass occupying the pelvis. Magnetic resonance imaging (MRI) showed a 80.65.40 mm mass showing papillary projections, loculations and variable echogenicity. Her AFP level was 1200 ng/ml and BhCG level was 140 ng/ml. She underwent a fertility sparing surgery. Left salpingo-oophorectomy, appendectomy and partial omentectomy was performed. Peritoneal washings were also taken. Histopathology of the adnexial mass revealed grade 2-3 immature teratoma with immature neuroepithelial tissue. Surgical staging was 1C1 because of the breached tumor capsule.

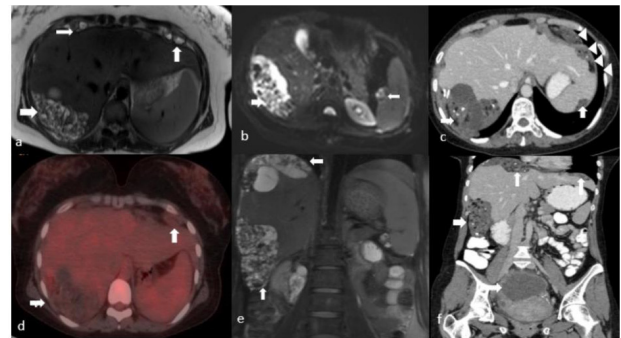
In December 2003, after 7 cycles of BEP (bleomycin, etoposide, cisplatin) therapy, tumor markers were within normal ranges but imaging revealed carcinomatosis peritonei with lesions around liver, peritoneum of the right diaphragm, mesentery of the small bowel and a 3 cm suspicious mass in the left pelvic region. Secondary debulking was performed with no residual tumor. Pathology was consistent with

a more mature teratoma compared with the previous mass. ICE (ifosfomide, carboplatin, etoposide) protocol was planned for the patient as the first chemotherapy regimen was thought to be unsuccessful. Only one and a half cycles of chemotherapy were completed because of the renal toxicity. Control imagings and tumor markers in every 6 months after the surgery were within normal ranges and consistent with no signs of recurrence.

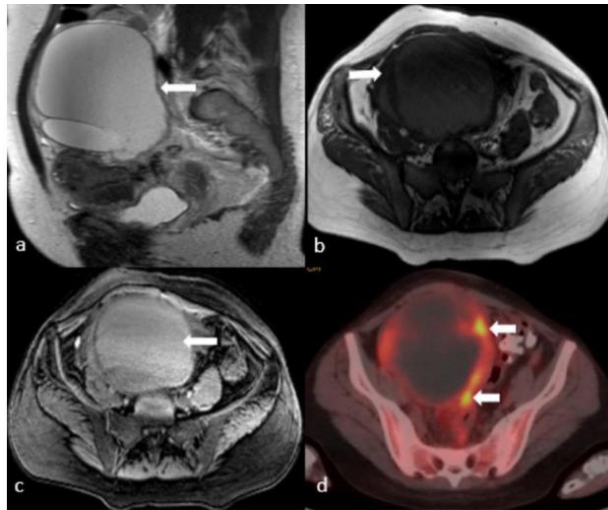
In August 2005, MRI of the abdomen showed lesions around liver, omentum and a 4 cm pelvic mass. Right paracolic and right subdiaphragmatic mass extirpation, residual omentum removal and left pelvic mass resection was performed. Histologic examination was consistent with only mature cystic teratoma. All three pathologic evaluations were performed by the same experienced professor in a tertiary care center in İstanbul. She did not receive any chemotherapy after the third operation due to the lack of any immature elements in the extracted specimen and she was followed with imagings and tumor marker levels in every 6 month.

In August 2018, MRI revealed some lesions around liver ranging between 2 to 3 cm, a 3 cm mass at the splenic hilus and bilateral suspicious adnexial lesions ranging approximately 4 cm. MRI did not show any contrast accumulation and PET/CT imaging pointed out no pathologic FDG take-up in the lesions. Tumor markers were beyond the normal range. ( B-hCG:4, AFP: 2 , CEA:16 , CA125: 284, CA19-9: 74 ). She was informed about the recurrence risk of immature teratoma and also about GTS. She was unwilling for another operation. Thus, surveillance with frequent hospital visits was planned.

MRI in February 2020 showed the lesions around liver segments spreaded over to the left subdiaphragmatic area and were numerous and bigger than before. Imaging studies also showed new lesions around ascending and descending colon that were not present in the previous studies ( Figure 1). The diameter of the right adnexial lesion increased to 12 cm showing multiple septa and nodular thickenings (Figure 2). Besides, transvaginal ultrasound showed rich blood flow around the septa and nodular areas. Tumor marker levels were also increased (B-hCG:4, AFP:1, CEA:9, CA-125: 598, CA19-9: 104).



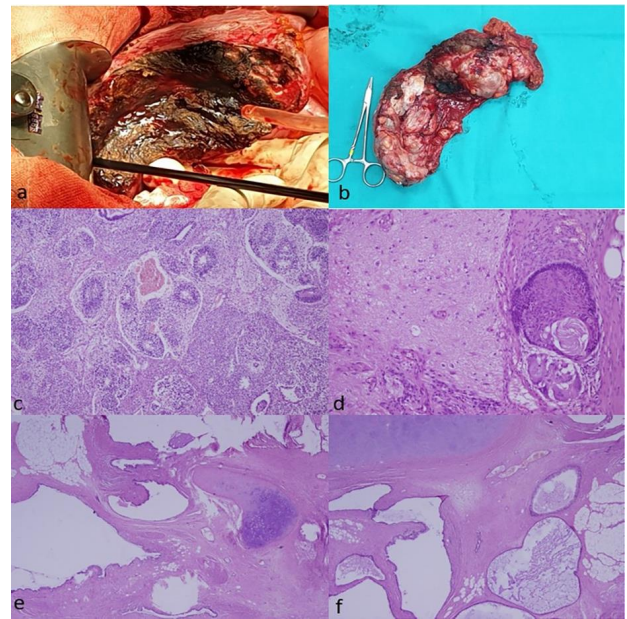
**Figure-1(a-f):** Imaging studies ( contrast enhanced computerized tomography, magnetic resonance, positron emission tomography ( May 2020, February 2020, February 2020 respectively ) ) from preoperative evaluation **a)** Axial T2W image shows heterogeneous, hyperintense, mixed lesions with solid and cystic areas adjacent to the posterior segment of the right lobe of the liver and adjacent to the anterior of the right and left liver lobes (white arrows) **b)** DWI-MRI image shows hyperintense lesions in the right upper quadrant and splenic hilum due to solid components (white arrow) **c)** Axial contrast enhanced CT image which is obtained two months later, shows coarse macrocalcifications in the lesion located in the right upper quadrant (white arrow), also new left diafragmatic lesion and peritoneal lesions are seen in this image (white arrow and arrowheads) **d)** Axial PET-CT image shows no FDG uptake **e)** Coronal fat-sat T2W image shows the lesion in the right upper quadrant extended through the right paracolic area (white arrows) **f)** Coronal contrast enhanced CT image shows both upper abdominal lesions and a right ovarian thick walled, hypodense lesion in the lower abdomen (white arrows).



**Figure-2(a-d):** Imaging studies (contrast enhanced computerized tomography, magnetic resonance, positron emission tomography ( May 2020, February 2020, February 2020 respectively )) from preoperative evaluation **a)** Sagittal T2W image shows the longest diameter of right ovarian lesion(white arrow) **b)** Axial T1W non-fat-sat **c)** T1W fat-sat images show hyperintensity relevant with hemorrhage products, not suppressed in fat-suppressed sequences (white arrows) **d)** Axial PET-CT image shows FDG uptake at the periphery of the lesion (white arrow).

The patient was informed about the risk of immature teratoma recurrence, GTS and a possible new malignant lesion growing from the right adnexa. We performed a debulking surgery (partial resection of the right liver lobe, partial resection of the diaphragm peritoneum and cyst removal from right ovary) with multiple frozen examinations. Right ovarian mass was compatible with endometrioma and the rest of the specimen was mature cystic teratoma without any immature elements (Figure 3).

Her follow-up visits were performed in every 6 months after the last surgery and no disease recurrence have been detected with imaging and clinical evaluation. Although oocyte cryopreservation was offered to preserve her fertility, she was unwilling after her last surgery. Now, she is planning to get married and she will be evaluated for fertility options at Istanbul University Reproductive Endocrinology and Infertility Department.



**Figure 3(a-f):** **a)** Resection from the right liver lobe **b)** Resected specimen **c)** Immature neural tissue with rosette formation (January 2003 – left adnexial mass) **d)** Neural and epidermoid tissue showing mature characteristic (December 2003 – peritoneal lesions around liver) **e)** Mucinous epithelium with cartilage, lipid and connective tissue showing mature features (December 2005 – right paracolic lesions) **f)** Mucinous epithelium with cartilage, lipid and connective tissue showing mature features (June 2020 – liver resection)

## DISCUSSION

Surgery followed by BEP ( bleomycin, etoposide and cisplatin ) is the accepted treatment of immature teratomas (1). Prognosis depends on the grade and stage of the tumor. Survival rates are %94 for stage 1 grade 1 tumors and falls off to %82 for grade 2 and 3. Recurrence rates also correlate with the grade of the tumor (2). Equal survival rates are stated with fertility sparing surgeries compared to bilateral salpingooforectomy with or without hysterectomy (2, 12, 13). These findings suggest the need for fertility sparing surgeries in eligible patients such as the presented case with conserving at least one ovary, tube and uterus. Assisted reproductive technologies could be offered after the index surgery due to the recurrent nature of the disease and possible need for additional operations. Different treatment modalities, such as oocyte/embryo

cryopreservation or fresh IVF cycles, has to be discussed depending of the fertility evaluation of each patient.

GTS treatment is primarily composed of surgery to abstain from malignant transformation (9) and mechanical compression symptoms. This was an exceptional case of growing teratoma syndrome requiring debulking surgery for three times after the first fertility preserving operation for immature teratoma. Although GTS recurrence after complete resection is profoundly low, it can reach up to %72-83 after partial resection (10). Complete surgical resection is especially critical for GTS because teratomas are highly resistant to chemotherapy and radiation. Also, capsule of the immature teratoma has to be kept intact as surgical spillage is associated with worse prognosis (10). Besides our patient, the only patient required 3 subsequent surgeries after immature teratoma diagnosis was reported in 2004 by Nimkin et al (14).

GTS diagnosis can be made up to 8 years after the first surgery for immature teratoma (10) and can be made even after 18 years for recurrent cases (15). Also, malign transformation is mostly seen in patients with a delayed diagnosis. This is the first case reported in the literature that reoccured such a long time after the last GTS surgery such as 13 years and having benign features on histopathological examination.

## CONCLUSION

GTS is a very rare non-malignant entity but better knowledge about the disease course and early diagnosis could help for a less invasive surgery and better prognosis. No internationally approved guideline exists for GTS and additional data from more cases is necessary for managing these patients optimally. This is a unique case reminding us the important aspects of

managing GTS. First, GTS has an unpredictable behaviour and recurrence could occur even after 13 years and with relatively small primary immature teratoma size. Besides, the need for 3 subsequent surgeries draws the attention for complete debulking to eliminate the risk of recurrence. Regular follow up for a long period is mandatory with imaging and tumor marker levels. Lastly, the presence of a new suspicious adnexial mass, peritoneal carcinomatosis and elevated tumor markers can be misleading for a malignity arising from teratoma origin or a new ovarian tumor. It is crucial to differentiate between GTS and recurrence of immature teratoma because it can lead to an inadvertent chemotherapy administration, which has no place for GTS.

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### Conflict of interest

Authors have no conflicts of interest relevant to this article.

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### Ethical Decleration

Helsinki Declarationrules were followed to conduct this study.

### Authorship Contributions

Concept: SBT, HY, KY, HS, ST, Design: SBT, HY, KY, HS, ST, Supervising: SBT, HY, KY, HS, ST, Financing and equipment: SBT, HY, KY, HS, ST, Data collection and entry: SBT, HY, KY, HS, ST, HS, Analysis and interpretation: SBT, HY, KY, HS, ST, Literature search: SBT, HY, KY, HS, ST, , Writing: BSBT, HY, KY, HS, ST, Critical review: SBT, HY, KY, HS, ST

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