

Review

## Growing teratoma syndrome after surgery for ovarian immature teratoma

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### Abstract

Growing teratoma syndrome (GTS) is a condition characterized by tumor growth during or after chemotherapy for a germ cell tumor, albeit with normal tumor marker levels in the absence of histopathological evidence of immature teratoma components. We encountered a 10-cm large GTS lesion in the para-aortic nodes after fertility-preserving surgery for a grade 3 ovarian immature teratoma. The patient was a 20-year-old woman who presented to the hospital with complaints of abdominal pain and swelling. Imaging examination revealed an ovarian tumor mass measuring 24 cm in the abdominal cavity, suspected to be composed of a mixture of fat and other components. The  $\alpha$ -fetoprotein (AFP) levels were elevated at 853 ng/mL. We elected to perform fertility-preserving surgery. The surgical findings included a tumor in the right ovary, which was excised without rupture with adnexectomy. The histopathological diagnosis was grade 3 immature teratoma. Palpation of the pelvic and para-aortic lymph node areas did not reveal significant lymphadenopathy. Subsequently, a para-aortic node metastasis (major axis: 8 cm) was discovered before chemotherapy (19 days after surgery). We confirmed that there was no swelling before surgery and assumed that the immature teratoma had recurred. Chemotherapy was initiated, and the serum AFP levels normalized after 4 courses of bleomycin, etoposide, and cisplatin (BEP) therapy. However, the para-aortic node metastasis had grown further (major axis: 10 cm). Another open surgery was performed. The nodal mass was completely excised and pathology revealed only mature teratoma. Growing teratoma syndrome should be considered in the setting of a recurrent mass with negative tumor markers.

**Keywords:** Growing teratoma syndrome; Ovarian immature teratoma; BEP

### 1. Introduction

Growing teratoma syndrome (GTS), first reported in 1982, is a condition characterized by the presence and proliferation of mature teratoma components in metastatic lesions during chemotherapy for immature teratomas or mixed germ cell tumors [1]. In Japan, retroconversion [2] was first reported in the 1989 [3], and is considered to be the same disease concept as GTS.

Grade 3 immature teratoma is a rare disease accounting for 0.5% [4] of all ovarian malignancies. It is most common in younger women, who are at an age that warrants consideration of fertility preservation.

We encountered a 10-cm GTS in the para-aortic nodes after fertility-preserving surgery for a grade 3 ovarian immature teratoma. Herein, we report the clinical and therapeutic course in a young patient, along with a discussion of the literature.

### 2. Case

The patient was a 20-year-old woman who presented with a chief complaint of abdominal pain and protrusion. She experienced menarche at 13 years of age. Her last menstrual cycle occurred 3 weeks before presentation. The

length of the menstrual cycle was 30 days. She had a medical history of autonomic imbalance but her family history was unremarkable.

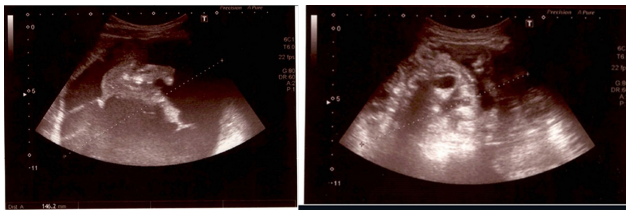
#### 2.1 Current disease history

The patient first experienced abdominal distention 2–3 months prior to presentation. The abdominal protrusion and pain worsened, 2 weeks prior to presentation, which led her to consult a local doctor. Transabdominal ultrasonography revealed a cystic mass the size of an adult head, and the patient was referred to our hospital on the same day (Fig. 1). The maximal diameter of the lesion was 20 cm or more and the proportion of solid tissue was 10 cm or more. The lesion contained more than 10 cystic locules and some papillary projections and ascites. Magnetic resonance imaging (MRI) was performed at the outpatient clinic, but the abdominal pain made it difficult for the patient to remain in the supine position, which in turn rendered imaging impossible under outpatient care. She was admitted to the hospital for symptomatic relief and further examination.

#### 2.2 Condition at admission

The patient was 149 cm tall and weighed 48 kg. Her vital statistics were as follows: blood pressure, 102/76





**Fig. 1. Transabdominal ultrasound image.** A mass with a mixture of cystic and solid components occupied the abdominal cavity.

mmHg; pulse, regular 60 beats/min ; body temperature, 36.4 °C. The abdomen exhibited generalized protrusion and a mass was palpable above the pubis and extended to the epigastric fossa.

Blood test findings (normal range in brackets):

<Blood count> WBC 8190/ $\mu$ L (3300–8600), Hb 10.8 g/dL (11.6–14.8), Platelets 300,000/ $\mu$ L (15800–34800)

<Biochemistry> LDH 234 U/L (124–222), AST 17 U/L (13–30), ALT 8 U/L (7–23), Creatinine 0.57 mg/dL (0.46–0.79), CRP 10 mg/dL (0–0.14)

<Tumor markers> AFP 853 ng/mL (0–10), SCC 3.0 ng/mL (0–1.5), CEA 1.5 ng/mL (0–5), CA125 35 U/mL (0–35), CA19-9 10.4 U/mL (0–37), STN 21.5 U/mL (0–45), HCG 1.3 mIU/mL (0–6)

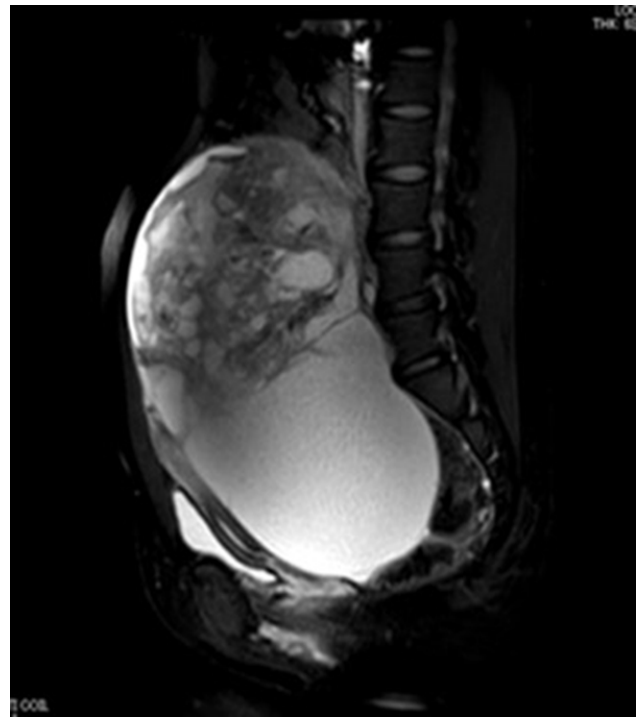
AFP and CRP levels showed marked elevation.

MRI depicted a multilocular tumor measuring approximately 118 × 187 × 220 mm with a variety of internal signal intensities, including solid and fat components, which suggested a germ cell tumor. It was not possible to identify whether the lesion originated from the left or right ovary (Fig. 2). Although preoperative MRI was acquired up to the upper abdomen, no swollen lymph nodes were found around the renal blood vessels at this juncture.

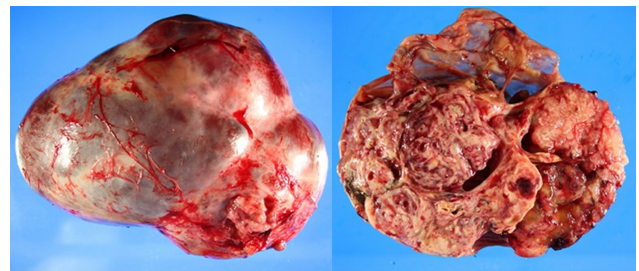
An ovarian immature teratoma was suspected before surgery. The tumor was resected 5 days after the first examination at our hospital.

### 2.3 Surgical findings

A tumor the size of an adult's head was found to occupy the abdominal cavity up to the upper abdomen. The border of the right ovary against the surrounding area was generally smooth, but adhesions to and invasion of the peritoneum near the suspensory ligament of the ovary were observed with the left ovary. Right sided adnexectomy, resection of the indurations on the abdominal wall side of the adhesions, omentectomy, and sampling of ascitic fluid were performed in order to preserve fertility. Palpation of the pelvic and para-aortic lymph node areas did not reveal significant lymphadenopathy. The extracted right adnexa measured 25 cm and weighed 3.1 kg (Fig. 3). The surgical grade was stage II, as per the 2014 International Federation of Gynecology and Obstetrics criteria.



**Fig. 2. MRI image.** A large mass occupied the abdomen from the xiphoid process to the pelvic cavity. The interior consisted of a cyst component, a solid component, and a fat component.

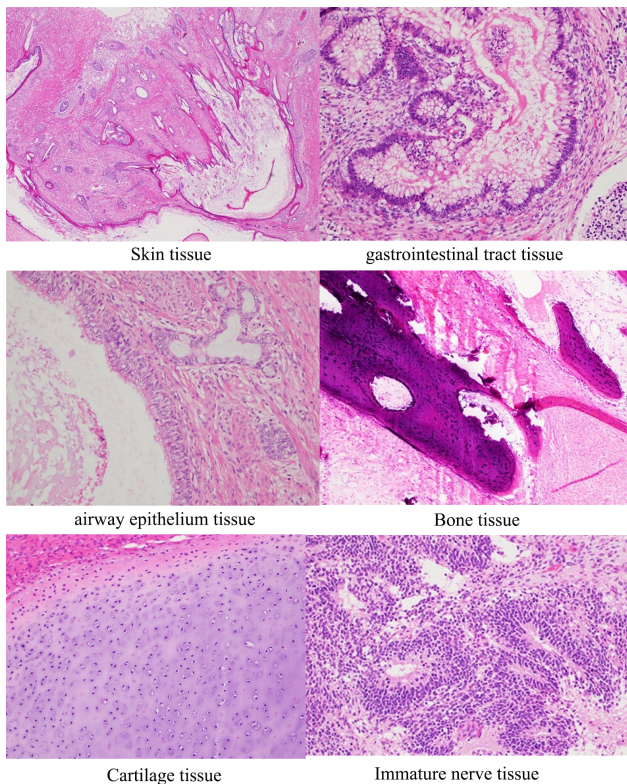


**Fig. 3. Gross findings.** The tumor was 25 cm and weighed 3.1 kg. The surface was relatively smooth, and a solid component was found inside the cyst with multiple septa. Findings indicating necrosis were found in the solid part.

### 2.4 Histopathological findings

Immature tissue containing skin, airway epithelium, cartilage, bone, adipose tissue, nerve tissue, choroid plexus, melanin-containing cells, gastrointestinal tract tissue, and neural tubes spanned multiple fields of view, as observed under a 4× objective lens. The histopathological diagnosis was grade 3 ovarian immature teratoma (Fig. 4). The main lesion and the adhesion lesion showed similar findings. There was a local invasion in the adhesion. There was no abnormality in the ascites and omentum.

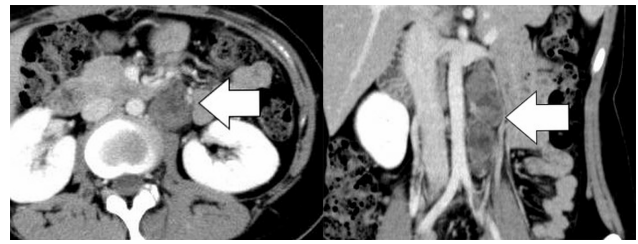
Contrast-enhanced computed tomography (CT) performed immediately before chemotherapy (19 days after surgery) revealed para-aortic node metastasis (81 × 25 × 30 mm) that had not been observed in preoper-



**Fig. 4.** The tumor was composed of immature tissues containing multiple germ layer components, and the immature nerve components could be easily confirmed in multiple visual fields in a quadruple visual field.

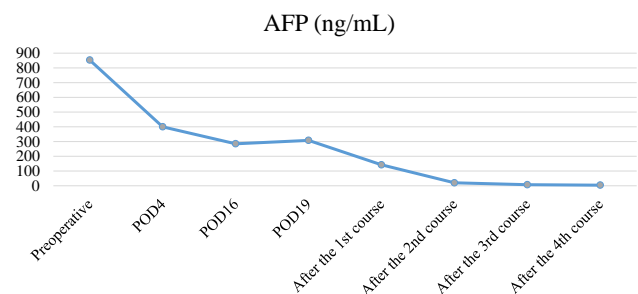
ative imaging (Fig. 5). Chemotherapy was prioritized because susceptibility to chemotherapy was presumed. Bleomycin, etoposide, and cisplatin (BEP) therapy was administered for postoperative chemotherapy, after obtaining sufficient induction chemotherapy, and assessing the risk of ovarian toxicity. Four courses of the following BEP regimen were administered: bleomycin (30 mg/body weight/day) was administered on days 2, 9 and 16, etoposide (100 mg/m<sup>2</sup>/day) was administered on days 1–5, and cisplatin (20 mg/m<sup>2</sup>/day) was administered on days 1–5. Gonadotrophin-releasing hormone (GnRH) analogues and oral contraceptives reportedly suppress ovarian function to protect against the ovarian toxicity of anticancer drugs [5–7]. Thus, GnRH agonists were used until the end of BEP therapy. Dehydration, hypotension, and facial contusion were observed due to the daily administration of diuretics, which improved after infusion and antibiotic use. No interstitial pneumonia or secondary leukemia was observed during the treatment period.

The patient's sample tested negative for AFP after the third course of BEP and remained negative thereafter (Fig. 6), although contrast-enhanced CT performed after chemotherapy showed further enlargement of the para-aortic nodes (101 × 57 × 51 mm) (Fig. 7). The differential diagnosis included recurrence of immature teratoma, malig-



**Fig. 5.** A tumor (81 × 25 × 30 mm) was found on the left side of the abdominal aorta and just below the left renal artery.

nant transformation of the teratoma components, and GTS. GTS had the strongest likelihood because of recurrence in the para-aortic lymph nodes after surgery, normalization of blood tumor markers, and growth of a metastatic lesion during or after chemotherapy. We decided to remove the tumor due to signs of exclusion of the left renal blood vessels.



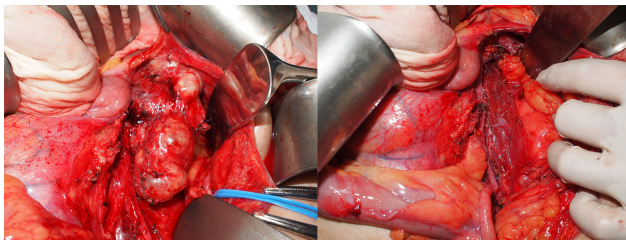
**Fig. 6.** Transition of AFP.



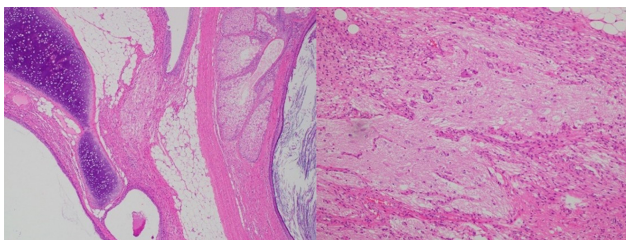
**Fig. 7.** The mass had grown (101 × 57 × 51 mm) and was compressing the abdominal aorta and the renal artery just above it.

Blood tumor markers after chemotherapy: <AFP 4.8 ng/mL (0–10), SCC 1.1 ng/mL (0–1.5), CEA 2.3 ng/mL (0–5), CA125 9 U/mL (0–35), CA19-9 23.3 U/mL (0–37), HCG 2.3 mIU/mL (0–6)>

A second open surgery was performed for complete removal of the tumor. The operative time was 3 h 43 min and the amount of blood loss was 150 mL (Fig. 8). Histopathological findings showed no immature nerve tissue and the diagnosis was grade 0 (Fig. 9).



**Fig. 8. This is a photograph of the retroperitoneum expanded.** A mass with fused multiple nodules was found. Many inflow vessels were observed, but the boundaries were relatively clear. The right photograph shows the retroperitoneum after removal of the tumor.



**Fig. 9. Excised para-aortic lymph nodes.** On left, the skin, cartilage, and multi-row ciliated epithelium are shown. On the right is nerve tissue, and no immature tissue was found in any of histological specimens.

The patient was placed under observation without any further treatment. At present, 15 months have elapsed since the removal of the GTS lesion, and no recurrence has been observed, as evidenced by tumor markers levels and contrast-enhanced CT. However, menstruation did not resume even 6 months after the end of chemotherapy. A blood test revealed reduced estradiol and increased follicle stimulating hormone levels. Hormone replacement therapy was initiated considering the risk of bone mineral loss and uterine atrophy.

### 3. Discussion

It is vital to initiate chemotherapy soon after surgery for ovarian germ cell tumors [8], owing to the rapid growth of malignant germ cell tumors. An 8-cm large para-aortic node metastasis that was not observed preoperatively was found immediately before postoperative chemotherapy (19 days after surgery) in our patient, which was attributed to the development of GTS in this area. The speed at which the grade 3 immature teratoma proliferated in our patient demonstrates the need for initiating chemotherapy soon after surgery.

Follow-up is essential after the treatment of immature teratomas due to the possibility of GTS. CT, MRI, and positron emission tomography (PET-CT) are the avail-

able imaging options, although PET-CT is not suitable for determining whether a lesion is benign or malignant because it reportedly depicts accumulations due to glucose metabolism in the nerve cells of teratomas [9,10].

The diagnostic criteria for GTS include normalization of blood tumor markers, growth of metastatic lesions during or after chemotherapy, and the histological presence of mature teratoma components [1]. An advanced stage III tumor, insufficient tumor reduction during surgery, and the presence of immature teratoma components in the primary tumor constitute the risk factors for GTS [11]. GTS does not respond to chemotherapy and can be the origin of secondary tumors. Surgical resection is performed to relieve pressure on surrounding organs [1].

Three differential diagnoses were possible in this case:

(1) GTS with an increased mature teratoma component, (2) increased immature teratoma component due to ineffective BEP therapy, and (3) secondary tumor caused by the teratoma component. Organ damage due to pressure on surrounding organs due to GTS was considered. Chemotherapy is a therapeutic option for residual immature teratoma, but is ineffective for GTS. Moreover, chemotherapy may have adverse effects such as ovarian toxicity and reduced quality of life. Thus, we think that tissue diagnosis should be prioritized in such cases.

We found 52 cases of GTS or retroconversion occurring after ovarian immature teratoma since 1987 (Table 1, Ref. [3,8–10,12–54]). We examined all 53 cases, including the present one. The mean age at initial onset of the immature teratoma was 20.8 years (median 19 years), and two patients underwent emergency surgery for acute abdomen due to torsion. A woman who was diagnosed at 18 weeks' gestation underwent termination of pregnancy. The mean AFP level before initial treatment was 4844 ng/mL (median: 900 ng/mL). All patients underwent postoperative chemotherapy: 31 with BEP and 6 with vinblastine, actinomycin D, and cyclophosphamide (VAC). The mean duration from treatment of the immature teratoma to the development of GTS was 39.9 months (median 12.0 months), the longest being 16 years, which shows the necessity of long-term follow-up. The most common location of the GTS lesion was peritoneal dissemination in 25 patients, followed by the para-aortic nodes in 5 patients, and the lungs in 2 patients, liver in 6 patients, and contralateral ovary in 2 patients each. Eight studies reported that patients underwent chemotherapy despite having suspected GTS. One patient was administered 12 courses of chemotherapy.

Since 2012, there have been 7 reports of laparoscopic biopsy for suspected GTS, which is considered to be a useful and minimally invasive approach for obtaining a definitive diagnosis in cases where GTS is strongly suspected.

Table 1. Previous reports of GTS.

Author	Year reported	Grade	AFP	Initial chemotherapy	No. of courses	Age at onset	Time from initial treatment to development of suspected GTS (months)	GTS site
Kaneko [3]	1989	3	29873	VAC	4	14	13	PAN
Miyasaka <i>et al.</i> [12]	1991	3	200	VAC	4	14	114	Peritoneal dissemination
Nakagawa <i>et al.</i> [13]	1991	2	Unknown	Chemo + radiation	Unknown	31	14	Lungs: 10 years follow-up
Yakushiji <i>et al.</i> [14]	1994	2	About 140	VAC	8	12	24	Peritoneal dissemination
Masuko <i>et al.</i> [15]	1995	Unknown	Unknown	VAC	Unknown	24	139	Peritoneal dissemination
Higaki <i>et al.</i> [16]	1997	Unknown	Unknown	VAC	9	15	36	Peritoneal dissemination, liver (left for 8 years)
Kobayashi <i>et al.</i> [17]	1999	1	Unknown	VAC	4	19	14	Peritoneal dissemination
Kumagaya <i>et al.</i> [18]	2000	1	166	Other	2	11	77	Contralateral ovary
Sakurai <i>et al.</i> [19]	2001	3	Unknown	Other	Unknown	17	156	Peritoneal dissemination
Itani <i>et al.</i> [20]	2002	2	21236	Other	3	24	4	PAN
Tagaya <i>et al.</i> [21]	2003	2	188	BEP	Unknown	21	2	Peritoneal dissemination
Rai <i>et al.</i> [22]	2004	3	2530	Other	5	15	12	PAN
Furudo <i>et al.</i> [23]	2004	3	2642	BEP	2	19	48	Peritoneal dissemination
Sunagawa <i>et al.</i> [24]	2007	2	397	Other	2	13	96	Peritoneal dissemination
Totake <i>et al.</i> [25]	2011	2	244	BEP	4	13	3	Peritoneal dissemination
Adachi <i>et al.</i> [26]	2010	2	12400	Other	3	18	192	Contralateral ovary, peritoneal dissemination
Kikawa <i>et al.</i> [9]	2011	2	11	BEP	3	36	8	Peritoneal dissemination
Terada <i>et al.</i> [27]	2013	1	28	BEP	3	20	5	Peritoneal dissemination
Abe <i>et al.</i> [28]	2012	3	4344	BEP	6	37	5	Peritoneal dissemination
Mariya <i>et al.</i> [29]	2013	Unknown	1134	BEP	3	30	26	Peritoneal dissemination
Morita <i>et al.</i> [30]	2014	3	1121	BEP	4	26	78	Peritoneal dissemination
Imai <i>et al.</i> [31]	2014	1	18743	BEP	4	11	6	Peritoneal dissemination
Hayashi <i>et al.</i> [32]	2015	Unknown	1052	BEP	4	41	5	Peritoneal dissemination
Sakamoto <i>et al.</i> [33]	2015	2	23352	BEP	3	11	6	Peritoneal dissemination
Ando <i>et al.</i> [34]	2015	3	1239	BEP	4	19	5	Peritoneal dissemination
Umezu <i>et al.</i> [35]	2015	2	2924	BEP	4	29	72	Peritoneal dissemination
Kojima <i>et al.</i> [36]	2019	1	288	BEP	3	18	3	Peritoneal dissemination
Tanaka <i>et al.</i> [37]	2020	2	Unknown	BEP	3	21	3	Peritoneal dissemination
Nakamura <i>et al.</i> [38]	2020	3	35464	BEP	4	24	4	Peritoneal dissemination
Byrd <i>et al.</i> [39]	2013	1	Unknown	BEP	Unknown	48	132	Uterus

Table 1. Continued.

Author	Year reported	Grade	AFP	Initial chemotherapy	No. of courses	Age at onset	Time from initial treatment to development of suspected GTS (months)	GTS site
Daher <i>et al.</i> [40]	2015	3	Elevated	etoposide, ifosfamide, and cisplatin	Unknown	4	7	Pelvic, omentum, appendix, broad ligament, abdominal wall
Djoordjevic <i>et al.</i> [41]	2007	3	2839	Unknown	Unknown	19	7	Periaortic, peripancreatic, perisplenic, omental, transverse colon, sigmoid, mesenteric
Han <i>et al.</i> [8]	2014	Unknown	Elevated	BEP	Unknown	13	5	Pelvic
Han <i>et al.</i> [8]	2014	Unknown	Elevated	BEP	Unknown	13	16	perihepatic space, pelvic
Han <i>et al.</i> [8]	2014	Unknown	Elevated	BEP	Unknown	27	83	subphrenic space, space, splenic hilum, paracolic gutter, rectouterine pouch
Hariprasad <i>et al.</i> [42]	2008	3	560	BEP	4	18	11	abdomino pelvic, uterus, rectum, sigmoid colon
Hariprasad <i>et al.</i> [42]	2008	3	1462	BEP	4	26	Unknown	pelvic
Hariprasad <i>et al.</i> [42]	2008	Unknown	6000	BEP	4	27	Unknown	pelvic, liver
Kampan <i>et al.</i> [43]	2012	1	Unknown	Unknown	Unknown	17	12	Bilateral adnexal, utarus
Kato <i>et al.</i> [44]	2013	3	Normal	BEP	Unknown	30	96	retroperitoneum, nodules in pelvicity
Kato <i>et al.</i> [44]	2013	3	Normal	vincristin, actinomycin D, carbonin	Unknown	22	264	peritoneal cavity
kurata <i>et al.</i> [45]	2010	2	107	non	Unknown	15	19	brain, liver, lung
Lorusso <i>et al.</i> [46]	2011	3	105	BEP	4	19	4	liver
Matsushita <i>et al.</i> [10]	2010	2	343	BEP	4	30	97	superior pole of kidney
Morency <i>et al.</i> [47]	2012	3	400	BEP	4	20	18	pelvic, liver
Mrabti <i>et al.</i> [48]	2011	Unknown	210	etoposide, cisplatin	6	18	6	abdmino pelvi, peritoneum
Pendlebury <i>et al.</i> [49]	2014	3	86	etoposide, cisplatin	2	21	2	Serosal surface of liver, hemidiaphragm, pelvic peritoneum
Rashmi <i>et al.</i> [50]	2010	3	5378	Unknown	3	19	36	Omentum, peritoneum, bowel loops
Sengar <i>et al.</i> [51]	2010	1	265	BEP	3	26	4	pelvic, abdominal wall
Tangitgamol <i>et al.</i> [52]	2006	3	900	BEP	2	5	5	Mass beneath diaphragm
Tejura [53]	2005	Unknown	154	Unknown	Unknown	21	12	pelvic, adnexal, para-aortic lymph
Tzortzatos <i>et al. et al.</i> [54]	2009	2	Unknown	BEP	3	20	24	Sacruterina ligaments, fossa douglasi
Present case	2019	3	853	BEP	4	20	5	PAN
average			4844			20.7	39.9	
mean			900			19	12	

PAN, Para-aortic lymph nodes; BEP, bleomycin, etoposide, cisplatin; VAC, vinblastine, actinomycin D, cyclophosphamide; AFP,  $\alpha$ -fetoprotein; GTS, Growing teratoma syndrome.

## 4. Conclusions

Tumorous lesions that develop after treatment for immature teratoma should be carefully examined for the possibility of GTS. Tissue diagnosis should be pursued aggressively since surgery is the only treatment modality for GTS.

## Author contributions

SS, YO, RS, YM, MS collected clinical data. TM collected histological data. SS, RS, YM compiled information collection and data on past reports. YO, TM, MS advised on the design of the paper. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript.

## Ethics approval and consent to participate

Not applicable.

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## Conflict of interest

The authors declare no conflict of interest.

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