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Journal of Endocrinology and Disorders
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Open Access

Research Article

Ectopic Thyroid in The Ovary, Uterus and The Pelvis: A Review and Update

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Received Date: 19 July 2023 | Accepted Date: 10 August 2023 | Published Date: 21 September 2023

Citation: Anthony Kodzo-Grey Venyo, (2023), Ectopic Thyroid in The Ovary, Uterus and The Pelvis: A Review and Update, *J. Endocrinology and Disorders*, 7(7): **DOI:10.31579/2640-1045/151**

Abstract

Ectopic prostate in the ovary, the uterus or within the female genital tract is a rare entity which majority of clinicians globally would not have encountered during their training as well as globally and may therefore not be familiar with the manifestations, diagnostic features and management of this rare clinical entity. Struma ovarii is a terminology that is used for a specialized or mono-dermal teratoma which predominantly is comprised of mature thyroid tissue. With regard to struma ovarii, it has been iterated that the thyroid tissue must comprise of more than 50 percent of the overall tissue I order to be classified as a struma ovarii. It has been stated that Struma ovarii does account for about5 percent of all ovarian teratomas. It has been iterated that depending upon the histology features, struma ovarii can be classified as either (a) benign or (b) malignant. Females who have struma ovarii have been documented to usually manifest with abdominal pain and/or a pelvic mass and less frequently with ascites. Ladies with ectopic thyroid tissue within the ovary or uterus may also be asymptomatic and they may be diagnosed incidentally based upon the investigation and treatment of a different clinical entity. A lady who has Struma ovari and a large pelvis mass that is compressing a ureter may also manifest with loin pain due to compression of the ureter that may simulate ureteric colic or with constant loin pain for which or rare occasions may be referred to a Urologist. A female with Struma ovarii or ectopic thyroid in the uterus may also manifest with vaginal bleeding. Depending the age of the female who has ectopic thyroid tissue in the ovary or uterus, she may initially be seen by her General Practitioner and referred to a paediatrician, a gynaecologist, a General Surgeon or Urologist depending upon the site and nature of her pain. The clinical and biochemical features of hyperthyroidism tend to be not common in women who have struma ovarii, which has been stated to occur in less than 5 percent to 8 percent of cases of struma ovarii. The clinical presentations of struma ovarii have tended to be based upon single case reports and small case series The ensuing summations had been made regarding Stuma ovarii:

- Struma ovarii is most common between the ages of 40 years and 60 years, but has been reported in patients as young as 10 years of age.
- In a case series of 20 patients to 30 patients who had histologically confirmed struma ovarii, abdominal or pelvic pain was documented to be present in 17 patients and a palpable lower abdominal mass in 22 patients.
- In one reported case series, no definite symptoms were present in 14 patients out of 34 patients, in whom the presence of an ovarian tumor was incidentally observed upon the undertaking of ultrasound scan for other medical reasons. Ascites was found in 4 patients. CA-125 level was raised in 4 out of 13 women in whom it was measured (and among these patients one of three were found to have malignant struma ovarii).
- It has been pointed out that with regard to hyperthyroidism, the clinical and biochemical features of hyperthyroidism have tended not to be common in women who have struma ovarii.
- It has also been iterated that in hyperthyroid patients, the serum thyroid-stimulating hormone (TSH) has tended to be low and free thyroxine (T4) and/or triiodothyronine (T3) had tended to be raised. It has been pointed out that the thyroid gland typically has tended not to be enlarged in cases of ectopic thyroid in the ovary or uterus, but serum thyroglobulin tended to be raised.
- It has been documented that radioiodine uptake is low or absent within the thyroid gland but present within the pelvis in cases of ectopic thyroid tissue in the ovary or uterus.

- It has additionally been pointed out that on rare occasions, women who have struma ovarii and hyperthyroidism also do tend to have a goitre and it has been explained that there are at least two possible explanations for this association had been promulgated including:
  - The coexistence of Graves' disease and struma ovarii, which had been reported on rare occasions in the literature.
  - Serum thyroid-stimulating immunoglobulins (thyrotropin-receptor antibodies [TRAb]) would be expected to stimulate the function of thyroid tissue within the ovary as well as within the neck.

Laboratory Studies that to be undertaken in patients who have ectopic thyroid in the ovary, uterus and genital tract include: Full blood count, routine biochemistry blood tests, blood type and screen, cancer antigen 125 (CA125), CA125 is a non-specific marker which is elevated in various benign clinical settings, including: menstruation, pregnancy, endometriosis. CA125 is raised in epithelial ovarian, endometrial, bowel, breast, and lung cancer. CA!25 was stated to be raised in only 8 cases reported in the literature in the setting of struma ovarii. Thyroid function tests need to be ordered only in patients who have symptomatic hyperthyroidism)

CT and MRI appearance of these tumours might demonstrate helpful diagnostic features. Triple-contrast CT scan of the abdomen and pelvis should be undertaken to evaluate the extent of disease and the involvement of lymph nodes and other adjacent structures (for example, bowel). Typically, struma ovarii does appear as a multi-cystic mass with no or moderate cystic wall enhancement. Ultrasound scan of the pelvis abdomen and trans-vaginal ultrasound could be undertaken as an optional radiology imaging if a CT scan has already been undertaken. With regard to patients who have pelvic masses of unknown origin, mammography should be undertaken.

For the vast majority of cases, surgical resection of the ovary has been stated to be sufficient to treat benign, unilateral disease. A paucity of evidence does exist in the literature regarding conservative management in cases with evidence of malignancy. In these patients, serum thyroglobulin levels could be followed as a marker for assessment for recurrence following fertility-sparing unilateral salpingo-oophorectomy. With regard to individuals who do not desire future fertility, it has been iterated that malignant struma ovarii necessitates the undertaking of surgical staging for ovarian cancer with pelvic washings, total abdominal hysterectomy, bilateral salpingo-oophorectomy, lymph node sampling, total thyroidectomy, and radioactive I-131 ablation. The recurrence rate in patients who have malignant struma ovarii who undergo surgery without subsequent radio-ablation had been documented to be as high as 50%. Some of the differential Diagnoses of ectopic thyroid in the ovary (Struma ovarii) include: (a) All other forms of ovarian neoplasms, both benign and malignant, (b) Ectopic Pregnancy, (a) Endometrioma; (d) Hydrosalpinx, (e) Hyperthyroidism and thyrotoxicosis, (f) Metastatic thyroid cancer to the ovary, (g) Physiological ovarian cyst, and Tubo-ovarian abscess. With regard to patients who have a benign struma ovarii, standard surgical follow-up is sufficient. With regard to patients who have malignant disease on surgical pathology, postoperative adjuvant therapy with radio-ablative iodine-131 has been recommended. After surgical staging, a thyroidectomy has been suggested to be undertaken before adjuvant therapy to potentiate the effects of radio-ablation. As normal thyroid cells preferentially uptake I-131, thyroidectomy would ensure delivery to the malignant cells. Additionally, it has been iterated that a thyroidectomy would provide pathological confirmation that the struma is indeed ovarian in origin. It has been pointed out that it is important for the surgeon to be aware of the intra- and post-operative complications of thyroidectomy which include hypocalcaemia, damage to the recurrent laryngeal nerve, and/or need for postoperative thyroid replacement, as well as to be comfortable with their management. Radioactive I-131 ablation had been reported to treat malignant disease in both its initial presentation and any subsequent recurrence with excellent efficacy, even though the rarity of the disease and lack of data surrounding its long-term management do prove challenging to clinicians. Thyroglobulin is stated by some authors to be the preferred tumour marker followed in patients with malignant struma ovarii and should be followed sequentially after surgery and ablation. It has also been advised that increases in serum thyroglobulin should be followed up with total body scanning in order to identify recurrence, which is treated with subsequent radio-ablation.

Key words: ectopic thyroid; ovary, uterus, abdominal pain; loin pain; bleeding; euthyroid; thyrotoxicosis; ultrasound scan; computed tomography scan; magnetic resonance imaging scan

Introduction

The finding of thyroid tissue outside the thyroid gland could occur in various clinical settings and anatomical locations and these include both benign as well as malignant differential diagnoses. [1] Some of these entities of the finding of thyroid tissue outside the confines of the thyroid gland include thyroglossal duct cyst, lingual thyroid, parasitic nodule, thyroid tissue within a lymph node, ectopic thyroid in the ovary. struma ovarii. With regard to the setting of routine daily clinical practice, these ectopic positions of the thyroid gland do tend to pose diagnostic challenges for the clinician and the pathologist. Differential diagnostic considerations do largely depend upon the location of lesion and the histology features of the ectopic thyroid tissue. A definitive diagnosis may remain not be clear in some cases of ectopic thyroid tissue while knowledge is still evolving in others for example, incidentally identified bland looking thyroid follicles within a lateral lymph node. Many patients who have ectopic thyroid in the ovary would be asymptomatic and the diagnosis would tend to be established incidentally during investigation of a non-related problem Nevertheless a number of individuals with ectopic thyroid in the ovary would manifest with non-specific symptoms and unless the clinician has a high index of suspicion for ectopic thyroid in the ovary, the diagnosis may be either delayed or missed. Large ectopic thyroid tissue within the ovary could obstruct the ureter and apart from manifesting as lower abdominal pain in all age groups that would require the patients initially being seen by General duty practitioners, pediatricians, emergency clinicians, or General Surgeons, manifestation of loin pain or impaired renal function may require that the patient is first seen by a Urologist for further assessment. The ensuing article on ectopic thyroid tissue in the ovary is divided into two parts: (A) Overview which has discussed General aspects of ectopic thyroid tissue and (B)

Miscellaneous Narrations and Discussions from Some Case Reports, Case Series and Studies Related to Ectopic thyroid in the ovary.

Aim

To review and update the literature on ectopic thyroid in the ovary, uterus and the female genital tract.

Method

Various internet data bases were searched including: Google, Google Scholar, Yahoo, and PUBMED. The search words that were used included: Ectopic thyroid in ovary; Ovarian ectopic thyroid; Struma Ovarii; Ectopic thyroid tissue in the ovary, benign thyroid tissue in the ovary, and malignant thyroid tissue in the ovary, ectopic thyroid in the uterus; uterine thyroid. Forty-two (42) references were identified which were used to write the article on ectopic thyroid in the ovary that has been divided into two parts: (A) Overview which has discussed General aspects of ectopic thyroid tissue and (B) Miscellaneous Narrations and Discussions from Some Case Reports, Case Series and Studies Related to Ectopic thyroid in the ovary.

Results

[A] Overview

Definition / general

- Even though generally thyroid tissue is found to be localized within the thyroid gland, ectopic thyroid tissue could be found with within the ovary and in pelvis organs of the female. [2]
- It has been pointed out that mono-dermal ovarian teratoma has tended to contain primarily (> 50%) or exclusively composed of benign thyroid tissue [2].
- It has also been iterated that ectopic thyroid tissue includes any mature teratoma with malignant thyroid tissue [2].

Essential features

- Ectopic thyroid tissue of the ovary refers to an ovarian teratoma which is either composed predominantly or exclusively of benign thyroid tissue or with any amount of malignant thyroid tissue [2].
- It has been iterated that majority of thyroid malignancy to occur within struma ovarii is papillary thyroid carcinoma which is followed by follicular carcinoma of the thyroid gland [2].

Epidemiology

- Ectopic thyroid tissue within the ovary is the most common type of mono-dermal teratoma occurring within the ovary [2].
- It has been iterated that ectopic thyroid tissue in the ovary does account for 3% of ovarian teratomas [3].
- Ectopic thyroid tissue in the ovary usually manifests within the fifth decade of life.

Sites

- Ectopic thyroid of the ovary tends to be found within the ovary [2].
- It is worth noting that ectopic thyroid tissue has been reported in the uterus on one occasion [4].

Pathophysiology / aetiology

- It has been pointed out that the actual aetiology / pathophysiology of ectopic prostate within the ovary is currently unknown [2].

Clinical features

- It has been documented that most often ectopic thyroid tissue within the ovary has tended to be an incidental and asymptomatic finding; however, ectopic thyroid tissue within the ovary may manifest as a pelvic mass with abdominal pain [3].
- It has been iterated that ectopic thyroid tissue in the ovary uncommonly manifests as hyperthyroidism or pseudo-Meigs syndrome with the development of ascites and pleural effusion [3].
- It has been iterated that ectopic thyroid tissue tends to be seen in association with Brenner tumour, serous and mucinous cystadenoma and fibrothecoma. [5].
- Other types of non-specific manifestations of ectopic thyroid tissue in the ovary or pelvis of a female include: lower abdominal pain, loin pain or discomfort, tachycardia, infertility.

Diagnosis

- It has been pointed out that diagnosis of ectopic thyroid tissue within the ovary is made or confirmed based upon microscopy pathology examination of specimens of resected ovarian tissue

Laboratory Tests

Urine Examination

- Urinalysis, urine microscopy and culture are routine tests that tend to be taken as part of the general assessment of patients who have ectopic thyroid tissue within the ovary and the results would tend to be normal but if there is any evidence of urinary tract infection, it would be treated accordingly to improve upon the general condition of the patient.

Haematology Blood Tests

- Laboratory tests including routine haematology blood tests that include full blood count and INR tend to be taken as part of the general assessment of patients who have ectopic thyroid tissue within the ovary and the results would tend to be normal but if there is any abnormality, it would be investigated and treated accordingly to improve upon the general condition of the patient.

Biochemistry Blood Tests

- Routine biochemistry blood tests tend to be undertaken as general assessment of all patients who have ectopic thyroid of the ovary and these tests include: CRP, Urea and electrolytes, liver function tests, bone profile, and random blood glucose. Generally, the results would tend to be normal but if there is any abnormality, it would be investigated and treated accordingly. For example, if there is an ovarian pelvis mass obstructing the ureter and causing impaired renal function, a per-cutaneous nephrostomy would be inserted or a double J ureteric stent would be inserted to obviate the obstruction so as to improve the renal function of the patient.
- In cases of ectopic thyroid tissue in the ovary, there tends to be mildly increased CA125 levels in up to 30% of cases [6].

Radiology description

- It has been pointed out that in cases of ectopic thyroid in the ovary, typically a lobulated and multiloculated solid cystic lesion of the ovary tends to be demonstrated on imaging. [7] [8].
- It has been iterated that Magnetic Resonance Imaging (MRI) is more specific, showing high and low signal intensity on T1 and T2 weighted images from the colloid [9].

- It needs to be realised that not all radiology units globally have MRI scan services and in establishments where MRI scans are not available, Computed Tomography (CT) scan and or ultrasound scan of the pelvis and ovary tend to be undertaken to demonstrate the features of the ectopic thyroid lesion in the ovary.

Prognostic factors

- It has been pointed out that most cases of ectopic thyroid in the ovary have a good prognosis, even when malignancy is present [2].

Treatment

The treatment options that tend to be utilized for the management of ectopic thyroid in the ovary had been summarized as follows: [2].

- Oophorectomy
- The undertaking of surgery for malignant struma ovarii which may include total abdominal hysterectomy and bilateral salpingo-oophorectomy with complete staging [10].

Gross description

- It has been iterated that macroscopy examination of ectopic thyroid in the ovary does typically tend to demonstrate unilateral and solid mass with a gelatinous, red-brown to green cut surface; and the examination may show goitre-like multinodular or cystic change [11].

Frozen section description

- It has been documented that frozen section examination of a sample of specimen of ectopic thyroid tissue in the ovary usually shows features of a mature teratoma or benign thyroid tissue; and rarely, a possible malignant component may be detected. [2].
- It is worth pointing out that globally, in some health service establishments, there are no pathology departments and the pathology departments are far away and hence the undertaking of frozen section intra-operative pathology examinations may not be possible or easy, and in such scenarios, it would be envisaged that radiology image-guided biopsy or FNA to obtain specimen from the ovary for pathology examination, may be necessitated [2].

Microscopy histopathology description

The microscopy pathology examination features of ectopic thyroid tissue within the ovary had been summarized as follows: [2].

- Microscopy examination of the ovarian specimen does demonstrate variably sized macro and micro-follicles often containing colloid
- Other architectural patterns that are seen upon microscopy examination of the ovarian specimen include solid areas that are composed of cells with clear to oxyphilic cytoplasm, trabeculae, cords and pseudo-tubular structures
- Rarely, microscopy examination of the ovarian lesion demonstrates stroma in between follicles which may be fibrotic or oedematous; and peripheral stromal leutinization, may also be seen
- Adenomatous hyperplasia or proliferative changes may be visualized, such as areas of densely packed follicles or papillary formations lacking nuclear features of papillary thyroid carcinoma.
- Birefringent calcium oxalate crystals might may demonstrated within colloid
- Most commonly associated malignancy in cases of ectopic thyroid in the ovary is papillary, and this is cytologically characterized by crowded and overlapping elongated nuclei with irregular contours and chromatin clearing, usually with papillary or follicular architecture
- Follicular carcinoma is the second most common malignancy; since ovarian lesions typically lack capsule, demonstration of tumour invasion into encompassing ovarian tissue, vascular invasion or metastases is required as evidence of malignancy
- It has been documented that ectopic thyroid in the ovary tends to be uncommonly associated with the more recently described highly differentiated follicular carcinoma of ovarian origin, characterized by extraovarian spread of thyroid elements histologically resembling nonneoplastic thyroid tissue [12].
- It has been iterated that undifferentiated (anaplastic) carcinoma and medullary carcinoma and had also been described in association with struma ovarii

Cytology description

It has been iterated that cytology examination of specimens of ectopic thyroid in the ovary does demonstrate the following: [2].

- Flattened to cuboidal / columnar cells with small round to oval nuclei, even chromatin and pale to eosinophilic cytoplasm [13].
- Clear cell change may occasionally be visualized.

Immunohistochemistry Staining

Positive stains

It has been documented that specimens of ectopic thyroid tissue in the ovary do exhibit positive immunohistochemistry staining for: [2].

- TTF1, thyroglobulin, PAX8, CK7, AE1/AE3. [14]

Negative stains

It has been documented that specimens of ectopic thyroid tissue in the ovary do exhibit negative immunohistochemistry staining for: [2].

- HNF1β, Napsin A, AMACR, inhibin A, SF1, S100, Melan A, HMB45.

Molecular / cytogenetics description

The molecular / cytogenetics description of ectopic thyroid of ovary specimens had been iterated to demonstrate the following: [2].

- BRAF mutations and RET / PTC rearrangements may be visualized in papillary thyroid carcinomas that arise from a struma ovarii [15] [16]

Differential diagnosis

The differential diagnoses of ectopic thyroid in the ovary had been summarized to include the following: [2].

- Metastatic thyroid carcinoma to the ovary:
    - It has been pointed out that in cases of metastatic thyroid carcinoma to the ovary clinical history of primary carcinoma tends to be available or obtained upon request.
- Strumal Carcinoid:
    - Strumal Carcinoid specimens depict corded, trabecular or follicular architecture with salt and pepper nuclear chromatin pattern and occasional eosinophilic granules
    - Strumal Carcinoid specimens upon immunohistochemistry staining exhibit positive staining for TTF1, PAX8, thyroglobulin in the follicular component and neuroendocrine markers: chromogranin, synaptophysin, CD56, and neuron specific enolase. markers
- Ovarian clear Cell Carcinoma:

- Tubulocystic, papillary and solid growth patterns with cytologically atypical cells, often hob-nailing into cysts
- Positive staining for HNF1β, Napsin A, and AMACR.
- Negative for TTF1, thyroglobulin.

- Sex Cord Stromal Tumour:
  - Sex cord stromal tumour of the ovary upon microscopy pathology examination demonstrates tubular, trabecular or corded growth without eosinophilic secretions
  - Sex cord stromal tumour of the ovary upon immunohistochemistry staining studies exhibit positive staining for inhibin A, Calretinin, and SF1.
  - Sex cord stromal tumour of the ovary upon immunohistochemistry staining studies exhibit negative staining for TTF1, PAX8 which is usually negative [17].
- Melanoma:
  - Melanoma of the ovary tends to exhibit nested growth with eosinophilic cytoplasm
  - Melanoma does exhibit positive staining for typical melanoma markers such as S100, Melan A. and HMB45.
  - Melanoma of the ovary tends to exhibit negative staining for keratin (AE1/AE3).

[B] miscellaneous narrations and discussions from some case reports, case series, and studies related to ectopic thyroid in the ovary.

Iranparvar Alamdari et al [18]. stated the following:

- Struma ovarii is an ovarian tumour with thyroid tissue as its predominant component.
- Struma ovarii usually occurs in older women and manifests with abdominal mass, pain and abnormal bleeding.
- Most patients who have Struma ovarii are euthyroid, but some reports had noted thyrotoxicosis originating from the malignant struma ovarii.

Iranparvar Alamdari et al [18]. reported **a** 10-year-old girl who had manifested with tachycardia, normal thyroid examination and thyrotoxicosis. She had thyroid scan which demonstrated no uptake with increased uptake within her right ovary which was indicative of struma ovarii. She underwent oophorectomy and thyroidectomy, Pathology examination of the excised specimens showed papillary thyroid carcinoma limited to the struma ovarii. Following TSH suppressive therapy and treatment with I131, she was totally symptom free at the time of publication of her case [18]. iterated that Struma ovarii should be a possible diagnosis in any female patient who has thyrotoxicosis manifestations with normal thyroid scan and examination. Detailed summation of the case report and educative summative discussions of Iranparvar Alamdari et al [18]. have been detailed out as follows:

Iranparvar Alamdari et al [18]. reported a 10-year-old girl who had presented with the complaint of palpitation to a cardiologist. She was found to have a normal clinical examination and laboratory tests, except for the fact that she had tachycardia with a heart rate of 130 per beats per minute, and low TSH levels (0.005) with normal T3 (9.46) and T4 [145]. She was referred to endocrinologist for possible evaluation for hyperthyroidism. Her thyroid gland was normal with regard to size, with no nodularity. She was diagnosed as having a possible thyrotoxicosis, but due to her normal physical examination finding, she underwent thyroid scan to exclude a possible thyroiditis, which did not show any uptake within the thyroid gland, while there was an increased uptake within her right ovary (see figure 1). She underwent pelvic trans-abdominal ultrasound scan which showed a heterogeneous complex solid mass that measured 113 mm × 112 mm × 100 mm with a volume of 670 cc in her right ovary with no ascites. She did not have any complaint of abdominal pain or pelvic pain or abnormal uterine bleeding.

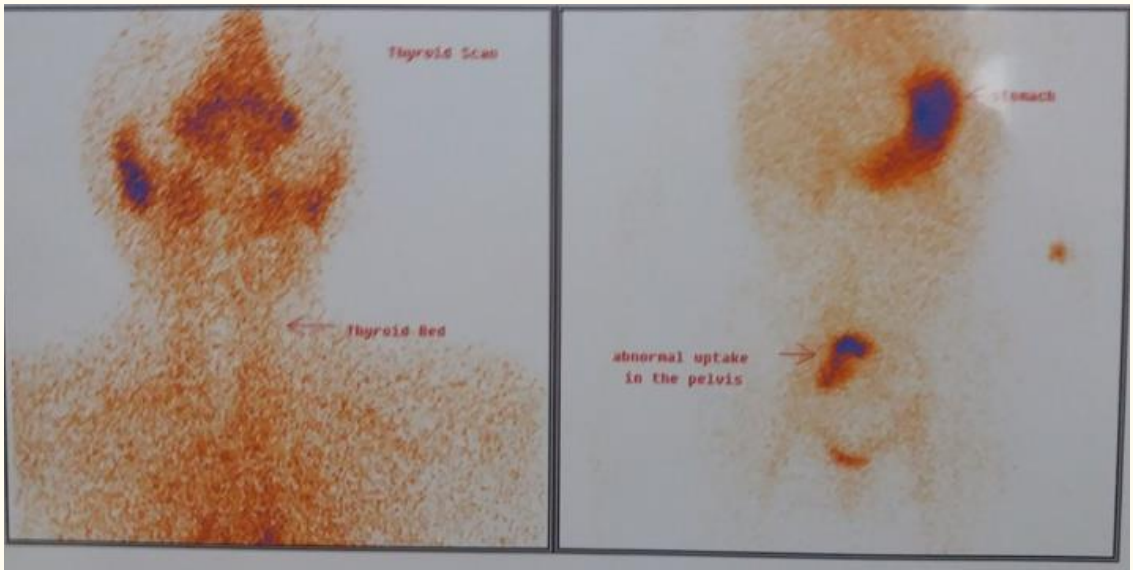

Figure 1: Reproduced from [18] Under Creative Commons Attribution License.

Thyroid scan showing no uptake in the thyroid gland, but increased uptake in the right ovary.

She was treated with methimazole 10 mg daily and propranolol 40 mg daily and she was considered to be a candidate for surgery after being euthyroid. She was referred to a gynaecologist with the possible diagnosis of struma

ovarii for further evaluation. She underwent right oophorectomy with the presumption of teratoma combined with thyroid-stimulating hormone (TSH)-suppressive therapy following treatment with I^{131}. Total thyroidectomy was undertaken in order to permit evaluation for metastatic disease and monitoring for recurrence by thyroglobulin levels. The pathology examination findings of the excised ovarian mass were reported to have indicated teratocarcinoma with 60% well-differentiated follicular thyroid carcinoma and 40% well differentiated follicular-variant with tumour necrosis, microscopic capsular invasion and peri-tumoral lympho-vascular invasion, which was considered to be a tumour stage IC of PTC (see figure 2) and the thyroid gland did not show pathology features of PTC.

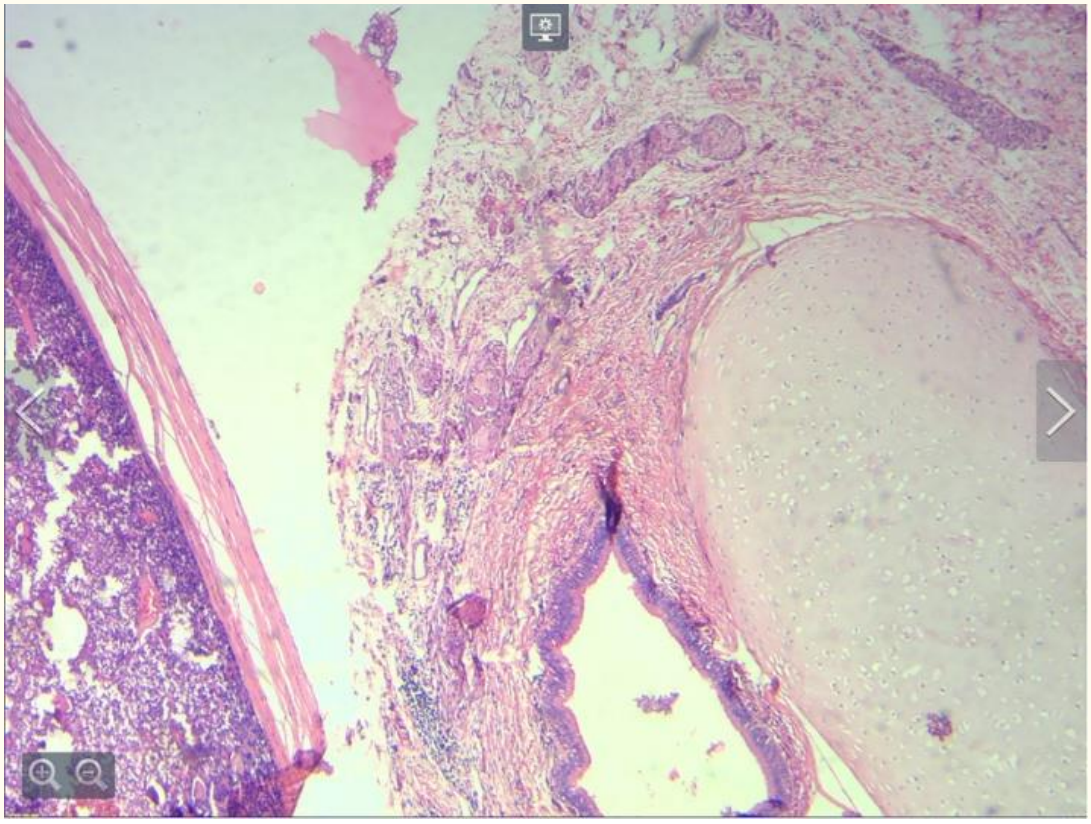

Figure 2: Reproduced from [18]. Under Creative Commons Attribution License.

Mature teratoma adjacent to tumour.

She underwent further evaluation with whole body scan with Iodine 123 [I123]. and the scan showed metastasis to lymph nodes. She had high levels of thyroglobulin and she received iodine therapy (150 mCi) twice. During her follow-up assessment, she had a follow-up whole body scan, which had demonstrated no trace of iodine uptake and the patient was symptom free. At the time of the report of her case, she was reported to be under treatment with levothyroxine 0.1 mg daily. Following 8 months after she had undergone surgery and iodine therapy, she was reported to be totally symptom free. Iranparvar Alamdari et al. [18] made the ensuing summating discussions:

- It had been pointed out that Struma ovarii could transform into malignant form [19].
- Struma ovarii is usually diagnosed in older patients, even though it had been reported in younger women [20] [21]. with symptoms of abdominal pain, abdominal mass, ascites and abnormal vaginal bleeding.
- Hyperthyroidism and thyrotoxicosis had also been reported in 5% to 15% of the cases. [19] [22].
- Struma ovarii in the young ages are very rare; their reported case was a 10-year-old girl with clinical and laboratory findings of thyrotoxicosis with no complaint of abdominopelvic origin.
- If malignant, the pathology examination of the specimen usually shows thyroid-related carcinoma with PTC as the most common type. But these patients usually tend to be aged between 40 years and 50 years of age with a mass that is confined to the ovary with a median size of 13 cm [23].
- Their reported young patient had PTC limited to her right ovary mass of 11 cm and the thyroid pathology was normal.
- It is important to evaluate the thyroid gland in order to differentiate the mass as a primary or a secondary tumour due to metastasis.
- As struma ovarii is diagnosed usually in women at older ages or menopauses, the recommended treatment for Struma ovarii is the undertaking of hysterectomy and bilateral salpingo-oophorectomy; nevertheless, the undertaking of unilateral oophorectomy is the choice to preserve fertility in younger patients if there is no extra-ovarian disease.
- The undertaking of thyroidectomy has usually been recommended to confirm the normal thyroid gland by excluding a primary thyroid carcinoma and to potentiate radio-ablation iodine therapy [24].
- It has been iterated that prophylactic thyroidectomy would allow for thyroglobulin monitoring of possible metastases, remained mass or recurrence [24].
- Nevertheless, there are no guidelines in performing prophylactic total thyroidectomy after the diagnosis of thyroid type carcinoma in struma ovarii.
- It had been stated that distant metastasis is very uncommon, while intra-abdominal metastasis could occur in almost 23%

of cases [24]. including: the peritoneum, fallopian tubes, contralateral ovary as well as omentum and pelvic and para-aortic lymph nodes [6].

- Their reported patient had regional lymph node metastasis which was eradicated after she had received her second iodine therapy.
- It had been pointed out that patients who have malignant struma ovarii have an excellent survival rate. Two large studies by Goffredo et al. [25] and Robboy et al. [23] reported a survival rate of more than 90% for the first ten years and 84.9% at 20 years and 79% and 25 years. Their patient was free of disease for eight months and was followed in routine three months periods [23].
- The pathophysiology of hyperthyroidism in struma ovarii was still unknown. With regard to the mechanisms underlying the pathophysiology of functioning struma ovarii, it had been postulated that struma ovarii is an autonomous hormone-secreting tumour or that the ovarian thyroid tissue is stimulated by thyroid-stimulating hormone receptor antibody [26].

Wu et al [27]. stated the following:

- Malignant struma ovarii is an extremely rare clinical entity.
- The diagnosis of struma ovarii and modalities of treatment of struvma ovarii were still controversial.
- They had described a case of extensive peritoneal implant metastasis originating from malignant struma ovarii which was discovered 14 years after ovariectomy and chemotherapy.

Wu et al. [27] reported a 48-year-old female who was admitted to their clinic due to haematochezia with a past history of left malignant struma ovarii. She had undergone an Enhanced computed tomography (CT) examination which had suggested multiple metastasis nodules within her abdomen and pelvic cavity. She underwent laparoscopy and laparoscopy biopsy results of intraperitoneal nodules showed a metastasis of papillary thyroid carcinoma. While pathological examination after total thyroidectomy did show no definite malignant tumour component within the thyroid tissue. Finally, combined with the patient's past history of malignant struma ovarii, peritoneal implantation metastasis derived from the malignant struma ovarii was adjudged to be the diagnosis. The patient was treated by the undertaking of total thyroidectomy and iodine 131 (I) therapy. Her post-therapy iodine scan and her single-photon emission computed tomography/computed tomography (SPECT/CT) fusion image showed iodine uptake within her distal descending colon, sigmoid colon, rectal lesions, and a larger lesion in the liver. Wu et al. [27] reported that after treatment, although the thyroid globulin had remained at a high level 3 months after her treatment, the patient's haematochezia was relieved. Wu et al [27]. iterated that thyroidectomy followed by adjuvant I treatment should be recommended in patients who have malignant struma ovarii as metastatic risk is difficult to predict based on histopathologic examination. Wu et al. [] made the ensuing conclusions:

- They had reported an extremely unusual case of peritoneal implantation metastasis from malignant struma ovarii 14 years after ovariectomy plus chemotherapy, which may arise debates about management of this kind of cases.
- Since malignant and benign struma ovarii do have different treatment and prognoses, it is highly significant to distinguish them—the former does require further iodine-131 intervention, while the latter does require postoperative follow-up only.
- Therefore, once malignant struma ovarii is confirmed, they would suggest undertaking of ovariectomy and postoperative adjuvant treatment including total thyroidectomy, radioactive iodine therapy, and thyroxine suppression therapy.
- Simultaneously, the findings in their reported patient had clearly demonstrated the similarity in the functional metastasis, treatment methods as well as follow-up between malignant struma ovarii and primary thyroid cancer.
- Additionally, they would speculate that molecular targeted anti-tumour medicaments could be utilized for radioactive iodine unresponsive malignant struma ovarii metastases.

Jin et al. [28] stated the following:

- Struma ovarii is an uncommon ovarian teratoma comprised predominantly of mature thyroid tissue.
- The combination of pseudo-Meigs' syndrome, and elevation of CA 125 to the struma ovarii is a rare condition that can simulate ovarian malignancy.

Jin et al [28]. reported a case of benign struma ovarii, manifesting with the clinical features of advanced ovarian carcinoma: complex pelvic mass, gross ascites, bilateral pleural effusion and markedly elevated serum CA 125 levels. The patient did total abdominal hysterectomy and bilateral salpingo-oophorectomy. Ascites and pleural effusion were not evident and the CA 125 levels had returned to normal level following surgical excision. They performed a systematic review of reported cases of coexistent benign struma ovarii, pseudo-Meigs' syndrome and elevated serum CA 125. They iterated that Struma ovarii accompanied by pseudo-Meigs' syndrome and elevated serum CA 125 should be considered in the differential diagnosis of ovarian epithelial cancer.

Gomes-lima et al [29]. stated the following:

- Struma ovarii is a rare ovarian teratoma which is predominantly composed of thyroid tissue.
- The simultaneous presence of thyroid carcinoma in the struma ovarii and the thyroid gland is extremely rare.
- It has remained unclear if these carcinomas represent independent primary tumours and whether the molecular mechanisms of the tumours that develop within the thyroid gland and ovarian tissues are similar.

Gomes-lima et al. [29]. reported the case of a patient who had two independent papillary thyroid carcinomas (PTCs) in struma ovarii and the thyroid gland that were driven by different *RAS* mutations. Gomes-lima et al. [29]. reported a 62-year-old woman who had a history of chronic lymphocytic leukaemia/small lymphocytic lymphoma which was diagnosed with a pelvic mass during a CT scan. She had undergone surgery which included removal of her ovaries. A 7.2-cm classical variant of PTC arising in a struma ovarii was identified within her right ovary. Two months after the pelvic surgery, total thyroidectomy was undertaken, and a small nodule (0.8 cm) in the left lobe was found which was diagnosed as a classical variant of PTC. Molecular analysis of tissues obtained from both the malignant struma ovarii and thyroid gland was undertaken. *RAS* mutations both in the PTC located within the thyroid and ovarian tissues were identified. Nevertheless, the thyroid gland tumour showed an *HRAS* Q61R mutation, the PTC in struma ovarii harboured an *NRAS* Q61R mutation. Gomes-lima et al. [29]. stated that **i**n this case, the finding of distinct types of *RAS* point mutation in thyroid cancers at two different locations had provided definitive evidence that these cancers are synchronously developed independent primary tumours. Gomes-lima et al. [29]. made the ensuing conclusions:

- The finding of distinct types of *RAS* point mutation in thyroid carcinomas at two different locations provides definitive evidence that these carcinomas are synchronously developed independent primary tumours.
- Nevertheless, in view of the fact that each of the carcinomas is driven by a *RAS* point mutation, it suggests a similar mechanism of carcinogenesis developing in thyroid tissue present in the same patient at the orthotopic and ectopic locations.

Sah et al. [30]. stated the following:

- Brenner tumours are uncommon ovarian neoplasms which occasionally do occur in combination with a mucinous tumour.
- On rare occasions, the combination of Brenner tumour and thyroid tissue (struma ovarii) had been reported.

Sah et al. [30] reported an ovarian neoplasm with components of Brenner tumour, mucinous cystadenoma and struma ovarii. Sah et al. [30]. stated that as they were aware, this combination had not been previously reported. Sah et al. [30]. speculated on the possible histogenesis of this combination of elements.

Wei at al. [5] stated the following:

- Thyroid tissue is a relatively frequent component of mature teratoma and could occur in 5% to 20 % of cases.
- Struma ovarii is defined as ovarian goitre which comprises either entirely or predominantly thyroid tissue of greater than >50 %. This also includes cases of mature teratoma with less than 50 % thyroid tissue but harbouring thyroid-associated malignancy.

Wei et al. [5]. reported that a total of 118 patients who had mature teratoma containing thyroid tissue were identified within their institution between 1989 and 2014. Ninety-six cases were diagnosed struma ovarii, including 10 cases of papillary thyroid carcinoma, 1 case of highly differentiated follicular carcinoma of ovarian origin (HDFCO), 5 cases of strumal carcinoid, and 80 cases of struma ovarii (53 cases of thyroid-only struma ovarii). Six of the cases had diffuse adenomatous hyperplasia, and seven cases had focal adenomatous hyperplasia. There was no recurrence upon follow-up except one of the papillary thyroid carcinomas. Concurrent primary ovarian lesions that were found included: serous cystadenoma--3, mucinous cystadenoma--4, Brenner tumour--3, thecoma--2, ovarian fibroma--1, and focal hilus cell hyperplasia--4 cases. Wei et al. [5]. iterated that in their case series, papillary thyroid carcinoma and strumal carcinoid were the most common well-differentiated neoplasm/malignancies arising in struma ovarii; these had demonstrated a minimal or no aggressive clinical behaviour.

Salibay et al. [31]. stated the following:

- Ovarian Brenner tumours, do account for about 5% of overall ovarian epithelial neoplasm, are often they tend to be reported in association with mucinous neoplasm.
- Histogenetically, the two tumours are thought to arise from similar precursors.
- Up to the time of the report of their case, fewer than 60 borderline Brenner tumours alone had been reported, and the concomitant presence of atypical proliferative components in Brenner and mucinous tumours was even rarer. Therefore, the clinicopathological characteristics and prognosis of patients with the borderline Brenner tumours alone or coexisting with mucinous neoplasm were extremely limited.

Salibay et al. [31]. reported a unique case of a 53-year-old woman who had a unilateral ovarian borderline Brenner tumour that was associated with focal atypical mucinous epithelial proliferation and her clinical presentations. Salibay et al. [31]. documented the clinicopathological features of the tumour and the literature review along with the clinical molecular advances were summarized in this study.

Xiao et al. [32]. stated the following

- Struma ovarii is a rare specific ovarian tumour.
- Struma ovarii is a highly differentiated mono-dermal teratoma with a malignant transformation rate as low as 5%.
- Hence, malignant transformation and metastasis are extremely rare.
- The clinical presentations of this disease are not typical and are easily misdiagnosed.

Xiao et al. [32]. reported a 55-year-old female patient who had presented with a history of pain within her right hepatic region for approximately 1 year. She had computed tomography scan and magnetic resonance imaging scan which showed a solid cystic mass within her right adnexal region and a solid mass with her the right retroperitoneum. She underwent surgical resection, and the combined morphology and immunohistochemical results led to the final diagnosis of right struma ovarii with papillary carcinoma and right retroperitoneal lymph node metastasis. Xiao et al. [32]. made the following conclusions:

- Malignant struma ovarii with distant metastasis is extremely rare, and the clinical presentations of this disease are non-specific.
- Accurate pre-operative diagnoses are difficult to obtain, and pathology examination is the gold standard for diagnosing this disease.
- Preoperative CT, MRI and thyroid function examinations, combined with the patients' clinical manifestations, can help improve the accuracy of the preoperative diagnosis and provide great assistance in developing an appropriate treatment plan.

Terada et al. [33] stated that ovarian tumour which is composed only of Brenner tumour and struma ovarii is very rare and by the time of publication of their case; only 6 cases had been reported in the English literature, to the best of their knowledge. Terada et al. [33]. reported a 66-year-old woman underwent who had undergone right oophorectomy because of torsion of her right ovarian cyst. Macroscopically, the ovarian cyst was noted to be haemorrhagic and red. Cystic content was haemorrhagic fluid. Microscopy examination of the specimen demonstrated that the cyst walls were composed only of Brenner tumour (50% in area) and struma ovarii (50% in area). Haemorrhage and ischemic changes were also seen upon the microscopy examination. Other elements were not recognized. No malignant transformation was found. These two elements were separately present, and no mergers between them were recognized. Immunohistochemistry staining studies had demonstrated that the Brenner tumour element was positive for cytokeratins (AE1/3 and CAM5.2) and Ki67 (labelling=3%), but negative for thyroglobulin, TTF-1, p53, CA125, and vimentin. The struma ovarii element was positive for cytokeratins (AE1/3 and CAM5.2), thyroglobulin, TTF-1 and Ki67 (labelling=5%), but negative for p53, CA125 and vimentin. The findings were documented to have suggested that there were cases of ovarian cyst composed only of Brenner tumour and struma ovarii, that such a case may be mono-dermal mature cystic teratoma or the Brenner tumour element had been derived from surface epithelium in the preexisting struma ovarii, and that such a tumour had manifested as cystic torsion.

Yilmaz et al. [4] stated the following:

- Ectopic thyroid tissue does occur mainly along the course of the thyroglossal duct (**1**). [34].
- Ectopic thyroid tissue had been found in various human organs including the tongue and the mediastinum [35].
- Intrauterine thyroid tissue; nevertheless, is an extremely rare occurrence.

Yilmaz et al. [4]. reported a case of an ectopic thyroid within the uterus without evidence of a primary thyroid gland tumour. Yilmaz et al. [4]. iterated that to their knowledge, their reported case was the first report of an ectopic thyroid within the uterus. Yilmaz et al. [4]. reported a 45-year-old woman who was admitted to the Gynaecology Department of the Dicle University Medical Faculty for a hysterectomy after the incidental finding of multiple uterine leiomyomas. The patient's thyroid gland was slightly enlarged upon palpation due to multinodular goitre. The patient had had fine-needle aspiration biopsy for diagnosis but the result of the aspiration was reported as benign. Macroscopy examination of the hysterectomy specimen showed a deformed uterus due to numerous intramural and subserous leiomyomas; the endometrial mucosa was found to be moderately atrophic

and the cervix was affected by erosion–re-epithelialization processes (Naboth cysts). The adnexa appeared normal. A sample was taken from a nodular, colloid–haemorrhagic-looking area of 8 mm in diameter in the basal lumina of the endometrium. Histopathology examination of this area had demonstrated a circumscribed lesion with follicles containing some colloid substance. The follicles on pathology were found to be uniform and lined with a monolayered cuboidal epithelium, with neither nuclear atypia nor hyperchromatism; no psammoma bodies or papillary structures were found. This thyroid tissue separated the surrounding tissue without infiltrating it. Immunohistochemistry staining studies by the peroxidase–anti-peroxidase (PAP) method was undertaken on formalin-fixed, paraffin-embedded sections, utilizing rabbit antiserum against human thyroglobulin (Dako, Carpinteria, CA, USA). Epithelial cells and colloid substance in the follicles were noted to have exhibited positive staining for thyroglobulin. The diagnosis was made of ectopic thyroid tissue in the uterus. Yilmaz et al. [4]. made the ensuing summating discussions:

- Ectopic thyroid tissue could be found anywhere along the thyroglossal duct, from the tongue to the mediastinum.
- Less frequently, thyroid tissue had been reported in the heart, the trachea, the oesophagus [36,37]. and even in the duodenum [38]. the biliary tract, the vaginal wall and the sellar region, [[39] but ectopic thyroid in the uterus had not been documented previously in the English literature.
- The incidence of clinically detectable ectopic thyroid is not known because the majority of cases tend to be asymptomatic.
- Ectopic thyroid tissue as measured by the presence of microscopically confirmed thyroid tissue in cadaver tongues might occur in up to 10% of the population [40].
- It is difficult to diagnose the ectopic thyroid tissue preoperatively.
- The histopathology findings in their reported case had demonstrated a close resemblance to the normal thyroid gland, and the immunohistochemical staining for thyroglobulin had confirmed that the follicles filled with periodic acid–Schiff-positive colloid were of thyroid origin.
- Immunohistochemically, calcitonin-positive cells (C-cells) were not detected in the ectopic thyroid tissue [34].
- The possibility that the intrauterine thyroid tissue might represent a solitary metastasis from an occult thyroid cancer needed to be considered.
- It had been iterated that occult thyroid carcinomas are frequent but they are mostly of the papillary type and usually metastasize to the regional lymph nodes rather than to distant organs. [39]
- Histology examination in their reported case could not demonstrate cellular atypia, papillary proliferation and psammoma bodies, which are commonly seen in metastatic occult carcinomas of the thyroid. The possibility of a metastasis from an occult thyroid cancer was unlikely in their reported patient. Nevertheless, there was slightly nodular enlargement of the gland.
- Another possibility is that the inuterin thyroid tissue does represent part of a teratoma, but inuterin teratomas are quite rare. [41]
- and despite examination of large numbers of sections, no elements other than thyroid tissue were noted in their reported case.
- Metaplasia to follicular cells of the endometrial epithelium had not been defined so far.
- Ectopic thyroid tissue within the uterus might be explained in two ways: firstly, and most probably, metastasis of the thyroid follicular epithelial cells via blood; and second, ectopia of the congenital thyroid tissue, which had not been defined up to the time of publication of their case.
- A sample of the patient's thyroid gland was obtained using fine needle aspiration. As a result, in their reported case, metastasis of the benign thyroid follicular epithelial cells through the blood would be the most likely explanation.

Frysak et al [42]. stated the following:

- Thyroid tissue ectopically located within the ovary could be reported accidentally after adnexectomy, but as a primary cause of hyperthyroidism this diagnosis is rare.
- The clinical search for a functional ectopic thyroid tissue requires intense clinical focus and a multidisciplinary approach.

Frysak et al. [42]. reported a patient who had a history of Graves' disease who had undergone thyroidectomy combined with postoperative 131I radioablation. Despite the previous treatment which she had undergone, she developed an outburst of hyperthyroidism ten years later. Only very close follow-up enabled Frysak et al. [42]. to disclose the right condition. The ovarian source of thyroid hormone production was removed by laparoscopic adnexectomy and a right sided benign ovarian struma was confirmed. Frysak et al. [42]. concluded that most patients who are treated by thyroidectomy and radioiodine do not require extended periods of follow-up or postoperative investigations, but when the clinical or laboratory signs change, clinicians should be prepared to perform the necessary re-evaluation in order to provide the best care.

Conclusions

- Ectopic prostate in the ovary (struma ovarii) and ectopic thyroid in the uterus and genital tract can be found in females on rare occasions and they tend to manifest with non-specific symptoms or they may be asymptomatic and diagnosed incidentally.
- A high index of suspicion is required to diagnose ectopic thyroid in the ovary, uterus or genital tract.
- Confirmation of the diagnosis of ectopic thyroid in the ovary and uterus or within the genital tract requires pathology examination of specimen of the lesion in the ovary, uterus or pelvis.

Conflict Of Interest - None

Acknowledgements

Acknowledgements to:

International Journal of Surgical Case Reports (Int J. Surg. Case Rep) and Elsevier Ltd on behalf of IJS Publishing Group Ltd., for granting permission for reproduction of figures and contents of their journal article under Creative Commons agreement under Copy Right © 2018 Published by Elsevier Ltd on behalf of IJS Publishing Group Ltd. This is an open access article under the CC BY license (http://creativecommons.org/licenses/by/4.0/).

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DOI:10.31579/2640-1045/151