Malignant Clinical Course of Histologically Benign Ovarian Struma: case report and literature review

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Case Report

Keywords: Struma ovarii, peritoneal strumosis, highly differentiated follicular carcinoma arising in struma ovarii

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Malignant Clinical Course of Histologically Benign Ovarian Struma: case report and literature review

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Abstract

Background: Struma ovarii is a variant of monodermal teratoma, consisting of morphologically benign, atypical, or frankly malignant thyroid tissue. Morphologic features may or may not correlate with biologic behavior. Albeit this case report is not unique, ovarian tumor developed with peritoneal dissemination and bone metastasis, which is highly unlikely clinical complication. Additionally, we summarized previously cases of struma ovarii with an emphasis on correlation between morphological appearances, clinical course and providing treatment.

Case presentation: We present the 38-year-old patient who was hospitalized for ovarian tumor. The diagnostic laparoscopy revealed lesions of peritoneum, sigmoid serosa and omentum and left ovarian mass. We diagnosed left ovarian mature teratoma without struma tissue and metastatic lesions with struma morphology which can be related to her history of left ovarian struma in 2016. Taking into account the metastatic lesions revealed in 2020, the tumor removed in 2016 was assessed as highly differentiated follicular carcinoma arising in struma ovarii.

Conclusions: Prediction of biologic behavior of struma ovarii is still to be to diagnostic challenge, therefore multidisciplinary approach including clinical and laboratory findings, radiologic details and histopathological features is required. Providing additional data, the present case report contributes to expending the knowledge of these peculiar neoplasms.

Key words: Struma ovarii, peritoneal strumosis, highly differentiated follicular carcinoma arising in struma ovarii.

Introduction

Struma ovarii is a monodermal ovarian teratoma composed predominantly of thyroid tissue, a rare neoplasm comprising 1% of all ovarian tumors and 3% cases of ovarian teratomas (1–3). The tumor is usually an incidental finding of a pelvic mass with or without abdominal pain. Uncommon clinical manifestations may include the following: hyperthyroidism, dropsy and Meigs' syndrome (1). Emerging evidence indicates that histological features and growth patterns of struma ovarii seem no to correlate with biological behavior. For instance, morphologically benign struma ovarii may be associated with extraovarian spreading, known as peritoneal strumosis. Peritoneal strumosis is an infrequent condition, where both peritoneal implants and primary ovarian tumor are morphologically bland (4,5). The phenomenon of extraovarian spreading is peculiar due to several reasons. Firstly, the mechanisms of dissemination are not well understood, albeit accumulating data suggests the molecular alterations occurring in benign peritoneal strumosis comprise *ALK, EGFR* and *BRAF* mutations may contribute to spread (6,7). Secondly, the treatment approaches are not standardized, and currently may include various doses of radioactive ablation with I-131 and thyroidectomy (4,8,9). Thirdly, the differential diagnosis includes secondary metastatic involvement by an adenocarcinoma, neuroendocrine carcinoma, follicular thyroid carcinoma etc. (10,11).

We report a clinical case of morphologically “benign” struma ovarii that subsequently progressed with development of peritoneal deposits and a remote osseous metastatic involvement following 4 years after struma ovarii resection.

Case report

A 38-year old woman with remote history of ovarian teratoma was admitted to gynecological surgery department due to ovarian tumor recurrence. She had been operated 3 times previously: in 1999 due to mature teratoma of the right ovary (right-side salpingo-oophorectomy); in 2006 due to mature teratoma of the left ovary (ovarian cystectomy); and in 2016 during pregnancy due to proliferative struma of the left ovary (completion oophorectomy during caesarian section). The mature teratomas resected in 1999 and 2006 consisted of ectodermal derivatives (squamous epithelium and other adnexal structures) and mesodermal derivate (mature cartilage).

<u>Clinical presentation.</u>

In May of 2020 the patient was examined due to lower back pain. MRI revealed a lesion involving the body of the L5 vertebrum measuring 6.2x3.4x2.7 cm, associated with a vertical fracture line, spinal canal narrowing, left neural foramen reduction and nerve root compression. Then A99mTc SestaMIBI whole body scan was performed. It demonstrated bone tissue remodeling in the lumbar column but did not reveal any osteoblastic lesions. Core biopsy showed morphologically bland thyroid

tissue (Fig 1) and percutaneous image-guided vertebroplasty was done due to pathologic fracture L5 risk and severe back pain.

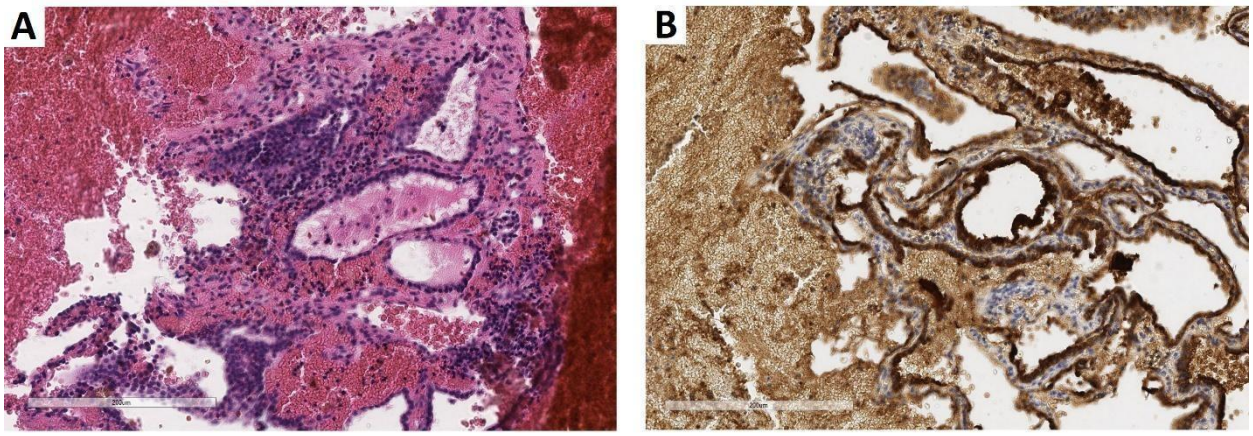

Figure 1. Core biopsy of the lumbar column. A. Hematoxylin and eosin stain, B. Thyroglobulin stain, x 200

PET-CT was performed for TNM classification, revealing an osteolytic lesion in L5 vertebral body, as well as clearly outlined left ovarian mass sized 3.0x2.2 cm with nonhomogeneous density and fat, highly suggestive of mature teratoma (Fig. 2).

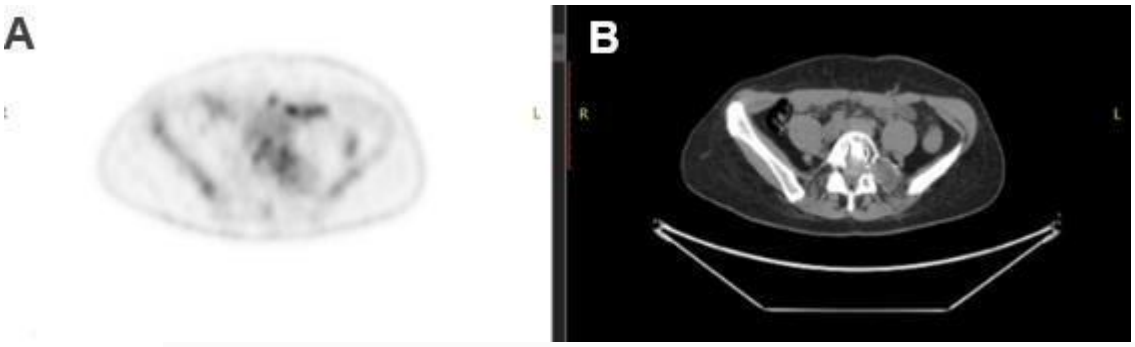

Figure 2. A. PET image in transverse plane, confirming abnormal FDG uptake within the metastatic lesion. B. CT image at the same level.

Taking into account the morphology of lumbar column metastasis thyroid gland USD was performed to exclude thyroid gland pathology. It revealed a small nodule, however fine-needle aspiration was benign (Bethesda diagnostic category II).

Given the patient's past medical history, a metastasis from ovarian neoplasm was suspected and the patient was admitted to surgery department of *National medical center for obstetrics, gynecology and perinatology named after V.I. Kulakov* in September of 2020.

For preoperative preparation the pelvic USD was done. The ultrasound scan demonstrated hyperechoic mass involving left ovary with the solid tumor sized 3.5 x 3.0 x 3.4 cm with increased echogenicity and clear smooth contour, without vascularization zones. We

compared the current USD scan with previous USD scan (2016). The latter demonstrated solid and cystic tumor with heterogeneous solid component, increased echogenicity and vascularization zones at the periphery, 7.5 x 5.0 x 3.5 cm in diameter.

Subsequent laparoscopy revealed ovarian mass, solid implants involving the serosa of greater omentum and sigmoid colon (Fig. 3). Laparoscopic left oophorectomy, peritoneal biopsy, omentectomy, and excision of sigmoid serosal lesions were performed.

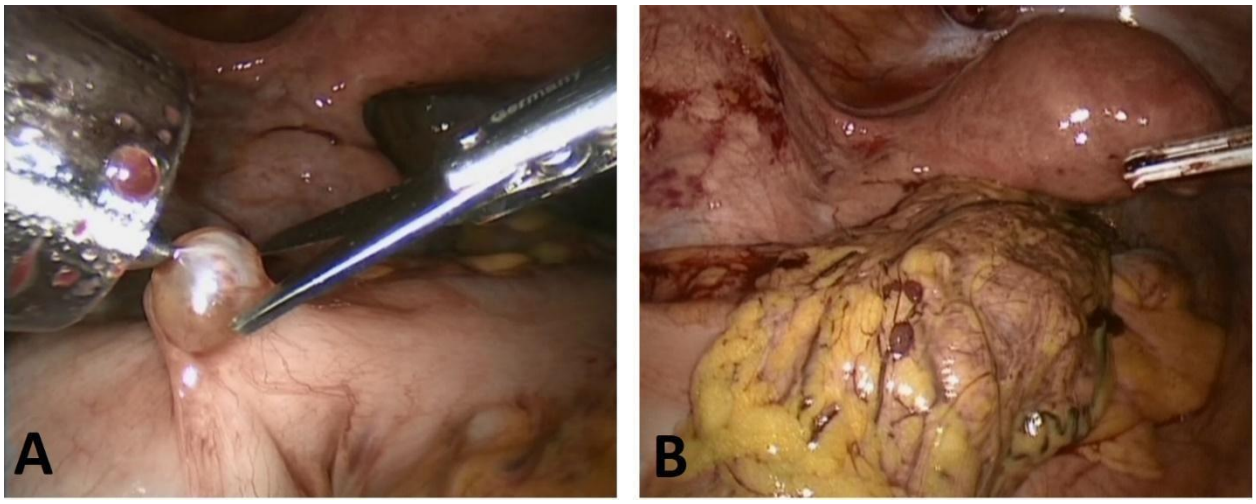

Figure 3. Macroscopic finding at laparoscopic surgery. Solid nodules were identified in the surface of the sigmoid colon (A) and (B) omentum

Pathologic evaluation.

Macroscopically, the specimen comprised an ovarian solid and cystic tumor measuring 3.5x2.0x1.0 cm, filled with hair shafts, fat tissue and mature cartilage, as well as four peritoneal implants from omentum and sigmoid serosa were submitted, ranging in size from 0.3-1.0 cm in diameter. Microscopically, the left ovarian tumor comprised mature elements (keratinized multilayer squamous epithelium, cutaneous adnexal structures, respiratory epithelium, fibroadipose tissue, mature cartilage, and glia). Peritoneal implants demonstrated follicles of various sizes composed of thyroid follicular cells devoid of histological features of papillary carcinoma (irregular contours, microcalcifications, loss of polarity, overlapping nuclei, nuclear grooves and pseudoinclusions etc.). Mild nuclear atypia and small-sized follicles were noted. Histologically, the implants resembled a benign thyroid follicular lesion rather than non-neoplastic thyroid tissue. These tumors were compared with the original ovarian struma operated in 2016. The slides were retrieved from the histological archive and scrutinized. The histological features of the primary struma ovarii and peritoneal metastases were identical. The lesional cells in the primary tumor as well as metastases were diffusely positive for TTF-1, PAX 8 и CK7, while negative for chromogranin, synaptophysin, inhibin-alpha, and calretinin. Ki-67 labeling index is

below 5% (Fig. 4). So, we demonstrated that the expression of investigated tissue markers was identical in these samples .

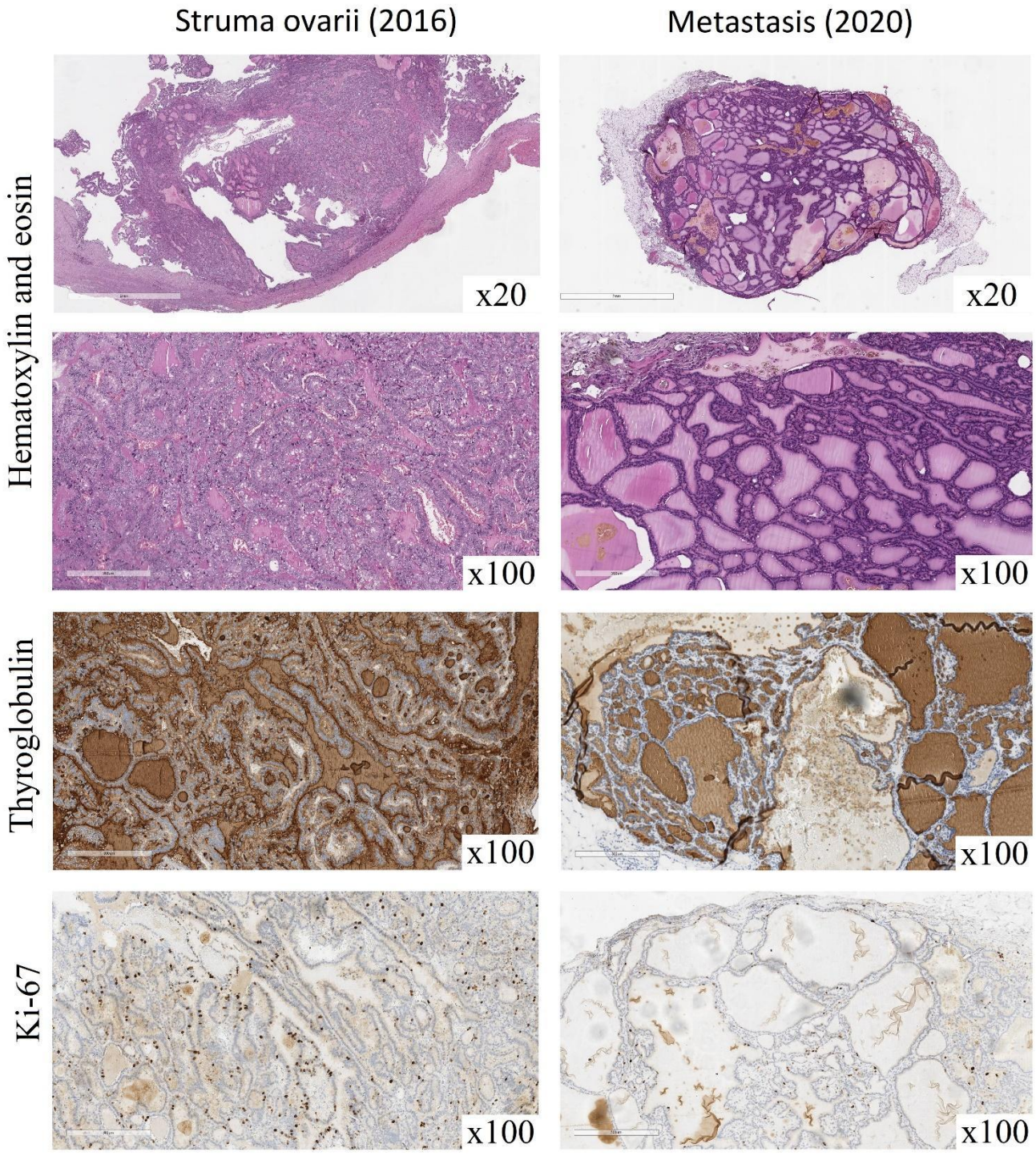

Figure 4. Morphology and immunohistochemistry of ovarian tumor and peritoneal deposits.

The differential diagnosis included strumal carcinoid, ovarian clear cell carcinoma, sex cord stromal tumors, and metastasis of thyroid gland tumor. Strumal carcinoid was ruled out due to negative chromogranin and synaptophysin, clear cell carcinoma was excluded due to immunoexpression of TTF-1, sex cord tumors were eliminated due to absence of expression of inhibin

A and calretinin negative stain, while thyroid gland tumor metastasis was rejected due to normal fine-needle aspiration cytology and normal thyroid-related hormones values. No *BRAF* mutations in ovarian struma or metastatic lesions were detected. Consequently, we can suppose that there is not molecular evolution between the primary ovarian struma and the metastatic lesions.

Discussion

Struma ovarii is the most common type of mature monodermal teratoma. The entity is of considerable interest because of its unique features. Foremost, histological appearance does not accurately correlate with biological behavior. Somewhat paradoxically, morphological features that characterized malignant potential for thyroid gland neoplasms cannot be extrapolated to struma ovarii in terms of prediction of extraovarian dissemination. Struma ovarii without any evidence of architectural or cytologic atypia could metastasize both to abdominal cavity and beyond (12,13). We present a case of recurrent struma ovarii with development of peritoneal and extraperitoneal spread following 4 years after the initial surgery. The resected tumor was devoid of histological features of malignancy. The peritoneal deposits were found both in omentum and on sigmoid serosa, histologically resembling a benign thyroid follicular lesion. Furthermore, an osteolytic metastasis involving L5 vertebral body reveled similar morphology. Currently, the terminology of morphologically benign struma ovarii with hematogenic, lymphogenic and peritoneal dissemination remains controversial. The term metastatic MSO (malignant struma ovarii) does not fit the benign or low-grade histologic appearances of the thyroid tissue in the anatomic sites of the tumor dissemination. Some authors used the term strumosis for a long time (4,14,15), whereas others suggested the term of "struma ovarii with extraovarian dissemination" (2). The most recent WHO classification of ovarian tumors the term of highly differentiated follicular carcinoma of ovarian origin (HDFCO)/highly differentiated follicular carcinoma arising in struma ovarii was coined as more appropriate for describing extraovarian spreading, so the International Classification of Diseases for Oncology (ICD-O) code is only presented for benign and malignant struma ovarii (16). It may seem feasible to use ICD-O code 1 to reflect the difficulty to accurately predict the biologic behavior of struma ovarii (17). Although it is exteremely difficult to suppose the further clinical course at the moment of struma original diagnosis it is very important to make frozen sections. M. R. Quddus et al. shown that it helps to improve the diagnostic accuracy when compared with gross examination, to differ ovarian struma from other malignant and benign ovarian tumors and to provide the important information to the surgeon in the operating room (35).

Due to the rarity of struma ovarii, the optimal management approaches and guidelines are not well-established nor standardized. Putative initial treatment is resection of the primary tumor,

supplementing with thyroidectomy and radioactive ablation with I-131 (8,9,18) in order to exclude metastatic thyroid gland malignancy, target the radioactive iodine to metastatic foci and to facilitate monitoring of thyroglobulin levels after surgery. However, it is rather difficult to accurately evaluate the benefits of the putative approach due to the rarity of the disease and, consequently, insufficient data on long term follow up. Primary hyperthyroidism in some cases may occur simultaneously with struma ovarii (19), providing additional diagnostic challenge in determining the cause of hyperthyroidism in such patients. Moreover, some thyroid gland carcinoma coincides with struma ovarii in the presence of circulating thyroid-stimulating hormone receptor antibodies (TSHR-Ab) (20,21). In the presented case a small thyroid nodule was detected, however, fine needle aspiration cytology was negative for neoplasia. Taking into account the FNA findings, as well as the patient's refusal of total thyroidectomy, the decision was made on "wait-and-see" approach, including delayed radioiodine therapy. The effectiveness of the approach will be determined over some time in this case, but it seems necessary to develop alternative management protocols due to certain disadvantages of lifelong hormone replacement therapy. Some of the previously reported cases, their features and outcomes are summarized in table 1. They demonstrated that benign strumas can have malignant clinical course and malignant strumas can show long progression-free survival (e.g. Garg K. et al. and Marti J.M. et al. described malignant strumas with no recurrence [13,26]; Akahira J. et al and .A.I. Karseladze et al. reported histologically benign strumas with multiple metastases [5,14]). In addition, morphology and clinical course did not correlate with patients' age (median age varied from 41 to 46 years).The localization of the metastases was different and also did not correlate with morphological features. Salpingoovarioectomy, thyroidectomy and hysterectomy were the most common treatment. Although progression-free survival did not depend on the treatment approach.

Conclusion

Despite histologically bland appearance of tumor at the primary site, minority of struma ovarii tumors are capable of extraovarian spread (peritoneal implants, distant metastasis). Due to this reason, the last WHO edition recommends the term of "highly differentiated follicular carcinoma arising in struma ovarii. The potential of late recurrences and extraovarian spread requires long-term follow-up. Treatment protocols have not been established, but radioiodine therapy, oophorectomy, and thyroidectomy remain as the most reasonable approach. The notorious challenge to predict the biologic behavior necessitates multidisciplinary approach in management of struma ovarii, with the meticulous correlation of clinical findings, laboratory data, radiologic details, and histopathological features.

List of Abbreviations

99mTc - Technetium 99m

FNA – Fine-needle aspiration

HDFCO -Highly differentiated follicular carcinoma of ovarian origin

I-131 – Iodine 131

ICD-O - International Classification of Diseases for Oncology

MRI – Magnetic resonance imaging

MSO - Malignant struma ovarii

PET-CT- Positron emission tomography–computed tomography

TSHR-Ab - Thyroid-stimulating hormone receptor antibodies

Declarations

Ethics approval and consent to participate:

Not applicable

Consent for publication:

The patient gave consent for publication.

Availability of data and materials:

All the data regarding the findings are available within the manuscript.

Competing interests:

The author(s) declared no conflicts of interest with respect to the authorship and/or publication of this article.

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Authors' contributions:

AA, AM and AT carried out the histochemical explorations; SM and JL participated in the USD, surgery and the design of the study; AV, AM, EK, VK and LA conceived the study and have been involved in the literature search. EK drafted the manuscript. All authors read and approved the final manuscript.

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Table 1. Clinical cases of ovarian strumas with clinical course and morphologic features.

Authors	Cases	Age	benign	Atypical	Malignant	Metastasis	Treatment	Follow up
Wei S. et al.(22)	96	median 46	80	0	16 (10-PTC, 1-	liver, cul-de-sac, fallopian tube, urinary bladder, pelvic wall	-TR -LT4	from 1 month to 20 years
Shaco-Levy R. et al , (2)	86	median 41	60	0	26	ovarian serosa, extraovarian spread	-TR -RAI	from 5 years to 20 years
Shaco-Levy R. et al. (23)	26	median 41	0	0	26	ovarian serosa, extraovarian spread (n=17), including pelvis, omentum, peritoneum, liver, lung, and bones	-SO with or without HY -RAI -chemotherapy (n=5)	from 1.5 to 33 years
Devaney K. et al (24)	54	mean 44	0	41	13	Peritoneal implants	-SO with or without HY	from 2 to 18 years
Wang Y. et al. (25)	68	mean 42	64	0	4	no recurrence	-TR - SO with or without HY -THY/RAI (n=2)	from 6 months to 20 years
Marti J.M. et al.(26)	57	median 44	0	0	57	no recurrence	- SO with or without HY -THY/RAI	from 6 months to 25 years
Garg K. et al (13)	10	median 41.5	0	0	10	Uterine serosa, pelvic sidewall, cul-de-sac, diaphragm, omentum and liver	-TR - SO with or without HY -THY/RAI	from 1 to 14 years
Muallem M.Z. et al. (27)	1	38	1	-	-	the para-colon gutter, left diaphragm, liver, spleen, gall bladder, omentum, ileocecal region, the mesentery of the appendix	-Right ovarian cystectomy, -THY/RAI	36 months
R.Ranade et al. (28)	1	55	1	-	-	liver, pelvic region and recurrence of bilateral adnexal masses.	-SO with HY -THY/RAI	3 months

Authors	Cases	Age	Benign	Atypical	Malignant	Metastasis	Treatment	Follow up
Hwua D.-W. et al (29)	1	28	1	-	-	bilateral ovarian tumors, metastases in the liver and peritoneal space	-SO with HY -THY/RAI	4 months
Akahira J. et al (5)	1	64	1	-	-	tumor tissue of the pelvic cavity including in the uterus, rectum and mesentery	-TR	17 months
A.I. Karseladze et al. (14)	1	49	1	-	-	contrlateral ovary, omentum	-SO with HY -3 consecutive cycles of polychemotherapy	36 months
McKayla J, et al. (30)	1	32	1	-	-	anterior and posterior peritoneal reflections of the uterus without evidence of malignancy	wait-and-see attitude	36 months
Sun-Ju O. et al (31)	1	60	1	-	-	12 level of the spine	-TR -THY+ spondylectomy/ (RAI)	not specified
R. Prasad et al. (32)	1	yearly forties	1	-	-	the right hemidiaphragm, adherent to the adjacent segment 8 of the liver, adjacent to the right adrenal gland, overlying the right perinephric tissue and on the porta hepatis	TR	96 months
Zekri J. et al. (33)	1	26	1	-	-	multiple pulmonary nodules	THY/RAI -	60 months after the initial dose of iodine therapy the mts appeared. (treated with bifrontal craniotomy)
Kobayashi K. et al (34)	1	39	1	-	-	osteolysis at the Th7 level	external beam radiotherapy at a dose of 37.5 Gy for the spinal lesion	9 months

*PTC- papillary thyroid carcinoma, HDFCO - highly differentiated follicular carcinoma of ovarian origin, SC- strumal carcinoid, TR- Tumor resection, LT4 – levothyroxine, THY/RAI - thyroidectomy/radioactive iodine, SO – salpingoovarioectomy, HY-hysterectomy

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