Inflammatory Myofibroblastic Tumor in the Thyroid Gland: A Retrospective Case Series Study and Literature Review

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Keywords
Thyroid cancer · Inflammatory myofibroblastic tumor · Ultrasonic examination · Surgery

Abstract

Background: The objective of this study was to investigate the clinical characteristics, diagnosis, and treatment of inflammatory myofibroblastic tumor (IMT) in the thyroid gland. Methods: A total of 17 patients with IMT by pathology from 2010 to 2020 were included in this study. Clinical features, imaging features, treatment, and prognosis were analyzed in this retrospective study. Results: The case series comprised 5 males and 12 females, with an average age of 49.6 ± 15.36 years. The patients were divided into two cohorts: with IMT without further pathological changes and with further pathological changes of the thyroid gland (e.g., nodular goiter or autoimmune thyroid disease). No significant differences were detected in tumor size and extrathyroid extension between the two groups. Fine needle aspiration biopsy examination before the operation was performed in 2 cases, and rapid freezing pathology examination during the operation was performed in 7 cases. Ultrasound images of 5 cases with only one type of pathology, IMT, presented a high and intermediate risk of malignancy. In the other 11 cases with further pathological changes of the thyroid gland, the image could be very low risk of malignancy or benign feature. Only 2 cases showed a high risk of malignancy ultrasound features. 5/17 patients underwent preventive cervical lymph node dissection additional to thyroid surgery. None of the lymph nodes were confirmed positive by postoperative pathology. Thyroid ultrasound, computed tomography scan of the lungs, abdomen ultrasound, and thyroid function tests were routine follow-up tests. During the follow-up period of 26–141 months, 2 cases were lost, and remaining 15 cases had no recurrence or metastasis and were considered cured. Conclusion: IMT in the thyroid gland is a rare disease with a good prognosis and surgical resection is the preferred treatment.

Introduction

An inflammatory myofibroblastic tumor (IMT) is a rare mesenchymal tumor. It is composed of differentiated myofibroblastic spindle cells with numerous plasma cells and/or lymphocyte infiltrates. Recently, IMT has been defined by the World Health Organization (WHO) as a low-grade or borderline mesenchymal tumor [1]. It often occurs in the visera and soft tissue, especially in the lung, and affects the whole body [2], but rarely in the thyroid gland. In previous studies, IMT has been referred to as plasma cell granulomas (PCGs) or inflammatory pseudotumors (IPTs) [3]. PCG is a pseudotumor-like lesion characterized by the polyclonal proliferation of plasma cells mixed with lymphocytes and other inflammatory cells in fibrous tissue. Therefore, we reviewed the previous literature and identified a total of 24 cases of thyroid IMT (17 cases of PCGs, 6 cases of IMT, and 1 case of IPT) (Table 1) [4–27]. Previous studies have shown that thyroid IMT is aggressive and can adhere to the recurrent laryngeal nerve, esophagus, or the surrounding muscles [28, 29]. Immunohistochemistry (IHT) indicated that activin receptor-like kinase-1 (ALK1)-positive thyroid IMT...
Table 1. List of previously reported cases as IMT of the thyroid gland

| Age at onset, years | Sex | Symptoms | Sonographic features | Treatment | ETE | Pathology results | LNM | Follow-up, months | Re-currence | Distant metastasis |
|---------------------|-----|----------|----------------------|-----------|-----|-------------------|-----|------------------|-------------|-------------------|
| Zhang et al. [4]    | 64  | Female   | No (touch the lump)  | Left lobe: single, hypoechoic mass | Left subtotal thyroidectomy + right partial thyroidectomy | No  | Left: IMT + NG    | – 4          | No               | No           |
| An et al. [5]       | 12  | Male     | Neck pain            | Left lobe: single, heterogeneous hypoechoic mass | Left lobectomy | Recurrent laryngeal nerve and esophagus | Left: IMT | – 48             | No          | No               |
| Trimeche et al. [6] | 18  | Female   | No (by physical examination) | Right lobe: single, hypoechoic nodule | Subtotal thyroidectomy | No  | IMT with sclerosing subtype of the thyroid | – 9          | No               | No           |
| Li et al. [7]       | 34  | Female   | No (touch painless neck mass) | Left lobe: single, hypoechoic mass | Left lobectomy | No  | Left: IMT         | – 10         | No               | No           |
| Kim et al. [8]      | 50  | Female   | No (touch the lump)  | Left lobe: oval hypoechoic mass Right lobe: lobulated hypoechoic mass | Total thyroidectomy | No  | Left: IMT Right: follicular adenoma | – 12         | No               | No           |
| Duan and Wang [9]   | 57  | Male     | No (touch painless neck mass) | Left lobe: a hypoechoic mass Right lobe: heterogeneous echo | Subtotal thyroidectomy | Unknown | IMT | – 17          | No          | Right thigh mass |
| Marylilly et al. [10]| 61 | Male     | No (touch painless thyroid swelling) | Right lobe: hypoechoic thyroid mass with cystic degeneration | Total thyroidectomy | Unknown | IMT | – 12          | No          | No           |
| Kojima et al. [11]  | 75  | Female   | No (touch the painless left-neck mass) | Unknown | Left lobectomy | Unknown | PIT | – 10          | No          | No           |
| Holck [12]          | 70  | Female   | Tracheal compression | Unknown | Subtotal thyroidectomy |Unknown | PCG | – Unknown | No          | No           |
| Yapp et al. [13]    | 61  | Female   | A goiter that had enlarged during the preceding year | – | Total thyroidectomy | Unknown | PCG | – 120         | No          | No           |
| Chan et al. [14]    | 35  | Female   | No (touch the neck lump) | – | Subtotal thyroidectomy | Unknown | PCG + colloid nodule | – Unknown | No               | No           |
| Talmi et al. [15]   | 51  | Female   | No                   | – | Hemithyroidectomy | Unknown | PCG | – 11          | No          | No           |
| De Mascarel et al. [16]| 55| Female   | No (touch left-sided neck swelling) | – | Subtotal thyroidectomy | No  | PCG | – 18          | No          | No           |
| Name et al. | Age | Sex | Symptoms | Sonographic features | Treatment | ETE | Pathology results | LNM | Follow-up, months | Recurrence | Distant metastasis |
|------------|-----|-----|----------|---------------------|-----------|-----|-------------------|-----|-------------------|-----------|-------------------|
| Zingrillo et al. [17] | 65 | Male | Tracheal compression | Isthmus and left lobe: a hypoechoic nodule | Total thyroidectomy | No | PCG + Hashimoto | – | – | No | No |
| Li Voon Chong et al. [18] | 29 | Female | Tracheal compression | – | Biopsy, spontaneous regression | RLN | PCG | – | 4 | No | No |
| Martinez et al. [19] | 46 | Female | No (touch a large painless neck mass) | – | Total thyroidectomy | Trap muscles | PCG | – | – | No | No |
| Mugler et al. [20] | 46 | Female | No | Total thyroidectomy | No | PCG + Hashimoto | – | – | No | No |
| Laurent et al. [21] | 35 | Male | Tracheal compression, asthenia, dysphagia | A hypoechogenic gland | Tentative thyroidectomy, corticosteroid | No | PCG + Hashimoto | – | 54 | No | No |
| Ferrer-Garcia et al. 41 [22] | | Male | Neck swelling and dysphonia | Left and right lobe: heterogeneous and hypoechoic mass | Immunosuppressive therapy | Unknown | PCG + Hashimoto | – | – | No | No |
| Kriegl et al. [23] | 50 | Male | Tracheal compression, asthenia, dysphagia | Left lobe: a goiter and the whole gland was hypoechogenic | Nearly total thyroidectomy | Unknown | PCG | 0/2 (left) | – | No | No |
| Deniz et al. [24] | 65 | Male | Large painless neck mass | Unknown | Total thyroidectomy | Unknown | PCG | – | 24 | No | No |
| | 44 | Female | Touch the cervical mass | Unknown | Total thyroidectomy | Unknown | PCG + Hashimoto | – | 12 | No | No |
| Fontenot et al. [25] | 55 | Female | 8-year history of an enlarging goiter | A substantially enlarged thyroid with heterogeneous echo texture without focal nodularity | Thyroidectomy | Unknown | PCG + Hashimoto | – | – | No | No |
| Barber et al. [26] | 89 | Female | Touch a left-sided neck lump | – | Thyroxine treatment | Unknown | PCG + Hashimoto | – | – | No | No |
| Cremonini et al. [27] | 47 | Female | Touch a right subhyoid mass | A hypoechoic, vascularized solid mass with sharp polycyclic margins | Subtotal thyroidectomy | No | PCG + Hashimoto | – | – | No | No |

PCG, plasma cell granuloma; IPT, inflammatory pseudotumor of the thyroid gland; ETE, extrathyroidal extension; LNM, lymph node metastasis.
Table 2. General clinical characteristics of the 17 patients

| Age at onset, Sex | Symptoms | Sonographic features | Treatment | ETE | Pathology results | IHC | LNM | Follow-up, months | Prognosis |
|------------------|----------|----------------------|-----------|-----|-------------------|-----|-----|-------------------|-----------|
| Only-IMT group   |          |                      |           |     |                   |     |     |                   |           |
| 62 Male          | No (touch the lump) | Right lobe: single, heterogeneous hypoechoic mass Left lobe: multiple cyst-solid nodules | Right lobectomy + left tumorectomy | No | Right: IMT Left: TA | (+): Vim, CK, TG, (-): EMA, CD56, Syn, Chr-A | – | 104 | Cure         |
| 63 Male          | No (by physical examination) | Multiple, patchy hypoechoical mass Right lobe: single, hypoechoic nodule | Bilateral partial thyroidectomy | No | Left: IMT Right: SAT + IMT | – | – | 85 | Cure         |
| 66 Male          | No (by physical examination) | Right lobe: single, hypoechoic nodule Left lobe: multiple, cyst-solid nodules | Right lobectomy + left partial thyroidectomy | No | Right: IMT Left: NG | (+): CD68, CD163, CD38, SMA, (-): S100, CD21 | – | 60 | Cure         |
| 29 Female        | 5 days after thyroid cancer surgery from other hospital | Postoperative changes | Right residual lobectomy + right CLN dissection | No | Residual right: IMT | (+): LCA, SMA, CD68, Cys, Vim (-): S100, Des | CLNM 0/2 | 41 | Cure         |
| 46 Female        | No (touch the lump) | Left lobe: single, extremely hypoechoic nodule Left lateral cervical region: abnormal lymph nodes | Left lobectomy + left LLN dissection | Surrounding tissue | Left: IMT | – | LLNM 0/3 | 85 (left) | Cure         |
| M-IMT group      |          |                      |           |     |                   |     |     |                   |           |
| 41 Female        | No (touch the lump) | Right lobe: single, cyst-solid nodule | Right lobectomy | No | NGCD + IMT | – | – | 127 | Cure         |
| 51 Male          | No (touch the lump) | Isthmus: single, cyst-solid nodule | Isthmus thyroidectomy | No | NGCD + IMT | – | – | 117 | Cure         |
| 22 Female        | No (touch the lump) | Right lobe: single, cyst-solid nodule Right central cervical region: abnormal lymph nodes | Right lobectomy + right CLN dissection | Surrounding tissue | NGCD + IMT | (+): Des, Lys, CD68, MSA, (-): CK, TG, EMA | CLNM 0/7 | Lost to follow-up | |
| 36 Female        | No (touch the lump) | Multiple, solid and cyst-solid nodules | Total thyroidectomy + right CLN dissection + right LLN dissection | No | NG + IMT | (+): Vim, SMA, (-): CK, TG, TTF1, CK19, Chr-A | – | 94 | Cure         |
| 61 Female        | No (touch the lump) | Multiple, cyst-solid nodules and patchy hypoechoic area | Right lobectomy + left tumorectomy | No | Left: SAT + IMT Right: NGAH | (+): MSA, Des, CK19, CD56, TTF-1, (-): MC, IgG, TgG4, PTH | – | 60 | Cure         |
| 66 Female        | No (by physical examination) | Multiple, hypoechoic masses, irregular shape, indistinct boundaries | Total thyroidectomy + left CLN dissection + left LLN dissection | Strap muscles | IFT + IMT | (+): Vim, CD38, IgG4, Calponin, (-): S100, ALK, TG, CK, CLNM 0/6 | LLNM 0/3 (left) | Cure         |
| 64 Male          | No (by physical examination) | Multiple, solid and cyst-solid nodules | Left lobectomy + right partial thyroidectomy | No | Left: NGAH + regional IMT Right: NGAH | – | – | 42 | Cure         |
| Age at onset, years | Sex | Symptoms | Sonographic features | Treatment | ETE | Pathology results | IHC | LNM | Follow-up, months | Prognosis |
|---------------------|-----|----------|----------------------|-----------|-----|-------------------|-----|-----|-------------------|-----------|
| 69                  | Female | No (by physical examination) | Left lobe: single, hypoechoic nodule All lobe: multiple solid and cyst-solid nodules | Left lobectomy + right tumorectomy | No | Left: NG + regional IMT Right: NG, TA | (+): SMA, Desmin, Calponin, ALK, CD163 (−): S100, CD69, CD117 | – | 26 | Cure |
| 31                  | Female | No (by physical examination) | Right lobes: single, hypoechoic and solid nodule | Right partial thyroidectomy + right CLN dissection | No | NG + IMT | – | CLNM 0/1 (right) | 97 | Cure |
| 40                  | Female | No (by physical examination) | Multiple, cyst-solid nodule | Total thyroidectomy | RLN | Right: NGAH + IMT Left: NGAH | (+): Vim, CD68 (−): Des, S100, D34, TG, TTF-1, CK | – | 60 | Cure |
| 36                  | Female | No (by physical examination) | Left lobe: single, cyst-solid nodule | Left partial thyroidectomy | Strap muscles | NGCD + regional IMT | – | – | 141 | Cure |
| 60                  | Female | No (touch the lump) | – | Total thyroidectomy (subternal) | No | Right: NGAH + regional IMT Left: NGAH | – | – | – | Lost to follow-up |

IMT, inflammatory myofibroblastic tumor; SAT, subacute thyroiditis; NG, nodular goiter; TA, thyroid adenoma; NGAH, nodular goiter with adenomatoid hyperplasia; NGCD, nodular goiter cystic degeneration; IFT, invasive fibrous thyroiditis (Riedel thyroiditis); ETE, extrathyroidal extension; RLN, recurrent laryngeal nerve; CLN, central lymph node; LLN, lateral lymph node; CLNM, central lymph node metastasis; LLNM, lateral lymph node metastasis; LNM, lymph node metastasis; IHT, immunohistochemistry; (+), positive; (−), negative.
was highly aggressive [7]. However, the current data suggest that most thyroid IMT has a good prognosis and does not show any evidence of recurrence or metastasis after surgical resection. Only 1 case showed recurrence with metastasis after surgery. The clinical data of 17 patients with pathologically diagnosed IMT in the thyroid gland at the Fourth Hospital of Hebei Medical University were collected. The clinical cases were analyzed retrospectively and summarized to improve the clinical understanding of IMT in the thyroid gland.

Materials and Methods

Patients
The clinical data of 17 patients with IMT in the thyroid gland diagnosed at the Fourth Hospital of Hebei Medical University between January 2010 and December 2020 were collected. The diagnosis was confirmed by 2–3 senior pathologists in our hospital. Fine needle aspiration biopsy examination was performed in 2 cases before the operation, and rapid freezing pathology examination was performed in 7 cases during the operation. The inclusion criteria: IMT in the thyroid gland was confirmed by histopathological examination. The exclusion criteria were as follows: (1) No surgical treatment, no pathological evidence of thyroid IMT; (2) IMT in the cervical tissue but not in the thyroid. To determine the differences in clinicopathological features, imaging, and prognosis between patients with IMT without further pathological changes and those with pathological thyroid gland changes (such as nodular goiter (NG) or autoimmune thyroid disease), the two groups were divided according to whether there was only one pathological type in the thyroid gland. The cases that presented only one pathological type, IMT, comprised the only IMT group (Only-IMT). The other types of pathological lesions, such as subacute thyroiditis, NG, thyroid adenoma, nodular goiter with adenomatoid hyperplasia, and invasive fibrous thyroiditis (Riedel thyroiditis), were also observed that were defined as the mix IMT group (M-IMT). Herein, 17 cases met the requirements. The main demographic characteristics, including gender, age, presentation symptoms, tumor size, extrathyroid extension, lymph node metastasis, imaging features, pathological results, surgical methods, and prognosis as well as clinical data of the patients, were collected retrospectively. The patients were followed up every 6 months through outpatient and/or telephone contact until September 2021. The baseline clinical characteristics are shown in Table 2. This retrospective analysis has been approved by the Ethics Committee of the Fourth Hospital of Hebei Medical University. All participants fully understood the experimental protocol and signed informed consent forms.

Imaging and Pathological Review
Sixteen cases underwent cervical ultrasound examination before operation. Of these, 2 cases underwent cervical computed tomography (CT) examination before operation. For pathological diagnosis, sections were reviewed to ensure that they met the criteria for the fifth edition of the WHO classification of soft tissue and bone neoplasms [30]. The pathologist assessed the cellular morphology, nuclear atypia, vascular invasion, and inflammatory components of the pathological sections. The specimens were fixed in 10% neutral formaldehyde solution at room temperature for 24 h and embedded in paraffin. Then, 3-mm thick glass slides were heated at 65°C for 2 h, the wax and water were removed, and the antigen was retrieved, according to the manufacturer’s protocols. The sections were conventionally stained with hematoxylin-eosin (HE) and observed under an optical microscope (magnification, ×10, ×20, ×40), and the images were analyzed by the EnVision method. The antibodies, smooth muscle actin (SMA), vimentin (VIM), and Desmin (Des), were purchased from Shanghai Biological Company to determine the pathological phenotype of IMT and identify the IPT's sarcomas, cancers, dendritic cell tumors, or vascular tumors.

Statistical Methods
SPSS 24.0 statistical software was used for data analyses. Normally distributed measurement data were expressed as X ± SD. The enumeration data were expressed as cases or percentages; χ² test and Fisher’s exact probability method were used for comparison between groups. All statistical tests were two-sided probability tests, and p < 0.05 indicated statistical significance.

Results

Patients’ Characteristics
The cohort comprised 5 males and 12 females, with a male to female ratio of 1:2.4. The mean age was 49.6 ± 15.36 (range, 22–69) years. Five cases presented only one pathological type IMT, of which 4 were confined to one side of the one lobe, and 1 case was the residual lobe of thyroid carcinoma. Multiple types of thyroid pathologies were observed in 12 cases in the M-IMT group. In addition to IMT, NG was observed in 4 cases, 4 cases also showed nodular goiter cystic degeneration, 2 cases exhibited nodular goiter with adenomatoid hyperplasia, 1 case displayed subacute thyroiditis, and 1 case showed invasive fibrous thyroiditis (Riedel thyroiditis) (Table 2).

Among the 17 patients, 1 had a history of Hashimoto’s thyroiditis, and 2 had a history of hyperthyroidism. However, none of the 17 patients had obvious clinical symptoms, such as obvious hoarseness, numbness in hands and feet, dyspnea, coughing while drinking water, and dysphagia. Moreover, 8 cases were identified by touching the painless neck mass, 8 were detected during physical examination, 1 case was required a second operation. Thyroid function was abnormal in 4 cases, 1 had subclinical hypothyroidism, 1 was subclinical hyperthyroidism, and 2 were abnormal with TgAb or TPOAb. None of them received thyroid-specific medication.

Imaging, Pathological Features, and Treatment
Using the American Thyroid Association (ATA) US pattern risk assessment [31], 16 patients underwent preoperative ultrasonography. The nodules of 3 cases were classified as high risk of malignancy feature, 2 were intermediate, 2 were low, and 2 were very low, while 7 cases were classified as benign. Moreover, 5 cases in the Only-IMT group presented a high or intermediate risk of ultrasonic malignancy feature of ATA guideline. The imaging
findings of them were extremely hypoechoic, hypoechoic mass, or heterogeneous echo with irregular shape and unclear boundary, accompanied by a strong echo plaque (Fig. 1a–d). 1/5 showed postoperative changes (Fig. 1d) while 8/11 cases of the M-IMT group showed signs that met the imaging of benign tumors of ATA guideline by ultrasonography or CT, such as cystic or cyst-solid nodules with clear boundaries and smooth surfaces. Some of these could occupy the entire gland, with or without calcification, and blood flow signals were visible in ultrasonic imaging (Fig. 1e–h). One case showed signs of inflammation: patchy low or high echo, irregular shape, and no calcification, usually confined to one gland lobe, with blood flow signal (Fig. 1l). Only 2 cases met signs of high malignancy of ATA guideline: the single low echo and solid nodule, aspect ratio >1, with obscure boundaries, with or without calcification, with visible surrounding blood flow signals, and with or without cyst-solid nodules. In conclusion, for thyroid nodules, ultrasound findings in the Only-IMT group were more similar to malignant nodules of the ATA guideline classification. But there was no significant difference between the lymph nodes imagings of two groups. The cortical medulla boundary of the central or lateral cervical lymph nodes was not distinct, and the doors of lymph nodes had disappeared (Fig. 1i–k). One case showed signs of inflammation: patchy low or high echo, irregular shape, and no calcification, usually confined to one gland lobe, with blood flow signal (Fig. 1l). Two cases showed benign lesions by CT (Fig. 2a–d).

All the patients were confirmed by pathology, except 1 case of thyroid cancer whose primary tumor size could not be tracked after surgery in another hospital. The remaining 16 cases had tumors with a diameter of 0.5–7.0 cm and a mean size of 2.72 cm. Gross examination revealed that the neoplasms were mostly located in glands and were ductile with the gray matter when incised. Conventional pathological staining revealed the loose or dense arrangement of fusiform muscle fibroblasts and fibroblast-like tumor cells with fascicular or layered structures and infiltration of acute and chronic inflammatory cells, mainly composed of plasma cells and lymphocytes (Fig. 3a–d). All 17 cases underwent conventional pathological staining, and IMT can be divided into three basic histological morphologies by fibroblast/myofibroblast, inflammatory cell, and stromal characteristics [16]: (i) mucus-vascular type, similar to nodular fasciitis; (ii) compact spindle cell type, similar to various spindle cell neoplasms; (iii) oligofibrous form resembling scarring or desmofibromatosis. According to the above analysis and classification, 11/17 cases were type II, and 6/17 cases were type III. IHT was only used for the diagnosis of 9 patients who could not be confirmed by conventional pathological diagnosis. According to the comprehensive

![Fig. 1. Ultrasonographic image of the cases in only IMT group (a–d) and M-IMT group (e–l). a Heterogeneous hypoechoes mass. b Patchy low echo-level mass. c Hypoechoic nodule. d Postoperative changes. e–g Mixed echogenic nodules. h Cystic nodule. i Low echo-level masses, the anterior capsule is interrupted. j Hypoechoic nodule. k Lateral cervical lymph node. l Patchy hypoechoic area.](image-url)
Fig. 2. Radiological analysis of the cases in M-IMT group. a The two lobes of thyroid gland are enlarged, with slightly lower density and less clear margins. b The enhanced scan is relatively low-density. c Multiple enlarged lymph nodes. d Multiple posterior sternal thyroid nodules were fused with each other, some of which were located posterior to the sternum.

Fig. 3. Cytomorphological analysis by HE staining of IMT in the thyroid gland. Thyroid follicular cells and long spindle cells contained small nuclei with vesicular chromatin and lymphocytes and scattered plasma cells. Magnification, ×10 (a, b), ×20 (c), ×40 (d).
immunohistochemical judgment, the positive rate of VIM expression was the highest (Fig. 4a) (5/9), followed by SMA (4/9; Fig. 4c), Des (3/9; Fig. 4b). All the 17 patients underwent surgical treatment, including partial thyroidectomy resection in 4 cases, unilateral thyroidectomy resection plus isthmus in 3 cases, unilateral thyroidectomy resection plus isthmus and contralateral part in 5 cases, total thyroidectomy resection in 4 cases, and residual lobectomy in 1 case after surgery. 5/17 cases were subjected to central or lateral lymph nodes dissection. No additional radiotherapy or chemotherapy was administered after surgery. Subsequently, 2 cases were lost to follow-up, with a follow-up rate of 88.2%. The median follow-up time was 79.4 (range, 26–141) months among the remaining 15 patients. All the patients received levothyroxine replacement therapy. Thyroid ultrasound, CT scan of the lungs, abdomen ultrasound, and thyroid function tests were routine follow-up tests. Thyroid-stimulating hormone (TSH), free tri-iodothyronine (FT3), and free thyroxine (FT4) were assessed in the thyroid function test. For only 1 patient with IMT and papillary thyroid carcinoma, we controlled TSH at 0.1–0.5 µIU/mL in the first year after surgery and adjusted the TSH dose at 0.5–2.0 µIU/mL after 1 year due to the thyroglobulin values and dynamic evaluation. Within 2 years of follow-up, thyroid function was tested every 1–3 months and imaging every 6 months. After 2 years of follow-up, the thyroid function was tested every 6 months and imaging every year. The TSH of the other patients was controlled at 0.5–2.0 µIU/mL. Within 1 year of follow-up, thyroid function was tested every 1–3 months and imaging every 6 months. After 1 year of follow-up, the thyroid function was tested every 6 months and imaging every year. All patients sur-

Table 3. Clinical characteristics between Only-IMT group and M-IMT group

| Clinical characteristics | Only-IMT, n | M-IMT, n | p value |
|--------------------------|------------|----------|---------|
| Sex                      |            |          |         |
| Male                     | 3          | 2        | 0.063   |
| Female                   | 1          | 10       |         |
| BMI, kg/m²               |            |          |         |
| <25                      | 2          | 9        | 0.547   |
| ≥25                      | 2          | 3        |         |
| Age, years               |            |          |         |
| <50                      | 1          | 6        | 0.585   |
| ≥50                      | 3          | 6        |         |
| Diameter, cm             |            |          |         |
| ≤1                       | 1          | 4        | >0.99   |
| >1                       | 3          | 8        |         |
| ETE                      |            |          |         |
| Yes                      | 1          | 3        | >0.99   |
| No                       | 3          | 9        |         |

BMI, body mass index; ETE, extrathyroidal extension. Statistically significant (p < 0.05). All calculated using χ² test.

Fig. 4. IHT analysis of tissues. a VIM(+). b Desmin(+). c SMA(+).
vived without death, recurrence, and metastasis were considered cured (Table 2).

Comparison of Clinical Features between Only-IMT and M-ITM Groups

The IMT group consisted of 5 cases, except 1 case was after local resection of thyroid cancer in another hospital, and the remaining 4 were primary. A total of 12 patients in the M-IMT group were IMT with additional pathological changes in the thyroid gland (e.g., NG or autoimmune thyroid disease). No significant differences were detected in gender, age, body mass index, tumor diameter, and extraglandular invasion (Table 3).

Discussion

IMT was first reported in 1939 and easily misdiagnosed as a highly malignant sarcoma. It usually occurs in children and adolescents, with a male to female ratio of 1:3 [32]. The most common organ is the lung [2, 33], and head and neck IMT usually occurs in orbital [34] and sinus [35]. The incidence of extraocular head and neck IMT constitutes about 5% of all cases [28] and is rare in the thyroid gland. Unlike other sites, thyroid IMT is predisposed in women (15/20) with a mean age of 51 (range, 18–89) years [5]. The statistical results are similar to those in the current study (Table 1). However, the exact etiology and pathogenesis of IMT remains unclear. The main factors leading to the development of IMT [36, 37] include inflammation, trauma, surgery, autoimmune etiology, viral infection, and abnormal repair (mainly myofibroblast proliferation). In addition, IMT is associated with chromosomal rearrangements involving 2p23 near or within ALK [38]. Among these cases, 9/17 patients were associated with inflammatory, traumatic, surgical, and autoimmune diseases consistent with the above developmental factors.

The clinical manifestations of IMT are closely related to the site of primary foci [39] and may be accompanied by systemic symptoms such as pain and fever. For example, pulmonary IMT may cause chest pain and dyspnea [40], while patients with the abdominal disease may present jaundice and gastrointestinal obstruction [41]. Head and neck IMT is mainly characterized by local pain and local tissue swelling [42]. IMT in the thyroid may be asymptomatic or present only as a diffuse mass in the thyroid region, which may be hard, fixed, and painful. If the mass compresses adjacent organs, such as the trachea and esophagus, corresponding uncomfortable symptoms would be appeared, such as shortness of breath and discomfort in swallowing [5]. Hypothyroidism may occur if Hashimoto’s thyroiditis is detected. None of the cases showed no obvious clinical symptoms regardless of the size of the mass. This is similar to previous studies.

The imaging features of IMT in clinical examination lack specificity, and neither CT nor MRI can distinguish IMT from inflammation. Ultrasounds are the most economical and simple means of examination that can elucidate the echo, location, boundary, blood supply, and the correlation of the lesion. IMT occurs in the thyroid gland and is easily detected by ultrasound because of its superficial location. Among the cases reported previously, 7 thyroid IMT showed hypoechoic nodules, isolated or multiple, with or without calcification, irregular boundaries, and blood flow signals, which were similar to the ultrasound findings of differentiated thyroid cancer. One case was cystic solid with unclear boundary and abundant blood flow signal, and 1 case was hyperechoic nodular. Based on the ultrasound results of 17 patients in 10 years, thyroid tumor with only one type of pathological IMT is manifested as hypoechoic nodules on ultrasound, which may be extremely hypoechoic or heterogeneous and tends to be malignant or inflammatory. However, the ultrasound images of the M-IMT group showed nonspecificity, but benign large-diameter nodules are common. Combined with the medical history, intracapsular hemorrhage is found in most cases, which might be related to IMT occurrence factors such as inflammation and traumatic stimulation. However, ultrasound images alone are difficult to identify the thyroid IMT. Based on the above images, we speculated that most ultrasound images of thyroid IMT present malignant signs and cannot be missed easily. However, combined with postoperative pathological reports, no cervical lymph node metastasis was observed, but combined with preoperative ultrasound, the biopsy during the operation broadens the patient’s surgical scope. Therefore, preoperative needle aspiration pathology is recommended to reduce this probability.

The diagnosis of thyroid IMT is based on pathological reports, and the pathological morphology is dominated by fibroblasts and smooth muscle cells [43], i.e., the proliferation of myofibroblasts. This disease type is different from other non-neoplastic or neoplastic pathologies [27]. According to the analysis of the three basic histological morphologies of IMT, the current study demonstrated that the second type of thyroid IMT was dominant. It was speculated that the pathological type of thyroid IMT differed from that of the other parts of the IMT, and most of the thyroid IMT infiltrated into the fibrous stroma via lymphocyte plasma cells to varying degrees, especially in thyroid PCG [10, 26]. The WHO classification of lung tumors recommends that PCG not be used as a synonym for IMT in the lung [1]. However, this guideline is not clear in the thyroid. Herein, fibrohistiocytic hyperplasia occurred in 8 cases of thyroid IMT, of which 6 were the second type of IMT. These results were similar to the findings of previous studies. In terms of immunohistochemical staining, IMT was diffusely positive for vimentin (Vim), locally or diffusely

DOI: 10.1159/000524489
IMT in the Thyroid Gland

positive for SMA and muscle-specific actin (MSA), and positive for ALK, Actin, Des, and calponin [42, 44]. S100, CD21, CD23, CD34, CD117, caldesmon, and myoglobin were negative. Immunohistochemical staining was employed to confirm the diagnosis and differential diagnosis. The positive expression of SMA, MSA, and Vim supports the diagnosis of IMT [45]. The above histopathological characteristics and immunohistochemical results were combined for a comprehensive clinical judgment. However, for patients with autoimmune diseases, such as Hashimoto’s thyroiditis, clinical manifestations need to be combined for differential diagnosis [46]. Herein, only 9 cases underwent immunohistochemical staining when conventional pathological staining could not confirm the diagnosis, which was pathologically insufficient. The differential diagnosis of IMT is based on conventional pathological staining, which could lead to misdiagnosis. Thus, clinical pathologists are suggested to perform routine IHT to confirm the diagnosis of IMT-type thyroid diseases.

IMT is a low-grade malignant or borderline tumor with slow progression, and surgery remains the preferred treatment based on the anatomic location. For patients who cannot be surgically resected, a combination of immunosuppressants, chemotherapeutic agents (cisplatin, doxorubicin, methotrexate, and vincristine), or radiotherapy may be used [47]. However, the patients with a single aggressive tumor do not respond satisfactorily to combination therapy [48]. Currently, there is no consensus on the effective treatment of head and neck IMT. Previous studies have shown that IMT is locally invasive and prone to recurrence. For example, the local recurrence rate of extrapulmonary IMT is about 25%. Although the metastasis rate is only 2%, the recurrence rate of head and neck IMT can be about 50% [42]. Thus, surgery is still the leading method for head and neck IMT [29]. The principle is to preserve the function during radical resection. Postoperative radiotherapy and chemotherapy are recommended for patients with incomplete tumor resection or positive tumor margin [29]. Some studies have shown that thyroid IMT is invasive and can adhere to the surrounding muscles, recurrent laryngeal nerve, and esophagus [5, 9]. However, most patients exhibit a good prognosis after surgery, with only 1 patient having a recurrence and soft tissue metastasis at 17 months after surgery [9]. In this study, patients who underwent intraoperative lymph node dissection showed no metastasis in the postoperative pathology. The imaging (thyroid and abdomen ultrasound and CT scan of the lungs) was tested for postoperative follow-up. To date, none of the 17 patients had a recurrence or distant metastasis. Also no significant difference was detected in the diameter and invasion between the two groups. Therefore, for the scope of thyroid IMT resection, resecting the thyroid gland lobe on the diseased side is recommended, and levothyroxine for replacement and supplementary therapy after surgery is administered for the postoperative thyroid function tests. Routine preventive cervical lymph node dissection, immunosuppression, radiotherapy, and chemotherapy are not recommended. On the other hand, preserving the function of vital structures such as nerves, trachea, or esophagus during operation is prioritized due to a good prognosis. Nonetheless, clinical, biological, and radiographic follow-up is essential. Since this study is a single-center retrospective study, it has limitations due to the small number of individuals. The follow-up of new cases will be continued, and a multicenter study will be conducted in the future.

Conclusion

In conclusion, thyroid IMT is a rare tumor composed of spindle muscle fibroblasts, but the etiology is yet unclear. It can be detected by preoperative ultrasound examination, and the definite diagnosis mainly depends on postoperative pathology and IHT. In order to determine an effective surgical range, needle aspiration pathological examination and intraoperative freezing should be added. Currently, thyroid IMT is considered to have a better prognosis than other IMTs. However, the number of IMTs is small, and long-term follow-up data are not sufficient, necessitating a close follow-up.

Acknowledgments

The authors thank the patients and healthy volunteers for their cooperation and participation in the study.

Statement of Ethics

The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. This study was approved by the Ethics Committee of the Fourth Hospital of Hebei Medical University and Hebei Tumor Hospital (2021KS028). All participants fully understood the experimental protocol and signed informed consent forms. Patient consent for publication is not applicable.

Conflict of Interest Statement

The authors have no conflicts of interest to declare. The authors do not have financial interests or conflicts to report.

Funding Sources

This study was supported by the Hebei Province Natural Scientific Fund (No. H2020206273) and Department of Health of Hebei Province Grant (No. 20190085).
Author Contributions

(i) Conception and design: Ping Shi and Yanzhao Wu; (ii) administrative support: Yanzhao Wu and Huijing Shi; (iii) provision of study materials or patients: Yanzhao Wu and Huijing Shi; (iv) collection and assembly of data: Ping Shi and Lan Zhang; (v) data analysis and interpretation: Ping Shi and Lan Zhang; (vi) manuscript writing: all authors; and (vii) final approval of manuscript: all authors.

Data Availability Statement

The datasets used and/or analyzed in the current study are available from the corresponding author upon reasonable request.

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