



Contents lists available at ScienceDirect

AAACE Clinical Case Reports

journal homepage: www.aaaceclinicalcasereports.com



Case Report

Metastatic Malignant Struma Ovarii and Graves' Disease: A Rare Occurrence



Brenda Chiang, MBBS, MRCP (UK), MMed (Int Med)^{1,*},
 Ray Lai, MBBS, MRCP (UK), MMed (Int Med)², Sorsiah Mansor, MB BCh BAO, FRCPath³,
 Brenda Lim, MBBS, MRCP (UK), MMed (Int Med)²

¹ Sengkang General Hospital, Department of Internal Medicine, Endocrinology Service, Sengkang E Way, Singapore

² Tan Tock Seng Hospital, Department of Endocrinology, Novena, Singapore

³ KK Women's and Children's Hospital, Department of Pathology and Laboratory Medicine, Kampong Java, Singapore

ARTICLE INFO

Article history:

Available online 6 January 2021

Key words:

Graves' disease
 struma ovarii
 metastatic follicular thyroid carcinoma

ABSTRACT

Objective: Malignant struma ovarii (SO) is a rare condition. Although there have been a few reported cases of malignant SO with coexisting Graves' disease (GD), the exact incidence of metastasis in these cases is not known. We report a rare case of metastatic malignant SO coexisting with GD.

Methods: Clinical examination, pelvic ultrasound, and histopathology of the resected tumor were performed, followed by iodine-131 (I-131) and whole body scan. Antithyroglobulin titers were post-operatively followed.

Results: A 43-year-old woman with a history of left ovarian cystic teratoma with SO resected 8 years ago and recently diagnosed GD presented with lower abdominal fullness. Pelvis ultrasound showed a 13.8-cm left adnexal mass, and she underwent left salpingo-oophorectomy. Histology confirmed an intra-ovarian thyroid tissue housing a highly differentiated follicular thyroid carcinoma, with metastatic peritoneal deposits. She underwent completion surgery and total thyroidectomy. Histology showed no evidence of intrathyroidal malignancy. I-131 therapy was administered, and posttherapeutic I-131 whole body scan revealed a remnant disease. She was started on suppressive levothyroxine therapy and remained clinically well at her 1-year follow-up with downtrending antithyroglobulin titers.

Conclusion: The coexistence of malignant SO and GD is very rare, and even rarer is the coexistence of metastatic malignant SO and GD. To the best of our knowledge, this is the first reported case of metastatic malignant SO in the setting of GD.

© 2021 AAACE. Published by Elsevier Inc. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

Introduction

Malignant struma ovarii (SO) with Graves' disease (GD) is rare. Although there have been reported cases of malignant SO with GD in the literature, the incidence of metastasis in such cases is not clear. Risk and prognostic factors are not well-defined, and the lack of consensus on optimal treatment can often render the management challenging. We present an interesting case of a metastatic,

highly differentiated follicular carcinoma of ovarian origin with coexisting GD and discuss therapeutic challenges faced and a possible mechanism of association.

Case Report

A 43-year-old woman presented to us with an enlarging left abdominal mass. She was recently diagnosed with GD 4 months prior to presentation. Free thyroxine level was 48.5 pmol/L (11.8–24.6), thyroid-stimulating hormone (TSH) level was <0.005 mIU/L (0.27–4.2), and thyroid-stimulating hormone receptor antibody (TRAb) level was 2.7 U/L (<1.8) at diagnosis, and she was started on carbimazole. Thyroid ultrasound revealed a heterogenous parenchymal echotexture and increased vascularity. Moreover, she had a significant history of a left benign ovarian teratoma with SO, which

Abbreviations: ATA, American Thyroid Association; GD, Graves' disease; I-131, iodine-131; SO, struma ovarii; TRAb, thyroid-stimulating hormone receptor antibody; TSH, thyroid-stimulating hormone.

* Address correspondence and reprint requests to Dr. Brenda Chiang, Department of Internal Medicine, Endocrinology Service, Sengkang General Hospital, 110 Sengkang E Way, Singapore 544886.

E-mail address: brenda.chiang@singhealth.com.sg (B. Chiang).

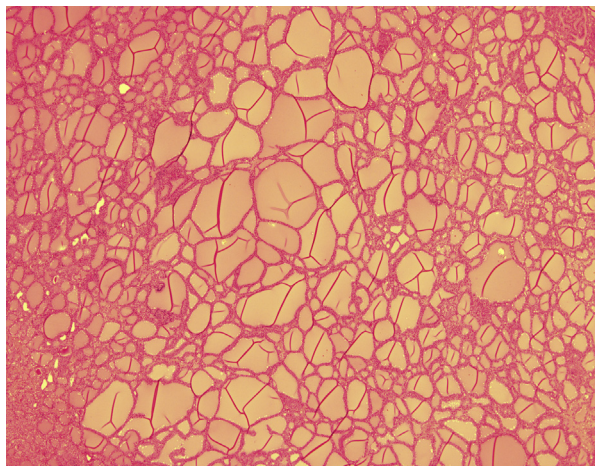


Fig. 1. Thyroid follicles of variable sizes containing luminal colloid in the left ovary.

had been resected 8 years ago. No record of thyrotoxicosis was noted at that time.

Pelvic ultrasound showed a heterogenous left adnexal mass, measuring $13.8 \times 11.6 \times 7.1$ cm. She was referred to a gynecologist and underwent left salpingo-oophorectomy. Intraoperative findings included a 12-cm left ovarian complex cyst, which was adherent to the bowel and mesentery, as well as scattered fibrous nodules on the bowel and peritoneal surfaces. Histology confirmed an intraovarian thyroid tissue housing a highly differentiated follicular thyroid carcinoma (Fig. 1). Although the ovarian tumor was not classical of a well-differentiated follicular carcinoma as no capsular or lymphovascular invasion was identified, the diagnosis of highly differentiated follicular carcinoma with metastatic peritoneal deposits was made in the presence of an extraovarian tissue resembling that of a nonneoplastic thyroid tissue (Fig. 2).

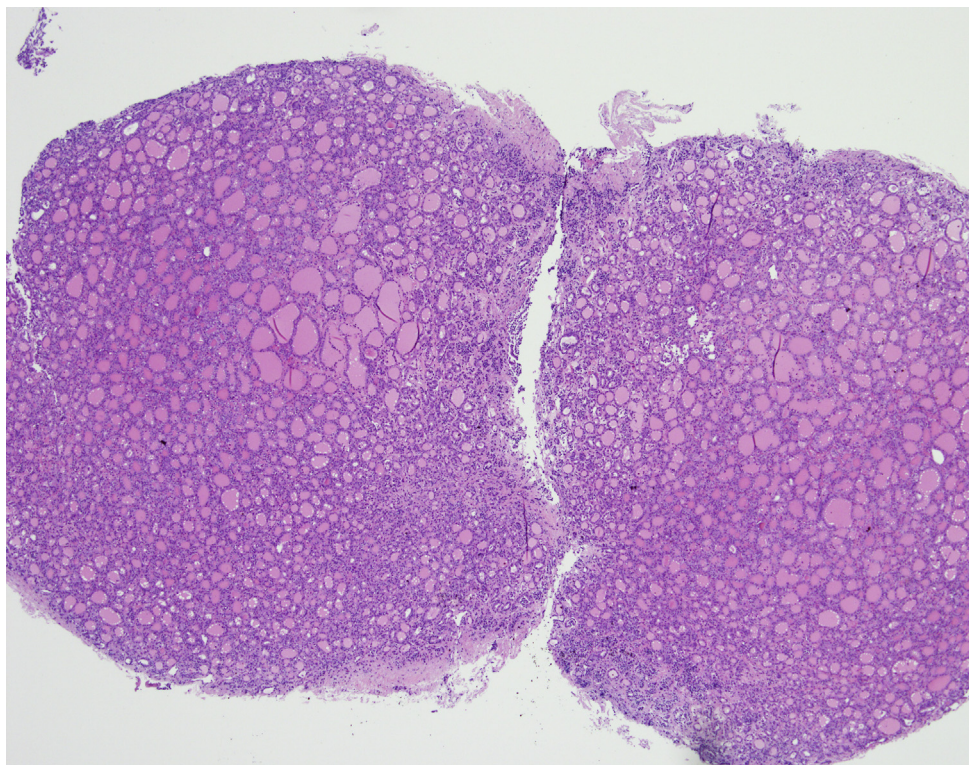


Fig. 2. Similar thyroid follicles in peritoneal nodule.

Computed tomography of the chest, abdomen, and pelvis did not show any evidence of distant metastasis. Completion hysterectomy, right salpingo-oophorectomy, omentectomy, and debulking surgery were performed. Intraoperatively, more metastatic foci were identified on the right fallopian tube, infundibulopelvic ligament, uterovaginal fold, bladder, rectal walls, and peritoneum.

Total thyroidectomy was performed to allow for iodine-131 (I-131) ablation therapy of the metastatic follicular carcinoma. It was histologically confirmed that no evidence of intrathyroidal malignancy was observed. Subsequently, 159.2 mCi of I-131 was administered. Posttreatment whole body scan revealed a remnant disease with multiple intraabdominal foci of uptake (Fig. 3).

She was started on TSH suppressive therapy (levothyroxine $2 \mu\text{g}/\text{kg}/\text{day}$) to target a TSH level of <0.1 mIU/L, as recommended by the guidelines from the American Thyroid Association (ATA) for differentiated thyroid cancer¹ for those with a high risk of disease recurrence and incomplete response to initial therapy.

At 1-year follow-up, the patient remains clinically well on suppressive levothyroxine therapy, with downtrending antithyroglobulin titers (Table). A repeat radioiodine scan is planned.

Discussion

We presented the case of a 43-year-old woman with coexisting GD and metastatic malignant SO. Interestingly, she had a prior history of benign SO, which was resected 8 years ago. She underwent complete staging surgery, total thyroidectomy, and adjuvant I-131 therapy. Antithyroglobulin titers, which were elevated on an account of concomitant autoimmune thyroid disease, were postoperatively followed to assess her biochemical response.

SO is a rare variant of ovarian teratoma that mainly contains thyroid tissue in more than 50% of the solid tumor, or as a tumor accompanying clinically evident hyperthyroidism owing to a

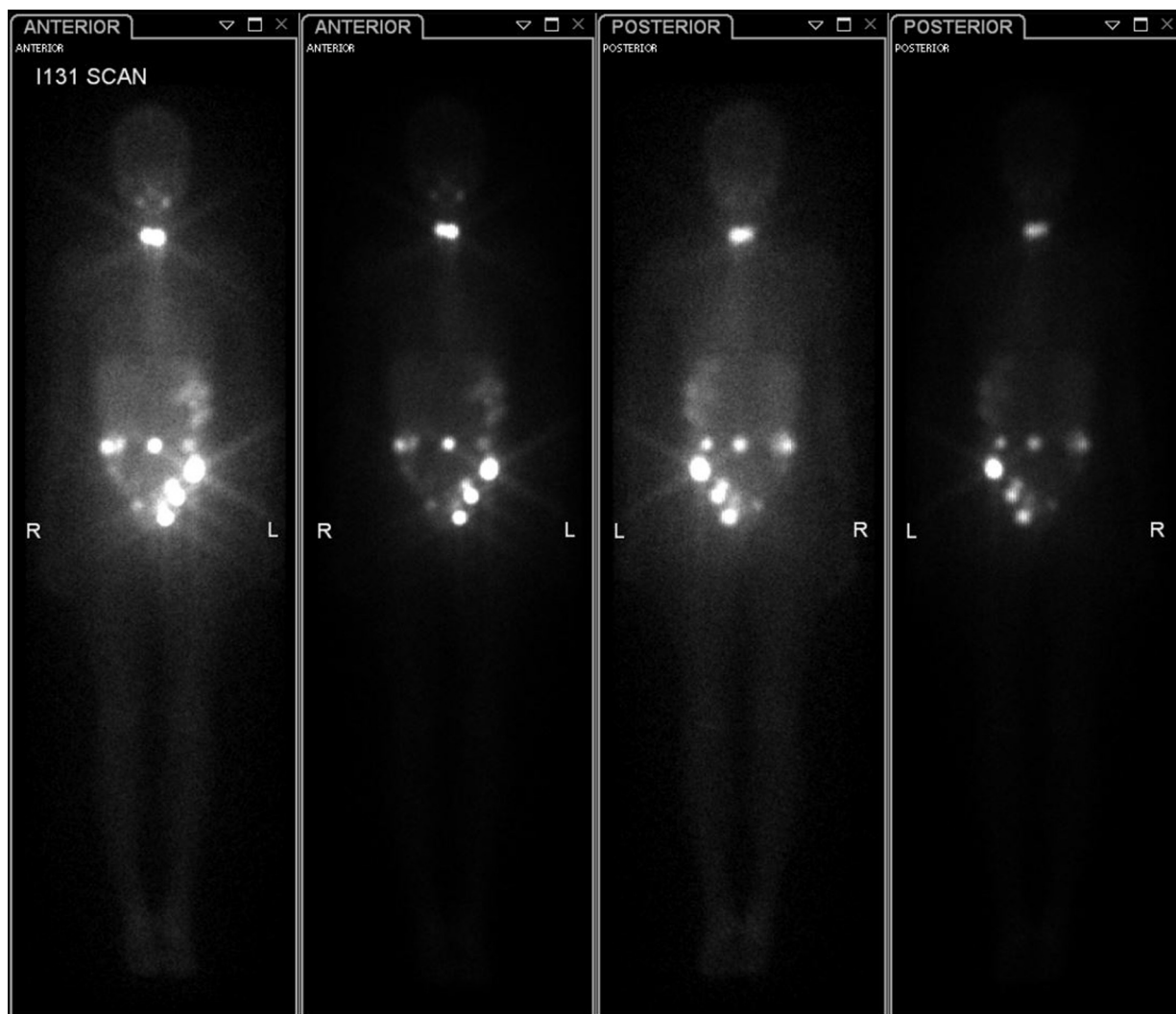


Fig. 3. The whole body scan with multiple intraabdominal foci of uptake.

Table
Trend of TG, Anti-TG, and Thyroid Function Tests

Test	Day 0 when RAI was administered	3 mo post RAI	6 mo post RAI	9 mo post RAI	15 mo post RAI	21 mo post RAI	Reference range (units)
Free T4 (pmol/L)	3.2	18.3	19.9	20.4	22.3	21.2	8.8–14.4
TSH (mIU/L)	120	0.196	0.014	0.018	0.078	0.056	0.65–3.7
TG (µg/L)	0.6	0.2	0.3	<0.17	0.2	0.3	2.0–70.0
Anti-TG (µ/mL)	477	409	232	145	98.4	87.1	0.0–60.0

Abbreviations: RAI = radioactive ablation; T4 = thyroxine; TG = thyroglobulin; TSH = thyroid-stimulating hormone.

significant production of thyroid hormone.² SO accounts for approximately 2% to 5% of ovarian teratomas and 0.5% to 1% of all ovarian tumors.³ SO frequently occurs during the fourth to fifth decades of life and is often asymptomatic, unilateral, and incidentally discovered.⁴ Patients may also present with a pelvic mass or abdominal pain. SO can undergo any of the pathologic changes that can be seen in the thyroid gland, including malignant transformation, wherein the 2 most common types are papillary carcinoma and follicular carcinoma.⁵

Of the 5% to 10% of SO that are malignant, only 5% to 6% metastasize beyond the ovary.^{3,6} Metastases from a malignant SO are commonly found in the peritoneum, bone, liver, omentum, and lungs.⁷ The spread of benign thyroid tissue beyond an SO was

previously believed to be benign “peritoneal strumosis,” although was later recognized to be an evidence of a low-grade malignant neoplasm; therefore, the term was changed to “highly differentiated thyroid follicular carcinoma of ovarian origin”.⁵ The incidence of coexisting GD and metastatic malignant SO is unclear owing to a lack of data, although is likely very low. To the best of our knowledge, this is the first reported case of metastatic malignant SO in the setting of GD.

In a case series and literature review of metastatic malignant SO, Li et al⁸ reported that 24% to 50% initially presented with a benign SO, and the time interval ranged from 2 months to 26 years. This adds to the challenge of a timely diagnosis and reinforced the need for regular follow-up even in benign SO.

It has been postulated that thyroid carcinoma occurs more frequently and more aggressively in the setting of coexisting GD. Patients with GD have an increased incidence of 17% to 33% of thyroid carcinoma compared with the general population.^{9,10} This may be because the stimulation of TSH receptors by TRAb promotes thyroid cancer growth, invasiveness, and angiogenesis by upregulating vascular endothelial growth factor, placental growth factor, and their receptors.¹¹ TRAb has also been shown to initiate cellular proliferation and prevent apoptosis by suppressing mitochondrial reactive oxygen species levels.¹² Interleukins 4 and 10, produced by infiltrating lymphocytes in patients with GD and concomitant thyroid cancer, may affect thyroid cancer biology and potentiate the role of other antiapoptotic factors, such as insulin-like growth factor, thereby resulting in an accumulation of mutations that eventually leads to a malignant transformation.¹³ These factors may have contributed to an increased risk of malignant transformation in SO in our patient.

Owing to the rarity of metastatic malignant SO, there is no consensus on the surgical and postoperative treatment of patients. Our management of this patient's metastatic SO was partly extrapolated from the 2015 ATA guidelines on the management of differentiated thyroid carcinoma.¹

The surgical approach can be individualized to the patient and disease profile. This might comprise conservative surgery, such as unilateral oophorectomy or cystectomy, in women who are concerned with fertility preservation and for lesions without gross metastasis or capsular invasion. Alternatively, a more aggressive approach, up to total abdominal hysterectomy with bilateral salpingo-oophorectomy and omentectomy, may be considered for postmenopausal women, for those who have completed their families, or in advanced diseases.¹⁴

The need for total thyroidectomy and radioactive ablation in cases of malignant SO has been debated. Various risk stratification models of malignant SO have been proposed to aid in management. Patients with high risk features, such as tumors >1 to 2 cm, extraovarian disease, or aggressive histologic features, should be considered for thyroidectomy and subsequent radioactive ablation therapy.^{15,16} Postthyroidectomy, serum thyroglobulin levels may be a valuable tumor marker to monitor tumor burden and recurrence.

Despite different management strategies, a recent study showed that patients with malignant SO have excellent disease-specific survival rates, whether or not metastases occurred.⁸ This was in agreement with previous reports of 89% to 94.3% 10-year survival rates for patients with malignant SO.^{17,18}

Conclusion

Metastatic malignant SO with coexisting GD is extremely rare. It is believed that TRAb and interleukin 4 may contribute to an increased risk of malignant transformation in GD. No consensus on

the treatment of metastatic malignant SO exists, and management can be extrapolated from principles laid out in the ATA guidelines on the management of differentiated thyroid carcinoma. Prognosis appears to be good with excellent survival rates.

Disclosure

The authors have no multiplicity of interest to disclose.

References

- Haugen BR, Alexander EK, Bible KC, et al. 2015 American Thyroid Association management guidelines for adult patients with thyroid nodules and differentiated thyroid cancer. *Thyroid*. 2016;26(1):1–33.
- Kempers RD, Dockerty MB, Hoffman DL, et al. Struma ovarii—ascitic, hyperthyroid, and asymptomatic syndromes. *Ann Intern Med*. 1970;72(6):883–893.
- Heintz AP, Odicino F, Maisonneuve P, et al. Carcinoma of the ovary. FIGO 26th annual report on the results of treatment in gynecological cancer. *Int J Gynaecol Obstet*. 2006;95(suppl 1):S161–S192.
- Mimura Y, Kishida M, Masuyama H, et al. Coexistence of Graves' disease and struma ovarii: a case report and literature review. *Endocr J*. 2001;48(2):255–260.
- Roth LM, Karseladze AI. Highly differentiated follicular carcinoma arising from struma ovarii: a report of 3 cases, a review of the literature, and a reassessment of so-called peritoneal strumosis. *Int J Gynecol Pathol*. 2008;27(2):213–222.
- Emge LA. Functional and growth characteristics of struma ovarii. *Am J Obstet Gynecol*. 1940;40(5):738–750.
- Leong A, Roche PJR, Paliouras M, Rochon L, Trifiro M, Tamilia M. Coexistence of malignant struma ovarii and cervical papillary thyroid carcinoma. *J Clin Endocrinol Metab*. 2013;98(12):4599–4605.
- Li S, Yang T, Li X, et al. FIGO stage IV and age over 55 years as prognostic predictors in patients with metastatic malignant struma ovarii. *Front Oncol*. 2020;10:1983.
- Boutzios G, Vasileiadis I, Zapanti E, et al. Higher incidence of tall cell variant of papillary thyroid carcinoma in Graves' disease. *Thyroid*. 2013;24(2):347–354.
- Weber KJ, Solorzano CC, Lee JK, Gaffud MJ, Prinz RA. Thyroidectomy remains an effective treatment option for Graves' disease. *Am J Surg*. 2006;191(3):400–405.
- Filetti S, Belfiore A, Amir SM, et al. The role of thyroid-stimulating antibodies of Graves' disease in differentiated thyroid cancer. *N Engl J Med*. 1988;318(12):753–759.
- Morshed SA, Ma R, Latif R, Davies TF. How one TSH receptor antibody induces thyrocyte proliferation while another induces apoptosis. *J Autoimmun*. 2013;47:17–24.
- Vella V, Mineo R, Frasca F, et al. Interleukin 4 stimulates papillary thyroid cancer cell survival: implications in patients with thyroid cancer and concomitant Graves' disease. *J Clin Endocrinol Metab*. 2004;89(6):2880–2889.
- Zhang X, Axiotis C. Thyroid-type carcinoma of struma ovarii. *Archives of Path & Lab Med*. 2010;134(5):786.
- Yassa L, Sadow P, Marqusee E. Malignant struma ovarii. *Nat Clin Pract Endocrinol Metab*. 2008;4(8):469–472.
- Jansenz EW, Van Doorn HC, Ewing PC, et al. Malignant struma ovarii: good response after thyroidectomy and 131-I ablation therapy. *Clin Med Oncol*. 2008;2:147–152.
- Goffredo P, Sawka AM, Pura J, Adam MA, Roman SA, Sosa JA. Malignant struma ovarii: a population-level analysis of a large series of 68 patients. *Thyroid*. 2015;25(2):211–215.
- Robboy SJ, Shaco-Levy R, Peng RY, et al. Malignant struma ovarii: an analysis of 88 cases, including 27 with extraovarian spread. *Int J Gynecol Pathol*. 2009;28(5):405–422.