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Liposarcoma of the Thyroid: A Case Report with a Review of the Literature

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What Is Known about This Topic?

- Liposarcomas of the thyroid gland are extremely rare, and there is no definitive consensus within the literature about a comprehensive treatment recommendation yet.

What Does This Case Report Add?

- This report presents a valid diagnostic and therapeutic approach to this rare tumor entity, including an analysis of the clinical and histopathological features concerning primary liposarcomas of the thyroid gland reported in the literature.

Keywords
Thyroid cancer · Liposarcoma · Review · MDM2 · Immunohistochemistry

Abstract
Background: Liposarcomas of the thyroid gland are extremely rare tumors, and, to our knowledge, only 12 cases have been reported in the English literature. An accurate diagnosis is challenging due to the nonspecific clinical presentation of this cancer, frequently defined just by a swelling of the neck. ***Patient Findings:*** We present an 82-year-old woman with liposarcoma of the thyroid, complaining of a fast-growing neck mass. MRI and neck ultrasound showed a large lipomatous mass, which corresponded to a *cold* nodule in the thyroid scan. After performing a total thyroidectomy, the diagnosis of a well-differentiated liposarcoma of the thyroid gland was made, showing an MDM2 amplification in fluorescence in situ hybridization. Since neither a metastasis nor a residual tumor was found, no further adjuvant therapy was needed. ***Results:*** We searched the literature for previous case reports and identified only 12 cases worldwide to form our database. A demographic as well as clinical and histopathological analysis was made. In most cases, the liposarcoma occurred in patients >60 years of age. All histological subtypes, such as well-differentiated and myxoid liposarcomas, and pleomorphic and dedifferentiated liposarcomas, were found in the literature. In only 38.46% of the cases, an infiltration of the adjacent organs was observed. Surgery was the most common treatment chosen. ***Conclusions:*** Our

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review provides clinical and histopathological features of a primary liposarcoma of the thyroid to enable the identification of this rare tumor entity and assist in the decision-making process regarding therapeutic options and tumor follow-up.

Introduction

Soft tissue sarcomas are tumors of mesenchymal cell origin and account for less than 1% of all head and neck neoplasms [1]. Liposarcomas represent about 20% of all soft tissue sarcomas and are consequently the most common histotype [2].

Primary sarcomas of the thyroid gland characterize less than 1.5% of all thyroid malignancies and include several histological entities such as angiosarcomas, malignant hemangioendotheliomas, malignant fibrous histiocytomas, leiomyosarcomas, fibrosarcomas, and liposarcomas [3]. Liposarcomas of the thyroid gland are extremely rare and only few studies have been performed, making an evidence-based management of patients challenging. In this study, we aimed to analyze clinical and histopathological features of primary liposarcomas of the thyroid gland reported in the literature as well as our 82-year-old female patient diagnosed with primary liposarcoma of the thyroid at our institution.

Case Report

An 82-year-old female presented to the ENT clinic to evaluate a fast-growing mass in the neck for more than 1 month.

At her initial ENT evaluation, she presented with a feeling of constriction of the neck and a muffled voice. Dysphagia, dyspnea, and pain were denied. The physical examination on admission revealed a palpable painless tissue mass in the right cervical area. Protrusion of the posterior pharyngeal wall was observed during the endoscopic examination but no fixation of the vocal cords or subglottic stenosis.

A neck ultrasound was performed and revealed a homogeneous hyperechoic mass involving almost the whole right lobe of the thyroid gland with a measured volume of 100 mL and a small hypoechoic node in the left lobe. There was no evidence of cervical adenopathy. The thyroid scan showed nearly no activity in the right lobe. Free T_4 and T_3 as well as thyroid-stimulating hormone levels were within normal limits.

A further radiographic evaluation with a contrast-enhanced MRI showed a semiliquid soft-tissue mass consistent with a lipomatous formation spreading from the thyroid to the right retropharyngeal space till the intrathoracic retrosternal area. It measured 10 × 4 × 8 cm, displacing and compressing both the trachea and the esophagus to the left, with no clear signs of infiltration (Fig. 1a, b). No pulmonary lesions were visible in the preoperatively performed chest X-ray.

Next, a total thyroidectomy was performed in order to relieve the pressure on the adjacent structures. A transverse cervical incision was used to approach the right retropharyngeal mass and the thyroid gland. Intraoperative nerve monitoring was used to identify and preserve the recurrent laryngeal nerve.

The histological examination demonstrated a neoplasm consisting of an adipocytic proliferation with significant variation in cell size. Focal adipocytic atypia and nuclear hyperchromasia were easily identifiable. Stromal broad septa contained stromal cells with nuclear hyperchromasia. Sporadic lipoblasts were found. In 10 high-power fields, no mitosis was identified, and tumor necrosis was absent. Areas of hypercellularity or rounded cell foci were absent. The surface was focally fibrotic delimitated. The adjacent thyroid gland showed regressive changes. MDM2 fluorescence in situ hybridization (FISH) (MDM2/CEN12 dual color probe; Zytovision) was performed and revealed high-level (cluster) amplification of the MDM2 gene locus. The tumor was diagnosed as well-differentiated liposarcoma, G1, FNCLCC score 1 + 1 + 0 = 2 (Fig. 1c, d).

The patient's postoperative course was uneventful. No residual tumor, lymph node metastases, or distant metastases were detected in the postoperative PET-CT. The case was discussed at the interdisciplinary thyroid board: based on the absence of metastases and residuum and considering the high differentiation grade of the histological findings, no postoperative treatment was recommended, and the patient was subjected to strict follow-up at our institution. So far, at the 1-year follow-up, there are no signs of recurrence, and the patient is in good health and physical condition.

Review

Methods

We screened PubMed and Ovid databases using *thyroid liposarcoma*, *liposarcoma of the thyroid*, and *primary thyroid liposarcoma* as key words. Secondary references were reviewed as well. We selected 9 articles and extracted 12 case reports of primary thyroid liposarcoma [4–12]. The case reported was also evaluated in our data analysis.

Two cases of liposarcoma metastatic to the thyroid gland, whose primary site was in both cases the right thigh, were not included in our investigation, as they were not defined as primary sarcoma of the thyroid [13, 14].

We collected demographic data from all case reports, and patients were grouped according to age: ≤60 and >60 years. The frequency of symptoms was noted, and the following tumor variables were assessed: local extension, local and distant metastases, histological features, and immunohistochemical staining. Tumor size was compared considering its greatest dimension. The choice of imaging methods and related findings were also analyzed.

Complications and treatment options like surgery or adjuvant radiochemotherapy were noted; patient out-

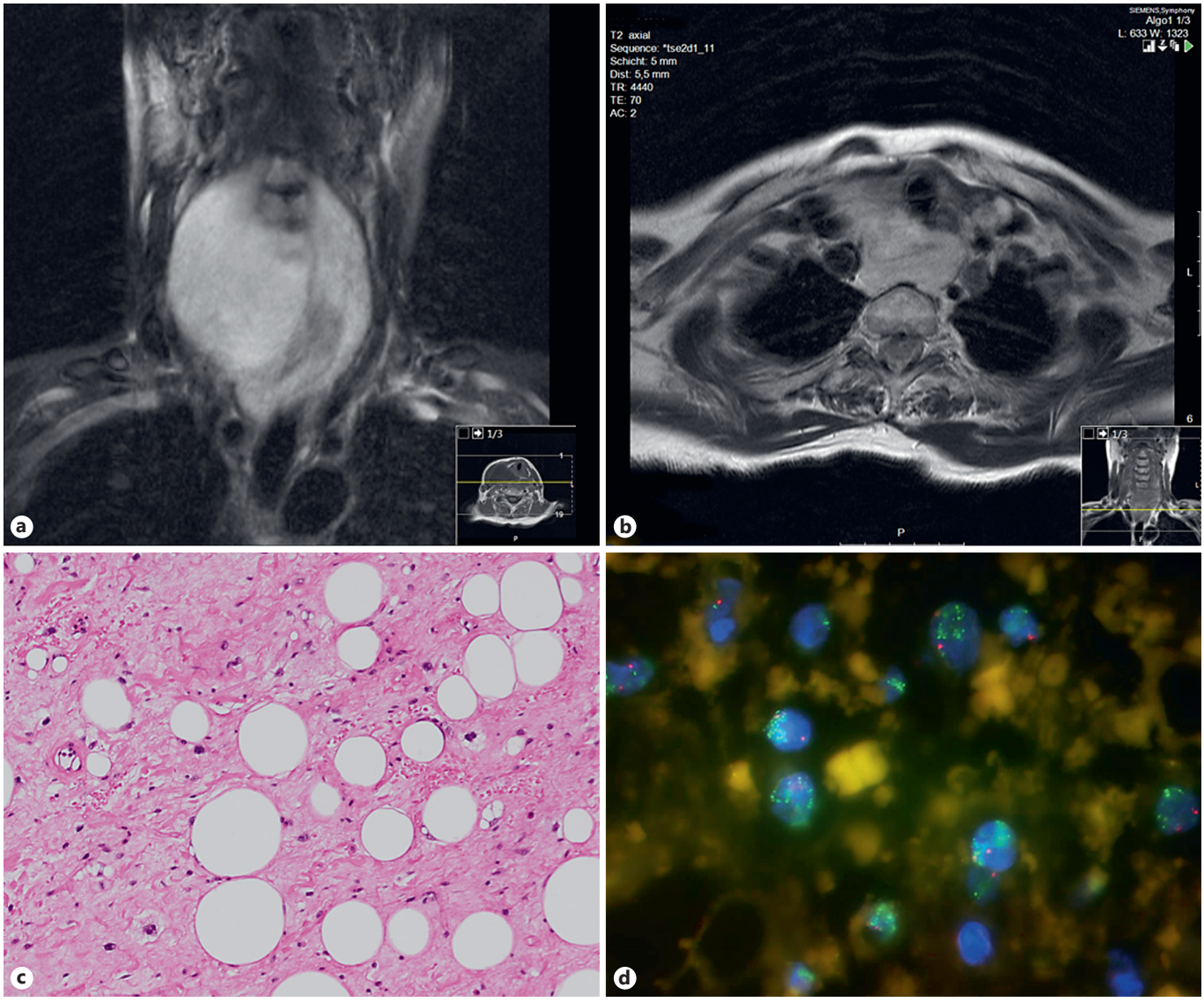

Fig. 1. Coronal section in short-T1 inversion recovery sequence (**a**) and axial section in T2 sequence (**b**) of a contrast-enhanced MRI scan of the neck demonstrating a lipomatous mass spreading from the thyroid gland to the right retropharyngeal space with tracheal and esophageal compression. **c** Representative H&E staining showing adipocytes with marked variation in size, stromal cells with hyperchromatic nuclei, and scattered lipoblasts. **d** MDM2 FISH with cluster amplification of the MDM2 gene locus (green signal). Red signal, CEN12.

come was categorized into dead, alive with no evidence of disease, alive with evidence of disease, and no follow-up. Evaluations of absolute and relative frequencies of categorical variables as well as the analysis of continuous variables were performed using Excel (Microsoft Office 2016).

Patients and Clinical Signs

A total of 12 cases were previously reported and analyzed in addition to our patient. No geographical clustering was observed, and gender distribution was equal: 53.85% were females and 46.15% were males. The mean age of the patients was 58.42 ± 15.99 years (median: 62 years).

All the patients (n = 13) presented with a rapidly enlarging mass in the neck as the main symptom. Other common symptoms involved dysphagia (n = 6), respiratory distress including dyspnea and shortness of breath (n = 5), alterations in the voice like hoarseness (n = 5), globus sensation (n = 1), weight loss (n = 1), coughing

(n = 1), and deafness of the ear (n = 1). A sensation of constriction of the neck caused by the swelling was mentioned in 2 cases; 4 patients (30.77%) had a history of a goiter. In just 1 case, radiation of the neck was performed previously [5]. Recurrent complications were a deviation and compression of the trachea caused by the tumor mass (76.92%), compression of the esophagus (23.08%), deep vein thrombosis including thrombosis of the jugular vein (15.38%), and vocal cord weakness (23.08%).

Imaging Findings and Characteristics of the Tumor

Five reports explicitly mentioned using a diagnostic neck ultrasound. In 2 cases, the sarcomas identified were described as hypoechoic, in 1 case it was hyperechoic, 1 case showed a heterogeneous echogenicity, and in 1 case this feature was not specified. A thyroid scan was performed in 4 cases (30.77%), with consistent findings of a *cold* area with no iodine uptake. A CT scan was obtained in 9 cases (69.23%), and MRI in just 1 case (7.69%).

As an initial diagnostic test, 7 patients underwent fine needle aspiration cytology (FNAC), which appeared to be nondiagnostic in 42.86% and nonspecific showing barely a suspect of malignancy in 57.14% of the cases. In 1 case, FNAC was suggestive of anaplastic carcinoma of the thyroid [6]. Four patients received a mass biopsy.

The thyroid gland was identified as the anatomical origin of the neoplasms based on ultrasound imaging (n = 4) as well as CT (n = 6) or MRI (n = 1), and on the results of the thyroid scan (n = 4), which displayed the lesions as intrathyroidal *cold nodes*. Intraoperative findings (n = 6) matched with a tumor arising from the thyroid tissue. In 1 case, the authors described a paratracheal mass in the CT scan that indistinctly appeared to grow from the left lobe of the thyroid [11].

The diagnosis of liposarcoma was made in 11 of the 13 cases based on the postoperative histological examination. Despite the expansive tumor properties described in the imaging findings (61.54%), no clear identification of this tumor entity was achieved preoperatively; in 2 cases, the diagnosis was made preoperatively based on biopsy results [7, 8]. The lipomatous nature of the neoplasm was identified by MRI in the case reported.

Tumor size ranged from 2.5 to 12 cm in 1 dimension. The majority of the tumors was >5 cm in their greatest dimension (n = 9, 69.23%). In 5 cases (38.46%), infiltration of the adjacent organs was observed, including the esophageal wall, the surrounding soft tissue, the recurrent laryngeal nerve, the pyriform fossa musculature, and the common carotid artery. No lymph node metastasis was seen at the time of diagnosis in all cases, but distant metastases occurred in 4 patients. The lung was the most frequent site (n = 4), followed by the bones (n = 3), skin (n = 2), and liver (n = 2).

Histologically, 3 of the reported tumors were diagnosed as well-differentiated liposarcomas, 3 as pleomorphic liposarcomas, 3 as myxoid liposarcomas, and 1 as a dedifferentiated liposarcoma. In 3 cases, the exact histological diagnosis was not mentioned. The majority of the tumors presented a myxoid stroma (n = 6) containing spindle-shaped cells (n = 8), multivacuolated lipoblasts (n = 5), and capillarization (n = 4). In 2 cases, signet-ring cells were described. The occurrence of areas of small, well-delineated, tight concentric meningothelial-like eddies of bland spindle and epithelioid cells was mentioned in 1 case [11]. Immunohistochemically, the diagnosis was confirmed in 6 cases; vimentin staining was positive in each of these cases. The weakly and focally expressed SKA, α_1-antitrypsin, and α_1-antichymotrypsin were considered to be spurious by the authors of the report [6]. Other negative markers were epithelial membrane antigen, AE1/AE3, Cam 5.2, EMA, Bcl-2, CD117, DOG1, GFAP, β-catenin, ALK, CD34, CD57, h-caldesmon, or CD68.

Therapy and Outcome

Surgical removal was performed in each case. Total thyroidectomy was selected as primary treatment in 53.85% of the cases: in 2 cases, total thyroidectomy was deployed to supplement a previous hemithyroidectomy due to multinodular goiter, while in 3 other cases it represented the method of choice after suspicious FNAC results indicating malignancy. In the remaining patients, total thyroidectomy was performed to obtain a greater decompression of adjacent organs.

Hemithyroidectomy was carried out in 38.46% of the patients mostly because the tumor was considered to be benign after normal FNAC findings or goiter history. In 1 case, the exact surgical approach was not specified.

In 7 reports, adjuvant radio- or chemotherapy was carried out (53.85%). Five patients died after the initial presentation of the disease, 4 of them from causes related to the tumor and 1 from pneumonia. Seven patients were alive with no evidence of disease, and 1 patient presented metastases/recurrence during the follow-up (Table 1).

Discussion

Liposarcomas are malignant adipocytic solid tumors representing a heterogeneous group of lesions classified into 4 major types by the World Health Organization

Table 1. Characteristics, treatment, and outcome of the thyroid liposarcomas reported

Study/ first author, year	Sex/ age, years	Size/side[a]	Local extension	Metastases		Surgery (resection margin status)	Adjuvant therapy	Outcome, last follow-up, months	Positive IHC staining/ histological
				nodal	distant				
Nielsen [4], 1986	M/80	12 cm/L	Capsule intact, deviation of the trachea	No	No	Left hemi-thyroidectomy	No	DUD, 24	NA
Griem [5], 1989	M/23	8 cm/L	Adherent to trachea, esophagus, left carotid artery, thyroid cartilage; no signs of infiltration	No	No	Subtotal thyroidectomy	NA	NED, 22	Vimentin
Andrion [6], 1991	F/56	8 cm/L, isthmus	Invasion of surrounding soft tissue	No	No	Surgery, not specified	NA	DOD, 2	Vimentin and S-100 protein
Awad [7], 2003	F/50	12 cm/R	Retrosternal extension to the aortic arch, invasion of the right pyriform fossa musculature and esophageal wall, tracheal compression	NA	Lung, bone, skin, liver	Total thyroidectomy (R1)	RCT	DOD, 9	NA
Awad [7], 2003	M/71	7 cm/L	Retrosternal extension to the mediastinum, invasion of the esophageal wall, tracheal compression	NA	No	Left hemi-thyroidectomy	RT	NED, 6	NA
Mitra [8], 2004	F/49	12 cm/R	Retrosternal extension, adherent to the tracheal and pharyngeal wall, infiltration of the carotid artery, internal jugular vein	NA	Lung, skin, liver	Total thyroidectomy (R1)	RCT	DOD, 10	NA
Mitra [8], 2004	M/71	NA/L	Extension from the thoracic inlet to the level of the aortic arch, adherent to the esophagus, tracheal compression	No	Lung, bone	Left hemi-thyroidectomy (R1)	RCT	AWD, 14	NA
Kilic [9], 2007	M/40	3.4 cm/ isthmus	Capsule intact	No	No	Total thyroidectomy	RT	NED, 24	NA
Huang [10], 2009	F/59	6 cm/L	Compression of trachea	NA	Lung, bone	Left hemi-thyroidectomy	No	DOD, 15	Vimentin
Blumberg [11], 2012	M/65	4.7 cm/L/ para-tracheal space	Compression of trachea and esophagus	NA	NA	Left hemi-thyroidectomy	NA	NED, NA	MDM2, CDK4, vimentin, SMA, and CD99
Kumar [12], 2014	F/72	NA/both, predominant effect on L	Infiltration of the right common carotid artery and prevertebral soft tissue	NA	NA	Total thyroidectomy (R2)	RT	NED, >24	Vimentin
Kumar [11], 2014	F/65	NA/R	Compression of the trachea	NA	NA	Total thyroidectomy	RT	NED, >24	Vimentin and desmin
This study 2018	F/82	10 cm/R	Compression of the trachea and esophagus, no signs of infiltration	No	No	Total thyroidectomy (R0)	No	NED, 12	Amplification of the MDM2 gene locus (FISH)

AWD, alive with disease; both, both thyroid lobes; CT, chemotherapy; DOD, died of disease; DUD, death unrelated to disease; F, female; IHC, immunohistochemistry; L, left thyroid lobe; M, male; NA, not available; NED, no evidence of disease; R, right thyroid lobe; R0, macroscopically complete resection without microscopic residual tumor; R1, macroscopically complete resection with microscopic residual tumor; R2, macroscopically incomplete surgery; RCT, radiochemotherapy; RT, radiotherapy.

[a] Greatest dimension of the tumor.

(WHO): atypical lipoma/well-differentiated liposarcoma, and myxoid, pleomorphic, and dedifferentiated liposarcoma [15]. Because of the strong correlation between tumor prognosis and aggressiveness in localized liposarcomas, tumor grading constitutes an extremely important approach for decision-making in treatment. Since well-differentiated liposarcomas are considered low-grade tumors, they have very little metastatic potential and a good prognosis but tend to be locally aggressive. On the other hand, pleomorphic and dedifferentiated liposarcomas are classified as high-grade tumors. Their mortality ranges from 28 to 50%, and they grow quicker and develop metastases, mostly to the lungs [16].

Apart from their genetic predisposition, well-known risk factors for soft-tissue sarcomas are iatrogenic factors such as a chronic lymphedema and previous radiation;

however, liposarcomas seem to be only rarely associated with these [5, 17]. A slight female preponderance was noted, in accordance with previous data [18]. There was no geographical clustering of the cases reported. Concordantly, no relevant association with iodine-deficient goiter was seen in liposarcoma patients, who presented a history of goiter in just 30.77% of the cases [19]. Clinically, the most common symptom reported was a rapidly enlarging mass in the neck, occasionally accompanied by other symptoms like dysphagia, dyspnea, coughing, and alterations in the voice. However, these signs have been generally identified as common symptoms of thyroid sarcomas and consequently nonspecific for liposarcomas [18]. Local lymph nodes were never affected in the reported cases. Distant metastases were more common in the lungs, consistent with results reported for other primary thyroid sarcomas [18]; skin, bone and liver metastases were also detected.

The ultrasound findings mentioned in the case reports were mixed: hypo- to hyperechoic. In agreement with previous reports, it is difficult to clearly assert typical imaging features of liposarcomas, because of the small number of ultrasound investigations reported [18]. When used, the thyroid scan could reliably identify liposarcoma as a *cold* nodule, indicating its malignant potential [20].

The initial diagnostic procedure was FNAC in 53.85% of the cases reported in our database, but FNAC was not able to provide reliable cytological findings for the identify the liposarcomas. These observations match the recommendation of preferring open biopsies over needle biopsies [16].

In histologically classified thyroid liposarcomas of this series, the most common types corresponded to well-differentiated, pleomorphic, and myxoid liposarcomas. Microscopically, the differentiation of the histologic types is very challenging in liposarcoma patients. This problem may call for the use of immunohistochemistry or molecular studies: staining for vimentin, a mesenchymal marker, was positive in 6/6 cases [21]. S100 positivity was observed in a myxoid liposarcoma, while a case of dedifferentiated liposarcoma presented nuclear positivity for MDM2 and CDK4 [22]. Furthermore, smooth muscle actin (SMA) positivity in dedifferentiated liposarcomas with meningothelial-like whorls proved to be typical for this tumor entity [23]. However, recent studies underline the higher FISH sensitivity for MDM2 amplification as a diagnostic solution in difficult lipomatous tumors [24]. Besides that, other cytogenetic studies would help establishing a definitive diagnosis, like the identification of the fusion gene FUS-CHOP in myxoid liposarcomas [15].

Although there is no definite consensus within the literature with respect to a comprehensive treatment recommendation in patients with a primary thyroid sarcoma, the first choice of therapy is surgical excision, which was also noted in our study (100%). In particular, Gerry et al. [25] showed that patients with head and neck liposarcomas receiving only radiation therapy had significantly a worse outcome than patients receiving either surgical resection or surgery plus adjuvant radiotherapy. Davis et al. [26] recommended surgery with negative margin resection as the treatment of choice in head and neck liposarcomas. Regular frequent follow-up after surgery can be chosen for patients with well-differentiated or myxoid liposarcomas with negative margins without local extension. Adjuvant chemo- and/or radiotherapy should be considered for high-grade tumors, positive margins, large tumors, local extension, and complex anatomic subsites. In sarcomas, the improvement in locoregional control and overall survival achieved by the addition of radiation has shown to be related to tumor grade and the narrowness of the surgical margins [27]. As extensive surgical margins are often difficult to accomplish in the neck region, it has been shown that postoperative radiation may improve local control rates [28]. Chemotherapy was included in 23.08% of the cases, as recommended for patients previously treated by surgery and/or radiation with metastatic or recurrent disease. However, no survival benefit has been established yet [8]. The clinical follow-up correlates mostly with the histological classification, with a better prognosis for patients affected by well-differentiated liposarcomas, and metastatic spread by high-grade types.

Statistical analysis was limited due to the low number of patients reported, which represents a considerable limitation of our study.

Conclusions

We present a further case of liposarcoma of the thyroid gland with a review of the literature concerning the diagnosis and treatment of this extremely rare tumor entity. The data summarized in this analysis should serve as a reference for future investigations.

Disclosure Statement

No competing financial interests exist.

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