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Case Report

Exception to rule of metastasis: Case report of growing teratoma syndrome in a paediatric patient

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Abstract

Growing Teratoma Syndrome (GTS) is a rare clinical entity associated with non-seminomatous germ cell tumors (NSGCTs) of the testis and ovary, initially described in the context of testicular tumors. GTS is exceptionally uncommon in the pediatric population, with only eight cases reported in the literature to date.

We report a case of a 6 years old paediatric patient diagnosed with immature teratoma, who later developed progressive disease during chemotherapy, despite normalization tumo-markers. Surgical excision was performed, and histopathological examination confirmed mature teratomatous elements without any viable immature component, establishing the diagnosis of Growing Teratoma Syndrome.

In the presence of a paradoxical clinical picture—showing radiological progression with normalized tumor markers after chemotherapy, the histopathology is key to confirming the diagnosis. Complete surgical excision is essential to prevent compressive complications. Prognosis is excellent, with <5% recurrence and minimal risk of malignant transformation after total resection.

Keywords: Alpha-fetoprotein (AFP), Growing Teratoma Syndrome (GTS), Lactate dehydrogenase (LDH)

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1. Introduction

Growing Teratoma Syndrome (GTS) is a rare condition associated with both testicular and ovarian germ cell tumors. The term was first coined by Logothetis et al.[1] in 1982 to describe a distinct phenomenon observed in patients with non-seminomatous germ cell tumors (NSGCTs) of the testis. It is characterized by the enlargement of metastatic masses during or after appropriate systemic chemotherapy, despite normalization of serum tumor markers. Histopathological examination of these masses typically reveals benign, mature teratomatous elements. In parallel, the gynecologic literature has reported similar cases in patients with ovarian germ cell tumors, with Amsalem et al.[2] Being among the first to describe this entity in the female population under the same terminology. The prevalence of growing teratoma syndrome varies in the literature, estimated at 1.9–7.6% following testicular non-seminomatous germ cell tumors 3 and up to 12% following ovarian germ cell tumors, though it is more commonly reported after testicular malignancies. Although growing teratomas are histologically benign, they tend to grow rapidly, with a median linear growth rate of 0.5–0.7 cm/month and a volumetric increase of 9.2–12.9 cm³/month, although individual growth patterns can vary significantly.

1.1. Criteria

Typically, any enlarging or newly detected mass following treatment for malignancy is presumed to represent disease recurrence until proven otherwise. However, *Growing Teratoma Syndrome (GTS) represents a notable exception* to this common clinical paradigm.

Logothetis et al[1] defined three diagnostic criteria:

1. Normalization of serum tumor markers, specifically alpha-fetoprotein (AFP) and human chorionic gonadotropin (hCG);
2. Enlarging or newly appearing masses despite administration of appropriate systemic chemotherapy;
3. Histopathological confirmation of mature teratoma components only in the resected specimen.

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It is postulated that intraoperative tumor spillage may contribute to the development of growing teratomas. Additionally, the presence of gliomatosis peritonei at the time of initial surgery has been suggested as a potential predictor of subsequent growing teratoma syndrome development.[4]

1.2. Etiology/Pathogenesis

The etiology of Growing Teratoma Syndrome (GTS) remains uncertain, with several proposed mechanisms. The transformation theory suggests chemotherapy alters cell kinetics of malignant germ cells, inducing differentiation into mature teratomatous elements.[5] The retroconversion theory (DiSaia et al.) proposes selective destruction of malignant cells, allowing benign components to proliferate.[6] The *differentiation hypothesis* (Hong et al.) proposes that spontaneous maturation of malignant cells during therapy, supported by murine teratocarcinoma models.[7] These mechanisms are not mutually exclusive, and the exact process remains unproven.

2. Case Presentation

A 6-year 9-month-old Bengali girl presented to the outpatient department of our institute in June 2023 with a gradually increasing abdominal swelling. A contrast-enhanced computed tomography (CECT) scan revealed a large, lobulated, encapsulated solid heterogeneous mass in the lower abdomen and pelvis, with areas of calcification and focal post-contrast enhancement, raising suspicion for an ovarian germ cell tumor, most likely a dysgerminoma.

Initial ascitic fluid cytology was performed to evaluate for malignant cells- was negative. Serum tumor markers were elevated: alpha-fetoprotein (AFP) – 1105 ng/mL, beta-human chorionic gonadotropin (β-hCG) – 42.6 mIU/mL, and CA-125 – 80.6 U/mL, while lactate dehydrogenase (LDH) was within normal limits (269 U/L).

Following appropriate preoperative evaluation, the patient underwent exploratory laparotomy with right salpingo-oophorectomy. Intra-operatively, a large right ovarian mass was noted, associated with hemorrhagic peritoneal fluid, peritoneal deposits, and pseudomyxoma peritonei formation. Intraoperative peritoneal fluid cytology and cell block preparation demonstrated immature elements.

Gross examination of the ovarian mass showed a solid-cystic tumor measuring 18 cm in greatest dimension, with variegated appearance, and areas of hemorrhage and necrosis. Histopathological analysis confirmed the diagnosis of an immature teratoma, WHO Grade 2 (moderately differentiated), FIGO Stage IA.

Separate specimens labeled as "peritoneal deposit" and "pseudomyxoma" were negative for malignancy. No lymph node metastasis was identified.

The patient was closely monitored postoperatively with serial tumor marker surveillance, which initially showed a downward trend. β-hCG and CA-125 normalized by postoperative day five, while alpha-fetoprotein (AFP) normalized by the end of the second postoperative week. However, AFP levels began rising again in the following month, prompting further evaluation.

A Positron Emission Tomography with Computed Tomography (PET-CT) scan demonstrated a likely complete metabolic response at that time. Given the prior elevation of tumor markers and clinical background, she was initiated on BEP chemotherapy regimen (Bleomycin, Etoposide, and Cisplatin), receiving a total of four cycles.

Following chemotherapy, the patient was clinically stable. However, a re-evaluation PET-CT scan revealed multiple solid-cystic lesions with heterogeneous enhancement and mild FDG uptake in the solid components. These lesions were located in the pelvis (adherent to the uterus), infraumbilical region, and subphrenic region, with the largest lesion measuring 8 cm. Compared to the previous scan, there was radiological evidence of disease progression, including significant enlargement of mesenteric deposits and the emergence of new abdominopelvic lesions.

Despite these radiologic findings, tumor markers remained within normal limits: β-hCG: 0.1 mIU/mL, LDH: 270 U/L, AFP: 1.46 ng/mL

Following comprehensive pre-surgical evaluation, the patient underwent a second exploratory laparotomy. Intra-operatively, a large, firm, multiloculated lesion measuring 5 × 4.5 cm was found adherent to the previous surgical suture line. Additional findings included multiple deposits on the upper pole of the spleen with hilar involvement and another pelvic lesion measuring 5 × 4.5 cm.

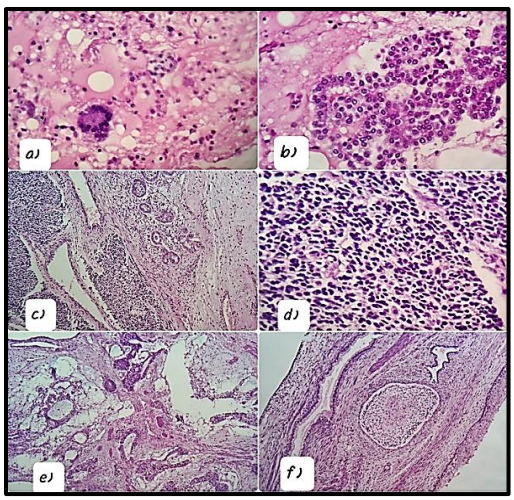

Figure 1: a,b:) Immature neural elements (rosette formation) in cell block preparation, **c,d,e:)** Immature neural components and **f :)** immature cartilage in resected specimen.

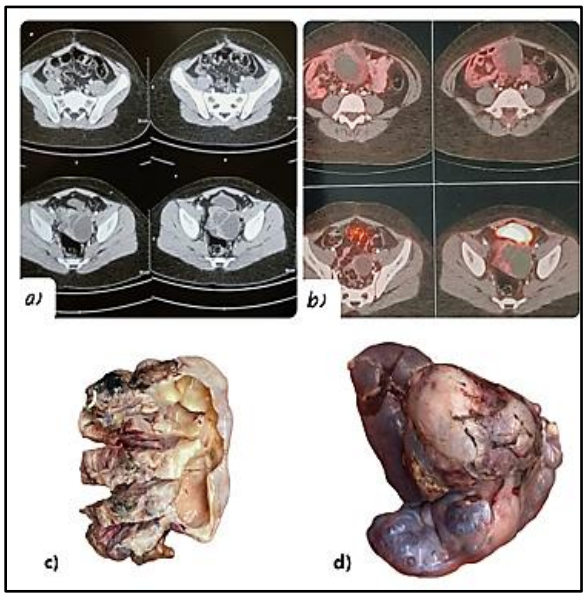

Figure 2: a) Multiple pelvic deposits in CT scan, **b)** Multiple non FDG avid pelvic deposits and FDG avid lesion adherent to uterus in PETCT scan, **c)** Gross image of deposit in peritoneum, **d)** Gross image of solid-cystic lesion in spleen.

Specimens from the spleen, umbilicus, pelvis, rectum, small bowel, and peritoneal deposits, along with right pelvic lymphadenectomy and peritonectomy tissue, were submitted for histopathological evaluation.

On gross examination, an encapsulated mass adherent to the spleen measured 7.5 cm at its greatest dimension and was composed of approximately 70% solid and 30% cystic areas. Additional solid-cystic encapsulated masses, labeled as "pelvic and peritoneal deposits," were also received. The largest tumor deposit measured 8.5 × 7 × 2.5 cm.

Cytological analysis of intraoperative peritoneal fluid revealed the presence of teratomatous components on smear examination.

Microscopic evaluation of the resected specimens from the spleen, pelvic, rectal, and peritoneal deposits showed well-circumscribed tumors composed of mature elements derived from all three germ layers, consistent with mature teratoma. No immature components or evidence of malignancy were identified.

A total of seven pelvic lymph nodes were examined, all demonstrating reactive hyperplasia with no metastatic involvement.

Tissue samples from the hemidiaphragmatic peritoneum, right and left pelvic peritoneum, small bowel, and umbilicus showed areas of moderate mixed inflammatory infiltrates and focal fibrinoid necrosis, but no teratomatous elements were identified.

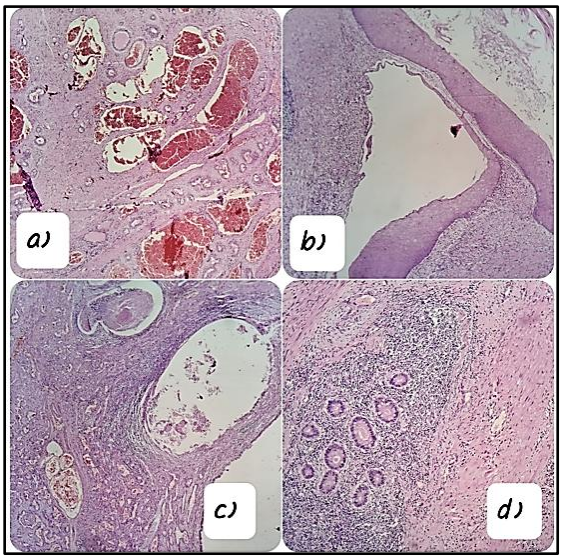

Figure 3: a,b,c,d) Post chemotherapy residual mature components only in the resected specimen

3. Discussion

The hallmark of Growing Teratoma Syndrome (GTS) is the normalization of serum tumor markers, including alpha-fetoprotein (AFP), beta-human chorionic gonadotropin (β-hCG), and lactate dehydrogenase (LDH). In our patient, all tumor markers remained within normal limits, consistent with the diagnostic profile of GTS.

Table 1:

	Literature review	**Our case**
Median age	Median age is 22 years (second decade), though it may be diagnosed in pre-menstrual females as well,[4,9] only 8 cases have been diagnosed so far in paediatric population[10,14]	Our case was in paediatric age group, under 7 years of age on initial presentation.
Clinical presentation	Mostly asymptomatic, though abdominal pain/distension may be seen.	Similar presentation as cited in literature
Interval between presentation and initial management	Average interval from receiving of initial treatment is around 8 months (although can appear during CT incidentally upto as long as 12 years after treatment). When surgery is delayed, complications related to local compression, including obstructive renal failure or bowel,	In this current scenario, patient required second surgery at an interval of 15 months, while mass lesion was evident at an interval of 13 months from initial surgery.

	duodenal, bile duct, or large vessel obstruction[11] is common.	
Organ involvement	Grow initially at the site of the tumor and then spread to more distant sites -most common site is the retroperitoneum[12] and has also been described in the lung, mediastinum, supraclavicular lymph nodes, inguinal lymph nodes, forearm, mesentery and liver[13]	Presented with pelvic organ involvement, lesion along previous suture area and involvement of spleen additionally. However, there was no lymph node involvement noted.
Chemotherapy regime association	Reported with conventional systemic chemotherapy regimens [bleomycin, etoposide and cisplatin (BEP)]	Our patient received 4 cycles of BEP regimen.

The definitive diagnosis is established through histopathological examination of the resected masses. The presence of mature teratomatous elements in these lesions strongly supports the diagnosis of GTS.[13] Notably, the teratomatous component is reported in up to 86% of primary germ cell tumors associated with GTS.[13] On gross examination, the tumors typically display a mixed cystic and solid appearance. Microscopic evaluation often reveals a variety of mature tissue types, including cartilage, bone, ciliated respiratory epithelium, enteric epithelium, and neurogenic tissue, along with undifferentiated mesenchymal spindle cell stroma.[7] Similar findings were observed in the current case.

Although malignant transformation within a GTS lesion is extremely rare, it has been reported in approximately 3% of cases.[8]

The gold standard treatment for GTS is complete surgical resection of all tumor masses, ideally at the earliest stage, to avoid inoperability due to local invasion or adhesion to surrounding structures.[15] To date, no standardized management protocol exists for GTS.

While medical therapy has limited efficacy, targeted agents such as Bevacizumab (a VEGF inhibitor)[16] and cyclin-dependent kinase inhibitors[17] have shown promising results in isolated cases and may have a future role in management.

Strict and regular follow-up is essential for early identification of recurrence or complications. Recurrence rates are significantly higher in cases of partial resection (72–83%) compared to those undergoing complete resection (0–4%).[8,11]

Postoperative management is guided by histopathological findings. Chemotherapy is re-initiated only if malignant elements are detected in the resected tissue. The prognosis of GTS is favorable, with a 5-year overall survival rate of approximately 89% in patients undergoing surgical treatment.

4. Conclusion

Growing Teratoma Syndrome (GTS) is a rare clinical entity, and its occurrence in the pediatric population is even more uncommon. However, it should be considered an important differential diagnosis, particularly in patients who present with radiological disease progression despite normal tumor markers, following adequate surgical intervention and chemotherapy.

Monitoring GTS poses a challenge due to the lack of elevated serum tumor markers, which typically guide disease assessment in germ cell tumors. Therefore, the definitive diagnosis relies on histopathological evaluation of the resected specimens, highlighting the critical role of tissue diagnosis in such cases.

5. Source of Funding

None.

6. Conflict of Interest

None.

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