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Review Article

Struma ovarii: a mini review

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Abstract: SO is a rare ovarian tumour with little clinical and imaging features. Most of the cases are benign and often associated with mature cystic teratoma. Increase of CA125 levels in the serum can potentially lead to a misdiagnosis of a malignant ovarian carcinoma preoperation. The diagnosis of a cystic struma ovarii is usually made on histopathology. Up to 5-10% of all cases of struma ovarii are reported to be malignant. Best treatment for benign struma is laparoscopic operation. Prognosis of benign strumosis and malignant struma ovarii without metastases is good. Malignant struma ovarii generally has a favorable prognosis while the prognosis of MSO with metastases is less favorable.

Keywords: Struma ovarii, papillary thyroid carcinoma, malignant struma ovarii

Introduction

The monodermal teratoma struma ovarii (SO) was originally described by Bottlin in 1888 as a rare form of ovarian tumor. Struma ovarii means ovarian goiter which originates from a single germ cell after the first meiotic division [1, 2] and is the most common type of monodermal teratoma in 3% of mature teratomas, 0.3-1% of ovarian tumour [3], 5-20% of mature teratoma has the component of thyroid tissue [4] and only 2% of these cases were diagnosed SO. According to the World Health Organization (WHO) classification, this disease was defined as ovarian goiter which comprises thyroid tissue either entirely or predominantly (> 50%). Malignant struma ovarii is even rarer as occurring in less than 5% of cases and metastases were seldom seen [5].

As to the low morbidity, lack of clinical and ultrasonographic features, misdiagnosis rate of SO before operation is high. Hence, radiological preoperative diagnosis is crucial for determining appropriate management, especially in patients of reproductive age who need fertility preserving therapy.

Clinical features

SO is a rare ovarian tumor with no specific clinical manifestations (**Table 1**). It has the similar age incidence with mature cystic teratoma. Onset age of the disease is extensive, mostly in women of fertile age with the peak age incidence in the fifth decade. It was found that 6% of the cases occur bilaterally [6] while most cases occur in one side as more often affect the left ovary [7, 8].

The clinical symptom may include a non-specific palpable pelvic mass and nearly 5% of cases may present with hyperthyroidism [9, 10]. Non-specific symptoms are described like abdominal pain, back pain, abdominal distension, vaginal bleeding and frequent urination has also been described. Acute severe abdominal pain may be caused by tumor rupture.

About 17% of the patients [11] developed pseudo-Meigs' syndrome with pleural effusion and ascites. Raised cancer antigen (CA)-125 levels can also be found in a few cases [12]. CA125 is a widely accepted tumor marker of ovarian carcinoma. This presentation may result in a misdiagnosis of malignant ovarian cancer in elderly patients which lead to unnecessary extensive surgery. The mechanism behind the raised cancer antigen levels in cases pseudo-Meigs' syndromes is still not well explained. However, CA-125 can found to be elevated in both benign and malignant ovarian carcinoma which means this clinical phenomenon of little value in struma ovarii patients.

Table 1. Clinical and pathological features of SO

Signs	Macroscopic examination	Scrape smears/frozen sections
Pelvic mass	Mostly < 10 cm in size	*Multicystic mass with lobulated surface**
Hyperthyroidism in 5% cases	Mixed cystic and solid nodular mass	Sometimes thickened septic
Pseudo-meigs' syndrome in 17% cases	Vascular networks	Occasionally has a dilated thyroid follicle
Raised CA125 in a few cases	3-10 mm of capsule wall thickness	Normal-appearing thyroidal tissue composed of *thyroid follicles**
Tumor rupture in few cases	Hemorrhage, necrosis, fibrosis	May associate with hyper/hypoactivity of thyroid tissue/ adenomatous nodule/nodular goitre
Non-specific symptons	Green or (and) brown solid/gelatinous/ transparent/liquid	Non-specific appearance of epithelium cells with flattened to cuboidal cells
	Dermoid background in non cystic tumors	

*Features of great value on pathological diagnose of SO.

Pathological features

On macroscopic examination, most cases of struma ovarri are solid with some extent of cystic, the tumors with predominantly or entirely cyst maybe lead to misdiagnose. The tumors are some mixed cystic and solid nodular mass encapsulated and mostly less than 10 cm in size, with vascular networks, sometimes adherent to surrounding tissues; The capsule wall thickness are mostly of 3-10 mm, contain brown or green-brown solid, gelatinous mass, transparent, green, or brown liquids. Hemorrhage, necrosis and fibrosis may be present. The dermoid background is found in some non-cystic tumors.

Scrape smears and frozen sections are quite important to the accurate diagnose of ovarian tumors and decision of surgical plan.

Typically, SO appears like a multicystic mass with lobulated surface and sometimes by thickened septic or cyst walls, occasionally has a dilated thyroid follicle representing thyroid tissue. The typical consists of normal-appearing thyroidal tissue composed of thyroid follicles and often is associated with mature cystic teratoma. Changes of the thyroid tissue may occasionally associate with hyperactivity, hypoactivity, or have the appearance of an adenomatous nodule or nodular goitre [13]. In cystic struma, the epithelium cells lining the cyst may have a non-specific appearance with flattened to cuboidal cells. The diagnostic difficulty of many cystic tumors is due to the non-specific histological appearance (**Table 1**).

Clues to the correct diagnosis of SO may include the detection of thyroid follicles in the cyst wall or in fibrous septa separating locules of mass, the identification of foci of typical struma through ample sampling, or the association with mature cystic teratoma.

The most common malignancy SO is papillary thyroid carcinoma (PTC) (carcinoma of follicular are second most frequent, some of these may represent follicular variant of papillary carcinoma) [4, 7].

Preoperative diagnosis of SO is difficult as it lacks clear clinical syndromes. Most of the cases are benign and often associated with mature cystic teratoma. Ignoring of the presence of small carcinoid lesions that are diagnosed only after pathological examination often occurs.

Radiological images

Ultrasonography

The ultrasound features of a struma ovarii are quite indistinct, such as mostly unilateral tumors, mixed cystic and solid mass, unilocular or multilocular with clear boundary. On transvaginal ultrasonography, struma ovarii typically appears as cystic tumors containing one or more well circumscribed roundish solid areas with smooth contour named as "struma pearls" [14]. Although struma ovarii presents with a variety of non-specific appearances and usually manifests as a multilocular cystic ovarian mass with solid components of various amounts, the ultrasound typically demonstrates these non-specific heterogeneous solid cystic features. Doppler results were described by Savelli [14] as differing between dermoid cysts and struma ovarii. The blood flow of struma ovarii was detected in the central part of the mass while in mature cystic teratomas

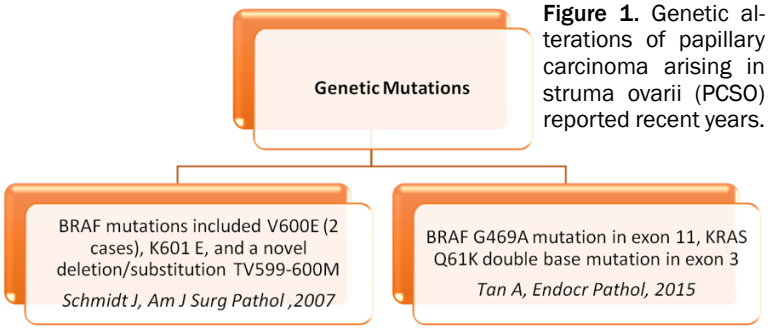

Figure 1. Genetic alterations of papillary carcinoma arising in struma ovarii (PCSO) reported recent years.

blood flow was detected only at the periphery of the ovary.

Computed tomography

Findings are generally non-specific on CT scan and demonstrates the complex appearance with multiple cystic and solid areas, reflecting the gross pathological appearance of the struma.

CT findings of struma ovarii are characterized by the presence of high attenuation area and calcifications [15]. The high-density cysts might be a characteristic feature of struma ovarii on CT. The CT features could show solid, cystic, or cystic-solid characteristics. Cystic-solid is the most frequent type while the solid type is the least on CT scan. Unlike the most common types of teratoma, struma ovarii does not demonstrate lipid material on either CT or MRI [8]. When struma ovarii is accompanied by foci of fatty tissue, they can be considered as areas of dermoid cyst associated with struma ovarii [16]. In these circumstances, the presence of dermoid cyst can be a strong clue to suspect struma ovarii. Recognition of these manifestations is helpful in the diagnosis of this tumor.

In summary, CT scan has such manifestations, ① Cystic-solid mass mostly occurred unilaterally, solid mass is rare. ② Tumor mostly present a lobulated shape with clear boundary, usually the diameter of OS mass is less than 10 cm, occasionally over 20 cm. ③ The density of single cystic mass is usually uniform, and the density of cystic density in polycystic type is different, which is generally higher than the density of bladder fluid, high attenuation areas and calcifications in the solid components of the struma are common findings, It has been hypothesised that the appearance of high-density values from CT scan are caused by both the thymoglobulin and thyroid hormones in the follicular thyroids that could attenuate the X-ray significantly [15, 16]. ④ The cyst wall and septum are usually thicker and about 0.3 to 1 cm, but the wall of the cyst is smooth, and the wall and septum are often calcified. ⑤ Imaging following an intravenous contrast agent is known to demonstrate marked enhancement of the thick septations and locally thickened wall seen in struma ovarii. The solid components, corresponding microscopically to thyroid tissue, also demonstrate strong enhancement. It may be related to the solid part of SO, which is composed of thyroid tissue and stroma rich in blood vessels and fibers [13, 17]. ⑥ SO was always complicated with small amount of ascites. Almost no distant metastasis of benign lesions, distant metastasis of malignant lesions is also rare.

Magnetic resonance imaging

The struma has features overlapping with those of malignant ovarian epithelial tumours, as it presents either as a unilateral complex adnexal mass often associated with ascites, or as a multi-cystic mass with solid components and multiple cystic locules. Thick septations, measuring 3-10 mm.

On MR imaging, the signal intensity of the various solid components varies. The SO cyst fluid signals are complicated, showing low signal in T1W1 and high signal in T2W1 [18]. MR findings include a multicystic mass with a multilobulated surface, some solid components representing thyroid tissue including thickened septi or cyst walls and cystic components showing a variety of signal intensities on both T1- and T2-weighted images [16, 18]. The cystic components occasionally have loculi of low intensity on T2-weighted images and the punctuate foci of high intensity on T1-weighted images. The solid components are of low signal intensity on T2-weighted images and intermediate signal intensity on T1-weighted images. The cystic spaces, on the other hand, demonstrated both high and low signal intensity on T1- and T2-weighted images. This pattern of signal

Table 2. Radiological image features

Ultrasonography	Mostly unilateral tumors; mixed cystic and solid mass; typically appears as ostruma pearls
Computed tomography	Mostly Cystic-solid type, solid mass is rare; uniform density; high-density cysts might be a characteristic feature; does not demonstrate lipid material; smooth cyst wall, calcified septum; marked enhancement of the thick septations/solid components/thyroid tissue with contrast agent; always show small amount of ascites
Magnetic resonance imaging	*Varies signal intensity**; low signal in T1W1 and high in T2W1 of cyst fluid; variety of signal intensities on T1-/T2-weighted images of thyroid tissue/thickened septi/cyst walls; very low intensity on T2-weighted MR and no enhancement on contrast-enhanced MR of cystic areas

*Radiological image features of great diagnostic value.

intensity on T1- and T2-weighted imaging was found to be due to the thick, highly viscous, gelatinous colloid material in large follicles of the struma. The areas of very low intensity on T2-weighted images were thought to be cystic, because they did not reveal any enhancement on contrast-enhanced MR studies. This may be of great diagnostic value. Joja et al. [18] stated that the variety of signal intensities seen on MR images in the cystic components depends on the degree of condensation of thyroglobulin and thyroid hormones, and it now recognised that this variable signal intensity is highly characteristic of struma ovarii.

Clinical diagnosis

SO is a rare ovarian tumour with no clinical and ultrasound specific features. Increase of CA125 levels in the serum can potentially lead to a misdiagnosis of a malignant ovarian carcinoma preoperation [14]. The diagnosis of a cystic struma ovarii is usually made on histopathology.

SO is mainly composed of thyroid follicles, sometimes characterized by small papillary hyperplasia or small follicles, so diagnosis is generally not difficult. The diagnostic criteria include ① the mass is entirely composed of thyroid tissue ② Teratoma with goiter, including thyroid composition accounted for more than 50% ③ or the symptom of hyperthyroidism occurs while thyroid composition of mass is less than 50% ④ thyroid tissue can be recognized by naked eyes in the mature teratoma [19]. In these criteria, ①, ② and ③ are commonly accepted by specialists.

Imaging does not allow the differentiation of non-functioning struma ovarii from other cystic masses. When struma ovarii is not associated with hyperthyroidism, the differential diagnosis includes: mucous or serous ovarian cystadenoma, mature cystic teratoma without fatty tissue and other primary ovarian cancer, endometriosis, metastatic tumors, and tubo-ovarian abscess.

Differentiation of benign and malignant struma ovarii

In total, up to 5-10% of all cases of struma ovarii are reported to be malignant, usually in the 6th or 7th decade of life. The diagnosis of malignant struma ovarii is usually based on histological features of the resected ovary, as no specific imaging features are available to detect malignant struma ovarii (MSO). There is no universally accepted standard for the diagnosis of MSO. As in the thyroid gland, papillary carcinoma is the most common histological type of MSO accounting for 70% of cases and of these one third are follicular variant papillary carcinomas. Papillary carcinoma arising in struma ovarii (PCSO) can be clinically malignant in the absence of conventional histological features of malignancy, most such lesions demonstrate follicular growth patterns and lack papillary cytological features. Criteria for malignancy in struma ovarii are the same as those of a thyroid carcinoma. Indicated by the histological classification of WHO in 2003, nuclear features such as nuclear grooves are more clearly visible on scrape smears and their absence rules out a papillary carcinoma. In addition, follicular carcinomas have capsular breaches and vascular invasion. Although diagnosis of papillary thyroid carcinoma in malignant ovarian goiter is definite, diagnosis of follicular carcinoma requires vascular and/or capsular invasion. Whether these criteria used for the thyroid gland are applicable to the cases of struma ovarii is still controversial [20].

Immunohistochemistry is frequently used to support a diagnosis of malignancy generally, or papillary carcinoma more specifically, using HBME-1, CK19 and CD56. Recently, absent CD56 expression has also been found to be

highly sensitive and specific for papillary thyroid carcinoma [21, 22]. CK and HBME-1 are characteristically positive in papillary thyroid carcinoma. Immunohistochemical staining with cytokeratin (CK) 19 and HBME-1 (Hector Battifora mesothelial cell 1) may help to confirm the diagnosis of PCSO. It should be noted that none of these antibodies are completely sensitive or specific, but they have proven valuable in diagnostic practice. However, the application of these three antibodies in combination is not known in PCSO.

Primary thyroid carcinomas have been found to harbor a variety of genetic alterations like the BRAF, RAS (KRAS, NRAS, and HRAS), PIK3CA, and RET genes, including point mutations and rearrangements [23]. BRAF mutations are seen in 40-45% of papillary thyroid carcinoma and up to 98% are V600E mutations. The V600E mutation and other closely located mutations (K601E and TV599_600M deletion) have also been identified in cases of PCSO. There are isolated reports of NRAS and HRAS mutations in these tumors [23]. Novel mutations in BRAF and KRAS were identified in A. Tan's research [24] in two cases and while additional larger studies are required, the findings suggested that there may be greater mutational diversity in PCSO than in eutopic thyroid papillary carcinoma. Data remain extremely limited on the molecular changes in MSO including PCSO (**Figure 1**).

For ovarian lesions which exceed the ovarian lesion itself, there is no consensus about the ovarian struma with the dissemination of the abdominal cavity, the greater omentum and the surrounding organs. There is a difference in understanding of ovarian goiter with benign changes beyond the ovaries and surrounding disseminated lenses. Roth [19] gave two explanations for this problem. One explanation is that the implant is due to rupture of the capsule of ovarian goiter or a mature cystic teratoma with thyroid components. Another explanation suggested that this may be caused by the spread of highly differentiated follicular carcinoma. One year later, Roth [25] described a new entity, highly differentiated follicular carcinoma of ovarian origin (HDFCO), which is characterized by extraovarian dissemination of thyroid elements that histologically resembles normal thyroid tissue. This entity comprises previously known peritoneal strumatosis with or without lymph node and/or distant metastasis.

Therapy

The gold standard treatment is surgery and prognosis is excellent. The best treatment for benign struma is laparoscopic operation. Complete removal of the tumor under laparoscope can not only remove the lesion, but also minimize the damage to the patient and recover quickly after operation. If the tumor is complete, smooth and without malignant component, resection of the ovary and fallopian tube or cyst removal alone are usually performed. During the operation, cysts should be removed totally, so as to avoid the omission and recurrence of the disease. Flushing the abdominal cavity and absorb all the fat/hair may help to recover the intraperitoneal environment. Careful operation should be done in order to reduce normal ovarian tissue damage. For women with fertility requirements, laparoscopic cystectomy can significantly reduce postoperative adhesions and infertility due to adhesions and pelvic pain.

Little is known about malignant struma ovarii due to its rarity and accordingly there are few guidelines to manage its treatment [26, 27]. Various treatment strategies have been suggested, but no treatment guidelines have been established. The intensity of treatment is a significant issue for clinicians to consider. This may include pelvic surgery, thyroidectomy and radioactive iodine (I^{131}), which must be balanced against the risks of infertility and the low rate of metastasis. A comprehensive assessment of the thyroid gland should be carried out to remove the metastasis of primary thyroid tumors once malignant ovarian goiter was diagnosed. In general, there is lack of consensus on the management of malignant struma ovarii (MSO) or papillary carcinoma arising in struma ovarii (PCSO), although some authors have suggested thyroidectomy and I^{131} therapy, particularly for patients with gross extra-ovarian extension or distant metastases [28, 29].

The surgical treatment of MSO is the main treatment which can be treated via total abdominal hysterectomy and bilateral salpingo-oophorectomy. The aggressive surgical management followed by radioiodine therapy is best to reduce recurrence risk and optimize

survival. For women wishing to retain fertility, unilateral salpingo-oophorectomy may still be a feasible option in the absence of extracapsular extension and distant metastases.

An adjuvant treatment technique that has been suggested for residual, metastatic or recurrent disease of malignant struma is radioiodine therapy, which has been reported to result in favourable outcomes [30]. In patients presenting with multiple metastatic lesions, or for those who absorb radioiodine poorly, external beam radiation has been proposed [31].

How to avoid misdiagnosis

OS is difficult to diagnose preoperatively for the following reasons. First of all, the incidence of this disease is low, and the clinical and imaging features are absent (**Table 2**). Second, the incidence of hyperthyroidism is low. Preoperative examinations usually do not perform a specific examination of thyroid function and thyroid composition. Finally, the tumor itself is composed of cystic and solid components, containing lipid, hair and skeletal components, which are difficult to identify with mature cystic teratoma. Radiologically, a benign ovarian mass presenting with *ascites* and raised cancer antigen (CA)-125 levels can be misdiagnosed as a malignant ovarian tumour [32]. In such cases, a correct intraoperative diagnosis can prevent extensive surgery.

Diagnosis must be made by pathological examination as diagnosis by naked eyes intraoperative is not reliable. In pathological examination, especially during the frozen section pathological examination, the tumor including the capsule should be completely removed so as to avoid missed diagnosis. Struma ovarii containing thyroid type carcinoma must be distinguished from rare cases of papillary or follicular thyroid carcinoma metastatic to the ovary which are mainly characterized by cervical lymph node metastasis, and less hematogenous metastasis. Since most malignant goiter is the pathological diagnosis, the extent of primary surgical resection is usually not enough. Hence, staging of reoperation to evaluate lymph node and other site metastasis is often unavoidable. Ovarian goiter sometimes has many morphological changes, a careful search for thyroid follicles should be undertaken. Immunohistochemical staining for thyroglobulin in difficult cases is recommended.

Prognosis

After treatment, the prognosis of benign strumosis and malignant struma ovarii without metastases is good. If ascites and/or pleural effusion are present, they usually disappear after surgery. Malignant struma ovarii generally has a favorable prognosis with overall survival of 92, 85 and 79%, at 5, 10 and 25 years [33]. The prognosis of MSO with metastases is less favorable. It has been suggested that BRAF mutation-positive papillary thyroid cancers, most commonly V600E, may show adverse prognostic features including invasive growth and lymph node metastasis and have worse clinical outcomes compared to papillary thyroid carcinomas which are negative for these mutations. The average duration of initial recurrence is 4 years, Because of the risk of long-term recurrence [29], long-term follow-up is required.

Strumal carcinoid of the ovary is a low-grade malignancy with slow growth. It was reported [34] that the malignant transformation rate is less than 0.1% and has a good prognosis. In a very rare occasion, strumal carcinoid can lead to metastasis [35]. Early surgical resection of stromal carcinoid can achieve the purpose of radical resection. In follicular thyroid carcinoma (FTC), mutations in the ras gene predict poor prognosis as the mutation rate of K-ras gene is about 9%.

Cases with histological benign tumors have better prognosis than those of histological malignant cases, and even if disseminated, the prognosis is still good. It is also related to the extent of adhesions and the size of the tumor. Thyroglobulin can be used as an indicator for the detection of postoperative tumor recurrence [36].

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Disclosure of conflict of interest

None.

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