Diagnostic Pathology

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A rare case of rib chondrosarcoma with purely mesenchymal cells metastases to thyroid

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Abstract

Metastasis to the thyroid gland is uncommon. The most common malignant tumors that metastasize to the thyroid gland include renal cell carcinoma, colorectal cancer, lung cancer, and breast cancer. Metastasis of chondrosarcoma to thyroid is extremely rare.

We describe a rare case of rib chondrosarcoma metastases to the thyroid gland. We reviewed patient characteristics, histological presentations, treatments, time of recurrence on chondrosarcoma, and metastasis situation. Additionally, we review all English articles reporting cases of chondrosarcoma metastasis to the thyroid gland that have been published in Embase, PubMed, and ISI WEB of Science databases (1981–2023) in this paper.

Only 7 cases of chondrosarcoma metastasis to the thyroid have been reported, including one report written in French. (Otmany et al. in Médecine Du Maghreb 53–54, 2001). We found that most patients are female adults, with compression signs or pain, most of whose metastases occurred after several years, and whom have poor prognoses. The main examinations are CT and ultrasound, the primary treatment is surgery, and the major pathological characteristic is coexistence of chondrocytes and mesenchymal cells.

The case we describe here is the first report of mesenchymal chondrosarcoma metastasis to the thyroid gland with only pure mesenchymal cells and no chondrocytes. Moreover, these rare cases highlight the necessary of communication between radiologists, histopathologists, and clinicians. It is meaningful to acquaint previous malignant tumor for diagnosing the metastases to the thyroid gland.

Keywords Chondrosarcoma, Metastasis, Thyroid, Histopathology, Treatment

Introduction

Thyroid gland is featured with fast blood flow. Its high oxygen saturation and iodine content discourage the growth of malignant cells. Malignancy metastasis to thyroid is extremely rare. The metastasis of chondrosarcoma is mainly hematogenous and the most frequently reported site is lung. To the best of our knowledge, only 7 cases of chondrosarcomas metastases to the thyroid gland have been reported yet, included one case in French. Here, we present a case which the thyroid metastasis from costal chondrosarcoma after 8 years of treatment.

Patients and methods

Our case is a 33-year-old woman. She experienced an underappreciated intermittent pain in the chest wall 12 years ago. Ten years ago, as the pain worsened, she underwent resection of mass in the left 6th rib. The pathology confirmed the diagnosis of high-grade chondrosarcoma which invaded the peripheral soft tissue with

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R0 resection, considering mesenchymal chondrosarcoma. Follow-up was done regularly with normal examination until 2015, when lung metastasis was detected with no interventions. From 2018, she received system treatment of molecular target therapy (Afatinib, 500 mg, oral, once daily, for 6 mouths), radiotherapy (100%GTV 66 Gy/15f for metastasis, 95%PTV 60 Gy/15f for expansion), and radiofrequency ablation (inferior lobe of right lung) during next years. The treatment response was defined as stable disease. In March 2021, ultrasonography detected a right-sided large, solid, isoechoic, and lobulated node with calcifications and peripheral vascularity and remarkable isthmus, as well as left thyroid lobe, with no local or specific symptoms of thyroid mass, primarily considering follicular neoplasm. The reexamination found that it grew fast during the 4 months follow-up interval. In July 2021, she underwent total thyroidectomy.

Analysis of the mass in our hospital showed a solid tumor measuring about 23 mm*17 mm*15 mm, with white gray cut surface and lobular contour. The tumor was uniformly composed of dense, short, and spindle-shaped cells that grew in solid sheets, with a high nuclear to plasma ratio, and mitotic figures were easy to see. The tumor infiltrated the thyroid parenchyma and as well as the adipose connective tissue around the thyroid with pushing border. Numerous intramuscular tumor thrombi could be seen around the tumor (Fig. 1A and B).

In the initial absence of medical history, this histological morphology required the identification of multiple possibilities, such as high-grade synovial sarcoma, rhabdomyosarcoma, spindle cell subtype of medullary thyroid carcinoma, among others. However, the results of immunohistochemistry and other work had ruled out the above possibilities.

After reviewing the patient's medical history, we resampled the whole rest of the tumor, and only irregular patchy scar tissue was observed in the center of the tumor nodule. No cartilage components were found.

From the sections of the patient's previous rib chondrosarcoma (sections provided form Center Hospital Chinese Academy of Medical Science), we found that the primary tumor was a typical mesenchymal chondrosarcoma, and the components of highly differentiated chondrosarcoma were very clear and significant. The mesenchymal components were highly similar to the morphology of this thyroid metastatic tumor (Fig. 1C and D).

Thyroid tumors were stained with S100, CD99, and SOX9 (Fig. 1E), all of which were diffuse positive. NCOA2 FISH detection showed gene breakage (Fig. 1F). All these above test results ultimately confirmed that the tumor in this case was a metastasis of the mesenchymal component of the rib mesenchymal chondrosarcoma.

By observing and collecting, we summarized and analyzed the characteristics of the case reports. We also searched for English articles published in Embase, PubMed, and ISI Web of Science databases by using "chondrosarcoma" and "thyroid" as the key words. The search results showed that only 7 cases of chondrosarcoma metastasis to thyroid have been reported yet, included 1 case published in French and its original article was not obtained, we have not discussed it in this paper. We reviewed and reported the following data: the demographic data, primary site, presenting symptoms, treatment of secondary carcinoma, type of chondrosarcoma, pathological features, and survival time (Table 1). Based on the literature review, we correspondingly analyzed and extrapolated, exploring the new findings and applying the value in clinical practice.

Results

Table 1 summarizes the clinical circumstances of the 6 cases previously published in English and our report of chondrosarcoma metastasis to thyroid [2–7]. The ages of the patients at presentation are all adults, most are females. The original sites in the reported cases are limbs; however, in our case, the tumor is located on rib. Most patients present clinical symptoms, such as large mass on the neck, dysphagia, dyspnea, even laryngeal paresis. The methods for detecting metastasis to thyroid include CT, ultrasound, and FNAB, and every patient underwent at least one of these examinations. Furthermore, surgeries are received by most patients and the types of chondrosarcoma are been confirmed with mesenchymal chondrosarcoma and dedifferentiated chondrosarcoma, and the prognosis is generally poor, that is the survival time of 5 patients are ranging from several days to two years. Interestingly, in the literatures that have been reported, pathological manifestations are included chondrocytes and mesenchymal cells; yet, in our case, the pathological manifestations have only mesenchymal cell component, deserving our attention.

Discussions

Metastasis to the thyroid gland is exceedingly rare [8, 9]. The average age of patients with thyroid metastatic cancer is 60 to 70, and most of them are female (female to male ratio = 1.4 to 1) [10]. Based on recent literature, the most frequent primary sites of tumors metastasizing to the thyroid are kidney, colorectal, lung, breast, skin, and sarcoma [11]. Chondrosarcoma is a rare malignant mesenchymal tumor of chondrogenic nature and predominantly metastasis to the lung, skin, and soft tissue by hematogenous spread, while metastasis to the thyroid is extremely infrequent [3].

The main clinical manifestations of the patients were goiters, neck swelling, dysphagia, dysphonia,

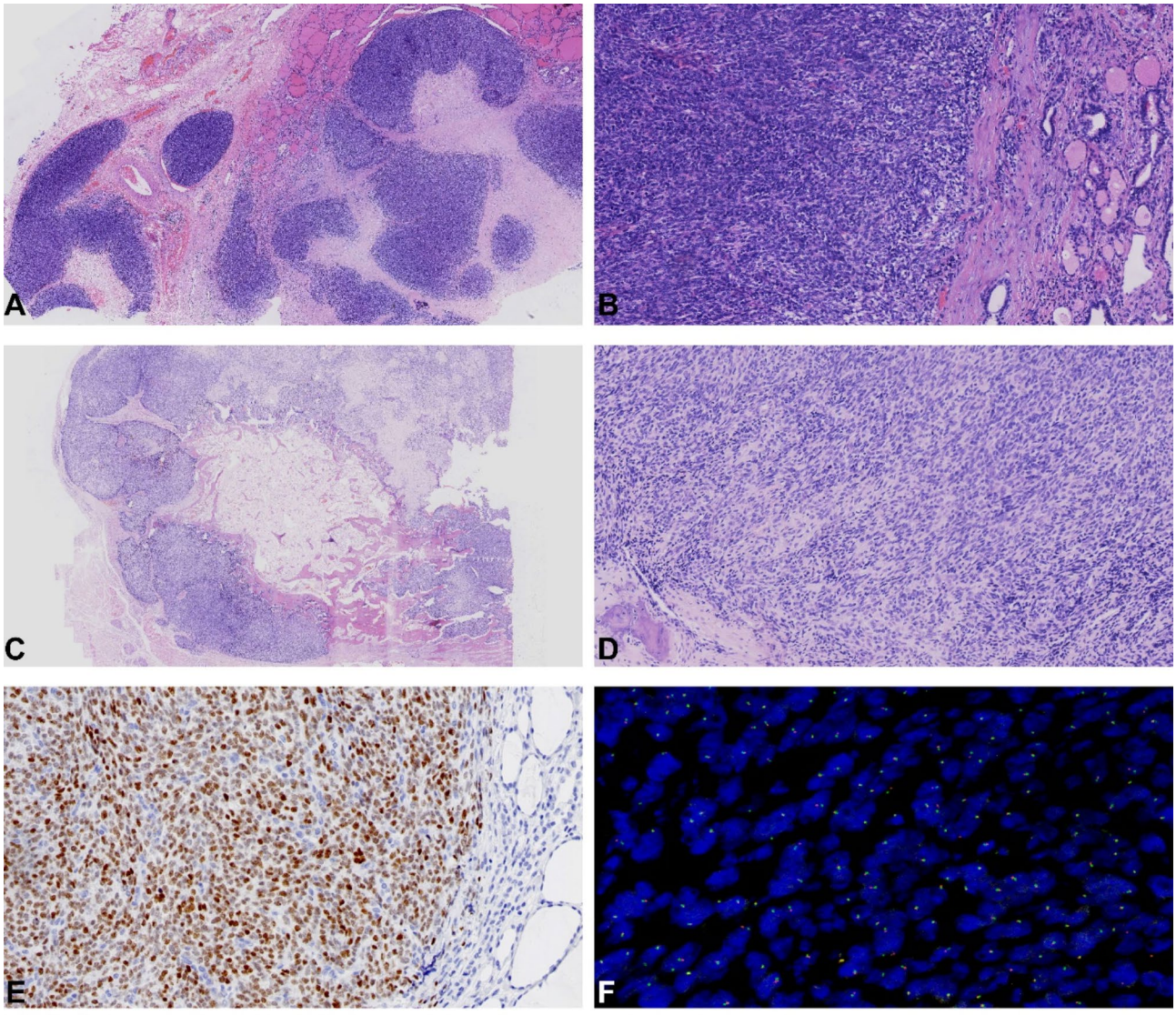

Fig. 1 (**A**) The tumor grew in a multinodular or lobular shape, with irregular fibrous scar formation visible in the center. The tumor involved the adipose connective tissue outside the thyroid gland, and several intra-venous tumor thrombi could be seen. (**B**) The tumor cells were arranged in solid large areas, with short spindle shaped cells with good consistency, high nuclear cytoplasmic ratio, and dark nuclear staining. (**C**) The pathological section of the patient's rib chondrosarcoma 8 years ago showed that the tumor also shows obvious lobulated growth, destroying bone tissue, and involving soft tissue outside the bone cortex. The tumor consisted of two types of tissue components, relatively mature cartilage tissue (upper and upper right in the picture), and dense short spindle like mesenchymal components. (**D**) The short spindle-shaped mesenchymal component was highly similar to the morphology of the thyroid metastasis. (**E**) SOX9 immunohistochemistry staining shows diffuse positive signals in tumor cell nuclei. (**F**) NCOA2 FISH separation probe detection shows a red green signal separation in the nucleus of the tumor (arrows), indicating NCOA2 gene breakage

hoarseness, and cough similar to primary thyroid tumors [12]. In the 6 cases, only 3 have reported varying degrees of the above symptoms, including goiters (3/3), neck swelling (1/3), dysphagia (1/3), and dysphonia (2/3). Some recent studies show that the thyroid function of most patients with metastases to the thyroid gland is normal, however, some patients may have hypothyroidism or hyperthyroidism. there was only one of these reports underwent lab test and recorded the function of thyroid gland is normal [2].

Ultrasound is the first choice for imaging examination of thyroid diseases. Suspicious features for thyroid cancer include microcalcifications, nodule hypo-echogenicity, irregular margins, and a taller-than-wide shape on a transverse view. However, compared with typical features of primary thyroid tumors, the typical ultrasonographic findings of secondary thyroid neoplasms include ill-defined hypoechoic nodules and intra-nodular angiogenesis [13]. In our case, the ultrasonographic findings is cystic-solid nodules, the causes of cystic degeneration been proved is the rapid growth

Table 1 Summary of reported cases of chondrosarcoma metastasis to thyroid

Reference	Nachawi et al[2]	Wu, et al[3]	Simon et al[4]	Ortiz at al[5]	Darouassi et al[6]	Bakx et al[7]	Our case
Age 1	N/A	51	48	23	51	N/A	25
Age 2	24	55	62	27	53	N/A	33
Sex	male	female	male	female	female	N/A	female
Primary site	N/A	left thigh	right femur	left lower limb	right tibia	N/A	right sixth rib
Presentation of metastasis to thyroid	right thyroid lobe enlargement	No	large mass, mild dysphagia, dyspnea	No	hard mass, dyspnea, a right laryngeal paresis	N/A	No
Diagnostic modalities	physical examination, ultrasound, CT	ultrasound	CT, ultrasound	CT	CT	N/A	ultrasound, CT
Ultrasound Features	solid hypoechoic nodules with coarse calcifications	N/A	heterogenic mass	No	No	N/A	cystic-solid nodules with microcalcifications
Treatment	chemotherapy	right subtotal thyroidectomy and left lobectomy	total thyroidectomy	right lobectomy	debulking surgery with tracheostomy	N/A	total thyroidectomy
Type	mesenchymal chondrosarcoma	mesenchymal chondrosarcoma	dedifferentiated chondrosarcoma	mesenchymal chondrosarcoma	dedifferentiated chondrosarcoma	N/A	mesenchymal chondrosarcoma
Specimen	core-needle biopsy	surgical specimen	surgical specimen	surgical specimen	surgical specimen	N/A	surgical specimen
Pathological features	Chondrocytes and mesenchymal cells	chondrocytes and mesenchymal cells	N/A	chondrocytes and mesenchymal cells	poorly differentiated with chondroid foci	N/A	pure mesenchymal cells
Survival time	N/A	died two years later	died several months later	N/A	died several days later	N/A	alive

Note:

Age 1: Age at diagnosis of primary

Age 2: Age at diagnosis of metastasis

El Otmany et al. [1] was reported by French and its original article was not obtained, we have not discussed it in this paper

of metastatic cancer and insufficient blood supply, followed by necrosis and liquefaction [14], indicating that the tumor is has high malignant degree.

The other imaging studies, including computer tomography (CT), positron emission tomography computed tomography (PET–CT), fine needle aspiration biopsy (FNAB), and core-needle biopsy (CNB), are reported to be the most important tool for differential diagnosis of secondary thyroid neoplasms from primary thyroid cancer. Specifically, CNB should be considered to aid further diagnosis whenever the FNAB results are not convincing. Immunohistochemistry (IHC) is instrumental in distinguishing secondary thyroid neoplasms from primary thyroid tumors, even to determine the source of primary tumors in metastases to the thyroid gland [15]. FNAB/CNB combined with IHC analysis is a specific method for the diagnosis of metastasis to the thyroid gland, it can also distinguish the primary location of the tumor and has high accuracy.

Conventional chondrosarcomas, which constitutes approximately 85% of all chondrosarcomas, can be categorized based their location in bone into central, peripheral, and juxtacortical chondrosarcomas. Central and peripheral chondrosarcomas are histologically similar, and for both, three different grades are discerned. Grade I chondrosarcomas are lowly cellular with chondroid matrix and absent mitoses, mitoses are found in grade II chondrosarcoma, a high cellularity with muco-myxoid matrix changes are found in grade III chondrosarcoma [16]. Aside from conventional chondrosarcoma, several rare subtypes of chondrosarcoma are discerned, including dedifferentiated, mesenchymal, and clear cell, together constituting 10–15% of all chondrosarcomas. The dedifferentiation chondrosarcoma develops in 10–15% of chondrosarcoma [17, 18], mesenchymal variant represents less than 3% of all chondrosarcomas [19]. Dedifferentiated chondrosarcoma is a high-grade, non-cartilaginous sarcoma next to a (usually low-grade) malignant cartilage-forming tumor, with a remarkably sharp, as reported by Darouassi et al. [6] Mesenchymal chondrosarcoma is a highly malignant, which occur in bone and soft tissue of relatively young patients. It has a characteristic biphasic histological pattern composed of highly undifferentiated small round cells and islands of well-differentiated hyaline cartilage. Histological diagnosis of mesenchymal chondrosarcoma is very difficult in the absence of well differentiated cartilage components, and its morphology is very similar to many other high grade soft tissue sarcomas, such as rhabdomyosarcoma, high-grade synovial sarcoma, malignant peripheral nerve sheath tumor, among others. Furthermore, differentiation from spindle cell subtypes of medullary thyroid carcinoma is more needed in the thyroid gland. IHC is conducive to differential diagnosis, as mesenchymal chondrosarcoma typically consistently express S100, CD99, and SOX9. More than 90% of mesenchymal chondrosarcoma have del (8) (q13.3q21.1), leading to *HEY1-NCOA2* gene fusion. These tests can assist in effective diagnosis and differential diagnosis of mesenchymal chondrosarcoma.

However, in our case, we only detected highly undifferentiated small round or spindle cells without islands of well-differentiated hyaline cartilage, which lead to an erroneous diagnosis of rhabdomyosarcoma. After comparing with the histology slides of thyroid and rib lesions from the Center Hospital Chinese Academy of Medical Science, the diagnosis was confirmed as metastases from rib mesenchymal chondrosarcomas. Lin et al. [20] reported a similar case diagnosed with mesenchymal chondrosarcoma arising in the central nervous system, which histological examination demonstrated a purely small, round cell appearance in specimen. The two characteristic components have a tendency in traditional mesenchymal chondrosarcomas; however, occasional cases show a gradual merging of the two elements. More importantly, the proportion of each element is highly variable as seen in our case where only the undifferentiated small cell element was present.

For all grades and subtypes of nonmetastatic chondrosarcoma, complete surgical treatment offers the only chance for cure, however, the most optimal type of surgical management is still debated due to. Wide, en-bloc excision is the preferred surgical treatment of intermediate- and high-grade chondrosarcoma cases [21]. Local adjuvant treatment can only be successfully used in lesions confined to the bone and some cases of low-grade chondrosarcoma, intralesional excision may not be adequate [22]. As chondrosarcomas has a relatively low fraction of dividing cells, and radiotherapy (RT) acts at dividing cells, chondrogenic tumors are considered relatively RT resistant. Therefore, doses > 60 Gy are needed in attempts to achieve local control after incomplete resection. Particle therapy has been proved to better sparing of critical structures close to the tumor, especially in skull base [23]. Chemotherapy is generally not effective in chondrosarcoma, especially in the most frequently observed conventional type and the rare (low-grade) clear cell variant [24]. Interestingly, both RT and chemotherapy seem to helping mesenchymal chondrosarcomas. Additional potential targets for systemic therapy for the different chondrosarcoma subtypes are being discussed [25]. Once metastasis to the thyroid gland is diagnosed or strongly suspected, surgical management should be considered. However, the indication of

thyroidectomy is still controversial because of the poor prognosis in such cases [13]. If the primary tumor is well-controlled and patients with metastases to the thyroid gland develop oppressive symptoms, there is no reason to avoid thyroidectomy. In case with poor control of the primary tumor, however, thyroidectomy for well-differentiated thyroid cancer is not recommended because the thyroid cancer may not be critical under such condition. Compared with primary thyroid tumors, secondary thyroid neoplasms are not sensitive to radioactive iodine. Therefore, for patients who cannot undergo surgical treatment, RT or chemotherapy is feasible, but like chondrosarcomas, the effect might not be ideal [9]. Recent studies have shown that immune checkpoint inhibitors and tyrosine kinase inhibitors may have greater application prospects in metastasis to the thyroid gland is diagnosed [26]. In our case, the female underwent RT and Afatinib (tyrosine kinase inhibitor), and obtained a relative better good effect. Over 6 cases, the prognosis is poor, most of them are died after several months even several days.

Conclusions

We report a very rare case of mesenchymal chondrosarcoma metastasis to the thyroid gland with a purely short spindle-cell appearance in slices. As in the few other cases reported in the literature, it appeared many years after the primary cancer. Metastasis to the thyroid gland itself is not common, and the clinical manifestations are not specific. FNAB combined with IHC analysis is a specific method for the diagnosis of secondary thyroid neoplasms. Surgical treatment is still the main treatment, supplemented by necessary RT, chemotherapy, and target therapy after surgery. However, the prognosis of patients with thyroid metastatic cancer is still not optimistic. Therefore, when thyroid abnormalities are found in patients with previous or present malignant tumors, the possibility of metastasis to the thyroid gland should be considered first, and more importantly, compared to previous pathologic sections to obtain a better diagnosis.

Author contributions

Jia Wang performed the conception and design of study, acquisition of data, performed data analysis and wrote the manuscript, Fang Mei performed data analysis and interpretation and wrote the manuscript and given critical revision, Mingcheng Li performed acquisition of data and given critical revision, Shibing Song given critical revision and approval of final version of manuscript, Xin Li performed the conception and design of study and approval of final version of manuscript. All authors have acknowledged the inclusion of the additional authors.

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Data availability

No datasets were generated or analysed during the current study.

Declarations

Competing interests

The authors declare no competing interests.

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