

Malignant struma ovarii: a case report and literature review

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Background: Struma ovarii accounts for 0.2–1.3% of all ovarian tumors and 2–4% of all teratomas. There is no guideline or international consensus for malignant struma ovarii treatment so far.

Case presentation: We report a case of a 42-year-old woman who was diagnosed with malignant struma ovarii 18 years prior and remains alive. The patient presented with uncommon features of primary malignant struma ovarii, locoregional recurrence and metastases and received radical treatments including cytoreductive surgery (CRS), hyperthermic intraperitoneal chemotherapy (HIPEC), and transcatheter arterial chemoembolization (TACE). **Conclusions:** We report a typical case of malignant struma ovarii successfully treated by radical comprehensive treatment, with CRS + HIPEC as the core procedure. At present, the patient remains in good condition, surviving for 18 years since the tumor was found. This case provides evidence that CRS + HIPEC may be a promising strategy to improve outcomes for struma ovarii patients.

Keywords

Struma ovarii; Liver metastases; Total thyroidectomy; ¹³¹I treatment; Cytoreductive surgery; Hyperthermic intraperitoneal chemotherapy

1. Background

Struma ovarii is a rare disease that accounts for 0.2–1.3% of all ovarian tumors and 2–4% of all teratomas [1–4]. The mean age of onset is approximately the 4th to 5th decades [2, 5]. Struma ovarii can be benign or malignant. However, malignant transformation only occurs in 5–37% of patients with struma ovarii [6–8]. Follicular carcinoma and papillary carcinoma are the most common pathological types of malignant struma ovarii, accounting for 2% of these cases. However, metastasis only occurs in a few patients. Diagnostic criteria for malignant struma ovarii, as suggested by Devaney *et al.* [9], include the presence of cytological atypia, “ground glass” nuclei, increased mitotic activity and/or vascular invasion.

Here, we report a primary malignant struma ovarii patient with unusual features who experienced locoregional recurrence and metastases and achieved long-term survival after multiple therapeutic modalities, including cytoreductive surgery (CRS), hyperthermic intraperitoneal chemotherapy (HIPEC) and transcatheter arterial chemoembolization (TACE). We also performed a comprehensive literature review on struma ovarii.

2. Case presentation

A 42-year-old female was found to have a 3 × 3 × 3 cm³ solid mass on the left ovary by Doppler ultrasonography during a regular medical checkup on November 4, 2000. The patient was asymptomatic and did not accept any treatments.

On October 8, 2001, ultrasonography showed that the mass had increased to 7.8 × 7.7 × 6.0 cm³. The patient underwent laparoscopic radical resection of both the tumor and left ovary 15 days later. The pathological diagnosis was malignant struma ovarii (clinical stage IV) (Fig. 1), with immunohistochemistry showing positivity for thyroglobulin (TG) and cytokeratin (CK7) and negativity for CA125 and CD99. After surgery, the patient was treated with 3 cycles of systemic chemotherapy consisting of VP-16 and carboplatin.

In September 2003, the patient was diagnosed with recurrence. An imaging examination showed multiple masses in the pelvic cavity and a subcutaneous mass on the navel. A laboratory examination showed a TSH level of 1.71 μIU/mL (normal range: 0.34–5.60 μIU/mL), an FT4 level of 0.9 ng/dL (normal range: 0.58–1.64 ng/dL), a CA125 level of 103 U/mL (normal range: 0–35 U/mL), and a thyroglobulin level > 1000 μIU/mL (normal range: 10–115 μIU/mL). The patient received another 3 cycles of chemotherapy (the first 2 cycles consisted of VP-16 plus cisplatin, and the last cycle consisted of paclitaxel plus ifosfamide). However, an imaging examination showed tumor progression.

On January 7, 2004, the patient received CRS, in which the pelvic masses, uterus, right ovary and fallopian tube, omentum, appendix, pelvic peritoneum, sigmoid colon mesentery and small intestinal mesentery tumor nodules were removed. Postoperative pathology showed thyroid follicular carcinoma invading the uterus, ovary, pelvis, sigmoid colon, mesentery, and omentum. CA125 and TG levels decreased to 10 U/mL and 100 μIU/mL, respectively, after surgery. Based on the drug sensitivity test, the patient was treated with gemcitabine plus oxaliplatin after surgery. However, this regimen was eventually stopped due to severe hematuria. Then, the patient received 5 cycles of chemotherapy with vinorelbine and epirubicin. During the course of chemotherapy, the CA125 level remained stable at approximately 10 U/mL, but the TG level decreased to 74 μIU/mL. The patient's condition was considered stable.

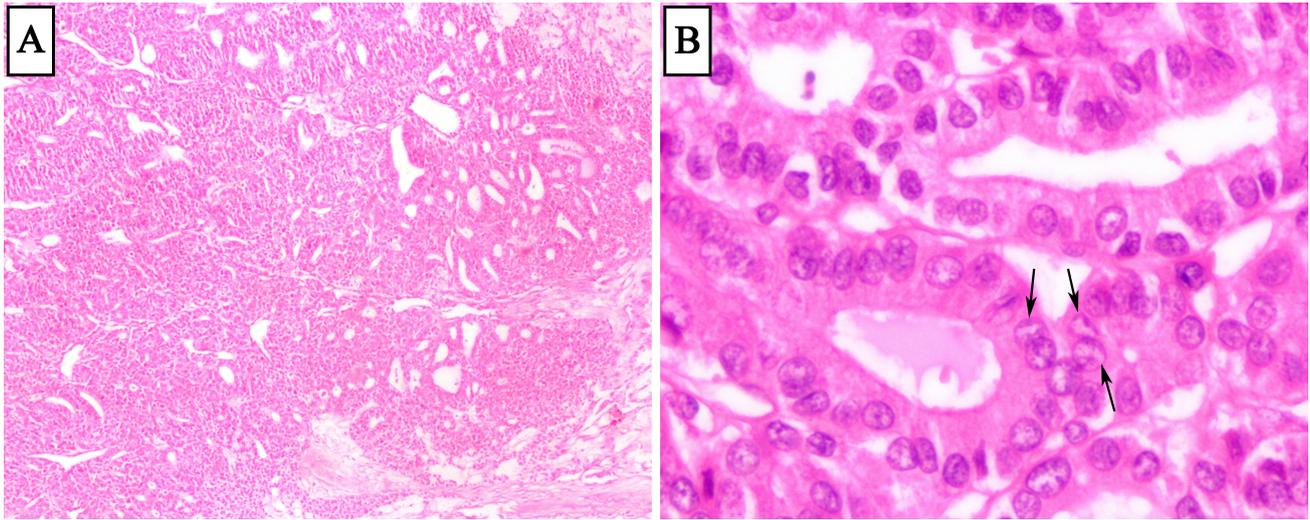


Fig. 1. Postoperative pathology showed malignant struma ovarii. (A) Thyroid follicular carcinoma in the ovarian tissue (H&E staining, 40 \times). (B) Infiltrative invasion in thyroid follicular carcinoma. Distinct atypia and a nuclear groove (black arrow) were observed in the cancerous epithelium (H&E staining, 400 \times). No ovarian tissue was obtained during pathological sampling.

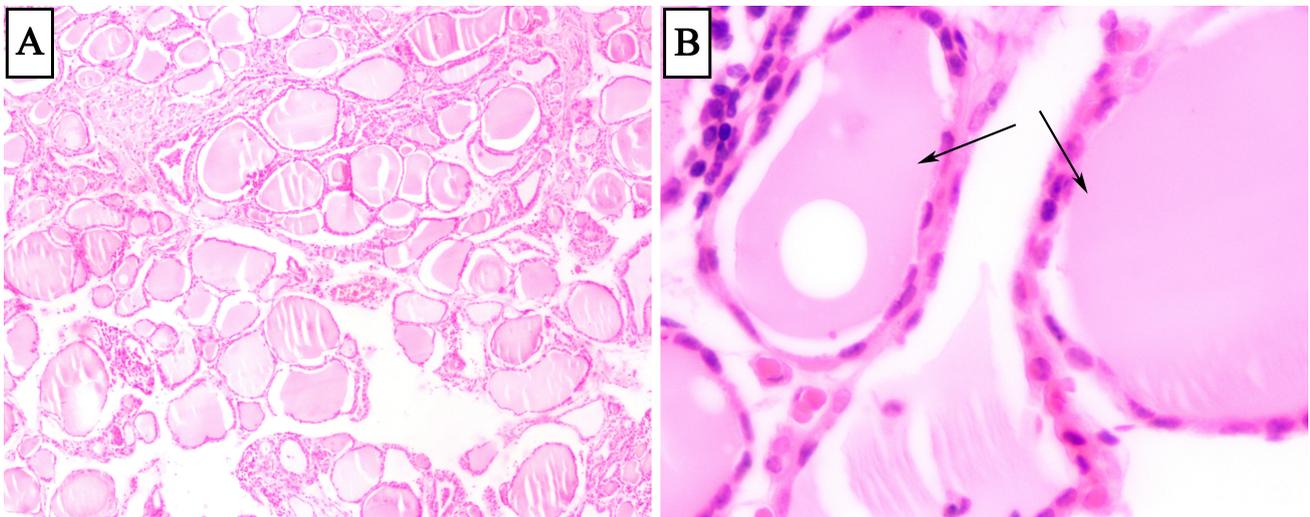


Fig. 2. (A) Postoperative pathology showed a normal thyroid gland (H&E staining, 40 \times). (B) An abundance of thyroglobulin (black arrow) inside thyroid follicles was observed (H&E staining, 400 \times).

In June 2004, however, the TG level increased to 86 μ IU/mL. From September 2004 thereafter, the patient was treated with levothyroxine at a dosage of 50 μ g per day. The serum TG level was reduced to 6.29 μ IU/mL. As a result, the dosage of levothyroxine was reduced to 25 μ g per day. The results of thyroid function tests were normal during the follow-up period, but Doppler ultrasonography showed a hypoechoic nodule in the vaginal stump measuring approximately 2.2 \times 1.7 \times 1.0 cm³. The serum CA125 level increased to 13.47 U/mL, and the TG level increased to 19.78 μ IU/mL. As a response to the elevation in serum tumor markers, the dosage of levothyroxine was again adjusted to 50 μ g per day. The patient remained in stable condition for 3 years.

In March 2008, a computed tomography (CT) examination revealed a neoplasm at the sigmoid colon wall measuring

approximately 1.2 \times 1.2 \times 1.0 cm³. The tumor at the vaginal stump remained almost the same size as before. On September 3, 2008, the serum TG level increased to 52.66 μ IU/mL, and the TSH level was normal at 1.49 μ IU/mL (normal range: 0.35–5.50 μ IU/mL).

On February 23, 2009, the patient underwent total thyroidectomy followed by ¹³¹I treatment. Postoperative pathology showed the absence of primary thyroid malignancy (Fig. 2). The patient received the first course of ¹³¹I treatment on May 5, 2009, at a dose of 100 mCi. Seven days later, radioiodine whole-body scans showed multiple iodine-avid foci in the thyroid bed, the left lower abdomen, the pelvis, and the right pleural diaphragm angle. However, the volume of the mass at the vaginal stump and the sigmoid colon decreased. From 2009 to 2013, the patient received ¹³¹I treat-

ment every year at a dose of 200 mCi. After 6 cycles of ^{131}I treatment, tumors in the sigmoid colon and vaginal stump continued to shrink. The patient lived without tumor progression for another 5 years.

In May 2014, the patient complained of thin stool, right lower extremity pain and limpness. A CT scan revealed that the pelvic mass had enlarged (Fig. 3). Another operation was performed to remove the pelvic tumor and the sigmoid colon. Postoperative pathology confirmed the diagnosis of a malignant monocortical teratoma-malignant goiter. The patient lived with a sigmoid colostomy and received ^{131}I treatment again on July 28, 2014, at a dose of 200 mCi.



Fig. 3. CT showed a very large mass (red arrow) in the pelvic cavity.

A follow-up examination in April 2015 revealed an enlarged pelvic mass with a rich blood supply and liver metastases. The patient received transinferior mesenteric arterial chemotherapy with oxaliplatin (150 mg) and gelatin sponge granule embolization with hydroxycamptothecin (5 mg), pirarubicin (10 mg) and iodized oil (10 mL). After the tumor blood supply had reduced and the tumor had shrunk, the patient underwent a more aggressive CRS + HIPEC regimen [cisplatin (120 mg) + mitomycin (30 mg)] on October 27, 2015. The rectum, ileocecum, sigmoid colon, and descending colon were resected during radical surgery. Postoperative pathology again revealed a malignant monocortical teratoma-malignant goiter. The patient presented with cachexia, weighing only 40 kg and losing the ability to walk. Surprisingly, the patient regained her appetite and gradually gained weight after surgery. The patient received ^{131}I treatment again on December 23, 2015, at a dose of 200 mCi. On June 28, 2016, the patient received internal iliac arterial chemoembolization treatment (cisplatin, paclitaxel liposome) + TACE [hydroxycamptothecin (10 mg) + pirarubicin (10 mg) + iodized oil (20 mL)]. Microwave ablation was performed to treat the liver metastases in June 2016; July, September, and December 2017; and January 2018. Key events during the course of treatment are presented in Ta-

ble 1. A tendency chart of the TG level and the relationship between treatment measures and the TG level is shown in Fig. 4.

From diagnosis to present, the patient has survived for 18 years, remains in good condition and is able to take care of herself.

3. Discussion

Struma ovarii is typically diagnosed before menopause. Benign lesions usually occur in the 4th decade, and malignant tumors usually occur in the 5th decade. The disease generally presents as a one-sided ovarian mass, and only approximately 6% of cases are bilateral [7, 9]. Most patients are asymptomatic or have nonspecific symptoms such as menstrual cycle changes, pelvic pain, or an abdominal mass. Struma ovarii may cause ascites and hydrothorax, similar to other ovarian tumors. Hyperthyroidism appears in 5–8% of struma ovarii patients. However, when hyperthyroidism occurs in a malignant lesion, the rate of metastases could reach up to 83%, and the tumor volume is usually large [7, 10, 11]. The survival rates of patients with malignant struma ovarii are high, with 5-year, 10-year and 20-year survival rates of 92–96.7%, 85–94.3% and 84.9%, respectively [12, 13]. Robboy *et al.* reported an 89% overall survival rate at 10 years and an 84% overall survival rate at 25 years for all patients [15]. Considering the high survival rate of struma ovarii patients, as well as the need to improve quality of life, we chose active but palliative treatment (tumor partial resection, intestinal fistula, etc.) after the occurrence of intestinal obstruction. For the treatment of thyroid cancer, recombinant human TSH has been used to increase the effectiveness of ^{131}I [7, 10, 11], and thyroglobulin has been used to prevent recurrence [14].

However, the treatment for struma ovarii is still controversial. There is no guideline or international consensus for this disease, with only published case reports or a small number of expert reviews. We reviewed the literature on the treatment of struma ovarii and found two options: conservative treatment or radical surgery combined with total thyroidectomy and ^{131}I ablation [15–17].

In regard to metastatic disease, there is a consensus to adopt aggressive management, including bilateral oophorectomy, hysterectomy, omentectomy and peritoneal washing followed by total thyroidectomy and ^{131}I ablation. However, the application of thyroidectomy and radioiodine therapy in nonmetastatic disease is quite controversial.

Based on our experience, it can be concluded that it is difficult to distinguish and make a diagnosis of malignant struma ovarii before surgery. Therefore, ovarian tumors should be closely observed in the case of struma ovarii. If necessary, ovaries and fallopian tubes should be resected to provide a clear pathologic diagnosis in the shortest time. Once the diagnosis is confirmed, patients who desire fertility are able to become pregnant if conservative surgery is performed as soon as possible [18].

Table 1. List of key events.

Date	Key event	Tumor marker	Surgical procedures	Pathology	Follow-up treatment
Nov. 4, 2000	Tumor found	NA ^a	NA	NA	NA
Oct. 14, 2001	First surgery	CA125: 103 U/mL	The left and right ovary wedge resection	Malignant struma ovarii	chemotherapy with VP-16 and Cisplatin for 3 cycles
Jan. 15, 2004	Second surgery	CA125: 10 U/mL	Uterine subtotal resection + right attachment resection + pelvic mass resection + omental total resection + pelvic peritoneum partial resection + appendectomy + peritoneal nodule resection + sigmoid colon intestinal wall nodule resection + mesenteric nodule resection	Thyroid follicular carcinoma infiltration to the ovarian surface	1. Vinorelbine and epirubicin for 5 cycles 2. Levothyroxine was administered beginning in Sep. 2004 until present
Feb. 23, 2009	Third surgery	CA125: 16 U/mL	Total thyroidectomy	Normal thyroid gland	¹³¹ I treatment every year from 2009 to 2013 (6 cycles)
May 2014	Fourth surgery	CA125: 31.7 U/mL	Pelvic tumor partial resection + intestinal adhesions release + rectal repair + sigmoid stoma surgery	Malignant monocortical teratoma-malignant goiter	¹³¹ I treatment
May, June, Aug. 2015	Pelvic mass increased and liver metastases were observed	CA125: 48.6 U/mL	DSA ^b bilateral internal iliac artery + TACE	NA	Levothyroxine
Oct. 27, 2015	Fifth surgery	CA125: 36.3 U/mL	CRS + HIPEC	Malignant monocortical teratoma-malignant goiter	Levothyroxine

^a: NA, not applicable; ^b: DSA, digital subtraction angiography.

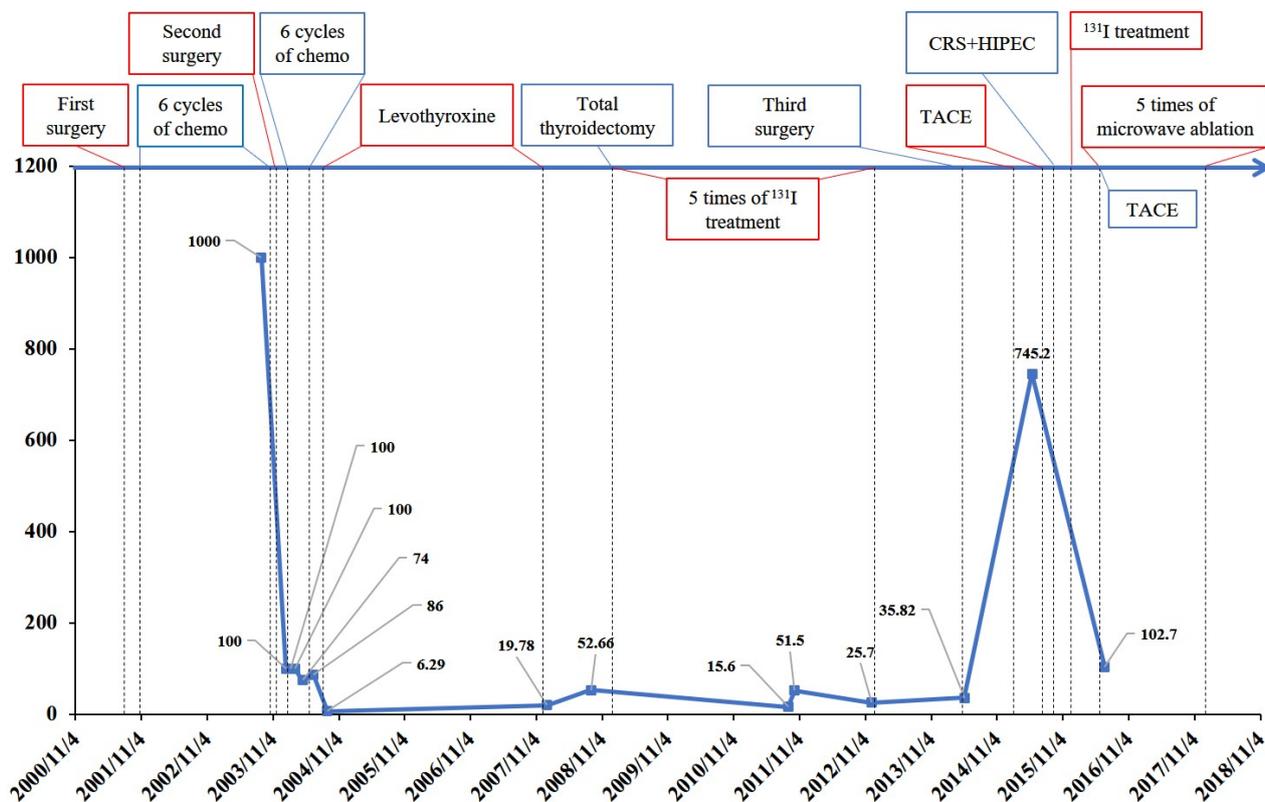


Fig. 4. Tendancy chart of the TG level and the relationship between treatment measures and the TG level. As shown in the figure, the TG level is related to the recurrence of struma ovarii, and tumor resection leads to a rapid decrease in the TG level. The application of levothyroxine, total thyroidectomy, ¹³¹I treatment and TACE helped the patient survive in a relatively stable condition for approximately 8 years.

Even though malignant struma ovarii has low potential for aggressive biological behavior, the risk of locoregional recurrence is high. Once recurrence occurs, it is difficult for patients to become pregnant. There are a few case reports on malignant struma ovarii during pregnancy, but none of them reported successful pregnancy after treatment [18].

The patient described herein was diagnosed with struma ovarii after the first operation but did not become pregnant. As the diagnosis was established, the patient was treated with chemotherapy to cure or even prevent the recurrence of the disease due to its rarity and lack of standardized therapeutic principles. However, the effect of conventional chemotherapy drugs was limited, and no other anticancer drugs were screened by drug-screening techniques. Nevertheless, the patient still chose to receive chemotherapy rather than become pregnant. When the disease recurred, the patient eventually lost the potential to become pregnant because of resection of the uterus and the right side of the adnexa. Patients who have given birth or who are infertile should be closely monitored on abdominal CT and/or abdominal color Doppler ultrasonography and for serum CA125, TG, and TSH levels. If locoregional recurrence occurs, the uterus, remaining ovaries, and fallopian tubes should be removed. Thyroidectomy should also be performed to prevent disease recurrence. The application of ^{131}I is also indispensable, after which levothyroxine is used for daily physiological requirements. During the follow-up period, radioiodine whole-body scans, abdominal CT and color Doppler ultrasonography should be performed, and serum CA125, TG, and TSH levels should be monitored to evaluate therapeutic efficacy and predict recurrence. Based on the treatment course of our patient, it is obvious that CRS + HIPEC is beneficial even though locoregional recurrence in the abdominal cavity, distant metastasis, intestinal obstruction and cachexia developed before surgery. Considering the good efficacy of gelatin sponge granule embolization through both the bilateral internal iliac artery and inferior mesenteric artery in our patient, these procedures are recommended as adjuvant treatment before surgery. An intra-arterial injection of chemotherapy drugs remains to be discussed in view of the limited effect of conventional chemotherapeutic drugs on struma ovarii. The efficacy of transcatheter arterial chemoembolization for liver metastases requires further evaluation.

In conclusion, we report a typical case of struma ovarii successfully treated by a radical comprehensive treatment method, with CRS + HIPEC as the core procedure. At present, the patient remains in good condition. CRS + HIPEC may be a promising strategy to improve outcomes for struma ovarii patients.

Abbreviations

CT, Computed Tomography; CRS, Cytoreductive Surgery; HIPEC, Hyperthermic Intraperitoneal Chemotherapy; TACE, Transcatheter Arterial Chemoembolization Embolization; TSH, Thyroid-Stimulating Hormone.

Author contributions

JHY organized the patient's medical records and was the major contributor in writing the manuscript. YLL collected the patient's medical records. ZHJ collected the patient's medical records. YZC performed the pathology analysis and provided the corresponding pathological image. YL designed the project, monitored project progress, and contributed to data evaluation.

Ethics approval and consent to participate

All subjects gave their informed consent for inclusion before they participated in the study. The study was conducted in accordance with the Declaration of Helsinki, and the protocol was approved by the Ethics Committee of Beijing Shijitan Hospital, Capital Medical University (approval number: 2018 Research Ethics Review No. (73)).

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Conflict of interest

The authors declare no conflict of interest.

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