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CASE REPORT

Thyroid papillary cancer elements arising from struma ovarii with benign peritoneal strumosis: Utility of iodine-123 imaging in diagnostics and treatment planning

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Key Clinical Message: In this case of struma ovarii a right-sided ovarian mass contained features of papillary thyroid cancer. Diagnostic iodine-123 revealed multiple foci of extraovarian spread, likely as a manifestation of concomitant peritoneal strumosis. Unilateral oophorectomy, partial peritonectomy, and adjuvant iodine-131 treatment were performed for successful curative treatment.

Abstract: Struma ovarii is a rare form of mature teratoma defined by a predominance of thyroid tissue. Approximately 5% of all ovarian strumae exhibit malignant transformation. Due to their extreme rarity, there has been a lack of consensus concerning uniform diagnostic criteria. Appropriate, risk-stratified treatment strategies also remain widely unelaborated, based only on a small number of cases reported in the literature. We describe the case of a 35-year-old female, who presented after undergoing unilateral oophorectomy for a right-sided ovarian mass. Histological workup revealed a struma ovarii containing papillary thyroid cancer (PTC). Postoperative I-123 scintigraphy with single photon emission computed tomography (SPECT) detected multifocal extra-ovarian spread to the peritoneum, containing likely benign strumosis upon pathological examination. The subsequent treatment strategy involved an ablative concept including total thyroidectomy and subsequent I-131 radioiodine therapy. Throughout a 3-year follow-up, the patient has remained without recurrence with thyroglobulin levels ranging below detection limits. Surgical resection with adjuvant radioiodine therapy is a curative therapeutic strategy in cases of struma ovarii with thyroid-type carcinoma and peritoneal strumosis. Its benefits lay in avoiding more extensive surgery, potentially maintaining fertility, facilitating follow-up, and minimizing the risk of recurrence. Reliable criteria for risk stratification are needed to identify patients who are most likely to benefit from this treatment approach.

KEYWORDS

I-123, peritoneal strumosis, radioiodine therapy, SPECT, struma ovarii

1 | INTRODUCTION

Struma ovarii is a rare presentation of ectopic thyroid tissue first described by Boettlin in 1888 and subsequently characterized as a form of mature teratoma in the early 20th century by Ludwig Pick.[1] Thyroid tissue, to any extent, has been found present in up to 20% of all mature teratomas, but a predominant portion of at least 50% thyroid tissue is the defining criterion of struma ovarii.[2] In total, struma ovarii accounts for less than 3% of all ovarian teratomas.[3]

In analogy to its orthotopic counterpart, thyroid tissue in struma ovarii can be subject to thyroid disorders. Thyrotoxicosis has been estimated to occur in 5%–8% of all cases.[4] Graves' disease, toxic nodular goiter, and Hashimoto's thyroiditis arising from ovarian teratomas have been reported.[5,6]

Approximately 5% of all strumae ovarii develop features of malignant transformation.[7] As for intrathyroidal malignancies, papillary thyroid cancer (PTC) occurs most frequently, displaying typical histological characteristics such as overlapping ground glass nuclei, vascular invasion, or the presence of psammoma bodies.[8] The follicular variant of papillary carcinoma (FVPTC) shows a loss of papillary architecture and has historically been misinterpreted as follicular carcinoma. Follicular thyroid carcinoma (FTC) is the second most frequent type posing diagnostic challenges since, in the absence of a thyroid capsule, its only defining characteristic in struma ovarii is vascular invasion.[7]

Clinical decision-making is complicated by the fact that histologic features of malignancy show only a poor correlation with clinically malignant behavior. A study reviewing 86 cases conducted by Shaco-Levy et al. concluded that clinical outcomes could not be predicted based on microscopic criteria.[9] Features of biological malignancy including extra-ovarian spread, tumor infiltration of the ovarian serosa, and recurrence after initial local therapy seem to occur regardless of initial histologic findings. Accordingly, there have been several cases of clinically widespread peritoneal disease with no histologic signs of malignancy. This phenomenon has been attributed to intraperitoneal spread of benign thyroid tissue by capsular rupture of teratomas or dissemination during embryogenesis. So termed 'benign ovarian strumosis' can be present in up to 5% of all ovarian strumae and may mimic disseminated malignant disease.[7]

Thus, in the presence of either sign of malignancy – histological or biological – authors have adhered to the term malignant struma ovarii (MSO) – leaving its definition an ongoing challenge.[10] We herein present a case of struma ovarii exhibiting both features of thyroid-type malignancy and benign peritoneal tumor spread.

2 | CASE REPORT

A 35-year-old patient presented after having undergone right-sided laparoscopic oophorectomy and partial salpingectomy. Upon presentation, the patient complained of infrequent abdominal pain. There were no signs of ascites or pleural effusion and no clinical evidence of hyperthyroidism. The patient's family history was unremarkable for ovarian or thyroid malignancy. The initially resected tumor mass measuring 13 cm in diameter was histologically classified as struma ovarii containing papillary thyroid cancer (PTC) measuring 30 mm. A postoperative MRI of the pelvis was performed detecting a small nodular lesion in the recto-uterine pouch (Figure S1). Thyroglobulin was 42.3 µg/dL (reference: ≤1.0 µg/dL after thyroidectomy), the TSH level was normal (2.04 mU/L, institutional reference range 0.17–4.0), and CEA level within normal limits. Ultrasound of the thyroid gland showed no nodular disease. For complete staging, I-123 scintigraphy with 185 MBq and single photon emission computed tomography (SPECT) was included in the diagnostic workup (Figure 1). This revealed multiple iodine-avid lesions adjacent to the peritoneal wall and in close proximity to the bladder. Peritoneal tissue samples were obtained by laparoscopic local peritonectomy showing nuclear irregularities, but no certain signs of malignancy. Further assessment for BRAF V600E-mutations was negative. Cytopathological analysis of peritoneal fluid was negative for malignant cells.

Given the presence of proven PTC, the large diameter of the resected struma ovarii, and multifocal extra-ovarian spread, the patient was treated in accordance with guidelines for PTC.[11] The patient underwent total thyroidectomy, which revealed no evidence of further – primary or secondary – manifestations of PTC. After exogenous TSH stimulation with recombinant human TSH (rhTSH) she received ablative I-131 treatment with 5.4 GBq (TSH level > 100 mU/L). Posttherapeutic whole-body scintigraphy showed multifocal uptake to the peritoneal lesions (Figure 2A). Stimulated thyroglobulin levels were elevated to 83.5 µg/L. A second treatment with 3.7 GBq I-131 was carried out 3 months after initial radioiodine therapy (cumulative radioiodine treatment activity: 9.1 GBq). Posttherapeutic whole-body scans showed no evidence of residual disease and thyroglobulin levels ranged below the detection threshold (<1.0 µg/L) after rhTSH-stimulation (Figure 2B). Thyroglobulin antibodies were not elevated. The patient has maintained hormone-suppressive substitution therapy. Throughout the course of a 3-year follow-up, she has been free of recurrent disease on both iodine imaging and thyroglobulin monitoring and has since given birth to a healthy child after uncomplicated pregnancy.

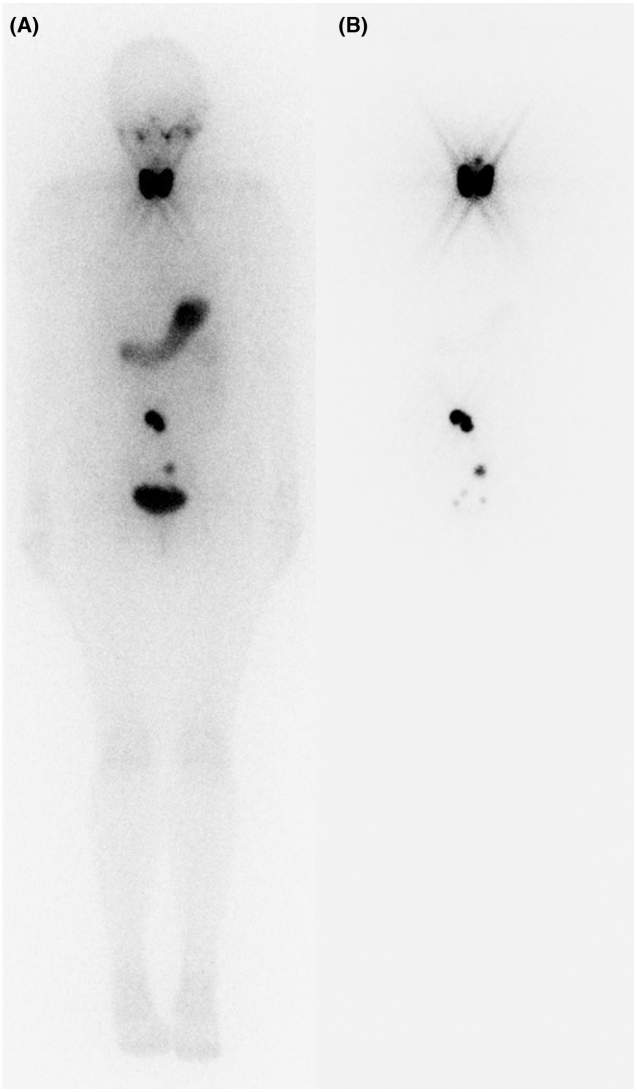

FIGURE 1 (A) I-123 scintigraphy with 185 MBq (anterior view) 4 h after injection shows intense uptake in the thyroid gland and bifocal intraperitoneal lesions, gastric uptake is unspecific, physiological tracer accumulation in the bladder (B) late acquisition 24 h after injection: three more focal lesions become detectable in close proximity to the bladder after voiding.

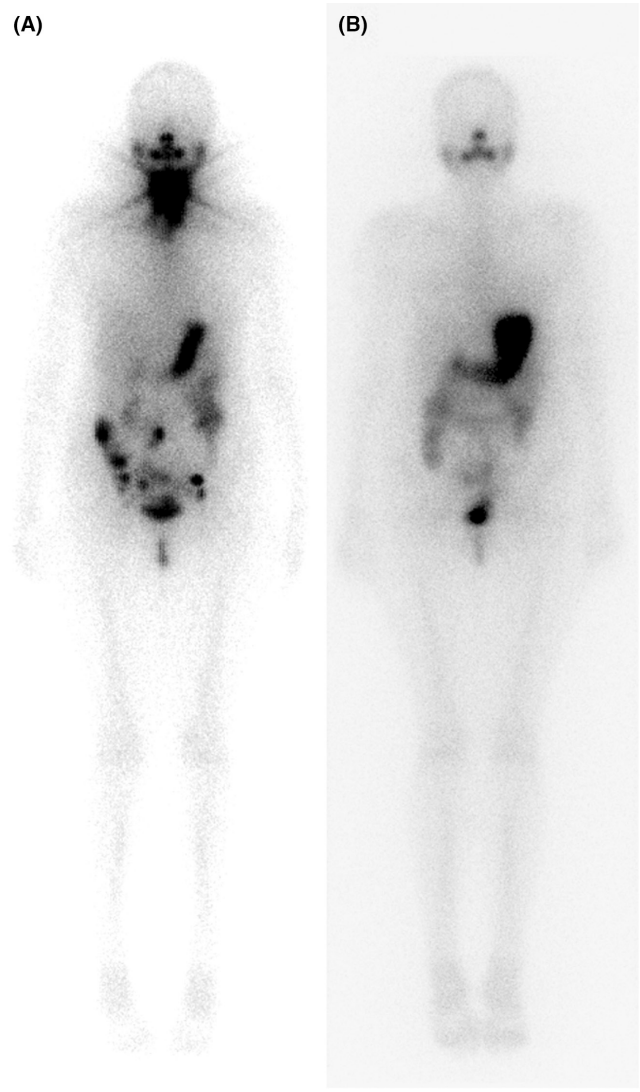

FIGURE 2 (A) Posttherapeutic whole-body scan (anterior view) after I-131 therapy with 5.4 GBq reveals multifocal peritoneal lesions with additional lesions as compared to previous I-123 scans and intense cervical uptake due to remnant thyroid tissue, non-specific intestinal accumulation. (B) Posttherapeutic whole-body scan, 3 months after primary treatment showing no evidence of residual disease.

3 | DISCUSSION

The natural history of struma ovarii with thyroid-type differentiated carcinoma is poorly understood. A series of 68 patients from a population-level database was examined by Goffredo et al.[12] The authors concluded that so-termed malignant struma ovarii (MSO) is associated with excellent disease-specific survival, with overall survival reaching 96.7%, 94.3%, and 84.9% after 5, 10, and 20 years respectively. Yet, it was also demonstrated, that once diagnosed with MSO, patients had a higher risk of developing aggressive orthotopic thyroid cancers. It has to be pointed out, that the vast majority of the examined cases (80%) was staged as localized disease. Thus, the impact of thyroidectomy and radioiodine therapy was only documented for very few patients (7.7%), not allowing for general conclusions in subgroups with extra-ovarian spread.

Roth et al. have discussed the difficulties in assessing malignant characteristics in struma ovarii, arguing that the term malignant struma ovarii (MSO) no longer be used, given the lack of uniform criteria for its diagnosis. The extra-ovarian spread should be carefully differentiated: it can arise from benign peritoneal strumosis, from typical thyroid-type carcinoma, or minimal deviation follicular carcinoma (MDFTC).[7] BRAF V600E gene mutation analysis can be helpful in distinguishing benign implants from malignant peritoneal spread.[13] In cases of

benign peritoneal strumosis overtreatment should be generally avoided, especially in the absence of histologically proven thyroid-type malignancy.

De Simone et al. reviewed a series of 24 cases, 4 of which had undergone thyroidectomy and radioiodine therapy. In patients treated conservatively, the recurrence rate was as high as 50%, while all patients treated with radioiodine therapy remained disease-free throughout follow-up.[14] The authors suggest that in struma ovarii with thyroid-type carcinoma, radical surgery with total abdominal hysterectomy, bilateral oophorectomy, thyroidectomy, and radioiodine therapy be considered as treatment of choice, especially in patients beyond child-bearing age.

In younger patients, where preservation of fertility is a core aspect, unilateral salpingo-oophorectomy, and conservative management has been advocated. Yassa et al. presented a case of a young patient with struma ovarii revealing PTC and benign peritoneal strumosis. Small tumor size (<2 cm) was considered a favorable criterion allowing for unilateral surgery and conservative management. The authors call for a risk-stratified approach, adhering to a careful follow-up routine including periodical thyroid and pelvic imaging in lower-risk cases.

A number of criteria have been put forth to define high-risk features for aggressive behavior. These include large ovarian mass upon diagnosis (>120 mm), extra-ovarian spread, adhesions, evidence of nodal, or distant metastases, or presence of ascites.[3,9,15]

For early risk stratification and staging, the use of I-123 scintigraphy proved beneficial in the presented case. Its incorporation into standard diagnostic workup in cases of struma ovarii can be encouraged from various points of view:

- Especially by addition of SPECT/CT, I-123 scans may help differentiate benign extra-ovarian spread from cases, where lymph-node involvement or distant metastases make malignant course of disease more likely.[16] The latter should be considered as an ablative treatment concept. In cases of diagnostic uncertainty, PET/CT with I-124 can increase sensitivity.[17,18]
- In younger patients, where preservation of fertility is a major consideration, a negative I-123 scan may be reassuring after unilateral salpingo-oophorectomy (SO). On the other hand, candidates for more radical pelvic surgery can be identified once contralateral or nodal involvement is present.
- In cases with oligofocal nodal involvement, I-123 may pave the way to radio-guided surgical re-intervention or sampling.[19]
- If thyroidectomy and ablative radioiodine treatment are to be performed, pretherapeutic I-123 scintigraphy may be useful for dosimetric purposes. Patients in child-bearing age with high pelvic tumor burden can be considered for prior cryoconservation and treatment with GnRH-analogues.[20]
- Lower whole-body radiation doses and the avoidance of a potential 'stunning effects' make I-123 scintigraphy a more adequate tool for primary assessment than diagnostic I-131 scintigraphy.[21] If I-123 uptake proves to be too low, an ablative concept might be excluded as a whole, thus avoiding potentially harmful therapeutic doses in the absence of benefit.

For high-risk settings, several authors have argued in favor of an ablative treatment strategy including thyroidectomy and radioiodine therapy.[22–24] Thyroidectomy is the safest path to ruling out primary or coexisting thyroid cancer in the thyroid gland and is a prerequisite for later radioiodine treatment.[25] Furthermore, only after thyroidectomy and ablative radioiodine treatment can thyroglobulin serve as a reliable marker for follow-up and early detection of biochemical recurrence. In cases with abundant extra-ovarian spread, endogenous TSH stimulation may pose a challenge after thyroidectomy due to ectopic hormone production. In these patients, recombinant human TSH (rhTSH) has successfully been used.[24]

Yet, to some patients, thyroidectomy may seem a radical choice to make, especially in the absence of suspected intrathyroidal malignancy. Perioperative risks of thyroidectomy, general anesthesia, and the necessity of lifelong levothyroxine substitution therapy have to be addressed and carefully weighed against the advantages of an ablative concept.

In the presented case, based on the literature available and the uneventful post-therapeutic course, the above risks were most likely outweighed by the benefits of better disease control and a safer follow-up routine.

4 | CONCLUSION

The treatment of struma ovarii with malignant features lacks randomized evidence for clinical decision-making. In the presence of high-risk features including large tumor size, extra-ovarian spread, or distant metastases, thyroidectomy followed by radioiodine therapy is a safe and effective treatment strategy. I-123 SPECT is a valuable tool in the assessment of newly diagnosed struma ovarii to identify patients with disseminated peritoneal findings or distant metastases, who will most likely benefit from an ablative treatment approach.

AUTHOR CONTRIBUTIONS

Daniel Groener: Investigation; visualization; writing – original draft; writing – review and editing. **Justus**

Baumgarten: Visualization; writing – review and editing. **Christian Happel:** Visualization; writing – review and editing. **Nicolai Mader:** Visualization; writing – review and editing. **Christina Nguyen Ngoc:** Visualization; writing – review and editing. **Amir Sabet:** Writing – review and editing. **Frank Grünwald:** Conceptualization; supervision; writing – review and editing.

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CONFLICT OF INTEREST STATEMENT
The authors declare that they have no competing interests.

DATA AVAILABILITY STATEMENT
The data used and/or analyzed during the current study are available from the corresponding author on reasonable request.

ETHICAL APPROVAL
All procedures performed were in accordance with the ethical standards of the 1964 Helsinki declaration and its later amendments or comparable ethical standards. All patients gave written informed consent prior to each therapy cycle and retrospective data analysis was approved by the ethics committee of Goethe University Frankfurt (approval number: 310/18).

CONSENT
The patient gave written informed consent to participation and publication.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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