Clinical Case Report

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Extensive peritoneal implant metastases of malignant struma ovarii treated by thyroidectomy and ^{131}I therapy

A case report

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Abstract

Rationale: Malignant struma ovarii is extremely rare in the clinic. The diagnosis and modalities of treatment are still controversial. Here we describe a case of extensive peritoneal implant metastasis originating from malignant struma ovarii discovered 14 years after ovariectomy and chemotherapy.

Patient concerns: A 48-year-old female was admitted to our clinic due to hematochezia with a past history of left malignant struma ovarii. Enhanced computed tomography (CT) examination suggested multiple metastasis nodules in the abdomen and pelvic cavity.

Diagnoses: Laparoscopy biopsy results of intraperitoneal nodules showed a metastasis of papillary thyroid carcinoma. While pathological examination after total thyroidectomy showed no definite malignant tumor component in the thyroid tissue. Finally, combined with the patient's past history of malignant struma ovarii, peritoneal implantation metastasis derived from the malignant struma ovarii was diagnosed.

Interventions: The patient was treated by total thyroidectomy and iodine 131 (^{131}I) therapy. Post-therapy iodine scan and the single-photon emission computed tomography/computed tomography (SPECT/CT) fusion image showed iodine uptake in the distal descending colon, sigmoid colon, rectal lesions, and a larger lesion in the liver.

Outcome: After treatment, although the thyroid globulin remained at a high level 3 months after treatment, the patient's hematochezia was relieved.

Lessons: Therefore, thyroidectomy followed by adjuvant ^{131}I treatment should be recommended in patients with malignant struma ovarii as metastatic risk is difficult to predict based on histopathologic examination.

Abbreviations: ^{131}I = iodine-131, TG = thyroglobulin, TSH = thyroid stimulating hormone.

Keywords: chemotherapy, iodine 131 treatment, malignant struma ovarii, peritoneal implant metastases, thyroidectomy, tyrosine kinase inhibitor

1. Introduction

Struma ovarii is a kind of specific teratomas in ovary germ cell tumors mainly consisting of thyroid tissue and was first formally described by Gottschalk in 1899.[1] It represents <3% of all ovarian teratomas. So far, fewer than 200 cases about struma ovarii have been reported abroad.[2] Malignant struma ovarii is even uncommon and it accounts for about 5% of all struma ovarii.[3] According to the literature, metastasis from malignant struma ovarii has only been reported in 5% to 6% of cases.[4] Owing to its rarity as well as the difficulty in distinguishing between biologically benign and malignant cases, optimal treatment strategy of malignant struma ovarii remains controversial. Even malignant struma ovarii with distant metastases has a relatively well prognosis. However, unlike most other malignant germ cell tumors, malignant struma ovarii poorly respond to combination chemotherapy.[5,6] More and more reported cases demonstrate that the patient should not only undergo comprehensive surgical staging for the primary tumor but also received postoperative adjuvant treatment including total thyroidectomy and iodine 131 (^{131}I) radio-ablation therapy, especially when there is a distant metastasis.[7,8] Here we report the case of a malignant struma ovarii that presented with extensive peritoneal implant metastasis 14 years after ovariectomy plus chemotherapy. We review the literature and discuss the therapeutic strategies emphasizing the possible benefit of using molecular targeted anti-tumor drugs in the management of such cases.

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MW and FH contributed equally to this work.

Written informed consent was obtained from the patient for publication of this case report and accompanying images.

The authors report no conflicts of interest.

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2. Case presentation

A 48-year-old woman was admitted to our clinic in December 2017 for medical advice. She presented with constipation during the past 2 months, accompanied by hematochezia for 2 weeks. Her blood cytology indicated that she had mild anemia. The red blood cell (RBC) was 3.22×10 ^ 12/L (3.80–5.10), and hemoglobin (Hb) was 92.0 g/L (115.0–150.0). Digital rectal inspection touched a fixed mass, occupying a circle of the intestine cavity, which was located 10 cm away from the edge of the anus, approximately 30 mm × 30 mm size, with smooth surface but partial rupture and bleeding viewed through the colonoscopy. Transanal rectal tumor biopsy just showed the acute and chronic inflammatory cell infiltration of the rectal mucosa with a few foreign bodies and a multi-nuclear giant cell reaction, which was probably caused by failing to definitely extract tumor tissue.

However, a computed tomography (CT) and enhancement scan of the whole abdomen and pelvic cavity revealed in addition to a markedly inhomogenous thickened mass of upper rectum, with partial cauliflower-like protruding out of the lumen, multiple nodules measuring 2 to 5 cm each were seen in the liver, spleen, and on the surface of the distal descending colon, sigmoid colon, pelvic peritoneum, mesorectum. These nodules were highly suggestive of secondary metastases and small speckle calcification was observed in some nodules (Fig. 1 A–F and Fig. 2 A–F).

The patient is a gravida 0, para 0. Her past medical history involves a left ovariectomy for an ovarian cyst in 2004 and a right salpingo-ovariectomy and hysterectomy in 2010 for a right ovarian serous papillary cystic adenoma. A review of the pathological gross inspection revealed that the left ovary contained a 10cm × 8 cm dermoid cyst with inclusions consisting of teeth, hair, scalp, and sebaceous material. The microscopic examination showed a left malignant struma ovarii with local epithelial papillary hyperplasia active. The patient underwent 7 times of chemotherapy with the PVC regimen (cisplatin 100mg + etoposide 200mg + cyclophosphamide 400mgD1, D2). On follow-up, the patient was clinical stabilization.

To evaluate the nature of the nodule, a laparoscopy was performed. Slightly reddish ascites was found in the pelvic cavity and the nodules from the liver and peritoneum within sight were taken for histologic examination. The pathological histology of the nodules showed thyroid tissue with a papillary structure and the papilla axis filled with fibrous vascular tissue, without follicle

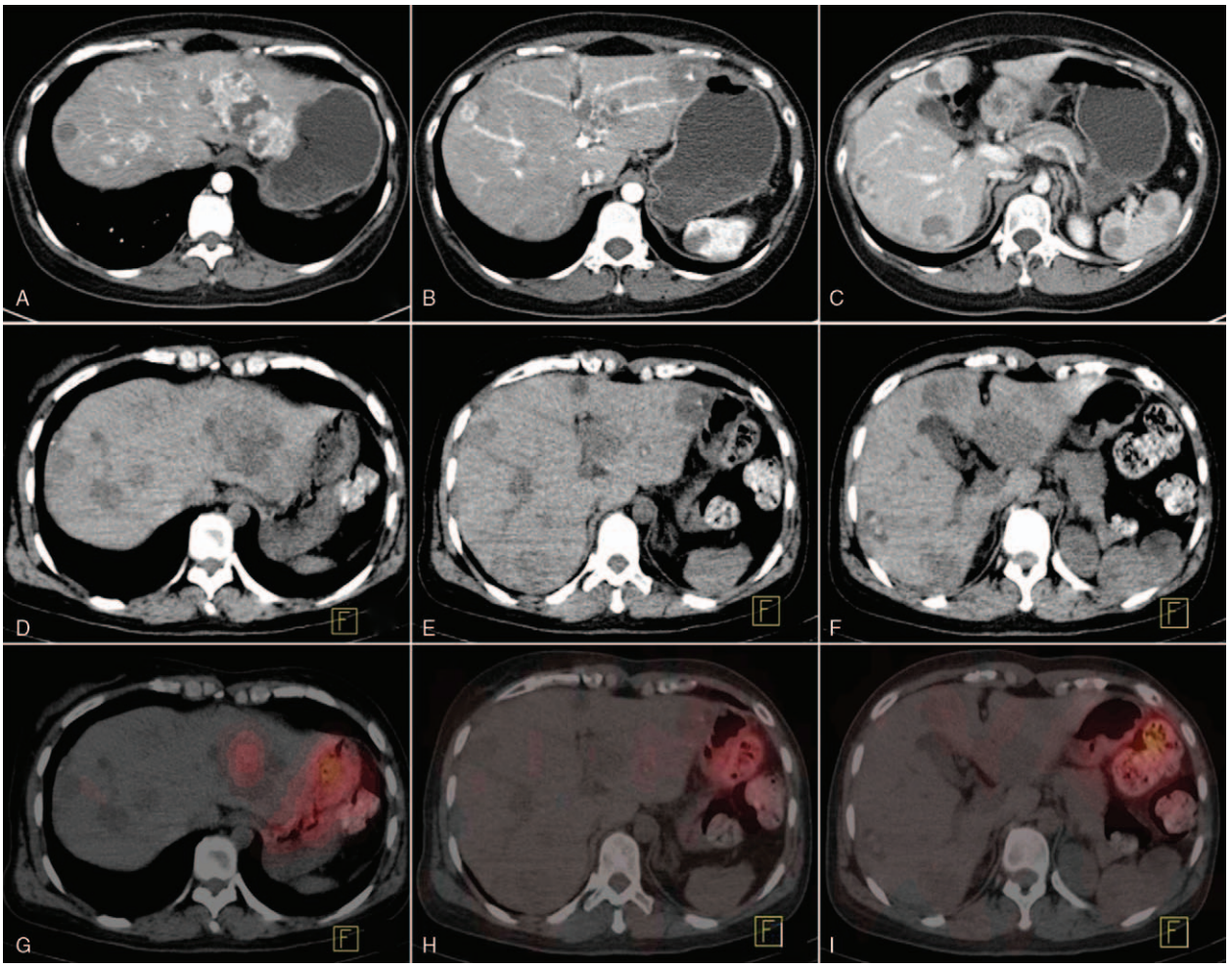

Figure 1. Abdominal computed tomography enhanced images (A, B, C) indicate multiple various-sized metastases in the liver and spleen, with inhomogeneous enhancement and small speckle calcification in some nodules. Iodine-131 post-therapy abdominal computed tomography images (D, E, F) and corresponding SPECT/CT fusion images (G, H, I) indicate metastatic lesions in the liver and spleen almost have no radioactive iodine uptake except for a larger lesion in the left lobe of liver with a slight uptake (G). Normal physiological uptake in the stomach also could be noted. SPECT/CT = single-photon emission computed tomography/computed tomography.

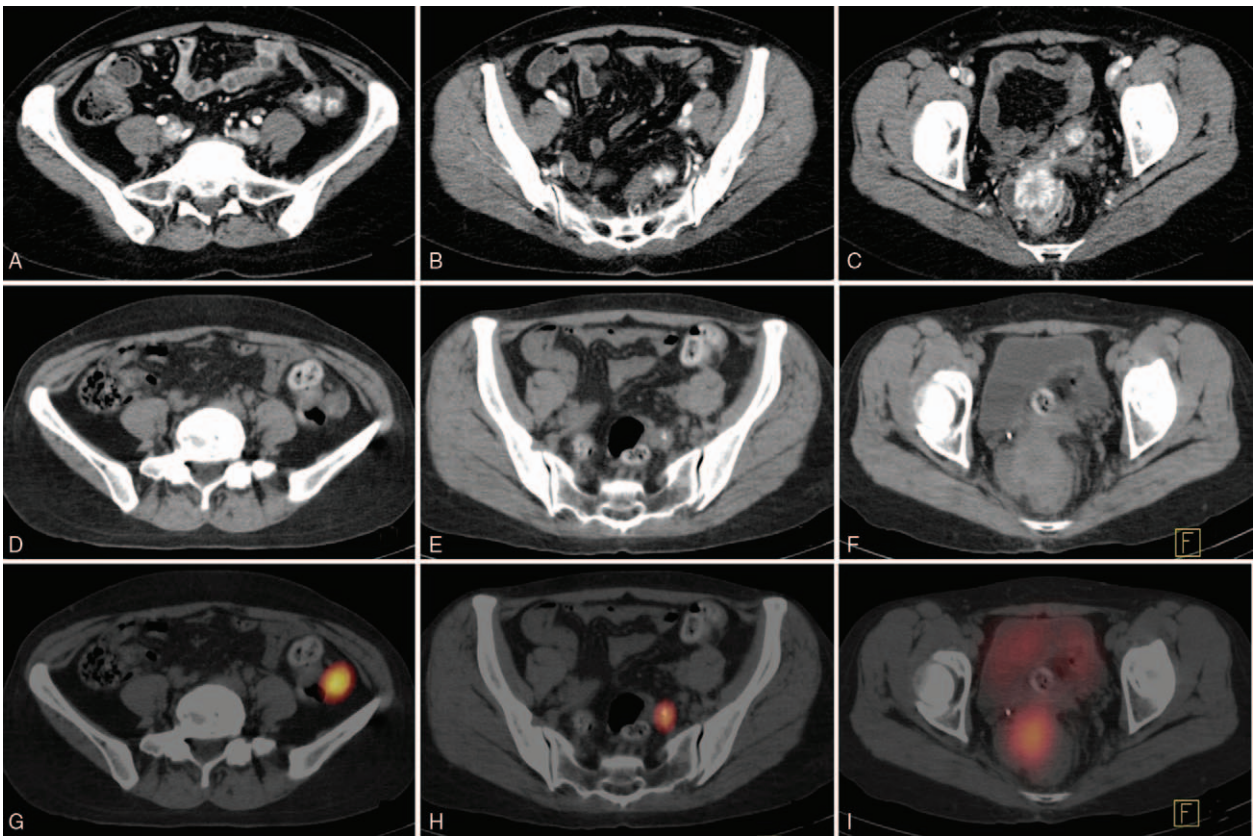

Figure 2. Pelvic computed tomography enhanced images indicate thickened soft tissue nodule and mass of the distal descending colon (A), sigmoid colon (B), and rectal (C), with inhomogeneous enhancement. Iodine-131 post-therapy pelvic computed tomography images (D, E, F) and corresponding SPECT/CT fusion images (G, H, I) indicate the above lesions all have a strong uptake of radioactive iodine. Normal physiological uptake in the bladder also could be noted. SPECT/CT = single-photon emission computed tomography/computed tomography.

(Fig. 3B, C and D). Both thyroglobulin (TG) and thyroid transcription factor-1(TTF-1) immunohistochemical staining showed strong reactions within the tumor tissues (Fig. 4C, D). CD34 and PAX-8 staining were also positive (Fig. 4A and B). However, staining result for Wilm's tumor-1(WT-1) which is usually positive in ovarian serous carcinoma was negative. The metastasis of papillary thyroid carcinoma was considered in combination with histological morphology and immunohistochemistry.

Due to this surprising pathological finding, a series of examinations were performed to evaluate for thyroid tumor. Neck ultrasonography was performed and several cystic nodules were noted in the bilateral thyroid lobes. According to the thyroid imaging reporting and data system (TI-RADS), these nodules belonged to the third classification, which was thought to be benign lesions with 95 percent possibilities. The assessment of central and lateral neck lymph nodes also showed a negative result. ^{131}I whole-body diagnostic imaging with a dose of 0.37GBq (10mCi) was performed and revealed no abnormal radiation uptake anywhere else in the body except for thyroid normal iodine uptake (Fig. 5A). Her thyroid function tests indicated that she was slight hyperthyroidism. The serum thyroid stimulating hormone (TSH) was 0.26uIU/mL (0.49–4.91), the FT4 was 1.27 ng/dL (0.59–1.25) and the total thyroxine (TT4) was 12.72 ug/dL (5.44–11.85), the free triiodothyronine (FT3) and total triiodothyronine (TT3) were normal. But the serum TG level was greater than 464.00 ng/mL (0–50.03) and anti-thyroglobulin antibody (TGAb) were negative.

Considering the history of left malignant struma ovarii and the multiple metastasis nodules of papillary thyroid carcinoma in the abdomen and pelvic cavity, the doctor made the final strategy of operation and iodine-131 treatment. Subsequently, a total thyroidectomy was performed followed by ^{131}I therapy with 5.55GBq (150mCi). Microscopically, no definite malignant tumor component was found in the thyroid tissue (Fig. 3A) and central lymph nodes just showed reactive hyperplasia. Post-therapeutic total body iodine scan and single-photon emission computed tomography/ computed tomography (SPECT/CT) fusion image showed that, in addition to uptake within the thyroid bed, which is usual after total thyroidectomy, uptake in the distal descending colon, sigmoid colon, and rectal lesions also can be noted (Fig. 5C and Fig. 2 G, H, and I). These findings were similar to the results of postoperative iodine-131 diagnostic scan (Fig. 5B). However, multiple nodules in the liver and spleen did not have any radioiodine uptake excluding a larger lesion in the liver left lobe with a slight uptake (Fig. 5C and Fig. 1 G, H, and I). The patient was given TSH suppression therapy with levothyroxine replacement. She will undergo serial examinations of ultrasound and TG level during follow-up and may be repeatedly treated with ^{131}I ablation. On follow-up, her hematochezia symptom was improved 2 months after her initial diagnosis, and her latest serum TG concentration is still greater than 464.00 ng/mL.

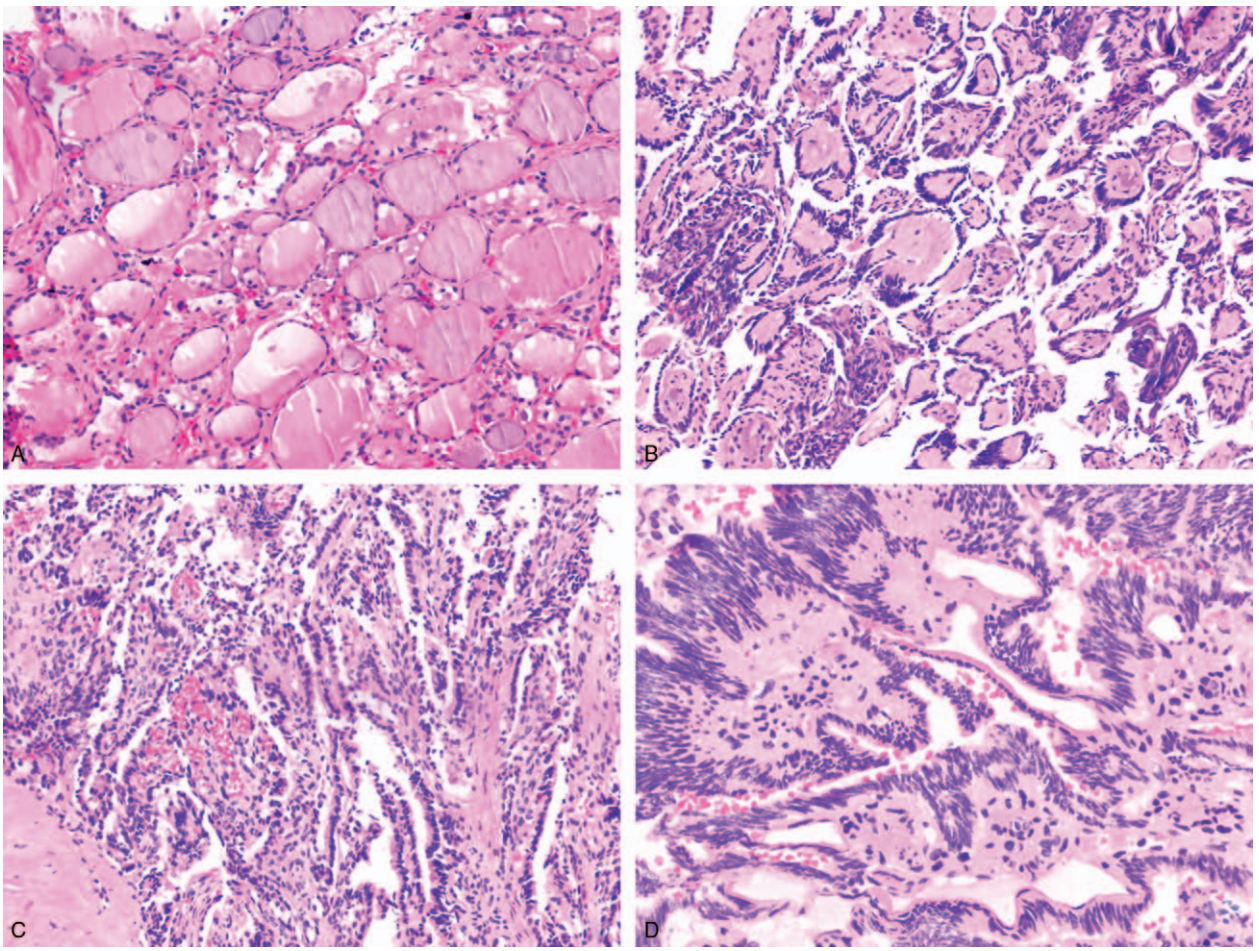

Figure 3. (A) The thyroid contains normal thyroid follicles filled with colloid and the follicles epithelial cells showed no atypia. Cytological features of papillary thyroid carcinoma are absent (hematoxylin and eosin, 200 × magnification). (B, C) The metastatic nodules in the abdominal cavity showed tumor cells with a line of papillary structure and vascular invasion. In the center of the papilla are fibrous connective tissue and capillaries (hematoxylin and eosin, 200 × magnification). (D) The tumor follicular epithelial lined with high columnar cells are so compressed that the nuclear features of papillary carcinoma are blurred (hematoxylin and eosin, 400 × magnification).

3. Discussion

Struma ovarii is a mature teratoma with high specificity of monodermal differentiation, which is predominantly composed of thyroid tissue with a potential of cancerization.[5] Struma ovarii could induce hyperthyroidism,[9,10] which may demonstrate that any pathologic features occurring in the normal thyroid tissue can be seen in struma ovarii. The incidence of malignant struma accounts for only 5% in all cases of struma ovarii.[3] The diagnosis of malignant struma ovarii remains controversial. Currently, the commonly accepted pathological diagnostic criteria are consistent with those for thyroid cancer. However, histological malignancy in struma ovarii does not necessarily mean a biological malignancy.[6,11] Robboy et al[12] analyzed 88 patients of malignant struma ovarii. There were 27 cases classified as biologically malignant, however, of these only 12 cases also showed histologically malignant. Therefore, the clinical outcome of struma ovarii cannot be effectively predicted based on histological malignant. Furthermore, malignant struma ovarii has a similar molecular pathogenesis to malignant tumors originating in the thyroid, such as BRAF (b-raf proto-oncogene), RAS (retrovirus-associated DNA sequence) gene point mutations, and RET/PTC (RET proto-oncogene/papillary thyroid carcinoma) gene rearrangement, etc.[2,13–15] In our patient, the extensive abdominal and pelvic metastasis were detected 14 years after surgery for a left malignant ovarian ovarii. In addition, the patient had mild hyperthyroidism. Considering that no recurrent lesion in the uterus and accessory area was found by the patient's pelvic ultrasound examination, we must exclude the presence of a primary thyroid carcinoma. However, pathological examination after total thyroidectomy found no thyroid cancer, and occult thyroid carcinoma also seems very unlikely because it is extremely rare to metastasize to distant organs. Therefore, combined with the patient's past history of a left malignant struma ovarii with local epithelial papillary hyperplasia active and pathological examination results of metastatic lesions, peritoneal implantation metastasis derived from the malignant struma ovarii was diagnosed.

Metastasis of malignant struma ovarii usually occurs in differentiated thyroid neoplasms, such as papillary carcinoma or follicular carcinoma.[16] The tumor may metastasize to the peritoneum,[17] lymph nodes,[5] liver,[18] lung,[3] bone,[19] and brain,[20] and may manifest itself as ascites or pleural effusion.[21] Indeed, our patient's pathological microscopy of the metastatic focuses in the peritoneum and liver was consistent with papillary

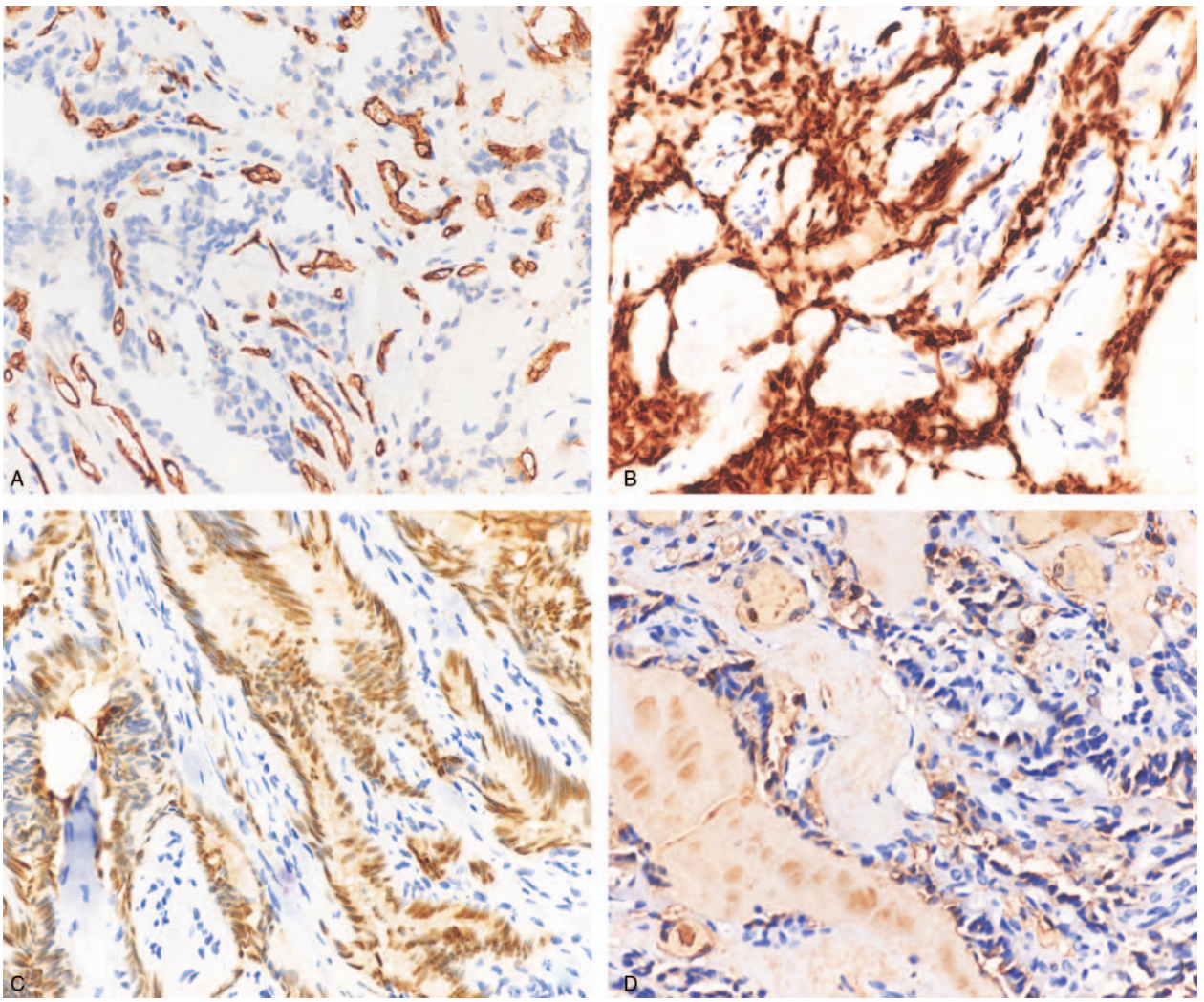

Figure 4. The CD34 (A), PAX-8 (B), TTF-1 (C), TG (D) immunohistochemistry staining reveals a positive reaction of metastatic nodule tissues, respectively (400 × magnification). TG = thyroglobulin, TTF-1 = thyroid transcription factor-1.

thyroid carcinoma. Although the rectal lesion causing the patient's hematochezia failed to get a biopsy, the post-therapeutic whole body iodine scan showed iodine uptake in the rectal lesion. Given that it had a similar iodine uptake function with thyroid tissue, we thought the rectal focus was a metastasis coming from cancerous thyroid tissues in struma ovarii, rather than a rectum primary tumor.

As malignant struma ovarii is extremely rare in clinical practice, there is still a lack of clear diagnostic criteria and treatment principles. However, metastases respond to ^{131}I therapy in most cases.[7,8] DeSimone et al[8] reviewed 24 cases in the literature, in which no recurrence occurred in the 4 patients who had undergone ^{131}I treatment, and 7 of 8 patients who had relapsed disease initially achieved a complete response after ^{131}I treatment. Therefore, it was advocated that comprehensive surgical staging and postoperative adjuvant treatment should be recommended as the optimal management strategy for malignant struma ovarii to avoid local recurrence and distant metastasis. Postoperative adjuvant treatments included total thyroidectomy, radioactive iodine therapy, and thyroxine suppression therapy, which were identical with the treatment of thyroid cancer.[22] However, the above postoperative adjuvant treatment has not been reliably performed, just like our patient. Notably, tumors that have no respond to ^{131}I may progress very slowly due to the high differentiation of thyroid tissues in struma ovarii. Thus, some patients with metastases have lived for longer than 20 years.[7] In a recent population-level analysis of literature, overall survival rates of the malignant struma ovarii at 5, 10, and 20 years were 96.7%, 94.3%, and 84.9% respectively.[2] McGill et al[23] and Marti et al[24] suggested that total thyroidectomy and radioactive iodine ablation should be reserved for metastases or recurrent disease and surgical resection of the ovarian tumor may be adequate for those cases absence of extraovarian metastases. On the other hand, Yassa et al[25] and Janszen et al[26] proposed a risk stratification of malignant struma ovarii in which patients with tumors measuring over 2 cm, extra-ovarian extension or distant metastases, or aggressive histological features should be considered for a thyroidectomy followed by ^{131}I ablation therapy. In the present case, the patient only underwent chemotherapy after ovarian surgery without further treatment of ^{131}I. However, the tumor developed a peritoneal implantation metastasis 14 years after surgery, which indicated chemotherapy

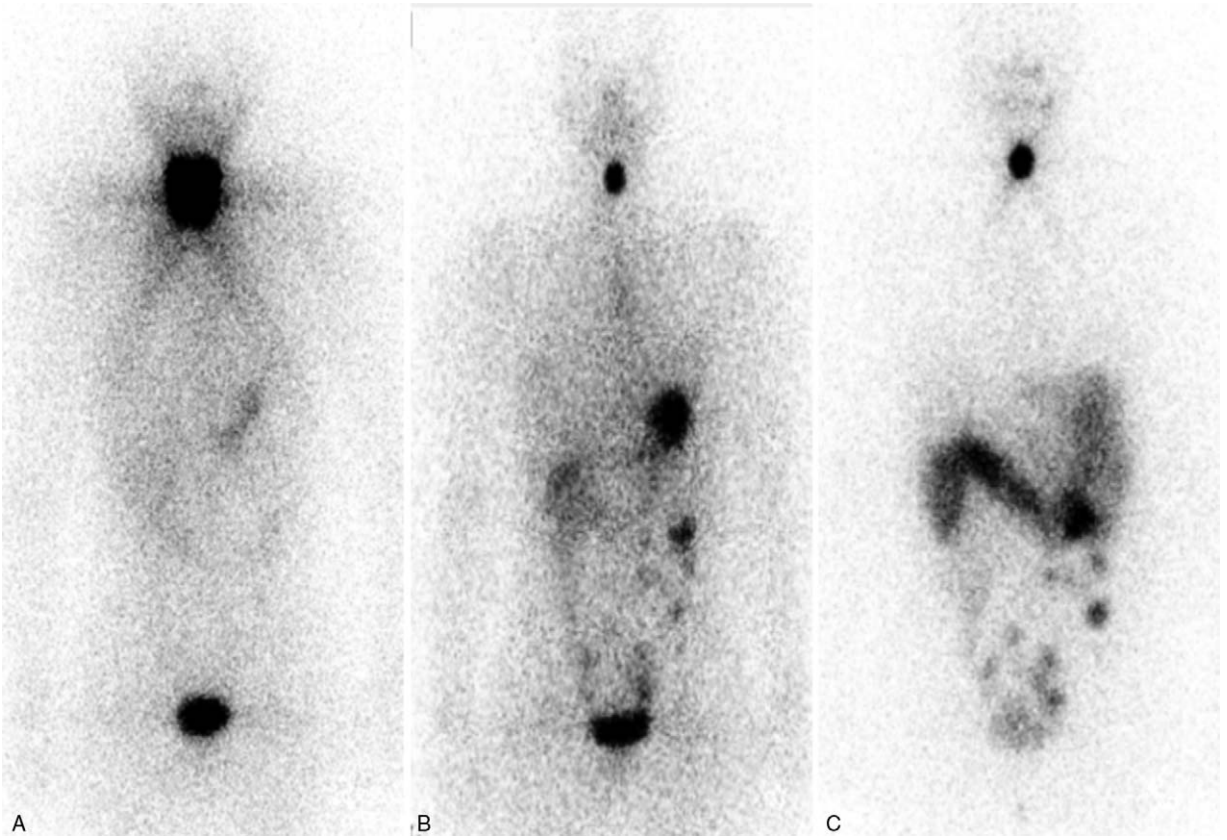

Figure 5. (A) Iodine-131 whole-body diagnostic imaging, before total thyroidectomy, revealed thyroid and bladder normal iodine uptake without other abnormal uptakes anywhere else in the body. (B) Iodine-131 whole-body diagnostic imaging, after total thyroidectomy, revealed uptake in the residual thyroid tissue, abdominal and pelvic lesions. Normal physiological uptake in the stomach and bladder also could be noted. (C) Post iodine-131 therapy whole body iodine scan showed a stronger uptake in the abdominal and pelvic lesions than Iodine-131 diagnostic imaging.

maybe not effective for malignant struma ovarii. This time, the patient had undergone total thyroidectomy and ^{131}I therapy. The post-therapy whole body iodine scan showed iodine uptake in the majority of the lesions except for multiple nodules in the liver and spleen. For lesions with iodine uptake, ^{131}I therapy may have a relatively good effect, and the exact effect is still under observation. For nodules without iodine uptake in the liver and spleen, because malignant struma ovarii metastases have similar biological behaviors to primary thyroid cancer metastases, we believe that molecular targeted anti-tumor drugs like Sorafenib, an orally active multi-tyrosine kinase inhibitor (TKI),[27] which benefits patient presenting with radioactive iodine-refractory thyroid cancer, can be applied for treatment. Besides, recombinant human thyrotropin (rhTSH) can be administrated before radioiodine therapy to enhance the uptake of ^{131}I by the tumor, if it is difficult to increase the endogenous thyrotropin (TSH) level as a result of functional thyroid metastases.[3,28] Finally, after thyroidectomy, dynamic monitoring of serum TG levels can be used to observe and confirm the tumor burden progression and the response to treatment.

4. Conclusions

In conclusion, we report an extremely unusual case of peritoneal implantation metastasis from malignant struma ovarii 14 years after ovariectomy plus chemotherapy, which may arise debates about management of this kind of cases. Since malignant and benign struma ovarii have different treatment and prognoses, it is highly significant to distinguish them—the former requires further iodine-131 intervention, while the latter requires postoperative follow-up only. Therefore, once malignant struma ovarii is confirmed, we suggest conducting ovariectomy and postoperative adjuvant treatment including total thyroidectomy, radioactive iodine therapy, and thyroxine suppression therapy. Simultaneously, the findings in our patient clearly demonstrate the similarity in the functional metastasis, treatment methods as well as follow-up between malignant struma ovarii and primary thyroid cancer. Additionally, we speculate that molecular targeted anti-tumor drugs could be used for radioactive iodine unresponsive malignant struma ovarii metastases.

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Author contributions

MW and FH wrote the first draft of the manuscript and contributed equally to this work, XH, ZT and CL carried out the data collection, literature review and images processing, DD modified the manuscript and wrote the final version. All authors

read and met the ICMJE criteria for authorship and approved the final manuscript.
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Supervision: Dong Duan.
Validation: Dong Duan.
Writing – original draft: Mengxue Wu, Fengqiong Hu.
Writing – review & editing: Mengxue Wu, Dong Duan.

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