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# Hashimoto thyroiditis onset after laparoscopic removal of struma ovarii: an overview to unravel a rare and intriguing finding

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**Summary**

Struma ovarii is an uncommon type of ovarian tumor derived by germinal cells, characterized by the predominance of thyroid tissue (>50%); 90-95% of these formations are benign and mainly affect the left ovary, while in 6% of the cases struma ovarii is bilateral. The malignant transformation is a rare condition that often occurs after 50 years. In most instances, diagnosis of malignant struma ovarii is made postoperatively during histological analysis. This tumor appears to derive by one germinal cell through loss of heterozygosity of the androgen receptor gene and of the X chromosome. Clinical symptoms comprise abdominopelvic mass, lower abdominal pain, abnormal vaginal bleeding, and ascites (the occurrence of this condition has been observed in one-third of the cases). The patients with struma ovarii generally do not manifest symptoms related to thyroid hyperfunction, reported only in 8% of the cases, and due to hyperstimulation of the thyroid by auto-antibodies. Thyroid tissue of the struma ovarii, often embedded in a teratoma, may be papillary, follicular or with mixed pattern and it can include elements of mucinous cystoadenomas, Brenner's tumor or carcinoid or melanomas cells. Here the authors report their experience with an unusual case of Hashimoto thyroiditis onset after laparoscopic removal of struma ovarii.

*Key words:* Struma ovarii; Ovarian tumor; Laparoscopy; Hashimoto thyroiditis.

## Introduction

*Definition and epidemiology*

Struma ovarii is an uncommon type of ovarian tumor derived by germinal cells (mature teratoma), characterized by the presence of thyroid tissue for more than 50% of the overall mass [1-5]. It uncommonly occurs in pre-pubertal girls and the peak of incidence is the fifth decade [6]. The first Authors who described struma ovarii were Von Kalden in 1985 and Gottschalk in 1899 [7]. It comprises 1% of all ovarian tumors and 2.7 % of all dermoid tumors [8]. Ninety to 95% of these formations are benign [9] and mainly affect the left ovary, while in 6% of cases it is bilateral[10]. Sometimes, thyroid tissue is organized in small foci on the peritoneal surface: this particular and rare condition is defined as "strumosi" [8, 11-13]. The malignant transformation is a rare condition that often occurs after 50 years [10], and causes metastasis in 5% of cases [14]. In most instances, diagnosis of malignant struma ovarii is made postoperatively during histological analysis [15]. The etiology of this tumor is still not clear. Ciccarelli *et al.* [16] have shown loss of heterozygosis (LOH) for the androgen receptor and on X chromosome (LOH on Xp22.1-Xq21.32), suggesting the monoclonality of this tumor. Furthermore, they have identified multiple loss of region in chromosomes 4, 7, 10, 13, 14, 16, and X, but they could detect no chromosomal anomalies by using comparative genomic hybridization (CGH). There are useful genetic tests to address the diagnosis of malignant struma ovarii:

1) immunohistochemical staining of Hector Battifora mesothelial-1 (HBME-1) cells and Galactin 3, often positive in papillary thyroid carcinoma [17, 18];
2) BRAF mutation (v-raf murine sarcoma viral oncogene homolog B1) including V600E, K601E, and TV599-600M variants, found in two-thirds of malignant struma ovarii with papillary histology [19, 20];
3) REarranged during transfection (RET) rearrangements, found in 70% of follicular variant papillary thyroid cancer [20, 21];
4) RAt sarcoma (RAS) mutation;
5) Neurotrophic tyrosine kinase receptor 1 (NTRK1) mutation [22, 23];
6) Cytokeratin 19 expression [21].

*Clinical characteristics and diagnosis*

Benign struma ovarii's symptoms and signs comprise palpable pelvic/abdominal mass, pelvic/abdominal pain, abnormal vaginal bleeding, and ascites (observed in one-third of cases), although most of the cases are totally asymptomatic [24-26]. As the benign counterpart, malignant struma ovarii are often asymptomatic: when symptomatic, the patient usually presents palpable abdominal mass (45%), pelvic pain (40%), menstrual irregularities (9%),

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hyperthyroid symptoms (8%), ascites (17%), and deep vein thrombosis (4%) [27, 28]. In laboratory tests it is not rare to find, both in benign and malign form, serum increased carbohydrate antigen (CA) 125 levels [29]. Clinical manifestations of hyperthyroidism occurs in 5% - 8% of patients [26, 30, 31], rarely with overt thyrotoxicosis [15]. Generally, this tumor is functionally inactive, and when hyperthyroidism occurs, it is due to the presence of thyroid-stimulating hormone receptor stimulating antibodies (TSHR-ab), which stimulate hormone production in the thyroid [6, 25]. Struma ovarii may be suspected also by radiologic imaging:

– Pelvic ultrasonography (especially performed by transvaginal approach) could identify adnexal mass characterizing the size, the location, the presence of solid areas, and relationships of contiguity. Savelli *et al.* [32] have shown that the most characteristic ultrasonographic feature is the presence of one or more "struma pearls", i.e. well circumscribed roundish areas of solid tissue with a smooth surface. However, as literature reports, the ultrasonographic pattern of struma ovarii are usually non-specific; it is possible to observe a multilocular cystic or solid adnexal mass [33, 34] and the presence of low resistance blood flow in the central portion of tumor and free fluid in the pelvis are frequent findings [35-37].
– Computerized tomography (CT) of pelvis could evidence a complex mass containing various size of cystic and solid components [34, 36]. After intravenous (i.v.) injection of contrast medium, the solid portion intensely enhance [34, 36], while most cysts contain non-enhancing fluid with Hounsfield values (HU) > 20 and calcifications [38].
– Magnetic resonance imaging (MRI) clearly shows a strong enhancement of the solid component in the tumor after i.v. injection of gadolinium- diethylenetriaminepentacetate (Gd-DTPA) [39], and also cyst with a low signal on T1-weighted images and a very low signal on T2-weighted are a typical findings in struma ovarii [33].
– I 131 scan is useful to evaluate active thyroid tissue when struma ovarii is suspected [16, 40].

Occasionally, struma ovarii is associated with Meigs' syndrome for the presence of ascites, pleural effusion, and serum increased CA 125 levels. In these cases, it is important to make a differential diagnosis with other malignant ovarian neoplasms [41-49]. Overt hypothyroidism rarely follows the resection of struma ovarii tumor [50], as well as it is uncommon to find evidence of concurrent autoimmune thyroiditis. The following has been reported: struma ovarii with patient's thyroid tests normal [51]; struma ovarii with the presence of antithyroid antibodies [52]; struma ovarii with severe postoperative hypothyroidism [53, 54]; struma ovarii with Hurtle cells, positive antithyroid antibodies, and normal thyroid function [55], and struma ovarii without Hurtle cells [56].

Literature describes rare cases of association of ovarian struma with toxic thyroid adenoma [16, 25] or Graves's disease [57]. Particularly, an interesting uncommon clinical case was reported that showed the coexistence of Graves's disease, papillary thyroid carcinoma incidentally found after thyroidectomy, and unilateral benign struma ovarii accompanied by ascites, pleural effusion, and elevated CA 125 levels, with the immunohistochemical identification of TSHR-ab that supported the functional struma ovarii tissue [58].

*Histologic findings and prognosis*

On gross examination, the struma is brown or green-brown, partly or entirely cystic, filled with gelatinous fluid [59]. Ninety-four percent of malignant struma ovarii is monolateral, commonly affect left ovary, and is macroscopically similar to the corresponding benign counterpart [60]. Thyroid tissue is the major component of the mass; it may be papillary, follicular or mixed pattern and it can include elements of mucinous cystoadenoma, Brenner tumor, carcinoid or melanoma. Birefringent crystals of calcium monohydrate are present in most cases. Immunohistochemical staining for thyroglobulin, triiodothyronine, thyroxine can confirm the diagnosis [61]. Malignancy is defined by histological features of tumor, including cellular atypia and hyperplasia, nuclear pleomorphism, high mitotic activity, microinvasion into surrounding vessels and/or ovarian capsule, and discovery of metastasis by imaging [62, 63]. Nevertheless, there is still controversy about the defying characteristics of a malignant struma ovarii by using the pathological criteria applied in diagnosing thyroid carcinoma [14, 21, 62]. As Bhansali *et al.* [40] revealed, in malignant struma ovarii histopathology, the presence of solid areas mixed with cysts without teratomatous elements. Final pathology review is diagnostic for this condition in 5-37% of cases [11]. Malignant form is classified into different categories by histology [28, 30, 64]: papillary type is the most common and identified by ground glass or overlapping nuclei; follicular variant of papillary carcinoma, which shares the same nuclear characteristics as the papillary type but has a follicular architecture; follicular carcinoma; "highly differented follicular carcinoma of ovarian origin" (HDFG) characterized by metastasis with innocuous histological appearance, resembling that of non-neoplastic thyroid [65]; undifferentiated anaplastic carcinoma, and medullary carcinoma.

In general, malignant struma ovarii appears to have good prognosis with low metastatic potential (5-6 % of the cases). Upon review of literature [56, 64], patients with follicular carcinoma have a survival rate of five years after diagnosis, those with papillary carcinoma eight years, and those with undifferentiated carcinoma 13 months, whereas, patients with HDFG seem to have a survival rate similar to the general population. Papillary and follicular carcinoma are the most frequent of malignancy to occur in ovarian struma, while other

forms occur only rarely. Typical follicular carcinoma is more aggressive than the somewhat more common papillary carcinoma, the HDFC is the least aggressive of these tumor types, while the undifferentiated carcinoma is the most aggressive. The most common metastatic sites reported include other pelvic structures as the contralateral ovary, or other sites as omentum, liver, lungs, bone, and brain [11]. While follicular cancer preferentially metastasizes to the lung, liver and brain, papillary carcinoma metastasizes to the organs of the abdominal cavity, lymph nodes, and rarely to the liver. Roth *et al.* [65] reported that in malignant struma ovarii bone metastases occur in 26% of patients with typical follicular carcinoma, in 17% of patients with HDFG, and in 4% of patients with papillary carcinoma. These tumors may metastasize up to ten years after initial surgery. In view of the long period between the initial diagnosis of malignant struma ovarii and the possibility of recurrence (typically within four years), as reported in the literature, it should be used for long term follow up to ten years [28].

*Treatment*

Therapy for benign struma ovarii is surgical resection. Due to rarity of malignant struma ovarii, there is a paucity of data in past literature regarding the optimal treatment modality for such patients. For women desiring further childbearing, unilateral salpingo-oophorectomy may be a feasible option in the absence of capsular invasion or distant metastasis [27]. Total abdominal hysterectomy and bilateral salpingo-oophorectomy should be performed in postmenopausal women or premenopausal women in which fertility is not desired. In any cases in which disease has spread outside the ovary, complete staging for ovarian cancer with pelvic washings, omentectomy, and pelvic and para-aortic lymph node dissection should be performed [40]. Adjuvant therapy consisting of total thyroidectomy and 131 ablation should only be considered in cases of residual and metastatic disease. In these cases, sequential serum thyroglobulin level measurement as follow-up every six to 12 months to detect recurrence has been recommended. Postoperative work-up should include serum thyroglobulin level and total body 131 scan to evaluate residual intra-abdominal disease in patients who have undergone total thyroidectomy. In malignant ovarian struma, iodine-131 ablation has been applied both as a therapeutic and preventive measure against local and distant recurrence [28]. This is supported by the evidence of 50% recurrence rate in those women who were treated with pelvic surgery only [27]. In these cases, medical therapy with synthetic levothyroxine appears to be appropriate in order to suppress the secretion of TSH and maintain inactive any residual cells [10, 50]. However, for patients with multiple metastatic lesion or those who do absorb radioiodine poorly, external beam radiation has been proposed. Chemotherapy and radiotherapy have been used for recurrent metastatic struma ovarii which does not concentrate radioiodine [10, 50].

## Case Report

*Patient's data and anamnesis*

The patient was a 67–year-old Caucasian female. Anthropometric parameters: weight 72 kg, height 154 cm (BMI: 30, first degree obesity). Familiarity for metabolic disease (her father had type 2 diabetes). First menstrual cycle when she was ten-years-old, followed by regular menstrual cycles for all characters. Parity 2012. Physiologic menopause at age 50. Personal history positive for tobacco use (ex-smoker of 20 cigarettes/day, suspended seven years ago). Remote pathological history: tonsillectomy, cholecystectomy, uterine curettage for abortion, rectal prolapse surgically treated, knee prothesis, surgical correction of carpal tunnel syndrome, essential hypertension, neuropathic pain, gastro-esophageal reflux, anxious depressive syndrome. Drug history: acetylsalicylic acid, Omeprazole, Pregabalin, Sotalol, Rosuvastatin, Venlafaxine, perindopril/indapamide, alprazolam, and felodipine. She presented herself to the current authors' observation for the incidental finding on pelvic ultrasound of right ovarian cyst. She, therefore, underwent preparation for laparoscopic surgery. Prior to surgery, she underwent routine blood tests and assay of tumor markers, chest x-ray, electrocardiogram (ECG), and pelvic ultrasound re-evaluation.

At the admission, the patient was informed in a comprehensive and complete way regarding her clinical condition and procedures that the authors were going to perform, and signed an informed consent to allow the data collection for research purposes (a subsequent formal approval by the Institutional Review Board was obtained before initiating the report). The following report is in accordance with the Helsinki Declaration, conforms with the Committee on Publication Ethics (COPE) guidelines (http://publicationethics.org/) and the CARE (Consensus-based Clinical Case Reporting) Statement [66], available through the EQUATOR (Enhancing the QUAlity and Transparency Of health Research) network (http://www.equator-network.org/).

*Preoperative tests*

The laboratory tests were all within normal range except for a slight increase of the enzyme lactate dehydrogenase (LDH), which was 682 U/L [normal value (n.v.) 152-460]. Chest X-ray and ECG were negative. Tumor markers were are all within normal range: alpha feto protein (AFP) was 1.6 U/L (n.v. 0-10), carcinoembryonic antigen (CEA) 1 ng/ml (n.v. <5), CA 15.3 13.8 U/ml (n.v. < 39,5), CA 19-9 6.7 U/ml (n.v. 0-37), CA 125 4.1 U/ml (n.v. 0-35). The transvaginal pelvic ultrasound (Figure 1 a-e) showed retroverted uterus in moderate flexion, nonhomogeneous echo pattern, widespread fibrosclerosis, and atrophic involution (longitudinal diameter: 58 mm; anteroposterior diameter: 62 mm; transverse diameter: 50 mm.). Endometrium presented finely uneven margins and greater echogenicity at the isthmus (Figure 1a). Normal vascularity at color Doppler sampling. Left ovary was 19.7 x 12.9 mm (Figure 1b) and right one 86.2 x 56.9 mm (Figure 1c). In particular, right ovary was occupied by multiple irregularly roundish formations: the greatest was 67.4 x 49.8 mm and presented transonic ecopattern and finely corpuscular aspect (Figure 1d). Other lesions in the right ovary showed complex structure, characterized by alternating hyperechoic and vacuolar anechoic areas (Figure 1e). No free fluid in Douglas.

*Gynecological examination, surgery, and histologic findings*

The preoperative gynecological examination evidenced external genitalia and vagina of primipara, regular uterine body, right ovary increased in volume, no appreciable left ovary, small cervix, and no atypical bleeding. Subsequently, the patient underwent laparoscopic surgery. During surgical procedure, the authors performed lysis of adhesion between the right ovary, the peritoneal wall and the bowel, and then bilateral salpingo-oophorectomy.

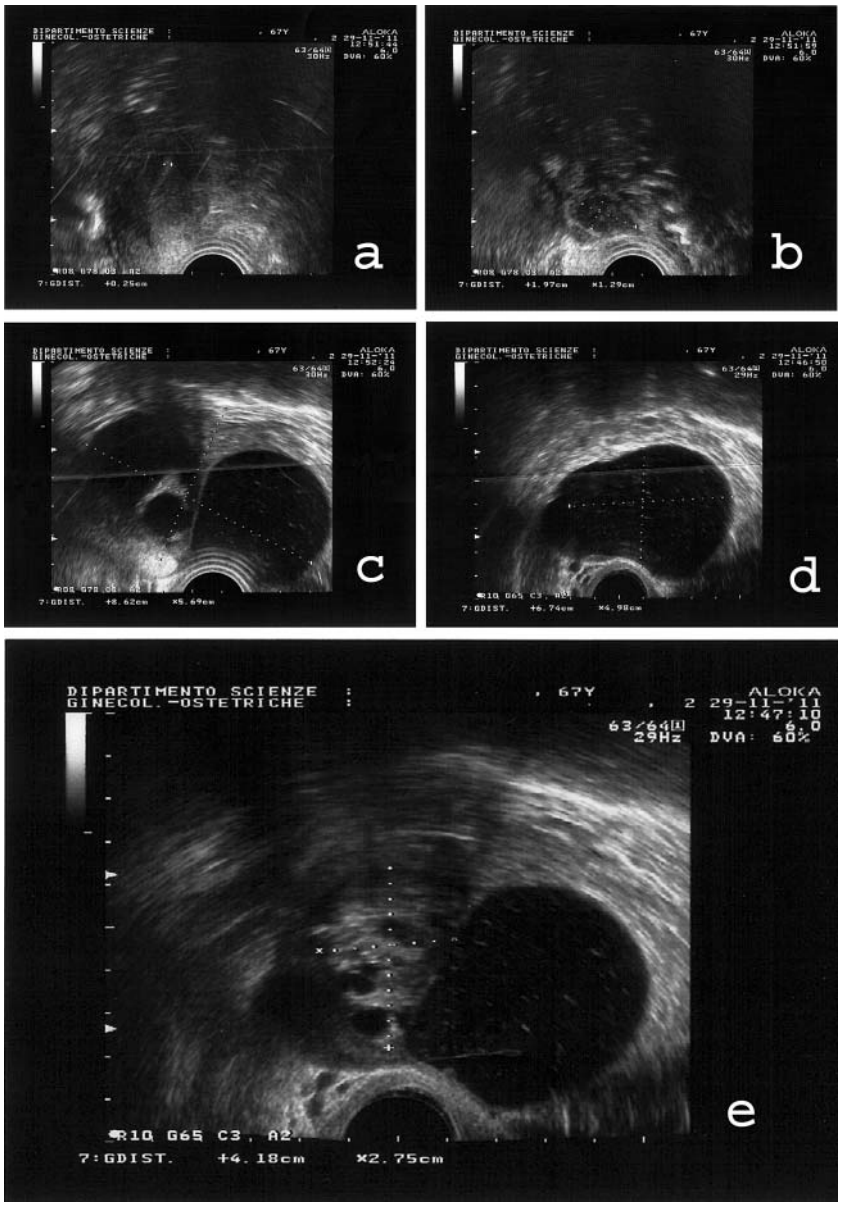


Figure 1. — Transvaginal ultrasonographic imaging. a) Left ovary: 19.7 x 12.9 mm. b) Endometrium. c) Right ovary: 86.2 x 56.9 mm. d) Major roundish irregular formation in the right ovary: 67.4 x 49.8 mm. e) Minor formations in the right ovary.

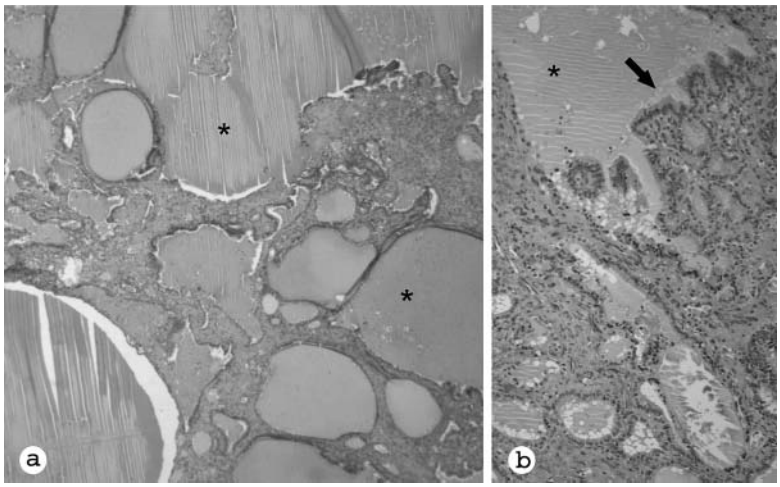


Figure 2. — Histologic examination. a) Thyroid tissue with dilated follicles (asterisk). Haematoxylin-Eosin staining. Original magnification x 40. b) Thyroid tissue with evident papillae (arrow) protruding into dilated follicles (asterisk). Haematoxylin- Eosin staining. Original magnification x 150.

Histologic examination of the left ovary showed diffuse fibrotecal hyperplasia and albicans bodies. Both fallopian tubes were sclero-atrophic. Right ovarian cyst showed the presence of a typical teratoma with prevalence of thyroid tissue with dilated follicles (Figure 2 a-b).

*Follow-up*

The patient had regular post-surgical course and was discharged home on the second day, in full health. Two and a half months after surgery, patient underwent morpho-functional thyroid evaluation. During this follow-up, she reported since the surgery, the onset of hyperthyroidism-like symptoms as flushing, profuse sweating, and tachycardia. The indices of thyroid function were normal: thyroid-stimulating hormone (TSH) was 2.010 mIU/ml (n.v. 0 0.27 - 4,2), free thyroxine (FT4) 14.04 pm/L (n.v. 12 - 22), but free triiodothyronine (FT3) was modestly increased (5.12 pg/ml; n.v. 2-4). The research of organ-specific antibodies was positive for anti-thyroglobulin (AbTG 245.5 IU/ml; n.v. 0-115), negative for anti-thyroid peroxidase (AbTPO < 5 IU/ml; n.v. 0 - 34) and anti-TSH receptor (Trab 0.10 IU/L; n.v. <1). The thyroid gland sonogram, postoperatively performed, was also normal. Transvaginal pelvic ultrasonography performed after three and a half months after surgery did not reveal any significant findings. The patient was therefore sent to the attention of the endocrinologist. Considering the clinical and laboratory findings, the authors diagnosed Hashimoto thyroiditis in euthyroidism, and patient is currently not taking any drug and undergoes periodic biochemical and instrumental checks.

## Discussion

Struma ovarii in an uncommon ovarian tumor is very rarely identified. Since the paucity of symptoms and signs, diagnosis occurs in most cases postoperatively after histologic analysis. As was evidenced from the present literature review, struma ovarii is difficult to diagnose on the basis of clinical manifestations or imaging studies; moreover, the presenting clinical features are widely nonspecific, and even if secondary conditions such as thyroid hyperfunction, ascites or hydrothorax are present, these usually regress spontaneously upon surgical removal of the primary tumor. Infrequently, it is possible to evidence clinical manifestations of hyperthyroidism or hypothyroidism associated or not with thyroid specific antibodies' positivity. In the present case, the authors report a case of coexistence of struma ovarii associated with post-surgical onset of thyroid autoimmune phenomenon (AbTG) and hyperthyroidism-like symptoms. Considering the clinical and laboratory data, they diagnosed Hashimoto thyroiditis. This scenario is similar to few others found in literature [54, 67-69].

In the present case, the correlation between excision of struma ovarii and post-surgical onset of Hashimoto thyroiditis remain to be elucidated: the authors could hypothesize that the laparoscopic removal of struma ovarii caused the activation of the antigen presenting cells (APCs), which processed and displayed thyroid-like antigens to T helper lymphocytes type 2 (Th2) and provoked the massive production of autoantibodies by B lymphocytes. Since the authors did not evidence any significant increase of T3 and T4, the cause of hyperthyroidism-like symptoms is still to be determined.

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