An Unusual Case of Malignant Struma Ovarii Causing Thyrotoxicosis

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What Is Known about This Topic?

- Struma ovarii (SO) is a specialized monodermal teratoma predominantly composed of mature thyroid tissue (>50%), accounting for approximately 5% of all ovarian teratomas. Thyrotoxicosis is seen in about 8% of patients with SO. Most SO cases are benign, with only 5–10% being malignant. Malignant SO causing thyrotoxicosis is very uncommon.

What Does This Case Report Add?

- This report adds to the limited number of cases of malignant SO causing thyrotoxicosis. It also illustrates the controversy concerning the management of malignant SO.

Key Words

Struma ovarii · Malignant struma · Thyrotoxicosis · Follicular carcinoma · Teratoma · Ovarian tumor

Abstract

Background: Struma ovarii (SO) is a specialized monodermal teratoma predominantly composed of mature thyroid tissue, accounting for approximately 5% of all ovarian teratomas. Thyrotoxicosis is seen in about 8% of patients with SO. Most SO cases are benign with only 5–10% being malignant, and malignant SO causing thyrotoxicosis is very uncommon.

Case: A 64-year-old woman had been diagnosed with thyrotoxicosis 2 years previously. The thyroid gland was palpable

with a micronodular texture, and the patient was euthyroid under carbimazole. She presented with abdominal pain and progressive enlargement of the abdomen over a 2-month period. An abdominal ultrasonography revealed a pelvic mass and a large fluid collection. Additional imaging confirmed the presence of a complex right ovarian mass measuring 13 cm. The patient underwent a total abdominal hysterectomy and bilateral salpingo-oophorectomy, omentectomy and appendectomy. The histological examination revealed the presence of 'follicular thyroid-type carcinoma arising in an SO of the right ovary, with metastatic infiltration in the tissue fragments from the pouch of Douglas'. Antithyroid treatment was discontinued 1 month after surgery in light of the pathology result. During the 4-year follow-up, the patient re-

mained euthyroid. **Conclusion:** There has been controversy about the management of malignant SO, which is a rare entity. Malignant SO causing thyrotoxicosis is even more uncommon. As clinical signs are nonspecific, other causes of thyrotoxicosis must be considered for a differential diagnosis. Our case is one of the very few cases ever reported.

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Introduction

Struma ovarii (SO) is a specialized monodermal teratoma predominantly composed of mature thyroid tissue [1]. Thyroid tissue must comprise more than 50% of the overall tissue to be classified as an SO. SO accounts for approximately 5% of all ovarian teratomas [2].

Most SO cases are benign, with only 5–10% being malignant [3, 4]. Due to the rarity of the malignant transformation there has been controversy regarding the management of malignant SO cases.

Thyrotoxicosis is seen in about 8% of patients with SO [5], but most cases are asymptomatic from a thyroid standpoint with the majority of patients presenting with symptoms attributable to a mass effect, such as pelvic pain. In thyrotoxic patients, serum thyroid-stimulating hormone (TSH) is low and free thyroxine (fT₄) and/or triiodothyronine (T₃) are elevated along with serum thyroglobulin (TG). The thyroid gland is typically not enlarged. Rarely, women with SO and thyrotoxicosis also have goiter [6], while the coexistence of SO with Graves' disease has rarely been reported in the literature [7, 8]. Malignant SO causing thyrotoxicosis is very uncommon [9]. Here we report a rare case of malignant SO causing thyrotoxicosis and discuss the relevant literature review.

Case Report

A 64-year-old woman presented with abdominal pain and progressive enlargement of the abdomen over a 2-month period. Her symptoms had initially been attributed to irritable bowel syndrome. Abdominal ultrasonography revealed a pelvic mass and a large fluid collection. Subsequently, computed tomography (CT) of the abdomen and magnetic resonance imaging of the pelvis confirmed the presence of a complex right ovarian mass measuring 13 cm, and the patient was admitted for surgery.

The patient's past medical history revealed multinodular goiter, irritable bowel syndrome and nephrolithiasis. Two years prior to her current endocrinological assessment the patient had been diagnosed with thyrotoxicosis, which had been attributed to a multinodular goiter, and was treated with carbimazole.

Fig. 1. Thyroid follicular carcinoma (clear cell variant) arising in SO. The tumor displayed predominately clear cell changes (90%) with a follicular and solid pattern. Higher magnification shows mild nuclear atypia, few mitotic figures and prominent clear cell cytoplasm.

The patient, euthyroid under treatment, underwent a total abdominal hysterectomy and bilateral salpingo-oophorectomy, omentectomy and appendectomy, and multiple biopsies were taken from the Douglas pouch. No peritoneal nodules were excised. Macroscopically in the anatomical position of the right ovary, a white-gray-tan mass was observed (12 × 7 × 7 cm) with elastic homogeneous consistency and focal areas of hemorrhage. Multiple sections were taken for histological examination. Microscopically, the neoplasm consisted of clear cells with a follicular and solid pattern, mild nuclear atypia, few mitotic figures and prominent clear cell cytoplasm (fig. 1). The tumor displayed predominately clear cell changes (90%) and only a small portion showed SO follicles. Capsular invasion was observed as well as several vessel invasions within the tumor (fig. 2). Immunohistochemical antibodies such as TTF1 (thyroid transcription factor 1), anti-folate receptor 4 antibody TH6 and monoclonal anti-mesothelial cell clone HMBE1 were positive, neuron-specific enolase (NSE) was focally positive, while pan-cytokeratin and cytokeratin 19 were negative. Metastatic infiltration was observed in the biopsies taken from the Douglas pouch. The left ovary, uterus and appendix were free of metastasis. Capsular invasion, vessel invasion and metastasis of the neoplasm to the Douglas pouch supported the diagnosis of carcinoma. The final diagnosis was given as thyroid follicular carcinoma, clear cell variant, arising in SO, with metastatic infiltration in the pouch of Douglas.

The patient's postoperative course was uneventful. A thyroid panel under carbimazole treatment revealed subclinical hypothyroidism: TSH 1.94 μIU/ml (reference range 0.5–4.8), T₃ 0.68 nmol/l (1.1–2.5) and T₄ 37.72 nmol/l (66–181). The carbimazole dose was therefore reduced and treatment was discontinued 1 month after surgery in light of the pathology result. The TG level at that point was elevated (132.7 ng/ml, range 3.5–77). Thyrotropin receptor antibodies were within the normal range (<1.58 U/l).

Fig. 2. Capsular invasion was observed (a) and several vessel invasions within the tumor (b) by clear cells supported the diagnosis of thyroid follicular carcinoma, clear cell variant, arising in SO.

During the 4-year follow-up the patient has remained euthyroid. The multinodular goiter remains unchanged on repeated ultrasonography thyroid scans and repeated pelvic CT scans have revealed no new findings. A whole body scan with ^{131}I was not performed since the thyroid gland is intact. TG levels remain stable (139.3 ng/ml) and carcinoembryonic antigen is normal (3.8 ng/ml, range 0–5). Thyroid peroxidase antibodies are elevated (112 IU/ml, normal level <35 IU/ml) and TG antibodies are normal (<20 IU/ml, normal level <40 IU/ml).

Discussion

SO is a highly specialized form of mature ovarian teratoma consisting of thyroid tissue that exhibits all the histological features of the thyroid gland. Malignant transformation of thyroid tissue in SO and metastases are extremely uncommon [10]. In rare cases, benign thyroid tissue may spread to the peritoneal cavity, and

pathologic examination of the peritoneal implants shows multiple nodules of varying sizes of mature thyroid tissue similar to SO, a condition termed ‘peritoneal strumosis’ [10]. Usually, patients with SO are asymptomatic or complain of nonspecific symptoms similar to other ovarian neoplasms. At the time of diagnosis, the most common symptoms are lower abdominal pain, a palpable abdominal mass, ascites and abnormal vaginal bleeding [2]. The incidence of thyrotoxicosis was reported to be 5–8%, and 17–33% of reported cases had ascites at diagnosis [9, 11]. In our case the patient presented with thyrotoxicosis 2 years before detection of the pelvic mass. The thyrotoxicosis was initially attributed to the multinodular goiter, and was well controlled by antithyroid drugs. The histology of the excised right ovarian mass revealed SO and the antithyroid treatment was therefore discontinued.

In patients with SO causing thyrotoxicosis the hormonal profile does not differ from that of patients with primary hyperthyroidism: TSH is low, fT_4 and/or T_3 are elevated and serum TG is also elevated. The thyroid gland is typically not enlarged. Radioiodine uptake is low or absent in the thyroid gland, but present in the pelvis. Rarely, women with SO and thyrotoxicosis also have goiter [6]. There are at least two possible explanations for this association: (1) the coexistence of Graves’ disease and SO, which has been rarely reported in the literature [7, 8], serum thyroid-stimulating immunoglobulins (thyrotropin receptor antibodies) would be expected to stimulate the function of thyroid tissue in the ovary as well as in the thyroid gland, and (2) the coexistence of toxic nodular goiter with autonomously hyperfunctioning thyroid tissue in an ovarian teratoma, these women would show radioiodine accumulation in both locations.

The diagnosis of SO is based on histopathological criteria and diagnostic guidelines for primary thyroid gland disease. Malignant SO consists of papillary thyroid carcinoma (PTC) cells, follicular variant of PTC or follicular thyroid carcinoma cells [12]. The most common type is PTC, followed by follicular thyroid carcinoma and the recent form of highly differentiated follicular carcinoma (HDFCO), which is characterized by extraovarian dissemination of thyroid elements [13]. Roth and Karseladze [14] introduced the term ‘follicular carcinoma with a high degree of differentiation’ in order to describe SO cases that had spread to the peritoneum. The differential diagnosis between benign and malignant follicular thyroid neoplasms is challenging, in particular in SO with a follicular growth pattern and undefined capsule. The incidence of malignancy is also difficult to assess due to the

rare nature of this case and the absence of standardized diagnostic criteria.

To our knowledge, the pathology report of our case, 'thyroid follicular carcinoma, clear cell variant, arising in SO with metastatic infiltration in the pouch of Douglas', has never been described before in the literature. When considering the differential diagnosis of SO with extra-ovarian dissemination, one must distinguish between HDFCO or peritoneal strumosis. HDFCO is a known entity in malignant SO cases associated with extraovarian spread, while peritoneal strumosis is a benign situation. The pathology report leaves no doubt about the diagnosis in our case: clear cells with a follicular and solid pattern, mild nuclear atypia, few mitotic figures and prominent clear cell cytoplasm (fig. 1). The HDFCO and peritoneal strumosis can therefore be excluded. In addition, malignant SO usually does not cause thyroid dysfunction [14]. However, in our case, 2 years prior to SO diagnosis, the patient had been diagnosed with thyrotoxicosis, initially attributed to toxic multinodular goiter, and was treated with antithyroid drugs. Antithyroid treatment was discontinued after the SO diagnosis. The thyroid function tests normalized postoperatively. Therefore, our patients' thyrotoxicosis seems to have been due to the hyperfunctioning ectopic thyroid tissue within the ovarian teratoma.

After presenting with a thyroid follicular carcinoma, clear cell variant, arising in SO, which also infiltrated the pouch of Douglas and was accompanied by ascites, our patient was diagnosed with malignant SO. We should always keep in mind that the diagnosis of follicular thyroid cancer in an ovarian teratoma (malignant SO) may be difficult, and parallels the difficulty in distinguishing between benign thyroid microfollicular adenomas and differentiated follicular thyroid cancer [6]. In our case, capsular invasion was observed along with several vessel invasions within the tumor (fig. 2), compatible with follicular thyroid cancer.

Another interesting finding in our case was the neuroendocrine component of the pelvic mass: the immunohistochemical antibodies, such as TTF1 and NSE, were positive. We were able to find another report in the literature documenting foci of follicular thyroid-type carcinoma arising in SO with a well-differentiated neuroendocrine component [12]. The clinical and prognostic significance of these findings remains unknown.

Concerning follow-up, the treatment of choice for these patients is local resection of the extraovarian tumor with subsequent thyroidectomy followed by radioactive iodine ablation. Thyroidectomy followed by radioactive

iodine ablation is not strictly applied, but is recommended because of the risk of recurrence in patients with peritoneal dissemination. No consensus has been reached in performing prophylactic total thyroidectomy after the diagnosis of thyroid-type carcinoma in SO. The decision to perform a thyroidectomy and administer radioiodine after oophorectomy should be based on the presence of metastatic disease and the risk of recurrence. Extremely high TG levels suggest metastatic disease. The risk of recurrence is higher in patients with a gross extraovarian extension of the tumor, large lesions (>4 cm, corresponding to T3 lesions), and the presence of BRAF mutation. BRAF-positive papillary cancer is more aggressive, and presumably this mutation in a malignant SO also indicates the potential for more aggressive disease. In a review of 24 cases of malignant SO, 4 out of 24 patients with an initial complete response were treated with adjuvant thyroidectomy and radioiodine after ovarian surgery; none of these patients had a recurrence [15]. There were eight recurrences (after an initial complete response to surgery), all of which occurred in the 16 patients treated conservatively after initial surgery. The median time to recurrence among those patients was 48 months. Seven out of 8 women with recurrences were treated with radioiodine at the time of recurrence, along with thyroidectomy. Four patients had no evidence of disease at 3, 5, 6 and 24 months following radioiodine. Three patients recurred after radioiodine (at 1, 3 and 6 months). One patient did not receive further therapy and died of disease 6 months after recurrence. Women with malignant SO confined to the ovary (low risk of recurrence, no metastatic disease) typically do not require radioiodine therapy after oophorectomy, and use of levothyroxine to suppress TSH to the lower limit or just below normal is suggested. In contrast, in patients with known distant metastases and the characteristics mentioned above (high risk of recurrence), thyroidectomy followed by radioiodine treatment is suggested. These patients also require TSH suppression therapy. The goal of T₄ therapy is to maintain the TSH at levels corresponding to those for conventional thyroid cancer, with TSH values maintained in the 0.1–0.5 mIU/l range for the first 5 years and then in the normal range thereafter in patients with no evidence of active disease. Patients with persistent disease following initial therapy require the maintenance of a serum TSH <0.1 mIU/l. Patients with malignant SO require long-term (at least 10 years) follow-up. Annual monitoring of stimulated serum TG is reasonable for the first 2 years postoperatively and, if negative, unstimulated levels annually thereafter. Patients with biochemical evidence of persistent disease

should have pelvic imaging with CT. In our case, we did not proceed to thyroidectomy because the patient declined the surgery. Hence, it was not possible to administer radioactive iodine either. Nevertheless, there are no signs of recurrence 4 years after surgery: the patient is euthyroid, with no new findings on pelvic CT. As malignant SO cases are rare, there is no standard follow-up protocol for patients who have not undergone thyroidectomy.

The literature also underlines the necessity to distinguish between SO containing thyroid-type carcinoma and ovarian metastases of papillary or follicular thyroid carcinoma. De Simone et al. [15] proposed thyroidectomy to exclude a primary thyroid carcinoma and potentiate radioactive iodine therapy. On the other hand, primary thyroid cancer rarely metastasizes to the ovary, and in such cases the ovarian tissue does not have teratomatous features [16].

In their literature review, Roth and Karseladze [14] found in total 18 cases of follicular carcinoma with a high degree of differentiation (HDFCO). Fourteen involved

the peritoneum and 4 were disseminated more widely. Among those with peritoneal dissemination, only 1 had overt hyperthyroidism [17] (this patient was initially diagnosed with peritoneal strumosis, which, according to the authors of the review, was rather a case of HDFCO). Five cases had ascites, 2 of which were with a negative cytological examination for malignant cells. Our patient presented with both hyperthyroidism and ascites, making this case rather unusual.

Overall, malignant SO is considered a very rare entity, and malignant SO causing thyrotoxicosis is even more uncommon. To our knowledge, the present case is one of the very few ever reported [9]. SO remains a challenge for the specialists involved. Although its prognosis is favorable, its clinical course is unpredictable and consensus on its optimal treatment has not been reached.

Disclosure Statement

The authors have no conflicts of interest to disclose.

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