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Original Article

Clinicopathological and immunohistochemical characteristics of struma ovarii: a retrospective study of 24 cases from updated 30-years experience

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Abstract: Background: Struma ovarii (literally: goitre of the ovary) is a rare form of monodermal teratoma that comprises either entirely or predominantly thyroid tissue (>50%). This also includes cases of mature teratoma with less than 50% thyroid tissue but harboring thyroid-associated malignancy. This study was to investigate the biological feature and immunohistochemical features of Struma ovarii. Patients and methods: This retrospective study enrolled 24 patients with Struma ovarii from 1986 to 2016, including 1 case of papillary thyroid carcinoma and 23 cases of benign struma ovarii. Results: The median age was 49.2 (ranged 24-79). Concurrent with primary ovarian lesions, 2 cases had ipsilateral mucinous cystadenoma, 8 cases had ipsilateral cystic teratomas and one case had ipsilateral mature cyst teratoma, whereas one case had contralateral Brenner tumor. Ascitic fluids were observed in four cases and hydrothorax fluids were observed in two cases. Nine cases were found by chance during a routine physical examination. The most common clinical manifestations were lower abdominal discomfort and palpable mass (10/24), menorrhagia (2/24), acute hypogastralgia (congenital ovarian cysts torsion, 3/24), cough and polypnea (2/24). Elevated CA125 was found in four cases. The tumors of all the cases had totally intact encapsulation. Tumor size ranged from 5-15.5 cm (average, 10.3) in greatest dimension. Twenty were multilocular, other four were unilocular. The cystic masses were typically filled with light yellow-brown or amber gelationous tissue and clear green-yellow fluid. Microscopically, the tumors consisted of thyroid follicular structure that were lined by flat-cuboidal cells and filled with eosinophilic colloid-like material. In one case, the epithelium cells exhibited malignant transformation, which was classified as a follicular variant of papillary carcinoma. Furthermore, endometrial polyps were found in two cases, one of them was post-menopause. Two cases were initially misdiagnosed as other ovarian tumors during intraoperative frozen section. Immunohistochemical stains for thyroglobulin and thyroid peroxidase were positive. Thirteen patients were cured without relapse and one patient was lost to follow-up. Conclusions: Struma ovarii is rare tumor and highly specialized form of monodermal ovarian teratoma, with a peak incidence in the fifth decade of life. Struma ovarii may manifest variant pathologic features presenting in the thyroid gland. They should be diagnosed on the same histological basis as thyroid carcinoma. Immunohistochemical staining for thyroglobulin and thyroid peroxidase contributed to the diagnosis of this disease. Principle of clinical treatment of malignant struma ovarii is commonly derived from the experience with thyroid carcinoma. Postoperative adjuvant radiation therapy and chemotherapy may be recommended to perform. The prognosis is generally favorable.

Keywords: Struma ovarii, teratoma, clinical features, immunohistochemistry, prognosis

Introduction

Struma ovarii is defined as ovarian goiter which comprises either entirely or predominantly thyroid tissue (>50%). This also includes cases of mature teratoma with less than 50% thyroid tissue but harboring thyroid-associated malignancy. Struma ovaii is rare tumor, accounts for 2.7% of ovarian teratomas and 0.3% of ovarian neoplasms [1-4]. Malignancy is even rarer and is reported in 5%~10% of all cases of struma ovaii [2]. The most common malignancy in struma ovarii is papillary thyroid carcinoma (PTC), followed by follicular carcinoma [5, 6]. Like ovarian mature teratoma, struma ovarii often occurs at reproductive age. Struma ovaii is a poorly

defined entity with variable non-specific clinical features and manifestations such as sizeable ovarian mass and abdominal pain. Being a rare disease, Struma ovaii has always lacked of literatures on the diagnosis and treatment. In this study we present our institutional 30-years experience of this disease and attempt to provide some diagnosis and treatment approach for clinicians reference. In this paper, the clinicopathological characteristics, immunohistochemical features, diagnostic and therapeutic strategy of 24 patients with struma ovarii are reviewed.

Materials and methods

From January 1986 to August 2016, 24 Chinese patients diagnosed of struma ovarii admitted to Xinhua hospital and Renji hospital, affiliated to Medicine School, Shanghai Jiao Tong University were enrolled in this study. The following diagnostic criteria were employed to diagnose cases in the present case cohort: struma ovarii was defined as a teratoma containing more than 50% thyroid tissue [6] or a thyroid-associated malignancy [7]. A detailed medical record containing clinical features, imaging data, serum tumor biomarkers, as well as cytological and histological confirmation was collected. None of the patients had a previous history of gonadal GCTs or non-CNS extragonadal GCTs. None of the patients had a primary disease of the thyroid gland. The study was approved by the ethics committee of Xinhua hospital and Ren Ji Hospital. There are 1 case of papillary thyroid carcinoma and 23 cases of benign struma ovarii (17 cases were entire struma ovarii, 6 cases were mixed struma ovarii in which several teratomatous tissues exist and thyroid tissue had occupied over 50% of entire tumor). These patients with struma ovarii account of 1.76% and 0.15% of ovarian teratomas patients and ovarian neoplasms patients respectively who admitted to Xinhua hospital and Renji hospital from Jan 1986 to Aug 2016.

Specimens were fixed in 10% neutral formalin, embedded in paraffin, and stained with hematoxylin-eosin. Immunohistochemical staining was performed by Envision method. Immunohistochemical analysis was performed employing the following antibodies: CK-19 (1:50, RCK108, DaKo), Thyroglobulin (TG, 1:200, Catalog No. A0251, DaKo), Thyroid Peroxidase (TPO, 1:40, MoAM7, DaKo), TTF-1 (1:200, Catalog No. M3575, DaKo).

Results

Clinical features

Among 24 patients, the median age was 49.2 years (mean 48.3, range 24-79 years). 9 patients were of postmenopause with mean menopausal time 13.4 years (range 2-20 years). Preoperative duration ranged from two days to two years.

The clinical manifestations of struma ovarii are lack of specificity. The most common clinical manifestations were lower abdominal discomfort and palpable mass (10/24), menorrhagia (2/24), acute hypogastralgia (congenital ovarian cysts torsion, 3/24), cough and polypnea (2/24). Nine cases were found by chance during a routine physical examination. All patients were found pelvic masses by bimanual examinations and ultrasound examinations. None of the patients had symptoms of hyperthyroidism. Elevated CA125 was found in four cases. 15 cases of struma ovarii located at left adnexa, 9 at right adnexa. Concurrent with primary ovarian lesions, 2 cases had ipsilateral mucinous cystadenoma, 8 cases had ipsilateral cystic teratomas and one case had ipsilateral mature cyst teratoma, whereas one case had contralateral Brenner tumor. Concurrent uterine leiomyomas were accompanied in four cases. Ascitic fluid was observed in four cases (light yellow-green fluid 3000 ml, light yellow-green fluid 2000 ml, light yellow-brown fluid 200 ml, and blood effusion fluid 100 ml, respectively) and hydrothorax fluid was observed in two cases. There was no tumor cell had been detected in ascitic fluid or hydrothorax fluid.

In 19 cases, serum tumor biomarker (CA199, CA50, AFP and CEA) were analyzed at baseline and after surgical resection. At baseline, all patients' tumor biomarkers such as CA199, CA50 and CEA levels were within normal range, while CA125 level was found elevated in four cases (ranged 45.72-503.14 u/ml, normal value <35 u/ml): one case of papillary thyroid carcinoma and three cases of benign struma ovarii. Two weeks later after operation, the CA125 level had decreased and one month later its level was within normal limit.

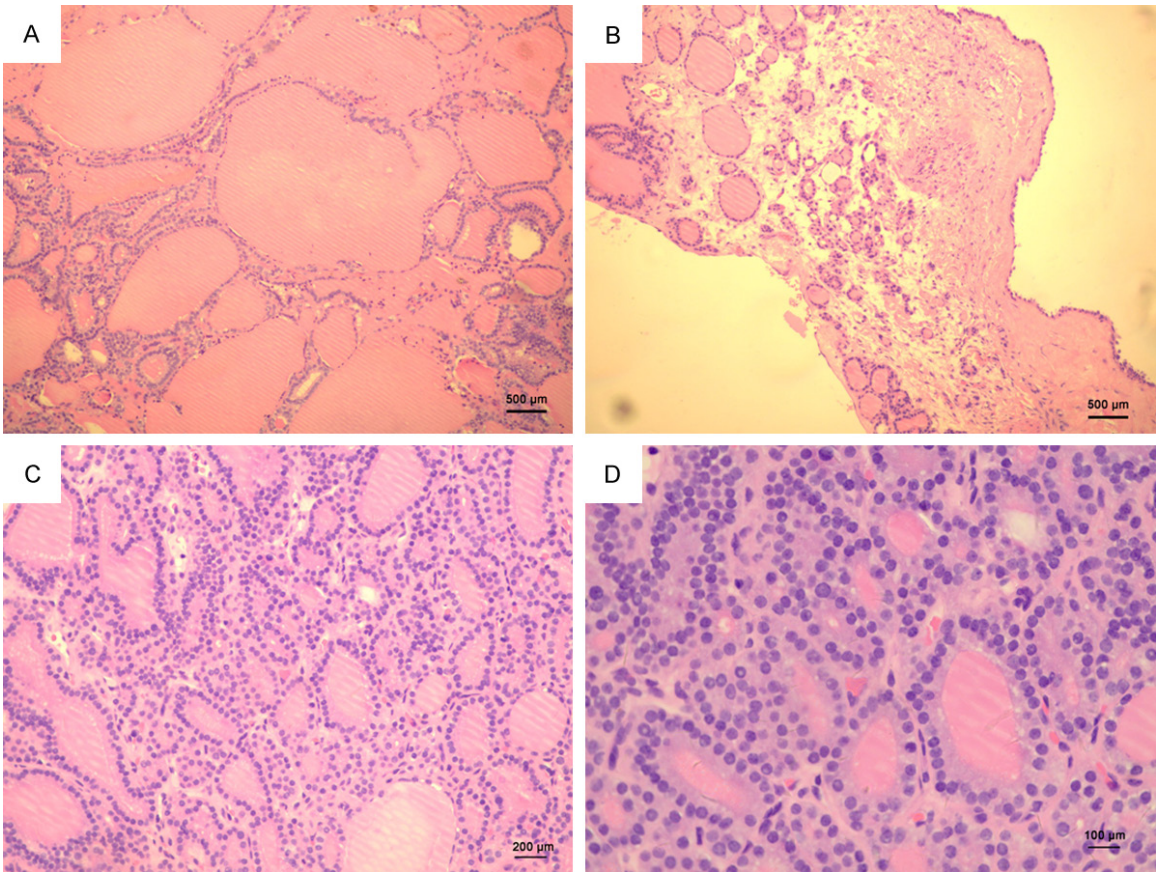

Figure 1. Pathological H&E sections in struma ovarii. A, B: Tumoural regions with normal thyroid parenchyma showed various thyroid follicular structures packed with eosinophilic colloid-like material. C, D: The tumor cells exhibited enlarged, overlapping nuclei, longitudinal nuclear grooves, and ground-glass appearance, with occasional mitoses.

Therapy

All patients underwent surgical treatments. In 23 benign struma ovarii patients: 6 patients underwent unilateral salpingo-oothecectomy, 1 bilateral salpingo-oophorectomy hysterectomy, 6 cystectomy, 9 total hysterosalpingo-oophorectomy, 1 patient received unilateral salpingo-oothecectomy + total hysterectomy + contralateral cystectomy + partial omentectomy + pelvis lymphadenectomy. The papillary thyroid carcinoma patient underwent total hysterosalpingo-oophorectomy + partial omentectomy + pelvis lymphadenectomy, and received 6 cycles of platinum-based chemotherapy (cisplatin, cyclophosphamide, vincristine and etoposide) after the operation.

Pathologic finding

Gross pathology

The tumors of all the cases had totally intact encapsulations and smooth surface, measured 5-15.5 cm (average 10.0 cm) in greatest dimension. Section illustrated slicing was solid and cystic neoplasm, cystic tumors predominated in 23 cases and solid tumor predominated in 1 case. 20 were multilocular, whereas 4 were unilocular. The cystic masses were typically filled with brown gelatinous solid mass and clear green-yellow fluid. The wall of the cysts ranged from 0.1 to 0.5 cm in thickness.

Microscopic findings

Microscopically, there were 23 benign struma ovarii and 1 malignant struma ovarii. The 23 benign tumors consisted of thyroid follicular structure lined by flat-cuboidal cells. The majority of the cystic lumens contained eosinophilic colloid-like material (**Figure 1**). Among them 7 cases had cystic degeneration, 6 cases showed adenomatous hyperplasia including 1 pseudopapillomatous hyperplasia without atypia. Focal calcification was present in 8 cases.

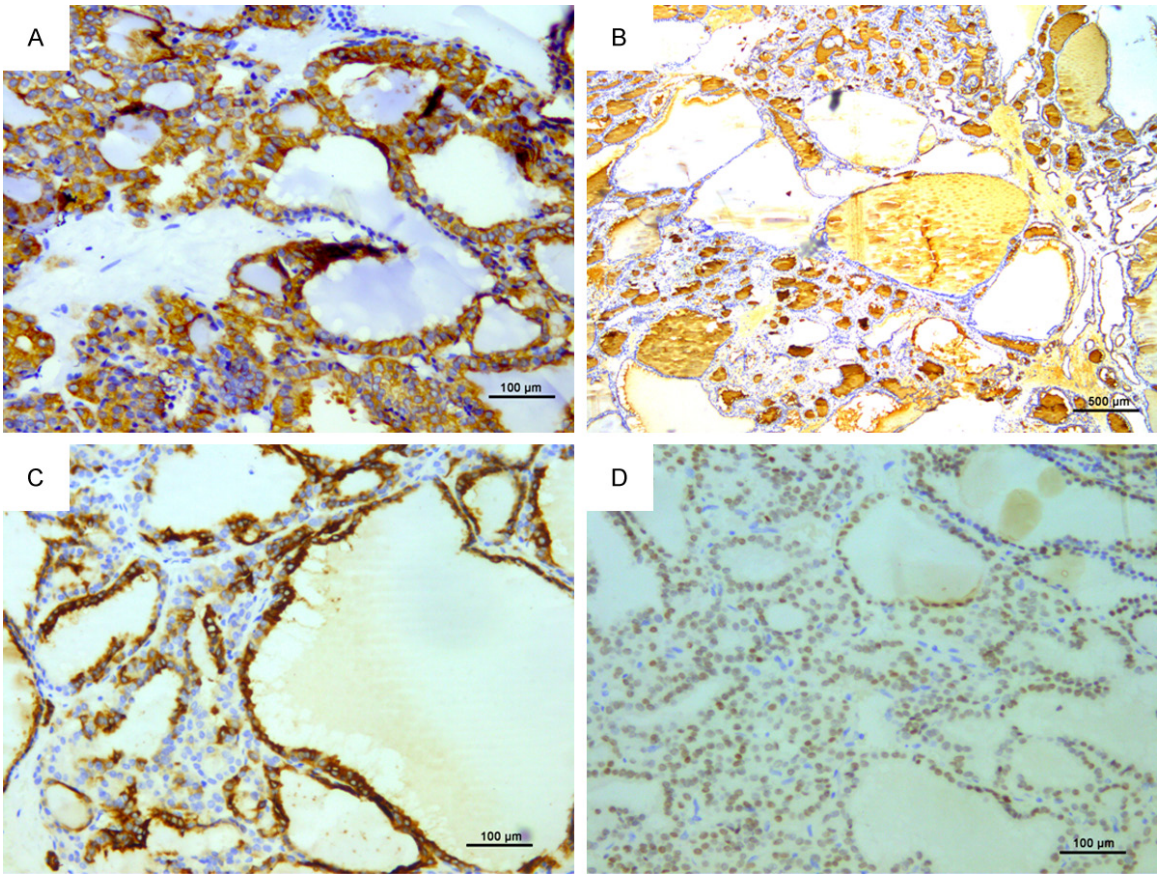

Figure 2. Immunohistochemical stains for (A) CK-19 were positive in malignant struma ovarii. Immunohistochemical stains for (B) Thyroglobulin, (C) Thyroid Peroxidase and (D) TTF-1 were positive in benign struma ovarii.

A total of two patients were misdiagnosed as other types of tumors. A 72-year-old patient, had two sequestration nodules, one measured 14×10×8 cm was misdiagnosed as Sertoli-Leydig tumor and then corrected as struma ovarii, and another one measured 31×30×14 cm was mucinous cystadenoma exhibiting focal atypia in epithelium cells. This patient had Brenner tumor located at contralataral ovary. Another case was initially misdiagnosed as mucinous cystadenoma at intraoperative frozen section. One patient had malignant struma ovarii located at left ovary, simultaneously had mature ovarian teratoma located at right ovary with a large amount of ascites. The tumor cells formed tightly packed follicles. Although these follicular growth patterns predominated, scattered primitive papillary formations were also presented (**Figure 1**). The tumor cells exhibited enlarged, overlapping nuclei with occasional mitoses, some of which displayed longitudinal nuclear grooves or ground-glass appearance (**Figure 1**). The uterus and pelvic lymph nodes were unremarkable. Considering these histological features, this case was classified as malignant struma ovarii (a follicular variant of papillary carcinoma of the thyroid).

Immunohistochemical stains for thyroglobulin, TPO were positive in all cases. In 23 benign struma ovarii patients, the positive rates for TTF1 and CK19 were 69.6% and 17.4%, respectively. Meanwhile, positive staining was observed for CK19, Ki-67 and TTF1 on one malignant patient (**Figure 2**).

Follow up

Twenty-three patients remain free of symptoms without relapse and one patient was lost to follow-up. The median follow-up time was 11.2 years (range, 1.86-30.55 years) in the cohort.

Conclusions

Teratomas account for approximately 95% of germ cell tumors, meanwhile approximately

15% of teratomas contain thyroid tissue [3, 8]. Struma ovarii, derived from germ cells, is a highly specialized form of monodermal ovarian teratoma with thyroid tissue as predominant or exclusive component. It is very rare with a peak often incidence in the fifth decade of life. Struma ovarii was firstly described by Von Kalden in 1895. Struma ovarii may manifest all pathologic features observed in the thyroid gland (cystic degeneration, hyperthyroidism, goiter, adenoma, Graves' disease and thyroid carcinoma, etc.). The tumors located more frequent at left ovary than right ovary. Only 6% of benign struma ovaries are bilateral. Struma ovarii related to teratoma contains a few thyroid tissues, dermoid cyst and cystadenoma. Moreover, Brenner tumor may be discovered in the contralateral ovary in a few cases of struma ovarii [1, 9]. Most of these struma ovaii are benign. Malignancy is very rare and the incidence was reported about 5%-10% of all cases.

The clinical presentations were nonspecific, some patients have incidental found in physical examination. The most common clinical manifestations were lower abdominal discomfort and palpable mass, menorrhagia, acute hypogastralgia, etc. Congenital ovarian cysts torsion can lead to acute abdominal disease in a few patients. The preoperative diagnosis of struma ovarii is very difficult. None of 24 patients was diagnosed preoperatively as struma ovarii. Two patients were misdiagnosed as ovarian carcinoma. Only one case diagnosed as struma ovarii preoperatively was described by Matsuda K, et al [10]. The diagnosis basis (a hormone-producing malignant struma ovarii) of struma ovarii includes clinical findings of thyrotoxicosis with no abnormal findings of the thyroid gland and the presence of a solid ovarian tumor. Meanwhile, microscopic morphology was consistent with malignant struma ovarii. Only 8% of patients with struma ovarii presents with clinical hyperthyroidism. Ascites may occur in 17% of cases and is usually not malignant. The associated pseudo-Meigs' syndrome has been reported [11]. Ascites and hydrothorax could significantly alleviate after the operation [12, 13].

Struma ovarii is generally round or oval cystic nodule with totally intact encapsulation, mimicking mature cystic teratoma. Occasionally, the nodule is predominantly solid. The section of strumas usually reveal multilocular, ranging from big to tiny cysts. The lumens are filled with yellow to brown or amber colloid-like material, and clear to light green-yellow fluid [1, 14]. There may be peritoneal disseminated metastatic lesions in malignant struma ovarii [15, 16].

Microscopic morphology reveals thyroid tissue, comprising varied thyroid follicles. They are lined by flat-to-cuboidal epithelium. The lumens were filled with eosinophilic colloid-like material with PAS positive stain. Nodular goiter, Hashimotos' thyroiditis, thyrotoxicosis and adenoma features can be found in the patients with struma ovarii. Follicular carcinoma or papillary carcinoma character in malignant region can be identified [10, 17].

Malignant struma ovarii can be diagnosed by the same histological guidelines as thyroid carcinoma. For example, colloid-like content decrease or absence from follicular lumens, vascular invasion, and cellular atypia can be present in follicular carcinoma of the thyroid; true papillary architecture, cellular atypia, nuclear grooves, and ground-glass can be present in papillary carcinoma. Psammoma body is useful to the diagnosis of malignant struma ovarii [3]. The benign struma ovarii shows a diploid DNA content, whereas the malignant struma ovarii has a hyperdiploid (aneuploid) DNA content [18]. The peritoneal and large omentum disseminated metastatic lesions may show benign-looking histological finding [18].

Clinically, absence knowledge of struma ovarii led to frequently an underdiagnosis, misdiagnosing as mucinous or serous cystadenoma, Sertoli-Leydig tumor, strumal carcinoid, and endometrioid adenocarcinoma, et al Immunohistochemical staining for thyroglobulin would facilitate the diagnosis [18, 19].

Due to mostly benign tumoral behavior, radical surgeries were the main mode of treatment. A total hysterectomy and bilateral salpingo-oophorectomy will be performed for menopause women. The patients with malignant struma ovarii would subject to radical surgery. Absence of uniform diagnostic criteria combined with the rarity of malignant struma ovarii contributes to various treatment modalities. It is commonly managed based on the experience with carcinoma of the thyroid. Posto-

perative adjuvant ^{131}I radiation therapy and chemotherapy may be performed [20]. A literature described one case of malignant struma ovarii that was diagnosed as stage IA and no further therapy was given [1]. Metastases and relapse rates are very uncommon. Metastases can occur only in 6% of all patients. The mode of spread fellows that of ovarian cancer, with the most common sites being adjacent pelvic structures including the contralateral ovary as well as more distant sites such as bone, liver brain, and lung. Sequential iodine scans and thyroglobulin measurements are recommended for follow-up and detection of recurrence [10]. Kempers described five cases of malignant struma treated with ^{131}I, with survival times of 8 to 20 years reported [3, 21]. The prognosis of struma ovarii is generally favorable.

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Disclosure of conflict of interest

None.

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