Castleman disease coexisting with papillary thyroid carcinoma: A case report

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Received September 19, 2024; Accepted January 22, 2025

DOI: 10.3892/ol.2025.14964

Abstract. Castleman disease (CD) is a rare lymphoproliferative disorder of unknown etiology characterized by lymph node enlargement. CD cannot be confirmed by preoperative puncture cytology, and definitive diagnosis depends on postoperative histopathology. Due to the lack of characteristic clinical manifestations and imaging features, in clinical practice, CD is often easily missed or misdiagnosed, and it is frequently mistaken for lymphoma or autoimmune diseases. Cases of CD that coexist with papillary thyroid carcinoma (PTC) are particularly rare and are often misdiagnosed as PTC with lymph node metastasis. The present study discusses the diagnosis, treatment process and prognosis of a case involving PTC that is complicated with unilateral, single-center CD. This patient was diagnosed with a right lobe nodal gland of the thyroid gland combined with a mass in the left supraclavicular fossa. The postoperative pathological examination revealed a right lobe papillary carcinoma of the thyroid gland with metastasis of the right cervical lymph node combined with CD in the left supraclavicular fossa. The immunohistochemical results of the right cervical lymph node were thyroglobulin (+), thyroid transcription factor-1(+). Immunohistochemical results of left supraclavicular fossa mass: Bcl-2 (low expression in the germinal center, high expression outside), Bcl-6 (germinal center +), Cyclin D1 (-), cluster of differentiation 38 (focally+). In future clinical practice, when encountering PTC with mediastinal masses, clinicians should consider not only common lymph node metastases but also the possibility of CD. Overall, this study aims to provide valuable insights and experience for clinicians regarding CD and PTC.

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Key words: Castleman disease, papillary thyroid carcinoma, mediastinum mass

Introduction

Papillary thyroid carcinoma (PTC) is the most common subtype of thyroid cancer, accounting for ~90% of the major histological types (1). The widespread use of imaging techniques has led to a year-on-year increase in the incidence of PTC among the general population of the world. Although thyroid carcinoma has a relatively low mortality rate compared with its incidence, due to its slow progression and effective treatment options, PTC has the highest relative survival rate among thyroid cancer types (1). Globally, the age-standardized incidence of thyroid cancer in 2020 was 10.1 per 100,000 women and 3.1 per 100,000 men, with age-standardized mortality rates of 0.5 per 100,000 women and 0.3 per 100,000 men (2).

Castleman disease (CD), first described in 1954 (3), is a heterogeneous lymphoproliferative disorder that commonly occurs in the neck, mediastinum and abdomen (4,5). Based on lymph node involvement, CD can be classified into unicentric CD (UCD) and multicentric CD (MCD). UCD involves the enlargement of a single lymph node or multiple lymph nodes within a single lymph node station, and most patients are asymptomatic (5). By contrast, MCD is a systemic, progressive and often fatal disease characterized by widespread lymphadenopathy (6). Histologically, CD can be divided into three types: Hyaline vascular (HV), plasma cell (PC) and mixed variant (MV), with the latter encompassing features of both HV and PC (7). Most UCD cases are histologically classified as the HV type (5).

PTC frequently metastasizes to the cervical lymph nodes. In previous studies, it was shown that lateral cervical lymph node metastasis was identified in 3,915 (20.9%) of 18,741 patients with papillary thyroid carcinoma (PTC) (8). Therefore, when PTC presents with lateral cervical masses, the possibility of tumor metastasis should be considered. However, mediastinal masses, which can be benign or malignant, require differential

diagnosis. Primary mediastinal tumors, such as congenital, inflammatory, neurogenic tumors, thymomas and benign cysts account for ~60% of surgically resected lesions. Lymphomas, teratomas and granulomatous diseases comprise for another 30%, while vascular lesions, typically aortic aneurysms, account for 10% in non-surgical series (9). Rare diseases such as CD and schwannomas should also be considered. The case presented in the current study initially suggested PTC with metastasis to different lymph nodes, but the patient was ultimately diagnosed as PTC combined with contralateral UCD, a rare occurrence. The present report aims to improve understanding, reduce the missed or incorrect diagnosis of CD, and enhance patient survival and treatment outcomes.

Case report

In May 2023, a 28-year-old Asian woman underwent a medical examination at Weixin County People's Hospital (Zhaotong, China). Her primary care physician's initial B-ultrasound of the thyroid revealed a solid hypoechoic nodule in the right thyroid lobe (class 4a) measuring 1.1x0.8 cm^2. The patient was initially monitored with follow-up observation and no further treatment. In October 2023, the patient came to the Affiliated Hospital of Southwest Medical University (Luzhou, China) for further evaluation and treatment. A thyroid B-ultrasound performed in the thyroid surgery clinic showed a slightly hypoechoic mass in the middle and upper part of the right thyroid lobe, measuring ~1.17x0.95 cm^2. The mass was located close to the capsule, with an aspect ratio >1, irregular shape, ill-defined boundaries, a solid internal structure and strong punctate echo (Fig. 1A). The left thyroid lobe and isthmus showed no apparent lesions. Multiple low-echo areas were found in the right neck region IV, with a regular shape and clear boundaries, the largest measuring 0.5x0.3 cm^2, and in region VI, the largest measuring 0.8x0.6 cm^2. A 4.6x1.9 cm^2 hypoechoic mass was detected in the left supraclavicular fossa (Fig. 1B), showing a regular shape, clear boundaries and poorly defined cortico-medullary boundaries. Clinical examination revealed an asymptomatic, enlarged, painless and fixed mass in the left supraclavicular fossa. Fine-needle aspiration under ultrasound guidance showed the following: A right thyroid nodule; Bethesda System for Reporting Thyroid Cytopathology (10) grade VI; papillary thyroid carcinoma; and a left supraclavicular mass. Microscopic evaluation showed numerous lymphocytes. A chest computed tomography (CT) scan showed tracheal diverticulum with no significant findings. Nasal fibrolaryngoscopy showed chronic pharyngitis and vocal nodules. The patient had no significant medical, surgical or social history, no known exposure to infection, and routine blood tests showed no significant abnormalities in liver and kidney function.

Based on preoperative findings, the initial diagnosis was papillary thyroid cancer with left supraclavicular lymph node metastasis. A preliminary plan was made for right lobectomy and isthmus thyroidectomy with central lymph node dissection and bilateral cervical lymph node exploration. Intraoperative frozen section results showed papillary carcinoma metastasis in the right cervical lymph nodes (2/18). No papillary carcinoma metastasis was detected in the left cervical lymph nodes. A complete capsular mass (Fig. 2) was found in the left supraclavicular fossa, suggestive of CD.

Following standard thyroid cancer treatment guidelines (11), the procedure was expanded to a total thyroidectomy and right cervical lymph node dissection. The patient experienced no significant complications postoperatively and was discharged on postoperative day 5. Postoperative pathology revealed papillary carcinoma in the right lobe of the thyroid. The tumor cells were arranged in a papillary, follicular structure. The tumor nuclei were enlarged and overlapped, round or oval, ground glass like, the nuclear membrane thickened, the karyotype was irregular and nuclear furrows were visible. Obvious interstitial hyperplasia and sclerosis were detected (Fig. 3A), measuring 0.6x0.4x0.4 cm^3, with capsular invasion but no vascular or nerve invasion. No malignancy was found in the left thyroid lobe. Cancer metastasis was detected in the central lymph nodes: A total of 6 lymph nodes were examined, with 2 showing cancer metastasis (2/6). No cancer metastasis was found in the left lateral cervical lymph nodes: A total of 15 lymph nodes were examined, with 0 showing cancer metastasis (0/15). Cancer metastasis was detected in the right lateral cervical lymph nodes: A total of 30 lymph nodes were examined, with 2 showing cancer metastasis (2/30). The left supraclavicular fossa showed a complete capsular tubercle that is characteristic of lymphoproliferative disease, and postoperative pathological examination showed that the lymph node follicles were increased, dispersed, the sheath area was widened, the germinal center was atrophic, and a sheath area surrounded multiple germinal centers. The small lymphocytes in the mantle area were widened, showing 'onion skin'-like changes, the interfollicular area and the germinal center showed hyalinous vascular hyperplasia, and the endothelial cells in the germinal center proliferated into a glassy shape. In addition, the small blood vessels were vertically inserted into the atrophied germinal center, resembling 'lollipop'-like changes (Fig. 3B and C).

Positive immunohistochemical results of right cervical lymph node supported metastatic papillary thyroid carcinoma with thyroglobulin (Tg)(+) (Fig. 4A) and thyroid transcription factor 1 (TTF-1)(+) (Fig. 4B). Immunophenotyping of the left supraclavicular mass suggested mixed-type CD with cluster of differentiation 3 (T region +), cluster of differentiation 20 (B region +), cluster of differentiation 79a (B region +), cluster of differentiation 5 (T region +), cluster of differentiation 10 (germinal center +), Bcl-2 (low expression in the germinal center, high expression outside) (Fig. 4C), Bcl-6 (germinal center +) (Fig. 4D), cluster of differentiation 21 (follicular dendritic network), CyclinD1(-) (Fig. 4E), cluster of differentiation 38 (focally+) (Fig. 4F), Ki-67 (high expression in the germinal center, low expression outside); *in situ* hybridization for Epstein-Barr (EB) virus-encoded small RNA (EBER) was negative.

At 21 days postoperatively, the patient returned for Iodine-131 radiotherapy. To rule out MCD, a comprehensive CT examination of the abdomen, chest and pelvis was repeated, showing no enlarged lymph nodes elsewhere, no abnormal symptoms and there were no laboratory abnormalities.

Discussion

CD was first described in 1954 (3), and its prevalence remains low, with an estimated annual incidence of 4,300 to 5,200 in

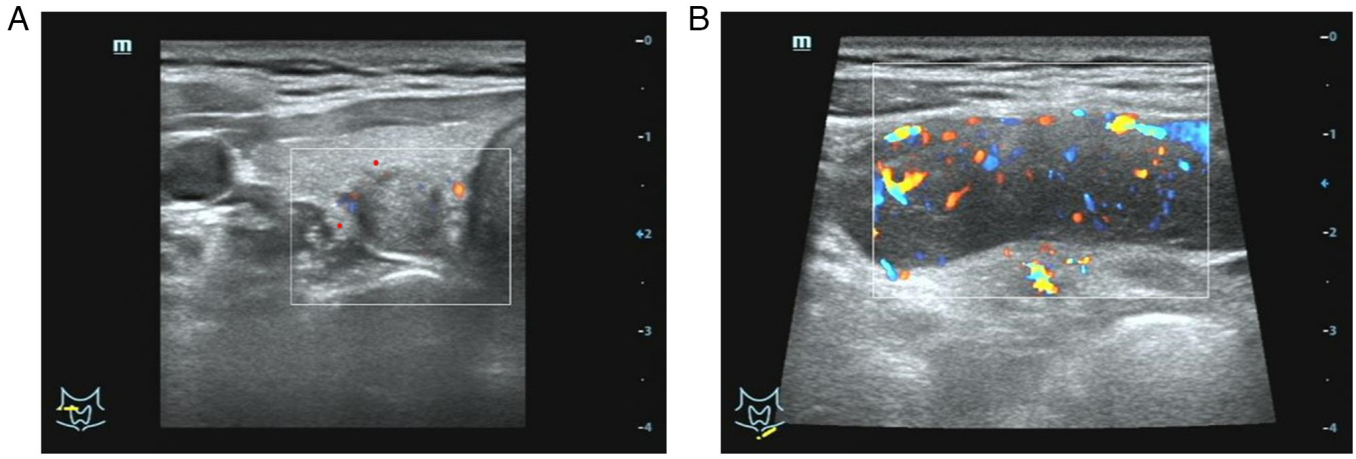

Figure 1. Preoperative ultrasound Doppler thyroid examination in October 2023. (A) hypoechoic nodules in the right thyroid gland. (B) An abnormal lymph node in the left supraclavicular fossa.

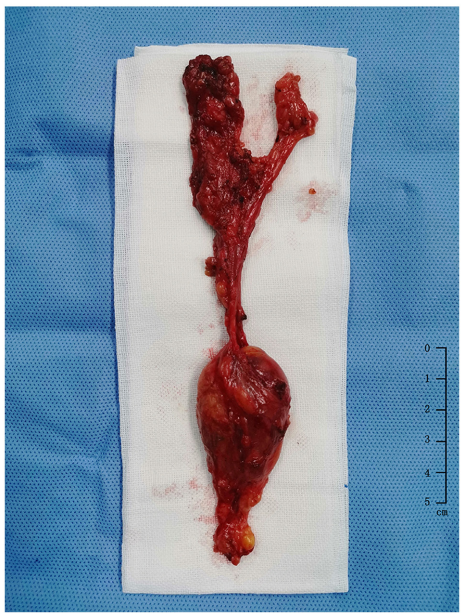

Figure 2. Gross surgical specimen. The mass was located in the left supraclavicular fossa with an intact envelope and was 4.6x3.0x1.9 cm^3 in size.

the United States (12). CD that coexists with PTC is even rarer, and in cases of PTC with a neck mass, CD is often overlooked. Initial assessments in the present case presumed PTC metastasis; however, the contralateral mass did not support this, ultimately leading to a diagnosis of PTC with contralateral UCD based on pathology.

UCD can occur at any age, and opinions on sex predilection differ. Some studies suggest no sex preference for UCD (5,13), while others suggest a slight female predominance (4,14). The average age of onset for MCD is higher than that for UCD, with a higher male proportion (12). Among 65 patients diagnosed with CD in the pathological database of Henan Provincial People's Hospital (Zhengzhou, China), 60% (n=20) of patients with UCD were female, while 65% (n=21) of patients with MCD were male, with mean onset ages of 36.1±18.0 years (UCD) and 40.9±19.9 years (MCD) (14). From a review of 775 articles from PubMed in 2017, 1,133 cases were extracted, and it was found that 58% of patients with UCD were female and 63% of patients with MCD were male, with mean ages of 34±17 years (UCD) and 48±18 years (MCD) (15). Both PTC and UCD are more common in female patients, and cases of PTC combined with UCD are rare. When PTC and UCD appear in female patients at the same time, evaluating whether there are potential pathogenic factors is worthy of further study.

UCD most commonly affects single lymph nodes or lymph node regions in the mediastinum, neck, abdomen and retroperitoneum (13). UCD can also occur in rare locations, such as the orbit, lungs, kidneys, nasopharynx and small intestine (16-20). UCD is typically asymptomatic, and produce normal laboratory tests. Severe complications such as paraneoplastic pemphigus (PNP), polyneuropathy, pulmonary complications and autoimmune hemolytic anemia may occur (21). By contrast, MCD presents a broader range of clinical and laboratory abnormalities (22). In a retrospective study, the most common symptoms and findings in MCD were shown as follows: i) Fever (78.8%); ii) inguinal lymphadenopathy (83.3%); iii) hepatomegaly (74.1%); iv) splenomegaly (90.3%); v) arthralgia (83.3%); vi) abdominal pain (40%); vii) fatigue (33.3%); viii) diarrhea (100%); and elevated serum C-reactive protein levels (63.4%) (22). The present case involved unicentric CD in the left supraclavicular region, with no symptoms and normal laboratory tests, and no complications observed post-surgery.

Preoperative diagnosis of CD is difficult. Currently, international consensus guidelines for diagnosis and treatment have been developed for idiopathic Multicentric CD (iMCD) and UCD (23,24). CD can only be definitively diagnosed by biopsy and microscopic examination (5). In addition, the guidelines recommend a series of laboratory and radiological tests such as CT or PET-CT, blood tests, bone marrow tests, inflammatory markers and organ function determination tests, EBER and latency associated nuclear antig-1 staining to exclude diseases with similar histopathological features to UCD, such as MCD, lymphoma, infection, autoimmune disease and primary or acquired immune deficiency (23). Preoperative imaging and fine-needle aspiration cytology often lead to misdiagnosis as lymphoma or autoimmune disease. However,

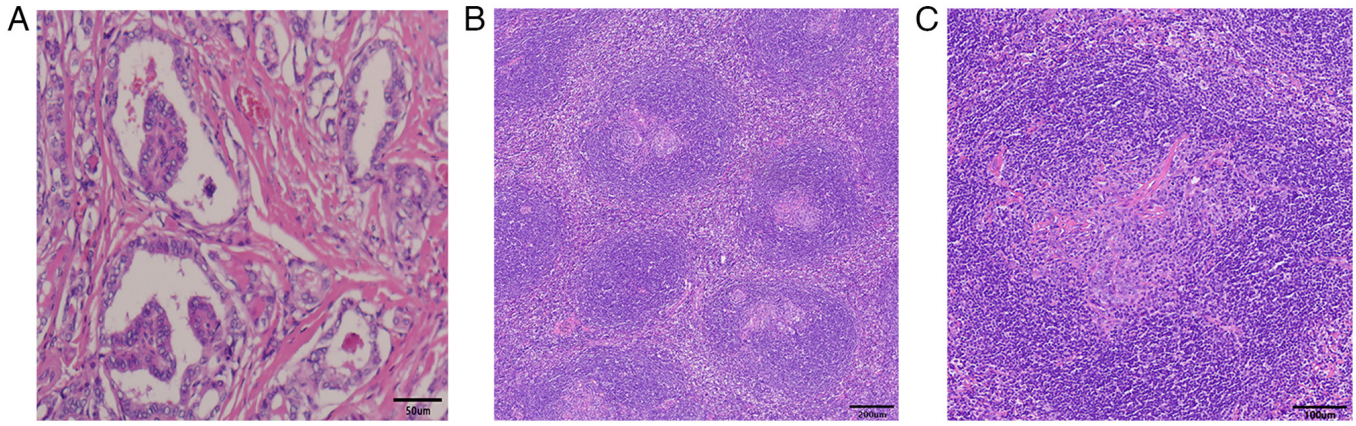

Figure 3. Histopathological examination. (A) The tumor cells are arranged in a papillary, follicular structure. The tumor nuclei were enlarged and overlapped, round or oval, ground glass-like, the nuclear membrane thickened, the karyotype was irregular and nuclear furrows were visible. Obvious interstitial hyperplasia and sclerosis (magnification, x200; scale bar, 50 μm). (B) The follicles of lymph nodes were increased, had a scattered distribution, the sheath area was widened, the germinal center atrophied and it was observed that one mantle area surrounded multiple germinal centers. The small lymphocytes in the mantle area were widened and showed 'onion-skin'-like changes, and the hyperplastic hyalinoid vessels were observed in the interfollicular area and germinal center (magnification, x40; scale bar, 200 μm). (C) Vascular endothelial cells in the germinal center proliferated and became glassy, and small blood vessels can be observed inserting vertically into the atrophied germinal center, a 'lollipop'-like change (magnification, x100; scale bar, 100 μm).

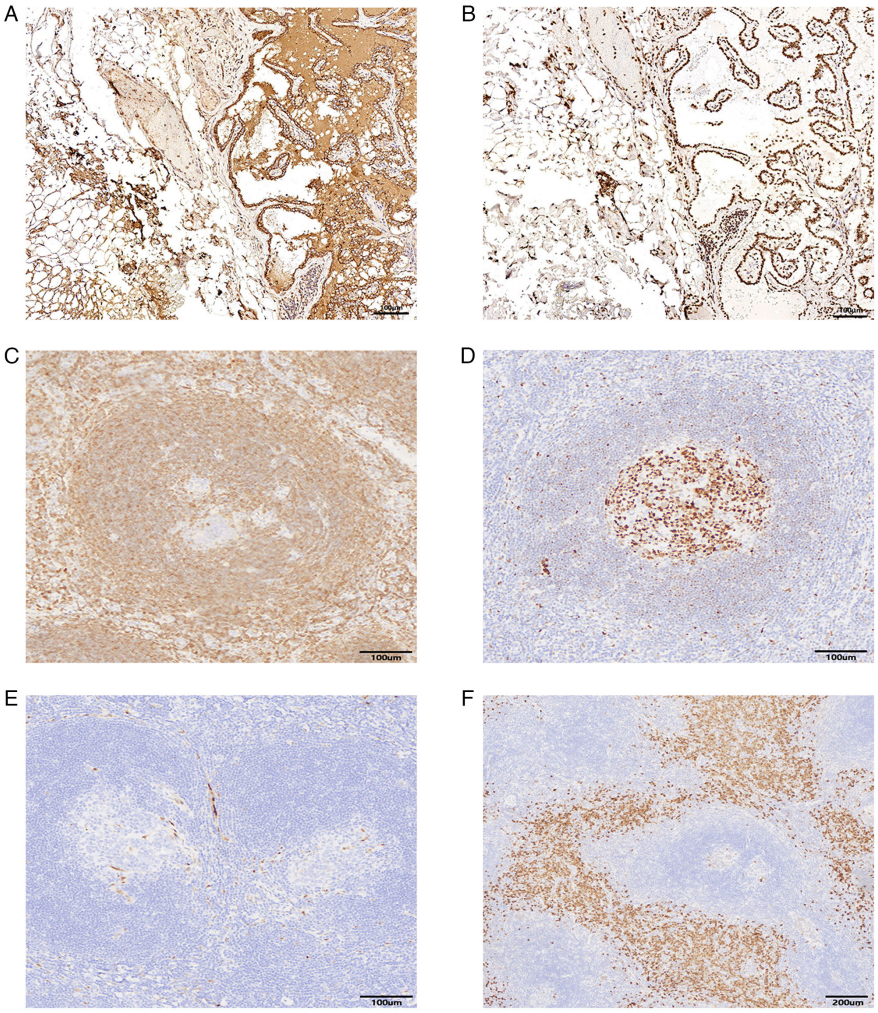

Figure 4. Immunohistochemical results of right cervical lymph node and Immunohistochemical results of left supraclavicular fossa mass. Right cervical lymph node: (A) Thyroglobulin immunohistochemical staining was positive (magnification, x100; scale bar, 100 μm); (B) Thyroid transcription factor-1 immunohistochemical staining was positive (magnification, x100; scale bar, 100 μm). Left supraclavicular fossa mass: (C) BCL-2 immunohistochemical staining showed that the sheath area widened significantly and atrophy of the germinal center (magnification, x100; scale bar, 100 μm); (D) BCL-6 immunohistochemical staining showed positive germinal center staining (magnification, x100; scale bar, 100 μm); (E) Cyclin D1 immunohistochemical staining was negative (magnification, x100; scale bar, 100 μm); (F) cluster of differentiation 38 immunohistochemical staining showed a large number of plasma cells in the interfollicular region (magnification, x40; scale bar, 200 μm).

imaging can assist in identifying lesion location and number to differentiate UCD from MCD and rule out other conditions. CD often shows well-defined, mildly hypodense or isodense, homogeneous lymph nodules on nonenhanced CT/MRI, with intermediate and marked enhancement on contrast-enhanced CT/MRI. Calcification and hypertrophied vessels may be valuable diagnostic features (25).

PC is the most common histological type in MCD, and HV is common in UCD, and the MV is rare for both (4,5). Analysis of 1,086 cases indicated that 77% of UCD cases were of the HV type, 16% of the PC type and 7% mixed type, while 62% of MCD cases were PC type, 20% HV type and 18% were of the mixed type (15). The results of immunohistochemistry also have certain significance for the diagnosis of CD. For mixed-type CD, Bcl-2 staining shows low expression in the germinal center and high expression outside the germinal center; Bcl-6 staining shows positive staining in the germinal center; and cluster of differentiation 38 staining shows positive staining of interfollicular plasma cells (26). In the present case, the immunohistochemical staining results of the left supraclavicular mass were: i) Bcl-2 (low expression in the germinal center, high expression outside); ii) Bcl-6 (germinal center +); and iii) cluster of differentiation 38 (focally+), which were consistent with the immunohistochemical results of mixed-type CD reported in the literature (26,27).

In addition, the diagnosis of CD needs to be differentiated, such as mantle cell lymphoma. Some articles have shown that the Cyclin D1 immunohistochemical staining of mantle cell lymphoma is positive (28). However, the Cyclin D1 staining result in the present case was negative, which can be used as evidence to exclude mantle cell lymphoma.

Compared with CD, the diagnosis of PTC lymph node metastasis is much easier. Among the immunohistochemical indicators, TG and TTF-1 are more important. TG is a protein secreted by thyroid follicular epithelial cells, and TTF-1 is a transcription factor expressed in the thyroid follicular epithelium and alveolar epithelium. When TG and TTF-1 are both positive, it strongly suggests that the tumor originates from thyroid tissue. In the present case, the immunohistochemical staining of TG and TTF-1 in the right cervical lymph node was positive, suggesting that the tumor originated from the right papillary thyroid carcinoma. This is consistent with the results reported in the previous literature (29,30). At 21 days after surgery, abdominal, chest and pelvic CT ruled out MCD, thereby confirming a diagnosis of PTC with mixed UCD based on international guidelines. To date, to the best of our knowledge, no similar case of PTC with mixed CD involving heterogenous regions has been reported.

Complete surgical resection is typically curative for UCD, making it the preferred first-line treatment (4,13,23). For unresectable UCD, patients with an inflammatory syndrome, the anti-interleukin-6 monoclonal antibody Siltuximab is recommended (23). For unresectable UCD with symptoms due to compression of nearby critical structures, medication treatment (such as rituximab or steroids) can be employed. After conservative treatment, if surgery becomes feasible, surgical resection is preferred (23). For patients who remain unresectable after conservative treatment, asymptomatic cases may be monitored, while radiotherapy may be considered for symptomatic cases (23). UCD treatment prognosis is favorable, with most surgically resected patients experiencing good survival and quality of life. In a retrospective study, it was shown that 43 of 47 surgical patients achieved complete remission post-surgery, while 11 out of 13 patients in the watchful waiting group remained stable for up to 17 years, with an estimated 5-year overall survival rate of 98.4% (21). However, patients with UCD have an increased risk of developing PNP, a rare and fatal autoimmune disease, which is considered an independent adverse prognostic factor (31).

MCD treatment typically involves systemic therapy, and surgery is generally not recommended. Patients MCD often have a poorer prognosis than patients with UCD. A Japanese study of 342 CD patients reported a median disease duration of 3.7 years, with 59.0, 40.6 and 20.1% surviving for more than 3, 5 and 10 years, respectively (32).

The present case study involved PTC associated with UCD. The patient underwent total thyroidectomy and resection of the Castleman mass. The patient was followed up for >21 days postoperatively without any significant discomfort or abnormal findings. With no complications or HIV infection, a diagnosis of UCD was favored, and further adjuvant therapy was deemed unnecessary, with follow-up observation considered sufficient. Based on this case, it is suggested that when imaging shows local enlarged lymph nodes, clinicians should not only consider thyroid cancer metastasis but also other possible causes of cervical lymph node enlargement, including CD.

In conclusion, in future clinical practice, when encountering PTC with mediastinal masses, clinicians should consider not only common lymph node metastases but also the possibility of CD. For the diagnosis of CD, postoperative histopathology is a necessary condition for the diagnosis of CD, but laboratory and imaging tests and clinical symptoms are still important.

Acknowledgements

Not applicable.

Funding

The present study was funded by The Southwest Medical University University-Level Project (grant no. 2020ZRQNB052).

Availability of data and materials

The data generated in the present study may be requested from the corresponding author.

Authors' contributions

FW and HL obtained and analyzed the patient's information and wrote the manuscript. RH, KC, JY, SL and XZ obtained and analyzed the patient's information and reviewed the discussion part of the clinical diagnosis and treatment. YL provided the pathological images and made pathological diagnosis. SL and XZ partially revised the article and generated the figures. FW and XZ confirm the authenticity of all the raw data. All authors have read and approved the final manuscript.

Ethics approval and consent to participate

The study was approved by the Ethics Committee of the Affiliated Hospital of Southwest Medical University (LuZhou, China; ethics approval no. KY2024265).

Patient consent for publication

Written informed consent to publish this case information and accompanying images was obtained from the patient and their family.

Competing interests

The authors declare that they have no competing interests.

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