Endocrinology, Diabetes & Metabolism CASE REPORTS

M L Gild and others | Malignant struma ovarii from FTC

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Malignant struma ovarii with a robust response to radioactive iodine

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Summary

Struma ovarii is a rare, usually benign ovarian tumour with malignancy occurring in <5% of cases. Metastases, particularly seeding to bone, are extremely rare. Presentation is variable but often features local pain and/or ascites and hyperthyroidism may occur. It is not established how to best treat and follow patients with extensive disease. Case reports of radioiodine (I^{131}) ablative therapy following thyroidectomy have shown reduced recurrence. We describe the case of a 33-year-old woman who presented with bone pain and was diagnosed with skeletal metastases with features of follicular thyroid carcinoma. However, thyroid pathology was benign. She recalled that 5 years prior, an ovarian teratoma was excised, classified at that time as a dermoid cyst. Retrospective review of this pathology confirmed struma ovarii without obvious malignant features. The patient was found to have widespread metastases to bone and viscera and her thyroglobulin was >3000 µg/L following recombinant TSH administration prior to her first dose of I^{131}. At 25 months following radioiodine treatment, she is in remission with an undetectable thyroglobulin and clear I^{131} surveillance scans. This case demonstrates an unusual presentation of malignant struma ovarii together with challenges of predicting metastatic disease, and demonstrates a successful radioiodine regimen inducing remission.

Learning points:

- Malignant transformation of struma ovarii (MSO) is extremely rare and even rarer are metastatic deposits in bone and viscera.
- MSO can be difficult to predict by initial ovarian pathology, analogous to the difficulty in some cases of differentiating between follicular thyroid adenoma and carcinoma.
- No consensus exists on the management for post operative treatment of MSO; however, in this case, three doses of 6Gbq radioiodine therapy over a short time period eliminated metastases to viscera and bone.
- Patients should continue to have TSH suppression for ~5 years.
- Monitoring thyroglobulin levels can predict recurrence.

Background

Struma ovarii is a monodermal teratoma comprised of >50% of thyroid tissue, found in <1% of ovarian tumours. Malignant transformation is rare, found in <5% of patients with struma ovarii (1). Papillary thyroid carcinoma (PTC) is the most common malignancy to occur in MSO (2). Follicular variant of PTC and follicular thyroid carcinoma (FTC) have also been described. Metastases are extremely uncommon.

Risk stratification of malignant struma ovarii (MSO) is comparable to differentiated thyroid cancer originating in the thyroid. Following surgical resection of the ovarian tumour, radioiodine treatment is recommended

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for those with MSO >4 cm; disease outside the ovary and aggressive histological features (3). Thyroidectomy is essential prior to radioactive iodine treatment. Thyroid remnant ablation renders thyroglobulin (in the absence of antibodies) a robust tumour marker. TSH suppression is also considered essential in these patients for at least 5 years similar to standard differentiated thyroid cancer guidelines.

The most common presentation of MSO involves pelvic mass symptoms such as ascites or pain (4). The case described is a unique presentation of this rare disease. It highlights how bone metastases can be the initial presentation of MSO arising from FTC and the importance of considering MSO following normal thyroid pathology. In FTC originating from the thyroid gland, bony metastases are uncommon and correlate with a poor prognosis (5). Of 26 cases of MSO reported in the literature associated with pathological features of follicular thyroid carcinoma, seven have described a bony metastasis. All but one had the MSO resected after the diagnosis of metastatic disease. To our knowledge, our case is the first to describe a retrospective diagnosis of MSO secondary to FTC.

Case presentation

A 33-year-old previously well woman presented with a 2-year history of a painful right shoulder initially diagnosed as a rotator cuff injury. Following more bone pain, notably at her sixth rib, she was investigated with serial MRIs that revealed lytic lesions which grew over several months. Concern about a primary bone tumour necessitated removal of the mass in the right scapula, and the pathology demonstrated metastatic FTC. Subsequent total thyroidectomy showed no evidence of malignancy. At 28, she had an ovarian cyst excised that was diagnosed at the time as a mature cystic teratoma. In light of the new diagnosis of metastatic FTC, the ovarian pathology was reviewed and revised to struma ovarii. She was subsequently treated with radioactive iodine (I^{131}). Stimulated thyroglobulin was initially 3010 µg/L. Extensive skeletal and soft tissue metastatic disease were apparent on the post I^{131} scan. Stimulated FDG-PET showed no uptake.

Investigation

Histological images of the ovarian cyst are shown in Fig. 1A. This confirmed the presence of 'struma ovarii' on the revised pathology report. The right scapula lesion demonstrating the FTC is shown in Fig. 1B and C. IHC was performed and both tissue samples were negative for $BRAF^{V600E}$, ALK and $NRAS^{Q61R}$.

Primary investigations that dictated treatment were the post dose I^{131} scans. These are shown in Fig. 2 together with the corresponding stimulated thyroglobulin.

Ongoing FDG-PET scans demonstrated no avidity in known areas of metastasis consistent with a well-differentiated malignancy.

Treatment

She underwent three cycles of radioactive iodine (I^{131}) over the course of 13 months. Each dose was 6 Gbq. Following the first dose of RAI, there was a mixed response to therapy with resolution at majority of the sites including deposits in her ribs and right ischium. There was stable disease along the thyroglossal duct and the right lateral wall of the orbit. Her stimulated thyroglobulin dropped three orders of magnitude (3 µg/L) (Fig. 2). She had two further doses and her thyroglobulin became undetectable (<0.1 µg/L).

Outcome and follow-up

Her final RAI post dose scan showed excellent metabolic response to therapy with resolution of uptake at almost all sites of metastatic disease apart from the right L3 pedicle, where there was mild residual uptake. No new sites of iodine-avid metastatic disease were demonstrated. Two years after her final dose, she had a recombinant TSH-stimulated whole body iodine scan that demonstrated no evidence of residual disease. She remains on replacement thyroxine with a suppressed TSH. She remains under

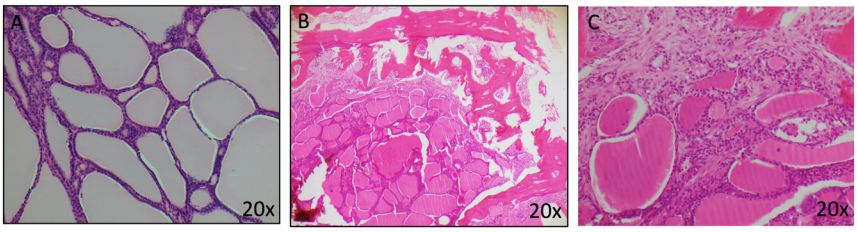

Figure 1
(A) H/E Struma ovarii identified in ovarian teratoma. (B) H/E Metastatic thyroid follicular carcinoma involving the right scapula. (C) H/E Scapula lesion demonstrating follicular thyroid carcinoma through follicles formed by uniform cells without features of papillary thyroid carcinoma.

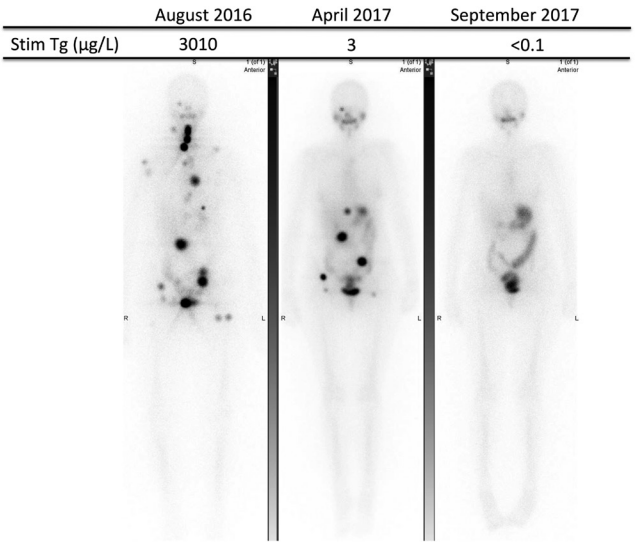

Figure 2
I^{131} post ablation scans and corresponding stimulated thyroglobulin levels over treatment time.

close surveillance with clinical review and thyroglobulin measurements

Discussion

The diagnosis of MSO can be challenging, and this case highlights a scenario where widespread metastatic disease could not be predicted. Even close retrospective analysis of the pathology could not describe any invasion or extraovarian extension predicting metastases. The pathology described the presence of struma ovarii which demonstrated no vascular space invasion or invasive growth; hence, the diagnosis of MSO was based solely on pathology of the bony metastases. This is a recognised challenge in patients who appear to have benign histology (6). Some data associate malignancy to the presence of $BRAF^{V600E}$ or RAS mutations (7), but these were absent in our case.

Preoperative diagnosis of MSO can be achieved with the presence of a raised thyroglobulin or concerning ultrasound appearance of the teratoma (7). In more classic cases than the one described, a similar and straightforward treatment strategy is employed (2). Fortunately, irrespective of whether the MSO is diagnosed with the ovary *in situ*, it appears that the prognosis is similar.

This case also highlights successful treatment of bone metastases from MSO using radioactive iodine. Despite widespread metastatic disease, it clearly remains differentiated, allowing for a promising prognosis. Literature review of FTC MSO cases shows that despite the lack of consensus, I^{131} treatment following thyroidectomy is favored. The majority of the cases required more than one dose and the range was 3–11.1 Gbq. Total abdominal hysterectomy with either unilateral or bilateral salpingo-oopherectomy was also performed in the majority of cases (1). Following these treatments most cases have good prognoses comparable to FTC originating in the thyroid (1, 3). In case reports of MSO originating from follicular variant PTC and presenting with bony metastases, a similar regimen with I^{131} has been successful (8).

Close follow-up of these patients should continue up to at least 10 years with regular thyroglobulin measurement (9). There are rare reports of metastases developing decades after the original struma ovarii was diagnosed, but even in these cases the outcome is favorable (10).

Declaration of interest
The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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Patient consent
Informed consent for the publication of clinical data and photographs has been obtained from the patient. Consent form is uploaded.

Author contribution statement
Dr Matti Gild wrote the case report. Dr Lauren Heath performed the literature review. Dr Julie Paik accessed and described the pathology. Associate Prof Clifton-Bligh reviewed the manuscript. Prof Bruce Robinson managed all care of the patient.

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