Papillary follicular variant thyroid cancer in a malignant struma ovarii: a report of a rare case

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Summary
A 33-year-old female presented in 2013 with left flank pain. Ultrasound and MRI pelvis showed a complex mass 9 × 7 cm arising from the left ovary suggestive of ovarian torsion. She underwent a laparoscopic cystectomy, but the patient was lost to follow-up. Three years later, she presented with abdominal distension. Ultrasound and CT scan revealed a solid left ovarian mass with ascites and multiple peritoneal metastasis. Investigations showed elevated CA 125, CA 19-9. Ovarian malignancy was suspected. She underwent total abdominal hysterectomy and bilateral salpingo-oophorectomy on November 2016. The histopathology confirmed a well-differentiated thyroid cancer of ovarian origin with features of a papillary follicular variant without evidence of ovarian cancer and the thyroglobulin (Tg) level was elevated, more than 400 consistent with the diagnosis of malignant struma ovarii. The follow-up post-surgery showed normalization of CA 125, CA 19-9 and Tg. The patient underwent total thyroidectomy on January 2017. The histology was benign excluding thyroid cancer metastases to the ovary. She was started on thyroxine suppression, following which she received two ablation doses 131iodine (131I) each 5.3 GBq. The Tg remains slightly elevated at less than 10. 131I WBS showed no residual neck uptake and no distant avid metastasis. She was planned for molecular analysis which may indicate disease severity. We describe a case of malignant struma ovarii with widespread metastatic dissemination and a good response to surgery and 131I treatment without recurrence after 5 years of follow-up. The Tg remains slightly elevated indicating minimal stable residual disease.

Learning points:
• Malignant struma ovarii is a rare disease; diagnosis is difficult and management is not well defined.
• Presentation may mimic advanced carcinoma of the ovary.
• Predominant sites of metastasis are adjacent pelvic structures.
• Thyroidectomy and 131iodine therapy should be considered. The management should be similar to that of metastatic thyroid cancer.

Background
Struma ovarii (SO) was first described in 1889 by Boëttlin when he detected follicular thyroid tissue in the ovaries (1). SO is a germ cell tumour of the ovary that consists of at least 50% thyroid tissue and accounts for around 2% of ovarian germ cell tumours (2, 3). It is predominantly found in women between the fourth and sixth decade of life (3). The neoplasm is composed of benign mature thyroid tissue in most cases and only around 5% contain malignant tissue (3, 4). SO may be asymptomatic or have a presentation similar to ovarian cancers, including pelvic mass and ascites, making it hard to differentiate a malignant SO from ovarian cancer based on imaging and clinical
presentation alone (1). The diagnosis of malignant SO is usually discovered on pathology, post-surgery. Based on the case series, the majority of malignant SO have papillary or follicular carcinoma, while the follicular variant of papillary carcinoma is less common (2). The diagnosis of SO remains challenging with no clear guidelines for the management of this entity as the cases are rare and few case series are only available in the literature (2, 5, 6).

**Case presentation**

We present a 33-year-old female with initial presentation of left flank pain in 2013 who was found to have a left ovarian cyst with possible torsion. Work-up revealed a 7 × 7 cm solid mass arising from the left ovary by ultrasound (Fig. 1). MRI pelvis showed a large complex mass 9 × 7 cm arising from the left ovary suggestive of ovarian torsion due to the presence of the dermoid for which she underwent a laparoscopic cystectomy but was lost to follow-up (Fig. 2). Three years later, she presented with abdominal distension. CT scan revealed a solid left ovarian mass with ascites with multiple peritoneal metastasis (Fig. 3).

**Investigation**

Investigations showed elevated CA 125: 1906 KIU/L (0.0–35) and CA 19-9: 1 14 KIU/L (0.0–37) with normal thyroid function tests FT4: 7.7 pmol/L (7.8–14), thyroid-stimulating hormone (TSH: 0.9 mIU/L (0.3–5) and Thyroglobulin (Tg): >466 ug/L (0–50).

Management: She underwent total abdominal hysterectomy and bilateral salpingo-oophorectomy (TAHBSO) on November 2016. The histopathology confirmed a well-differentiated thyroid cancer of ovarian origin with features of a papillary follicular variant without evidence of ovarian cancer consistent with the diagnosis of malignant SO (Fig. 4A, B and C).

The follow-up post-surgery showed normalization of CA 125: 14 KIU/L and CA 19-9: 60 KIU/L. FT4: 12 pmol/L, TSH: 0.22 mIU/L. Tg dropped to 7 ug/L (before >466).

**Treatment**

The patient was transferred under endocrine care and underwent total thyroidectomy on January 2017. The histology of the thyroid showed that no malignant tissue was identified in the excised thyroid gland.

She was started on thyroxine suppression, following which she received the first 131I iodine (131I) ablation dose (5.3 GBq) using recombinant-TSH on July 2017. Blood test showed her TSH: 208 mIU/L (0.3–5), FT4: 10 pmol/L and Tg: 31 ug/L (<1). 131I WBS and SPECT/CT post-
therapy revealed residual thyroid tissue uptake and no distant active metastasis. Four months later, she received the second $^{131}$I ablation therapy dose, 5.3 GBq, and $^{131}$I WBS showed no residual neck uptake and no distant avid metastasis (Fig. 5). She was planned for molecular analysis looking for BRAF, NRAS, KRAS, PIK3CA and c-KIT mutations which may indicate disease severity, but these were not available.

**Outcome and follow-up**

The follow-up of the patient on 14 September 2021 showed that the patient was well, had no recurrence and her clinical examination is normal. She was maintained on T4 100 mcg 6 days a week and the most recent blood test showed TSH: 0.3 mIU/L (0.3–5), FT4: 19 pmol/L (12–21) and stable mildly elevated Tg: 8.3 ug/L (<1.0), Tg antibodies 11, CA 125: 34 KIU/L (0–35) and CA 19-9: 26 KIU/L (0–37). US abdomen and pelvis was normal.
Discussion

The diagnosis of malignant SO is challenging and the patient’s presentation was in the third decade of life, much earlier than expected (3, 5). The patient initially presented with a large left ovarian mass for which cystectomy was performed, preserving the ovary. After 3 years, the mass recurred with metastasis to the peritoneum and omentum along with ascites. This indicates that conservative therapy in a large malignant SO presenting at a young age may not be the correct treatment. The most common metastatic site is the pelvic area (2). A literature review showed that among surgical options TAHBSO has the best clinical outcome for malignant SO (6). Unilateral salpingo-oophorectomy, unilateral oophorectomy and bilateral salpingo-oophorectomy also seem effective, but ovarian cystectomy seems connected with higher recurrence rates (6). While some recommend tumour resection alone, others recommend TAHBSO followed by thyroidecomy and 131I ablation. This allows the use of Tg for monitoring once the SO is larger than 1 cm (5). Another case report favours any ovarian surgery along with thyroidecomy followed by 131I ablation since without thyroidecomy and 131I WBS it is difficult to perform distant metastasis assessment (7). 131I ablation is effective in treating metastasis using an average of three doses (8). We prefer ovarian surgery along with thyroidecomy followed by 131I ablation to decrease the chance of recurrence in patients with malignant SO. In addition, this will allow the use of Tg as a long-term monitor for recurrence even after more than a decade of treatment (8). Our patient had an excellent response post TAHBSO with a drop in unstimulated Tg to 8 from more than 400. This indicates that the origin of Tg was from the ovarian mass. She underwent total thyroidecomy and received 2 doses of 131I ablation after which her Tg is currently less than 10 and she is clinically free of disease although she harbours residual tumour (2). The recurrence rate of malignant SO is low (7.5%) and the survival rate is (84%) high at 25 years (5, 7).

Our patient presented with ascites and markedly elevated CA 125 and Tg and mild elevation of CA-19 9 which shifted the clinical diagnosis initially towards ovarian cancer. Ascites is associated with malignant SO in 17–33% of cases, but the ascitic fluid rarely contains malignant cells and CA-125 is rarely increased (5, 9). CA 19-9 elevation was not mentioned in previous case reports of malignant SO but was mentioned to be elevated in a case of stromal carcinoid (10). Tg level was markedly elevated in the presented case which could suggest an ectopic form of thyroid tissue in a person with a normal thyroid gland on ultrasound (11).

SO and dermoid cyst are hard to differentiate based on ultrasound features, but a high Tg would suggest SO (3).

Molecular analysis of malignant SO showed positive BRAF in two-thirds of papillary cases, while RAS and cytokeratin 19 (CK-19) mutations were usually found in the majority of follicular variant (2, 5). These mutations may be similar to those found in thyroid cancers, but their absence or presence still does not have any clinical significance.

In conclusion, malignant SO diagnosis and management is still challenging. Performing TAHBSO and thyroidectomy followed by radioactive iodine ablation will help in decreasing recurrence. Close monitoring for more than 10 years is needed in order to detect recurrence.

Declaration of interest
The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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Patient consent
Written informed consent for publication of their clinical details and/or clinical images was obtained from the patient.

Author contribution statement
O Elshafie and N Woodhouse were involved in management of the patient; M Al Kabani performed the ovarian surgery; A Al Hamadani provided the pathology report; S Hussein treated the patient with radioactive iodine; O Elshafieand A B Khalid were involved in the literature review and writing of the paper; N Woodhouse was involved in the paper review.

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