



# Recurrent Metastasis of Ovarian Immature Teratoma in a 7-Year-Old Girl. Case Report of Uncommon Tumor and Brief Review of the Literature

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## Abstract

Ovarian teratoma is most frequently found in children and adolescents. It comprises a combination of adult and embryonic tissues from the three germ cell layers: ectoderm, mesoderm, and endoderm. According to the current WHO grading system, the tumor can be divided into mature (benign) and immature (malignant) based on the existence and quantity of the immature component. The microscopic grade of the initial tumor best predicts the chance of extraovarian dissemination, and size and stage have been linked to survival. Immature elements might be present in small foci or large amounts. An incorrect diagnosis of a benign teratoma with inadequate treatment and a poor prognosis can result from insufficient pathological sampling missing the immature tissue. No matter how they present clinically or grossly, all teratomas must be extensively sampled in the pathology lab to look for any potential immature components. A teratoma is challenging for pathologists to diagnose, much like every other gonadal germ cell tumor, and an accurate diagnosis has significant therapeutic and prognostic ramifications. Here, we present the case of a 13-year-old girl with a high-grade metastatic giant 23 cm immature teratoma and review the relevant literature. The patient had several peritoneal implants at the time of surgery, and the tumor had grown to the pelvic wall. Following surgical debulking and chemotherapy, the patient's tumor recurred after two years with liver and lung metastases.

**Keywords:** Immature teratoma, Malignant, Recurrent, Surgery, Immunotherapy

## Abbreviations

**IT:** Immature teratoma, **MCTs:** Mature cystic teratomas, **MOGCT:** Malignant ovarian germ cell tumors, **GTS:** Growing teratoma syndrome.

## Introduction

Ovarian teratomas are germ cell tumors derived from all three germ cell layers and contain different tissue types, such as hair, bone, and muscle. Teratomas can be classified into mature and immature teratomas (ITs) according to the type of differentiation. Immature teratomas contain varying amounts of fetal neuroectodermal tissue and are the second most

common ovarian germ cell tumors, leading to cystectomy and oophorectomy [1]. There are three types of ovarian teratomas; mature, immature, and monodermoid. Mature teratomas, also called dermoid cysts, account for 95% of all teratomas and are benign. Immature teratoma (IT), a malignant form of teratoma, is the second most common type. Eighty percent of cases are unilateral and primarily affect children and women of childbearing age. A third type is a mono dermal teratoma with a single structural element: ovarian goiter, neuroectodermal, and carcinoid. [2].

Adolescents and young adults of childbearing age are most affected. After germinomas, IT is the second most common malignant germinal tumor [3]. Immature teratoma is the only neoplasm containing germ cells that are histologically classified based on immature neural elements, an important prognostic factor for overall survival [3]. A definitive diagnosis is histological, with surgical staging. IT metastases are rare; the most common mode of spread is the hematogenous route, especially in the liver, retroperitoneum, omentum, mediastinum, and brain [2]. Here, we report a case of this uncommon tumor in a 13-year-old girl and review the pertinent literature.

## Case Presentation

A 13-year-old girl presented with intermittent pelvic pain and abdominal distention for five months. She gradually noticed enlargement of the pelvic swelling, which extended to the

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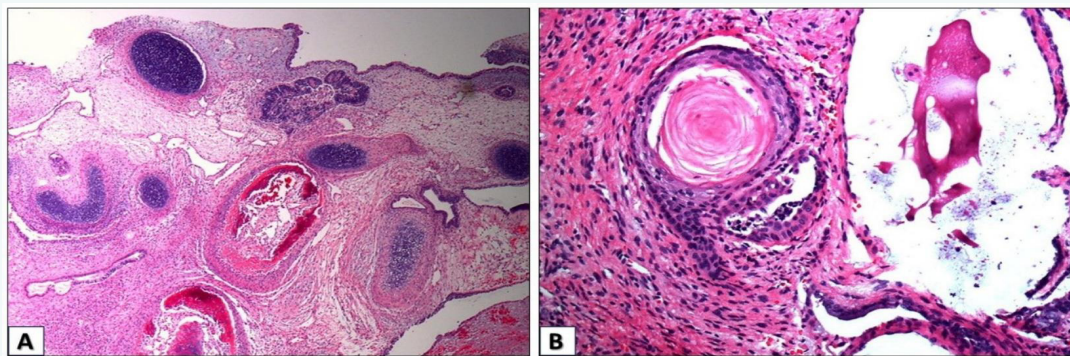
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abdomen. She also reported difficulty passing stool that became progressive with time. Past medical history was remarkable for removing a benign ovarian cyst before the current presentation. No significant family history was reported. Ultrasonography (U.S.) of the abdomen and pelvis revealed a large solid cystic mass at the site of the left ovary measuring 23 cm, confirmed with C.T. scan studies. Scattered retroperitoneal implants were also noted. A biopsy was obtained from the mass, which revealed various mature tissue components derived from different embryonic germ layers. The biopsy contained ectodermal tissue, such as skin, hair follicles, and nerve-like tissue, and included endodermal tissue, such as the digestive tract and respiratory mucosa, in addition to bone and cartilage mesodermal tissue (**Figure 1 A-B**). Although a mature benign cystic teratoma diagnosis was given, the pathology report indicated it was a small biopsy from a large mass and may not fully represent the entire mass.

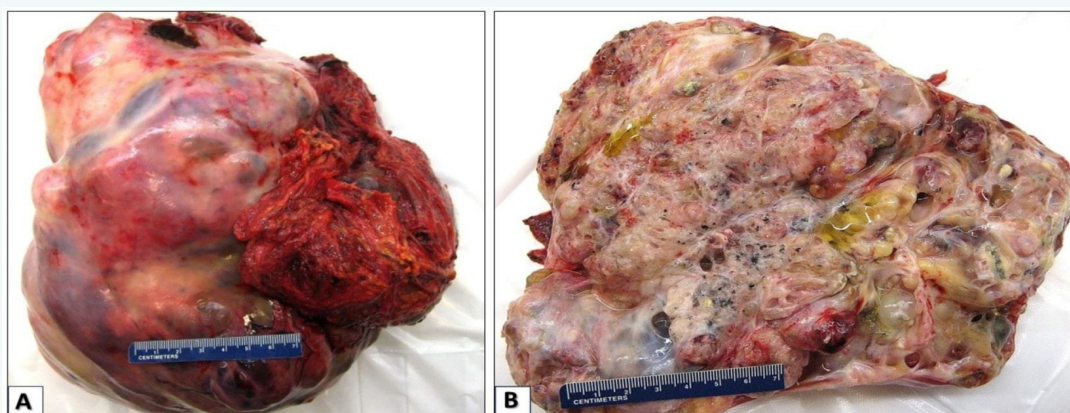
Due to the large mass size and the pathology report's concern, a germ cell tumor or immature teratoma could not be ruled out. Therefore, a decision was made to remove the entire mass and

the peritoneal implants surgically. The surgical excision included; the left retroperitoneal ovarian mass with the attached segment of the colon, omental nodules, and three peritoneal implants. There were foci of an immature high-grade teratoma (malignant teratoma) with a high-grade neuroectodermal component in the background of a benign cystic teratoma. The entire mass measured 23 x 14 x 9 cm. The tumor mass was attached to the colonic wall, but the colon was not involved by the tumor. The cut surface showed multilobulated predominately solid tumor and multiple cystic areas. Cystic spaces contained hemorrhagic tumor debris admixed with mucoid material and black necrotic tissue. Focal calcification was noted in the solid areas (**Figure 2 A-B**). No tumor was seen at the free peritoneal margins, but two of the three implants were involved by teratoma with immature malignant elements. The immature malignant component was seen as a high-grade neuroectodermal primitive tissue and foci of malignant osteoid and cartilage and was estimated to be scattered over at least 30% of the entire mass (**Figure 3 A-B-C**). Immunohistochemistry (IHC) studies ruled out malignant germ cell tumors with negative AFB, HCG, and PLAP (**Figure 3 A-B**).



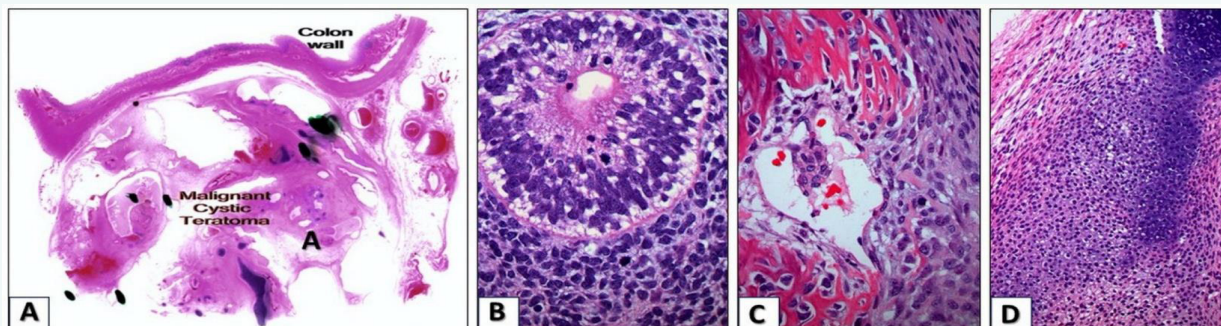
**Figure 1** Mature teratoma (first biopsy)

A: The biopsy shows mature elements of skin, bone, and nerve-like tissue, in addition to digestive tract and respiratory mucosa (H&E stain X 20)  
B: Biopsy shows mature bone, cartilage, and hair follicles (H&E stain X 40)



**Figure 2** Immature teratoma excision:

A: The tumor mass is attached to the colonic wall.  
B: The cut surface shows multilobulated predominately solid tumor and multiple cystic areas. Cystic spaces contain hemorrhagic tumor debris admixed with mucoid material and black necrotic tissue.



**Figure 3** Immature teratoma, microscopic examination  
A: Scanning view Showing teratoma attached to the colonic wall (H&E scanning view)  
B: High-grade neuroectodermal malignant component (H&E X40)  
C: Malignant osteoid (H&E X40)  
D: Malignant cartilage (H&E X20)

The tumor showed a DNA index ploidy of 1.0 Diploid, S-Phase 6.5. The malignant tumor showed high proliferation with 80% nuclear staining with Ki-67.

Postoperatively, three rounds of chemotherapy with bleomycin, etoposide, and cisplatin were given. The tumor recurred 28 months later with metastasis to the peritoneum, liver, and brain. As the metastatic foci were unresectable, another round of chemotherapy started, but unfortunately, the patient expired after three weeks of the treatment.

## Discussion

Mature cystic teratomas (MCTs) of the ovary, known as dermoid cysts, are the most common form of ovarian germ cell tumors. It is relatively common, accounting for approximately 20% of all ovarian tumors. They are benign tumors in their pure form [2]. Malignant transformation of an MCT is rare and occurs in only 1-3% of cases. In ovarian teratoma, it is essential to assess immaturity, which manifests as immature neuroepithelium, but in some cases, it can also display as mitotically active cellular glia. Semi-quantification of neuroepithelial abundance correlates with the survival of immature ovarian teratomas, at least in adult patients, and is the basis for grading these tumors [4].

There are differences in the approaches of international organizations related to the diagnosis, staging, and treatment management of ITs. All these organizations are attempting to reach a consensus. Regarding diagnosis, no biomarkers or apparent clinical or imaging factors distinguish it from other ovarian tumors, and histopathology is the only definitive diagnostic method. The actual incidence of IT is controversial due to its rarity. Some researchers reported an incidence of 2.3 per 100,000 patients, and others wrote an incidence of 0.05 per 100,000 in the population [2,5]. In a report by Jorge S et al., they studied 1045 cases with immature teratoma. They reported that African Americans had a higher mortality rate from malignant ovarian germ cell tumors (MOGCT) than Caucasians despite similar rates and modalities of adjuvant treatment. Additionally, lower-income people were more likely to be diagnosed with the disease at an advanced stage [6].

Symptoms of immature teratoma (IT) are not specific. Clinically, painful pelvic tumor swelling is more frequently observed. Symptoms may be acute with complications such as rupture, torsion, hemorrhage, and superinfection with peritonitis. However, these symptoms are less specific and can accompany other ovarian tumors [7]. Alpha-fetoprotein levels are elevated (AFP) but do not exceed 1000 ng/ml. Biomarkers are not used in children because values >100 ng/ml correlate with the presence of yolk sac elements [5]. Therefore, surgical intervention is essential to make the diagnosis. Imaging studies usually show mixed appearance, both solid and cystic, with calcifications. Usually, ultrasonography (U.S.) is used, but C.T. scans and MRIs are also used in cases where the US findings are not specific for ITs [2].

Macroscopically, immature teratomas are mostly or completely solid, typically unilateral, and their dimensions are variable, with a typical diameter of about 15 cm. This diameter is double the average diameter of mature teratomas. On sectioning, solid areas appear white, gray, or brown, but if cartilage or bone is present, the tissue has a different consistency (soft or hard). Dermoid cysts may occur in the contralateral ovary in 7.1% of the cases [8]. Extraovarian tumor implantations in the omentum, peritoneum, and lymph nodes are detected more frequently in patients with immature teratomas but only rarely in mature teratomas. Moraru et al. reported that about 100 such cases have been documented in the literature with such observations. Implants are called gliomatosis because immature tissue, consisting primarily of neuroepithelial tissue, may be present within the implant [2]. Microscopically, immature mesodermal tissue is hypercellular, predominantly composed of small, mitotically active spindle-shaped cells. The cells show hyperchromatic nuclei, immature cartilage, immature adipose tissue, osteoid, and even immature striated muscle cells [8,20]. The differential diagnosis of immature teratomas includes mature teratomas, mixed germinal tumors, melanoma, myxoid types of sarcomas, dermatofibrosarcoma protuberance, and mixed mesodermal tumors. Differentiating between mature and immature teratomas can be difficult because teratomas with rare



foci of immature tissue are difficult to classify. These tumors are recommended to be called mature teratomas with microscopic foci of immature tissue [9].

Immature teratomas are a subtype of malignant germ cell tumors of the ovary. Diverse errors are the key to forming immature teratomas, and epigenetic differences are critical to the variation in differentiation patterns in teratomas and the transformation from benign to malignant tumors [10]. The origin of immature teratomas has not yet been investigated, and their molecular and genetic etiopathogenesis is unknown and remains not fully studied. The etiopathogenesis of these tumors is not clear. Several hypotheses exist, such as their development from trapped oocytes following defective folliculogenesis [11]. They can also develop from pluripotent stem cells or residual fetal cells. They undergo a process of metaplasia under the influence of inflammatory factors that act as triggers [12]. However, these are all just postulations. The genetics of these tumors are being studied, and they show a common cellular origin from germ cells in various stages of development but with different pathogenic pathways and behaviors [13]. In their study, Heskett et al. used genome-level sequencing to explain the pathogenic mechanism of immature teratomas for the first time. They highlighted that meiotic nondisjunction events producing the 2Nnear-diploid genome and allelic imbalance are responsible for the rise of immature teratomas [10].

Despite the involvement of various international organizations concerning staging, a clear consensus has yet to be reached using a common FIGO and COG design [2,14,15]. There is no consensus on staging, but an agreement was made to combine FIGO staging with the TNM and COG (Children's Oncology Group) [15]. There are discrepancies between the proposed therapies, and this fact is due to the rarity of such a tumor and its characteristics. The preferred method is fertility-sparing surgery in pediatric IT, with complete resection to avoid tumor relapse. However, experience in such cases is limited [16].

There are no randomized trials with precise data in the literature. Pediatric cases have not received adjuvant chemotherapy except in rare situations, as there is disagreement regarding its usefulness compared to its long-term adverse effects [15]. For adults in stage I, grade 1, a surveillance policy is already imposed rather than adjuvant chemotherapy [14]. The primary therapy is fertility-sparing surgery, which maintains both menstruation and reproductive function, though there is no consensus regarding combination treatment with chemotherapy. Chemotherapy is not performed even for grade 3 tumors because it is considered that it does not prevent relapse, and the adverse effects are unacceptably high [17]. The reported chemotherapy with the best results is platinum-based (BEP-bleomycin-etoposide-cisplatin). The number of chemotherapy courses is not yet well defined, but three courses are preferred. There are relapses, which may take the form of immature teratomas, other germinal tumors, mature teratomas, glioblastomas of the peritoneum, or GTS (growing teratoma syndrome). The relapse treatment is surgical, with additional histopathological examinations performed [14,17]. The correct approach in the

case of resistance to chemotherapy is not known. Various targeted treatments that have been proposed are still being studied [15].

The chromosomal mapping of the histological tissue could be helpful in evaluating other family members regarding the possibility of the appearance of the pathology and in terms of finding an alternative targeted treatment [11]. Interesting to follow the results of fertility treatments. A study of 46 patients by Wang and colleagues concluded that residual disease contributes to poor prognosis in advanced disease [18]. The most important prognostic factor is tumor grading based on immature neuroepithelial components. In general, tumor stage, incomplete resection, and mixed elements of a yolk sac are prognostic factors and indicators of overall survival [2].

Growing Teratoma Syndrome (GTS) is a syndrome that appears after chemotherapy for germ cell tumors without elements of malignancy. Heskett and associates reported 26 immature teratoma (IT) patients with 69 months of follow-up, where 15 underwent chemotherapy and 6 developed GTS. The studied patients were between 17 and 38 years of age, with an average age of 24. Those with GTS required additional surgery, and no malignant elements were found in the histopathology [10]. In another study, out of 175 IT cases, 35 developed GTS. The interval from the initial diagnosis to GTS was 18.5 months [18] however; other studies disagreed with these findings [14]. The pathogenesis of GTS is controversial as chemotherapy is supposed to induce cell differentiation into mature tissue. According to another theory, chemotherapy selectively eliminates malignant tumor cells, called a therapeutic conversion. Tumor markers normalize in cases of GTS [18].

Peritoneal gliomatosis (Gliomatosa Peritoneii) is defined by mature glial tumor tissue in the peritoneum. Its exact etiopathogenesis is unknown, but it can be assumed that it is secondary to IT rupture. However, it was found that glial tissue is more reactive and genetically different from a primitive ovarian tumor, which raises more questions [15].

## Conclusion

Immature teratoma is a rare malignant embryonic tumor and the only one that can be graded among malignant germ cell tumors. There are discrepancies between the proposed therapies, and this fact is due to the rarity of such a tumor and its characteristics. With our case and literature review, we fully agree with prior investigators observations. There are no randomized trials with precise data in the literature. Urgent cooperation between pediatric and adult oncology is necessary to establish a generally accepted staging system and a reliable treatment strategy. Although there is no consensus on treating this type of tumor, it has a good therapeutic outcome. It is the only malignant germ cell tumor with good survival and high fertility preservation.

Further investigation is needed to provide additional insights into immature teratomas' pathogenesis and clarify the need for chemotherapy, especially in pediatric oncology. Given the side effects of chemotherapy, monitoring may be preferred. Our patients developed metastases and succumbed to the diseases



even with the use of sufficient cycles of chemotherapy. These efforts are necessary given the age at which these malignancies develop and the potential to cure the disease. Particular attention should be paid to the genetic mapping of the histological part for patient risk stratification, as it is crucial for prognosis and future treatment. Our report will raise awareness and knowledge of these uncommon tumors and help establish a multidisciplinary approach in specialized clinics regarding management for optimal patient care outcomes.

**Human subjects:** Ethical review and approval were not required for the study on human participants in accordance with the local legislation and institutional requirements. The paper has been sufficiently anonymized to keep patient's confidentiality

**Conflicts of interest:** In compliance with the ICMJE uniform disclosure form, all authors declare the following:

**Payment/services info:** All authors have declared that no financial support was received from any organization for the submitted work.

**Financial relationships:** All authors have declared that they have no financial relationships at present or within the previous three years with any organizations that might have an interest in the submitted work.

**Other relationships:** All authors have declared that there are no other relationships or activities that could appear to have influenced the submitted work.

## Patient's consent

Patients was lost to follow up, all attempts to reach the patient or family member are unsuccessful. Therefore, the paper has been sufficiently anonymized to keep patient's confidentiality.

## Author contributions

Study concept and design: Jessica Jahoda and Mohamed Aziz, Writing the manuscript: Carolyn Coles, Helen Diaz, Izunna Ezekwesili, Ashley Gonsalves, Chinenyenwa Okoye, and Keoni Campbell. Reviewing and editing the manuscript: Jessica Jahoda and Mohamed Aziz, Critical review, and final approval: Mohamed Aziz

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