Primary undifferentiated pleomorphic sarcoma of the thyroid
A case report and review of the literature

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Abstract
Rationale: Primary undifferentiated pleomorphic sarcoma is extremely rare in the thyroid, and can be easily misdiagnosed as anaplastic thyroid cancer.

Patient concerns: We present a case of a 71-year-old woman who presented with a rapidly growing painless mass in the neck.

Diagnoses-interventions-outcomes: Computed tomography showed a large hypointense mass with hyperdense areas involving whole of the right lobe of thyroid gland and fine-needle aspiration cytology found a few atypical cells. Surgical exploration was performed subsequently and frozen section showed malignant tumor. Therefore, a total thyroidectomy, central, and bilateral lateral neck dissection were performed and adjuvant radiotherapy of 60 Gy was administered. The patient was alive and had no recurrence at 6-month follow-up.

Lessons: Although primary undifferentiated pleomorphic sarcoma in the thyroid is extremely rare, patients who presented with a rapidly growing painless mass in the neck should be considered and it is essential to excise the tumor completely as soon as possible.

Abbreviations: ATC = anaplastic thyroid cancer, CT = computed tomography, MFH = malignant fibrous histiocytoma, PTS = primary thyroid sarcoma, UPS = undifferentiated pleomorphic sarcoma.

Keywords: malignant fibrous histiocytoma, sarcoma, thyroid, undifferentiated pleomorphic sarcoma

1. Introduction

Sarcomas are tumors that arise from transformed cells of mesenchymal origin. Primary thyroid sarcoma (PTS) is very rare with reported frequency ranges from 0.01% to 1.5%.[1-3] Based on the presence and frequency of certain cellular and subcellular characteristics associated with malignant biological behavior, sarcoma is classified as low grade for well differentiated, intermediate grade for moderate differentiated and high grade for poorly differentiated and undifferentiated. Undifferentiated pleomorphic sarcoma represents a group of malignances without any defined cell differentiation, previously known as malignant fibrous histiocytoma (MFH). MFH is a subtype of sarcoma often locating in the extremities, trunk, and retroperitonium, which rarely occurs in the thyroid gland. To our knowledge, there are only few well-documented primary MFH of the thyroid (MFH-T) cases in the literature.[4-10] However, after the term MFH was completely replaced by undifferentiated pleomorphic sarcoma in the 2013 World Health Organization (WHO) classification of soft tissue sarcoma,[11] there has been no report about primary thyroid undifferentiated pleomorphic sarcoma (UPS-T). Here, we report an extremely rare and first case of UPS-T with bilateral neck metastases, which was initially misdiagnosed as anaplastic thyroid cancer (ATC).

2. Case report

A 71-year-old woman presented with a rapidly growing painless mass in the right neck for one month. She reported no history of radiation to the neck and no family history of malignancy. On physical examination, a palpable, 4 cm, firm, poorly demarcated, nontender mass in the right lobe of thyroid gland, and several suspicious enlarged lymph nodes were found. Thyroid function tests showed: free thyroxine (FT4): 0.95 pg/dL (NL, 0.8–1.7); free triiodothyronine (FT3): 2.52 pg/dL (NL, 2.2–4.2); thyrotropin (TSH): 3.45 mIU/L (NL, 0.3–3.6); thyroglobulin (Tg): 280.80 ng/mL (NL, 0.2–70); thyroglobulin antibody (TRAb): 56.00 IU/mL (NL, 5–100); and thyroid peroxidase antibody (TPOAb): 12.20 IU/mL (NL, 1–16). Computed tomography (CT) showed a 5.6 × 4.7 × 4.5 cm inhomogeneous hypo-to-hyperdense mass with poorly defined border involving whole of the right lobe of thyroid gland (Fig. 1A and B). Fine-needle aspiration cytology
found a few atypical cells. Based on these suspicious signs, we performed surgical exploration. Intraoperatively the tumor was found that invaded the strap muscles, recurrent laryngeal nerve and carotid sheath. Given that the frozen section showed malignant tumor, a total thyroidectomy, central and bilateral lateral neck dissection were performed. Microscopic examination revealed anaplastic proliferation of spindle-shaped cells admixed with atypical giant cells arranged in fascicular and storiform patterns (Fig. 2A and B). The tumor also showed typical hyperchromatic nuclei with eosinophilic cytoplasm and focal necrosis. On immunohistochemistry, vimentin was strongly positive (Fig. 2C). Some tumor cells were weakly positive for epithelial membrane antigen (EMA) and smooth muscle actin (SMA), but they were negative for cytokeratin (CK) (Fig. 2D), S-100 (Fig. 2E), and CD34 (Fig. 2F). Based on histological features and the result of immunohistochemistry, diagnosis of UPS-T was made. Furthermore, cervical lymph node metastasis was confirmed by pathological examination (Fig. 2G). No metastatic lesions were detected on a positron emission tomography/CT scan. The postoperative course was uneventful and she received adjuvant radiotherapy (60 Gy/30 fr, 2 Gy/fr, 5 times per week). She was alive and had no recurrence at 6-month follow-up.

This study was approved by the Institutional Review Board of Sichuan Cancer Hospital and Research Institute and the written informed consent was obtained from the patient and her family.

3. Discussion

Differentiated thyroid carcinoma is the most common type of thyroid malignancy. Comparing with differentiated carcinoma, primary non-epithelial malignant tumors, namely sarcomas, are extremely rare in the thyroid. PTS mainly encompasses several subtypes, such as angiosarcoma, hemangiendothelioma, MFH-T was first described by Zahrada et al. in 1989 and several cases, including a series of 12 cases, have been reported in the literature subsequently. As immunohistochemistry found that the phenotype of the neoplastic cells is more aligned with a fibroblast than a histiocyte, undifferentiated pleomorphic sarcoma was regarded as an alternative name of MFH in 2002 WHO soft tissue sarcoma classification. However, after the term undifferentiated pleomorphic sarcoma has completely replaced the old MFH terminology in 2013 WHO classification of soft tissue sarcoma, there has been no report about UPS-T. Hence, our report represents a rare and first case of UPS-T with bilateral neck metastases after 2002 and 2013 WHO classification.

Undifferentiated pleomorphic sarcoma is extremely rare in the head and neck region, which has been reported in parotid gland, mandible and eyelid, and only accounts for about 3% of all undifferentiated pleomorphic sarcomas. Clinically, UPS-T has no specific signs and presents with painless large mass and can be accompanied by cough, dyspnea, and dysphagia in some patients. ATC is an extremely rare malignancy of thyroid, which most commonly presents with a similar clinical manifestation to UPS-T. Therefore, it is difficult to differentiate UPS-T from ATC by clinical features. Some studies showed that the radiological features of ultrasound (US) or CT were helpful to distinguish sarcoma from ATC. According to the literature, most UPS-T showed relatively regular margins accompanying with mixed hypo-to-hyperechoic in comparison to the normal thyroid tissue on US, while ATC had predominantly irregular margins. Therefore, radiological features of US or CT may facilitate the differential diagnosis, but more studies should be done to further investigate. It has been widely accepted that histopathologic morphology, immunohistochemical stains and molecular diagnostic test could accurately differentiate from carcinoma, melanoma, and lymphoma. Appropriate immunohistochemical markers could usually resolve diagnostic dilemmas in the distinction from PTS and ATC. In our case, based on histological features and immunohistochemical result, diagnosis of UPS-T was finally made.

The cause of UPS-T has not been identified in most patients in the literature, but some patients developed UPS-T after radiotherapy. However, there was no history of radiotherapy in our patient. Although there is no consensus within the literature on a comprehensive treatment plan for patients with undifferentiated pleomorphic sarcoma, surgery plays a central role in nearly all cases. In addition to the timing of surgery, the extent of surgery and the status of the surgical margins are important prognostic factors for undifferentiated pleomorphic sarcoma in the head and neck. It has been reported that inadequate resection of the sarcoma in the head and neck was associated with a high incidence of local recurrence and a poor prognosis, whereas the recurrence rate with radical resection was relatively low. Therefore, extensive surgical excision of the primary tumor and involved adjacent tissue is recommended to patients with UPS-T in order to get negatively surgical margins. However, due to the anatomical and functional complexity of the head and neck and high-aggressive potential of the sarcoma, resections with adequate margin are not easily obtained. As a result, there is a higher risk of local recurrence than patients with undifferentiated pleomorphic sarcoma in the extremities and trunk. Although there is no consensus argument on the
surgical type for patients with UPS-T, total thyroidectomy plus excision of involved tissue with or without neck dissection would be optimal. Neck dissection is not routinely performed because regional lymph nodes metastases are uncommon in UPS-T, but should be considered for patients who have enlarged cervical lymph nodes. In our case, neck dissection was performed because physical examination found enlarged cervical lymph nodes, and lymph nodes metastases were confirmed by pathological examination.

Radiotherapy or chemotherapy is usually administered as a part of cancer treatment. Due to the poor results of surgical treatment alone, adjuvant radio- and/or chemotherapy is also considered in bone and soft tissue sarcoma treatment, despite the fact that there is no proven benefit. Adjuvant or neo-adjuvant radiotherapy has been used to improve disease control for MFH in the head and neck. In a retrospective study, Huber et al. suggested that adjuvant radiotherapy should be recommended for large tumors (>4 cm), high histological grade, tumors close the resection-margins, or those with positive margins. Given that the tumors in our patient >4 cm in size, the patient underwent total thyroidectomy plus excision of involved tissue with negative margins followed by radiotherapy (60 Gy), and remained free of

**Figure 2.** (A) Microscopically, spindle and pleomorphic cells arranged in fascicular pattern with focal necrosis (H&E, ×100). (B) Pleomorphic spindle cells with numerous mitotic and interspersed giant cells (H&E, ×400). (C) Vimentin staining: positive. (D) Cytokeratin staining: negative. (E) S-100 staining: negative. (F) CD34 staining: negative. (G) H&E image of lymph node metastasis (H&E, ×200). H&E = hematoxylin and eosin.
recurrence at 6-month follow-up. Adjuvant chemotherapy for undifferentiated pleomorphic sarcomas remains unclear and has been usually used for metastatic cases. Additionally, limited data in the literature on evaluating the advantages of chemotherapy did not help to detect differences in overall survival. Therefore, the role of chemotherapy in UPS-T cannot be concluded and needs further investigation.

In conclusion, undifferentiated pleomorphic sarcoma is a rare subtype of thyroid sarcoma, "which clinically presents as a rapidly growing painless neck mass that can be easily misdiagnosed as ATC." Histological features and immunohistochemical stains are crucial to establish the diagnosis of UPS-T. Surgery plays a significant role in the management of this malignancy, while effect of combination with radiotherapy and chemotherapy is limited.

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