

Clinicopathological features of primary thyroid leiomyosarcoma without Epstein-Barr virus infection: A case report

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Abstract. Primary thyroid leiomyosarcoma (LMS) is a rare tumor type with an unusual location, the diagnosis is based entirely on histological and immunohistochemical evaluations. In the present study, a rare case of a 74-year-old female patient who exhibited a right anterior neck mass for 12 months, which rapidly enlarged for the last 3 months. Ultrasound of the thyroid revealed a 55x42 mm hypoechoic mass with clear margins in the right lobe. Histological examination of the tumor demonstrated malignant spindle cells in interlacing fascicles and whorls. Additionally, nuclear pleomorphism, tumor giant cells, necrosis and abnormal mitotic figures were observed. The immunohistochemistry indicated that the tumor cells were strongly positive for smooth muscle actin, desmin, p53 and vimentin expression, but negative for cytokeratin, epithelial membrane antigen, thyroid transcription factor-1, paired box-8, 34βE12, cytokeratin 5/6, cluster of differentiation (CD)117, myoglobin, S100, p16. The final histopathological diagnosis was primary thyroid LMS.

Introduction

Leiomyosarcoma (LMS) is a relatively rare soft-tissue tumor that can arise from any organ or structure containing smooth muscle, most often occurs in the retroperitoneum, the digestive tract, pelvis, skin and soft tissue (1,2). Primary thyroid LMS is rare, and may be associated with smooth muscle-walled vessels at the periphery of the thyroid gland capsule; however, the pathogenesis of primary thyroid LMS remains unclear (1-17). To the best of our knowledge, only 25 cases have been reported in English literature (1-17). LMS is composed of cells with distinct

smooth muscle histological differentiation, and the diagnosis is confirmed by immunohistochemical techniques combined with clinical history (4). It is difficult to produce a preoperative diagnosis of primary thyroid LMS and to differentiate it from anaplastic thyroid carcinoma or other spindle cell sarcoma types of either primary or metastatic origin (15). In 2016, Zou *et al* through retrospective literature review, reported that the prognosis of thyroid LMS is poor, with a 1-year survival rate of <10% (1). In the present study, a rare case of a 74-year-old female patient diagnosed with primary thyroid LMS was reported and a brief review of the literature is presented.

Case report

In October 2016, a 74-year-old Chinese female was admitted to Shaoxing People's Hospital due to her exhibiting a right anterior neck mass for 12 months, which rapidly enlarged for the last 3 months. The present study was approved by the Ethics Committee of the Shaoxing People's Hospital and the patient provided written informed consent.

Ultrasound of the thyroid revealed a 55x42 mm hypoechoic mass with clear margins in the right lobe (Fig. 1A and B). Color Doppler flow imaging (CDFI) indicated no abnormal blood flow signal. Computed tomography revealed a 66x46 mm soft tissue mass at the entrance of the thoracic trachea, adjacent to the right side of the soft tissue (Fig. 2A), and there was no notable reinforcement following enhanced scanning (Fig. 2B). There were no abnormal findings in the chest or pelvis as demonstrated by imaging examination. Physical examination demonstrated a hard mass of ~6.0 cm in the right lobe of the thyroid gland. There were no palpable cervical or supraclavicular lymph nodes. There was no history of radiation exposure or another primary tumor. Routine laboratory investigations were normal, including complete blood count and electrolyte levels. A serum thyroid function test was also normal. Tumor markers, including carcinoembryonic antigen, α-fetoprotein, carbohydrate antigen 125, carbohydrate antigen 19-9 and lactate dehydrogenase were all within normal limits. The patient underwent thyroid neoplasm resection and the frozen examination demonstrated a malignant spindle-cell tumor. Subsequently, the patient underwent bilateral thyroid radical resection and neck lymphadenectomy. Following surgery, the

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Key words: thyroid gland, leiomyosarcoma, spindle cell tumors, immunohistochemistry

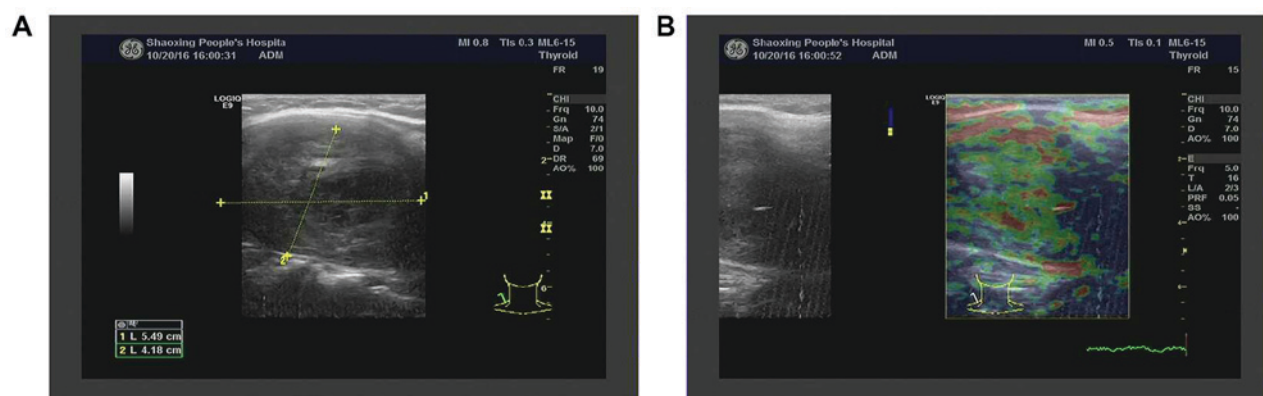


Figure 1. The findings of Ultrasound inspection. (A) Ultrasound demonstrated a 55x42 mm hypoechoic mass with clear margins in the right lobe. (B) CDFI indicated no abnormal blood flow signal.

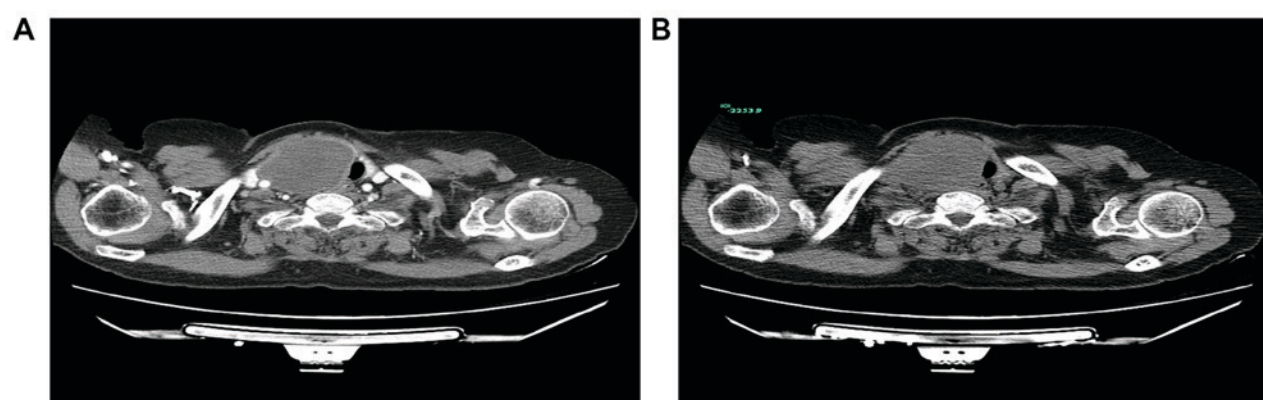


Figure 2. The findings of Computed topography. (A) Computed topography demonstrated a 66x46 mm soft tissue mass at the entrance of the thoracic trachea, adjacent to the right side of the soft tissue, (B) and there was no notable reinforcement following enhanced scanning.

patient refused all treatment and succumbed to the disease after 2 months.

The tissue was fixed in 10% buffered formalin for 6 h at room temperature, and embedded in paraffin, following which 4- μ m thin sections were cut and stained with hematoxylin (for 5 min at room temperature) and eosin (for 1 min at room temperature). Sections, which were deparaffinized and subsequently rehydrated in a descending alcohol series (100% alcohol for 5 min, 95% alcohol for 4 min, 85% alcohol for 2 min). Antigens were heat-retrieved at 98°C in EDTA solution. Following cooling to room temperature, the tissue sections were quenched with 3% hydrogen peroxidase and non-specific binding sites were blocked with 5% goat serum (Zhongshan Bio, Beijing, China) at 37°C for 30 min. Subsequently, the sections were incubated with the following primary antibodies (listed in Table I). Immunohistochemical staining was performed by EnVision (Zhongshan Bio, Beijing, China) according to the manufacturer's protocol. All antibodies were incubated at room temperature for 20-30 min, then observed under an OLYMPUS microscope at x40, x100 and x400 magnification. Immunohistochemical staining was performed using commercially available antibodies to the following antigens: Epithelial membrane antigen (EMA) (dilution, 1:100; cat. no. GP1.4; Guangzhou Ascend Biotechnology Co., Ltd., Guangzhou, China), pan-cytokeratin (CKpan) (dilution, 1:100; cat. no. V9; Ascend Biotechnology Co., Ltd.), vimentin (dilution, 1:100; cat.

AE1/AE3; Ascend Biotechnology Co., Ltd.), smooth muscle actin (SMA) (dilution, 1:800; cat. no. 1A4; Fuzhou Maixin Biotech, Fuzhou, China), desmin (dilution, 1:600; cat. no. D33; Zhongshan Bio, Beijing, China), paired box (Pax)-8 (dilution, 1:100; rabbit. no. IR1; Zhongshan Bio, Beijing, China), thyroid transcription factor-1 (TTF-1) (dilution, 1:400; cat. no. SPT24; Ascend Biotechnology Co., Ltd.), 34 β E12 (dilution, 1:200; cat.; Ascend Biotechnology Co., Ltd.), cytokeratin (CK)5/6 (dilution, 1:1,600; cat. no. 007; Zhongshan Bio, Beijing, China), cluster of differentiation (CD)117 (dilution, 1:1,000; rabbit. no. EP10; Fuzhou Maixin Biotech, Fuzhou, China), CD34 (dilution, 1:1,000; rabbit. no. QBEnd110; Zhongshan Bio, Beijing, China), CD68 (dilution, 1:400; cat. no. EP2; Ascend Bio, Guangzhou, China), myoglobin (dilution, 1:100; cat. no. MY018; Zhongshan Bio, Beijing, China), S100 (dilution, 1:800; cat. no. poly; Fuzhou Maixin Biotech, Fuzhou, China), p53 (dilution, 1:800; rabbit. no. EP9; Ascend Biotechnology Co., Ltd.), Ki-67 (dilution, 1:200; cat. no. MIB1; Ascend Bio, Guangzhou, China), progesterone receptor (PR) (dilution, 1:800; rabbit. no. EP2; Ascend Biotechnology Co., Ltd.) and estrogen receptor (ER) (dilution, 1:800; rabbit. no. EP1; Ascend Biotechnology Co., Ltd.). Simultaneously, *in situ* hybridization for the presence of small Epstein-Barr virus (EBV)-encoded RNA (EBER) was performed to identify the association between this tumor and EBV. All protocols were employed according to the manufacturer's protocols (Table I).

Table I. Summary of primary antibodies and results of immunohistochemistry.

Antibody	Source	Dilution	Result
CK	Ascend Bio, Guangzhou, China	1:100	-
EMA	Ascend Bio	1:100	-
Vimentin	Ascend Bio	1:100	+
TTF-1	Ascend Bio	1:400	-
S100	Dako; Agilent Technologies, Inc., Santa Clara, CA, USA	1:3,200	-
Pax-8	Ascend Bio	1:100	-
Desmin	Zhongshan Bio, Beijing, China	1:600	+
SMA	Dako; Agilent Technologies, Inc.	1:3,200	+
p53	Ascend Bio	1:800	+
34 β E12	Ascend Bio	1:200	-
CK5/6	Zhongshan Bio	1:1,600	-
CD117	Dako; Agilent Technologies, Inc.	1:1,000	-
CD34	Zhongshan Bio	1:1,000	-
CD68	Ascend Bio	1:400	-
Myoglobin	Zhongshan Bio	1:100	-
PR	Genetic Tech, Shanghai, China	1:1,600	-
ER	Epitomics; Abcam, Cambridge, MA, USA	1:800	-
Ki-67	Ascend Bio	1:200	40% in the most concentrated spot
EBER	Triplex International Biosciences, Fuzhou, China	RTU	-

CK, cytokeratin; EMA, epithelial membrane antigen; SMA, smooth muscle actin; TTF-1, thyroid transcription factor-1; EBER, Epstein-Barr virus-encoded RNA; RTU, ready to use; CKpan, pan-CK; Pax-8, paired box-8; CD, cycle of differentiation; PR, progesterone receptor; ER, estrogen receptor; +, positive expression; -, negative expression.

Results

The size of the surgical specimen was 7.0x5.5x5.0 cm, and the largest diameter of the tumor was 6.5 cm. In cross sections, the tumor was yellowish-white with focal areas of hemorrhage, cystic change and myxoid degeneration (Fig. 3). There was identifiable thyroid tissue around the tumor. Microscopically, there was no capsule between the tumor and the surrounding normal thyroid tissue, and the tumor infiltrated into the adjacent thyroid (Fig. 4A), fat and perineural (Fig. 4B). There was a visible thick-walled blood vessel located around the tumor, and the neoplastic cells scroll off the muscle wall, where tumor cells grew around the periphery of blood vessels (Fig. 4C), which indicated that the tumor may originate from smooth muscle of the walled vessels. The tumor consisted of spindle cells arranged in interlacing fascicles, and the cells had cigar shaped, blunt-ended nuclei (Fig. 4D). Additionally, in a number of areas, the appearance of neoplastic cells ranged from spindled to plump or pleomorphic cells (Fig. 4E), and they exhibited notable nuclear pleomorphism, atypical, giant cell formation (Fig. 4F), with >3 abnormal mitotic figures per each of 10 high-power fields (Fig. 4G), large areas of hemorrhage and coagulative necrosis (Fig. 4H).

Immunohistochemically, the tumor cells were strongly positive for desmin (Fig. 5A), SMA (Fig. 5B), p53 and vimentin expression, but negative for CKpan, EMA, TTF-1 (Fig. 5C), Pax-8, 34 β E12, CK5/6, CD117, CD34, CD68, myoglobin, S100 (Fig. 5D), p16, PR and ER. The Ki-67 labeling index reached

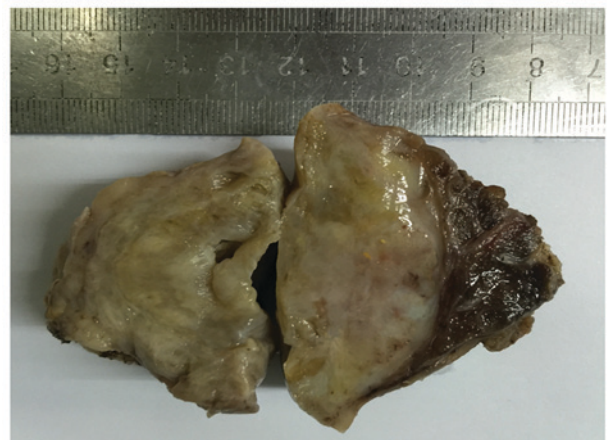


Figure 3. Gross examination results. Pathological observation demonstrated that the tumor was yellowish-white with focal areas of hemorrhage, cystic change and myxoid degeneration on cross-sections.

40% in the most concentrated location. Furthermore, EBV (*in situ* hybridization) was negative.

Discussion

Primary thyroid LMS is a rare malignant tumor type, and to the best of our knowledge, only 25 cases of primary thyroid LMS have been previously reported in English literature (1-17). The

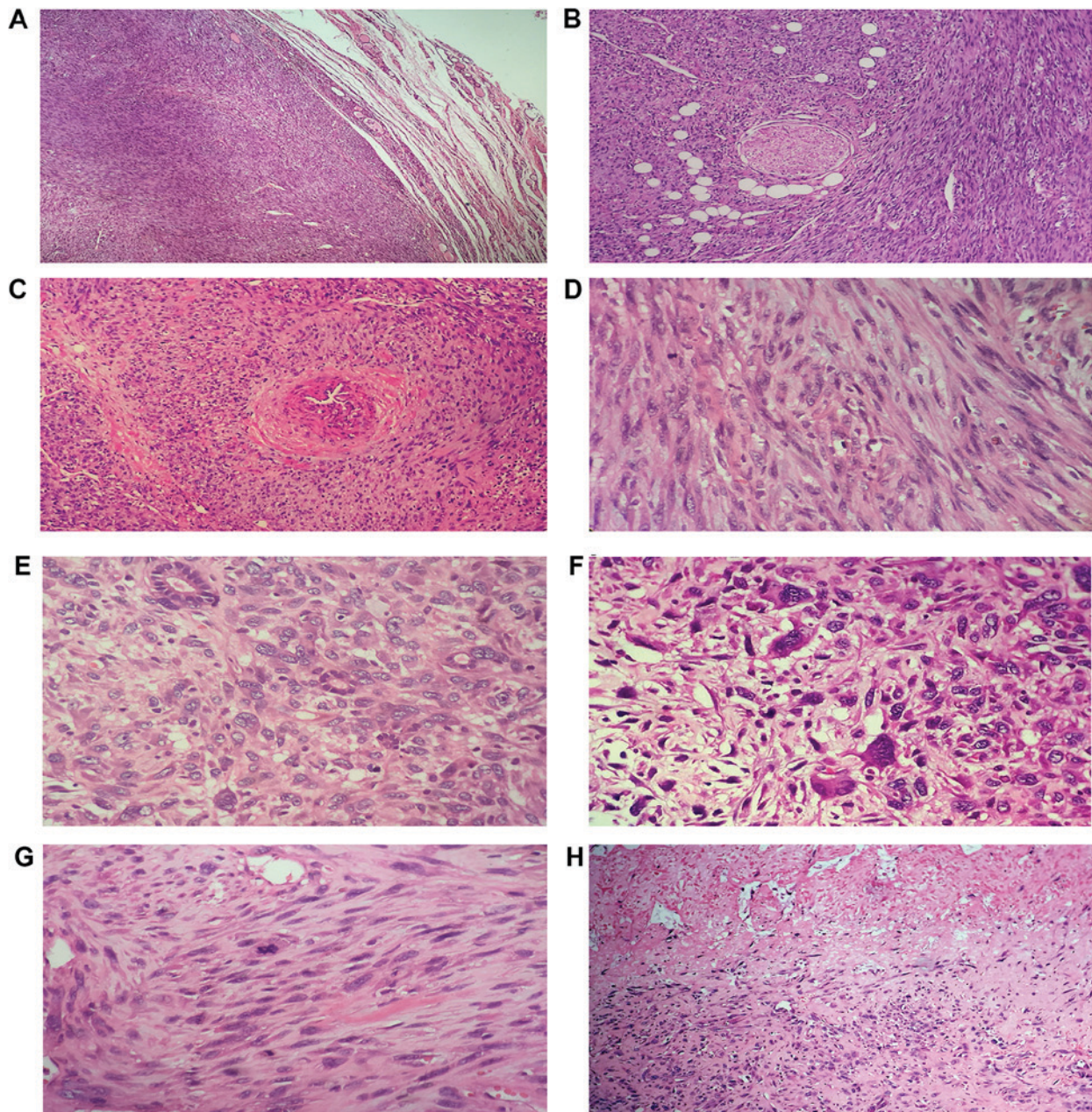


Figure 4. Morphological characteristics of LMS. Microscopically, there was no capsule between the tumor and the surrounding normal thyroid tissue, and the tumor infiltrated the (A) adjacent thyroid, (B) fat and perineural (H&E staining, x40). (C) There was a visible thick-walled blood vessel located around the tumor, and the neoplastic cells scroll off the muscle wall (H&E staining, x100). (D) The tumor consisted of spindle cells arranged in interlacing fascicles, and the cells had cigar shaped, blunt-ended nuclei (H&E staining, x400). (E) In a number of areas, the appearance of neoplastic cells ranged from spindled to plump or pleomorphic cells, and there were residual thyroid follicles (H&E staining, x400). (F) Additionally, it exhibited notable nuclear pleomorphism and atypical, giant cell formation (H&E staining, x400). Furthermore, the tissue exhibited (G) abnormal mitotic figures (H&E staining, x400) and (H) coagulative necrosis (H&E staining, x40). H&E, hematoxylin and eosin.

etiology of primary thyroid LMS remains unclear, particularly the role of radiation exposure (1,3,7,9,11). It may be associated with smooth muscle-walled vessels at the periphery of the thyroid gland capsule (1-5). A single case of an EBV-associated thyroid smooth muscle tumor has been reported in a child with a congenital immunodeficiency disease (12). A previous study demonstrated that LMS of other sites have also been associated with acquired immunodeficiency syndrome or EBV infection (12). It appears that LMS has a high probability of occurring in immunosuppressed patients (1,12). However, the present patient had no history of radiation exposure.

Microscopically, there was a visible thick-walled blood vessel located around the tumor, and the neoplastic cells scroll off the muscle wall, where tumor cells grew around the periphery of blood vessels, which indicated that the tumor may originate from the smooth muscle of the walled vessels. Additionally, the present patient was negative for human immunodeficiency virus and EBV; therefore, we hypothesized that there was no association between them.

In retrospective review of the small number of reported cases (1-17), limited information was available for 1 patient (16). The ages of all the patients ranged between 39 and 90 years,

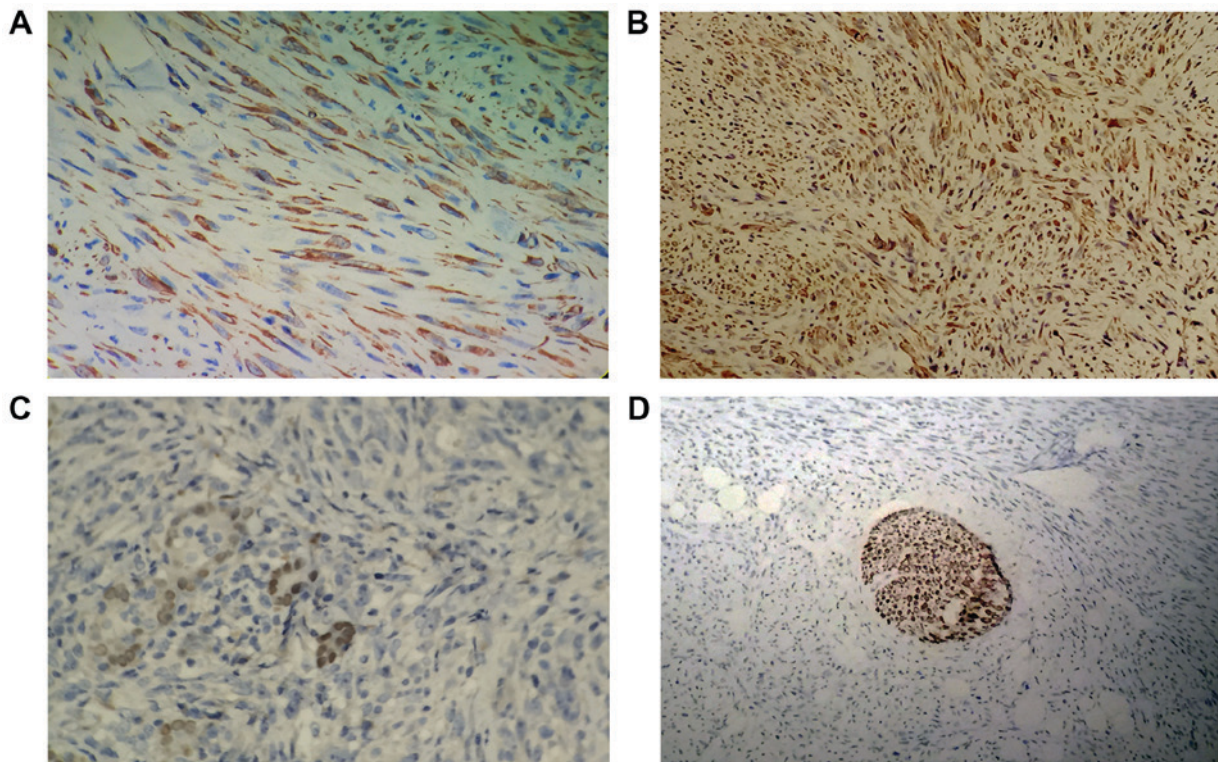


Figure 5. Immunohistochemical results of LMS. Immunohistochemically, neoplastic cells were strongly reactive for (A) desmin (EnVision, x400) and (B) smooth muscle action (EnVision, x100), but was negative for (C) TTF-1 (EnVision, x400) and (D) S100 (EnVision, x40). (C) Residual thyroid follicles were positive for TTF-1 and (D) perineural was positive for S100. TTF-1, thyroid transcription factor-1.

excluding a 6-year-old patient who had immune system deficiency, (mean age, 59.7; median age, 65), indicating that the tumor has been principally determined in adults. Additionally, the majority of patients were elderly and the female: male ratio was 1.5:1, demonstrating a slight predilection for female patients. The majority of thyroid LMS were unilateral, with only 1 patient exhibiting bilateral thyroid LMS (2). Clinical manifestations included a painless, rapidly growing neck mass, or dysphagia, hoarseness, odynophagia, dyspnea and weight loss (1-17). The majority of reported patients were euthyroid (1,3,5-17). The present patient was an older female, and exhibited a right anterior neck mass for 12 months, which rapidly enlarged over the last 3 months. Furthermore, a serum thyroid function test was also normal.

There are no imaging characteristics or tumor markers that allow a preoperative diagnosis, and all patients have been diagnosed following surgical resection. The diagnosis is based entirely on histopathological and immunohistochemical evaluations. Additionally, the tumor boundary was not clear, and the cross-sections were grayish white, or with hemorrhage, necrosis and cystic change (1,2,6). The tumor diameter range was 1.9-12.0 cm (average diameter, 6.3 cm), with a diameter of >5 cm in of cases (1-17). The tumor of the present patient exhibited a typical interlacing fascicular growth pattern with spindle cells, and the cells had cigar shaped, blunt-ended nuclei. Additionally, there were a number of areas with diffuse pleomorphic neoplastic cells containing large nuclei or osteoclast-like giant cells, and the nuclei was notably atypical and pleomorphic. Furthermore, the tumor infiltrated the adjacent thyroid, fat and perineural. The tumor cells were positive for

desmin, SMA, p53 and vimentin; therefore, the final diagnosis was primary thyroid LMS.

The major differential diagnosis included anaplastic (undifferentiated) thyroid carcinoma, metastatic LMS (18,19), spindle epithelial tumor with thymus-like differentiation (SETTLE) (20), spindle cell variant of medullary thyroid carcinoma (21) or other primary and metastatic malignant mesenchymal tumor types, including rhabdomyosarcoma (22), synovial sarcoma (23), malignant peripheral nerve sheath tumor (MPNST) (24) or undifferentiated pleomorphic sarcoma (25). Thyroid LMS should be diagnosed only when there is a complete lack of all epithelial differentiation and there is definite evidence (histologic, immunophenotypic, or ultrastructural) of specific sarcomatous differentiation (1,6,17). Anaplastic thyroid carcinoma also frequently occurs in older patients with longstanding history of a pre-existing thyroid lesion that has rapidly enlarged (26). Histologically, the presence of residual well-differentiated thyroid carcinoma favors anaplastic thyroid carcinoma (6,12,26). Anaplastic thyroid carcinomas frequently express epithelial markers to different degrees, and a few rare cases may lose the epithelial phenotype, and express SMA and desmin (27). Prior to the diagnosis of primary thyroid LMS, the possibility of LMS metastasising to other sites, including the uterus, lung, or gastrointestinal or soft tissue, must be ruled out (2,18,19). The clinical history and radiographic evaluations are beneficial to the differential diagnosis of LMS.

Immunohistochemistry has important value in the diagnosis and differential diagnosis of LMS. The lack of CD5, CD117 and p63 expression ruled out SETTLE. The

lack of calcitonin and neuroendocrine markers expression ruled out medullary thyroid carcinoma. The lack of S100 protein expression ruled out MPNST. The lack of MyoD1 and myogenin protein expression ruled out rhabdomyosarcoma. Synovial sarcoma is frequently expresses a different degree of CK and EMA. Additionally, undifferentiated pleomorphic sarcoma neither expresses epithelial markers nor mesenchymal markers. When tumors were positive for SMA and desmin, support the diagnosis of LMS. CD117 is rarely expressed in LMS, although a case of CD117 overexpression in primary thyroid LMS has been previously reported (9). A number of reports demonstrated that uterus LMS can express ER and p16; therefore, ER and p16 may have important value in identifying primary or metastatic uterine LMS (18,19,26). In the present case, the final diagnosis of LMS was supported by histopathological findings plus the positive immunostaining for desmin and SMA, and radiological and clinical observations.

There is no consensus on standardized treatment strategy for thyroid LMS, but radical surgical resection is considered to be the most effective treatment (1,2,6). Adjuvant chemotherapy, radiation therapy and immunotherapy have not proven beneficial. The prognosis of the patients with thyroid LMS is poor (3-5,7,16). According to the literature review, it was determined that 2 patients had lymph node metastasis (2,16), and 10/25 patients had distant metastases (1,11-14). In 2016, Zou *et al* (1) through retrospective literature review, reported that thyroid LMS is primarily fatal and survival rates are <10% in the first year worldwide (1). A total of 16/25 patients succumbed within 8 months due to the disease, with the longest disease-free duration of a patient being 5 years (17).

In conclusion, a thyroid mass with spindle cells and abnormal pleomorphic cells should raise the suspicion of LMS, particularly in older patients exhibiting a rapidly growing mass at the anterior portion of the neck. Immunohistochemistry is required to differentiate it from anaplastic thyroid carcinoma or other primary and metastatic malignant mesenchymal tumor types. The prognosis of thyroid LMS is notably poor, and the necessity of an aggressive oncological and effective treatment approach remains controversial.

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Availability of data and materials

All data generated or analyzed during this study are included in this published article.

Authors' contributions

All authors read and approved the final manuscript. JGW made substantial contributions to conception and design, or acquisition of data, or analysis and interpretation of data, and drafted the article and revising it critically for important intellectual content; JFY, WQL and CWX contributed to the acquisition of data or analysis and interpretation of data; YYW revised the article critically for important intellectual content, and contributed to the conception and design, approved the final version to be published.

Ethics approval and consent to participate

The present study was approved by the Ethics Committee of the Shaoxing People's Hospital and written informed consent was obtained from the patient.

Patient consent for publication

The patient signed written informed consent for the publication of any data and associated images.

Competing interests

The authors declare that they have no competing interests.

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