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CASE REPORT

Well-Differentiated Liposarcoma (Atypical Lipomatous Tumor) Presenting as an Esophageal Polyp

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Case Report

We present a case of a 61-year-old gentleman referred to our institution for investigation of a brief history of dysphagia, predominantly for solid foods, of 3 months duration. Of note, there was no associated weight loss, nausea, or vomiting described. There was no significant past medical history.

Gastroscopy and endoscopic ultrasound (EUS) revealed a massive polypoid esophageal lesion, extending from the level of the upper esophageal sphincter to the gastroesophageal junction. The lesion was ulcerated distally and had an inhomogeneous appearance at EUS. Representative biopsies taken with a linear EUS scope were non-diagnostic. CT imaging confirmed the endoscopic findings, with no evidence of regional lymphadenopathy (Fig. 1). Clinically and radiologically, the differential diagnosis included gastrointestinal stromal tumor (GIST) and leiomyosarcoma.

A minimally invasive three-stage (McKeown) esophagectomy was performed. Due to the bulk of the lesion, it was not possible to deliver it at the cervical incision and an extension of a midline laparoscopic port for retrieval was necessary. In adherence with our enhanced recovery program, he progressed on to liquids on day 2 and was tolerating a modified diet at day 5. He was discharged home on the seventh day. He remains well.

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Pathological Findings

Grossly, a 21 cm well-circumscribed tumor was seen, which had a solid, white, whorled cut surface (Fig. 2). Focally, myxoid change was present. The lesion was calcified in areas.

Histologically, the tumor was an unencapsulated, ill-defined, low to moderately cellular adipocytic and spindle cell lesion, located in the submucosa and muscularis propria of the esophagus. The adipocytic component comprised adipocytes of varying sizes and shapes. Unequivocal lipoblasts were not present. Bands of fibrous tissue traversed the adipocytic component, and occasional atypical hyperchromatic stromal cells were identified (Fig. 3). Collagenized stroma and myxoid stroma were present in areas (Fig. 4).

A large, distinct, more cellular focus was identified, consisting of spindled cells with mild cytological atypia (Fig. 4). Thorough examination yielded no mitoses. There was no evidence of necrosis or nuclear pleomorphism. Osseous metaplasia, comprising benign, metaplastic bone, with trilineage hematopoiesis, was seen focally, intimately admixed with this more cellular component (Fig. 5).

Immunohistochemistry with p16 and with retinoblastoma protein (pRb) showed strong and diffuse nuclear staining throughout all components of the tumor (Fig. 6). CD34, S100, and smooth muscle actin were negative in the lesional cells.

Fluorescence in situ hybridization (FISH) showed amplification of *MDM2* in both the adipocytic component and in the more cellular spindle cell component (Fig. 7).

This constellation of morphological, immunohistochemical, and cytogenetic features represents an atypical lipomatous tumor/well-differentiated liposarcoma (ALT/WDL) of the esophagus, with a focus of low-grade dedifferentiation.

Discussion

Rare cases of primary liposarcoma of the esophagus have been reported in the literature, most of them being of the

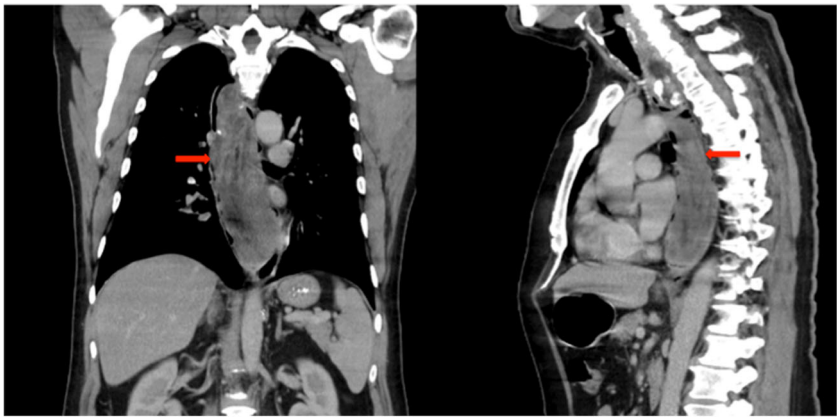

Fig. 1 CT imaging showed a large mass (red arrow) bulging into the lumen of the esophagus, extending along the entire length of the thoracic esophagus, commencing just below the cricopharyngeus and extending almost to the gastroesophageal junction

atypical lipomatous tumor/well-differentiated liposarcoma (ALT/WDL) type [1–4]. Esophageal dedifferentiated liposarcomas (DDLs) are extremely rare [1, 5]. Morphological, immunohistochemical, and cytogenetic features of esophageal ALT/WDL and DDL are the same as the features of these tumors occurring at more conventional sites. Unique to the esophagus, the morphological features of these entities raise the differential diagnosis of benign giant fibrovascular polyp (GFP). We review the clinical, histopathological, immunohistochemical, and molecular attributes of esophageal GFP, ALT/WDL, and DDL.

GFP of the esophagus (previously called "fibroma" or "fibrolipoma") was first proposed in 1957 as a unifying term for polypoid esophageal lesions lined by benign squamous epithelium, containing variable amounts of mature fat and fibrous tissue. GFPs of the esophagus are rare, reactive, non-neoplastic lesions [5]. They typically present as pedunculated polypoid masses, which partially obstruct the esophageal lumen. The clinical presentation can be dramatic, with reports of patients regurgitating tumors and descriptions of death from asphyxiation [6–8].

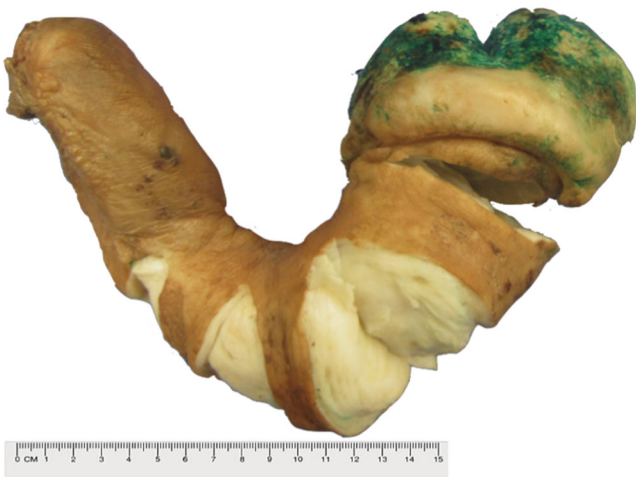

Fig. 2 The entire specimen consisted of a 21 cm elongated, sausage-shaped, well-circumscribed tumor, which had a firm, white, whorled cut surface

Histologically, GFPs consist of an admixture of mature adipose tissue and fibrous zones; the relative percentages of these two components are highly variable [5].

Immunohistochemistry shows that the lesional cells of GFPs are negative for p16, MDM2, and CDK4. Immunohistochemistry with retinoblastoma protein (pRb) shows diffuse nuclear positivity, indicating that there is no evidence of deletion of tumor suppressor gene *RB1*. *MDM2* fluorescence in situ hybridization (FISH) does not show amplification.

In recent years, it has become increasingly apparent that cases reportedly showing "classical" morphological features of GFP may show ring or marker chromosomes with regional amplification of chromosome 12q13-21 (the genetic hallmarks of ALT/WDL) [9]. In addition, there have been several case reports of morphologically typical ALT/WDL clinically mimicking GFP in the esophagus [3, 10, 11]. Thus, Graham and colleagues have suggested that most (if not all) esophageal GFPs represent well-differentiated and dedifferentiated liposarcomas, and they conclude that the diagnosis of GFP should be made with great caution in the esophagus, and only after careful morphological study and *MDM2* FISH has excluded the possibility of liposarcoma.

Atypical lipomatous tumor/well-differentiated liposarcoma (ALT/WDL) and dedifferentiated liposarcoma (DDL) form the largest subgroup of liposarcomas, and represent a morphological and behavioral spectrum of one disease entity [12, 13].

ALT/WDL is a locally aggressive mesenchymal neoplasm. The term "atypical lipomatous tumor" (ALT) is preferred in superficial soft tissue sites amenable to wide local excision. In deep-seated locations where curative resection cannot be achieved, such as in the retroperitoneum and mediastinum, the term "well-differentiated liposarcoma" (WDL) is used for the same lesion [14]. Graham et al. suggest that the term WDL, rather than ALT, should be used in the esophagus.

Esophageal WDLs are quite rare, with fewer than 50 reported cases, most commonly occurring in the 7th decade of life [3, 5]. They typically cause no symptoms until they reach a substantial size, impairing esophageal transit and,

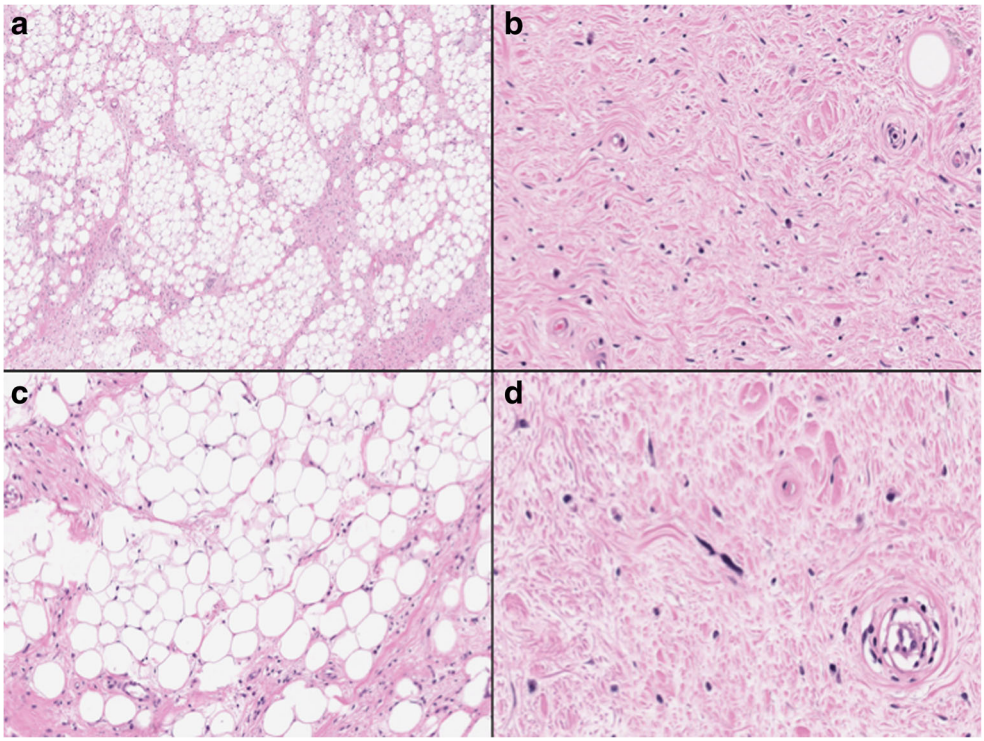

Fig. 3 The esophageal tumor was an unencapsulated, ill-defined, low to moderately cellular adipocytic and spindle cell lesion (**a**, 100× and **b**, 200×), located in the submucosa and muscularis propria of the esophagus. The adipocytic component comprised adipocytes of varying sizes and shapes (**c**, 100×). Occasional atypical hyperchromatic stromal cells were identified within the fibrous tissue (**d**, 400×)

thus, causing dysphagia. Other presenting symptoms include vomiting, weight loss, shortness of breath, chest discomfort, and anorexia [3]. Most ALT/WDLs of esophagus appear as large, elongated, smooth polyps within the esophageal lumen [3].

Microscopically, WDLs are composed entirely or in part of an adipocytic proliferation with significant variation in adipocyte size and a variable number of atypical, enlarged, hyperchromatic stromal cells, present in fibrous septae. Myxoid change is well recognized in WDLs. Lipoblasts are

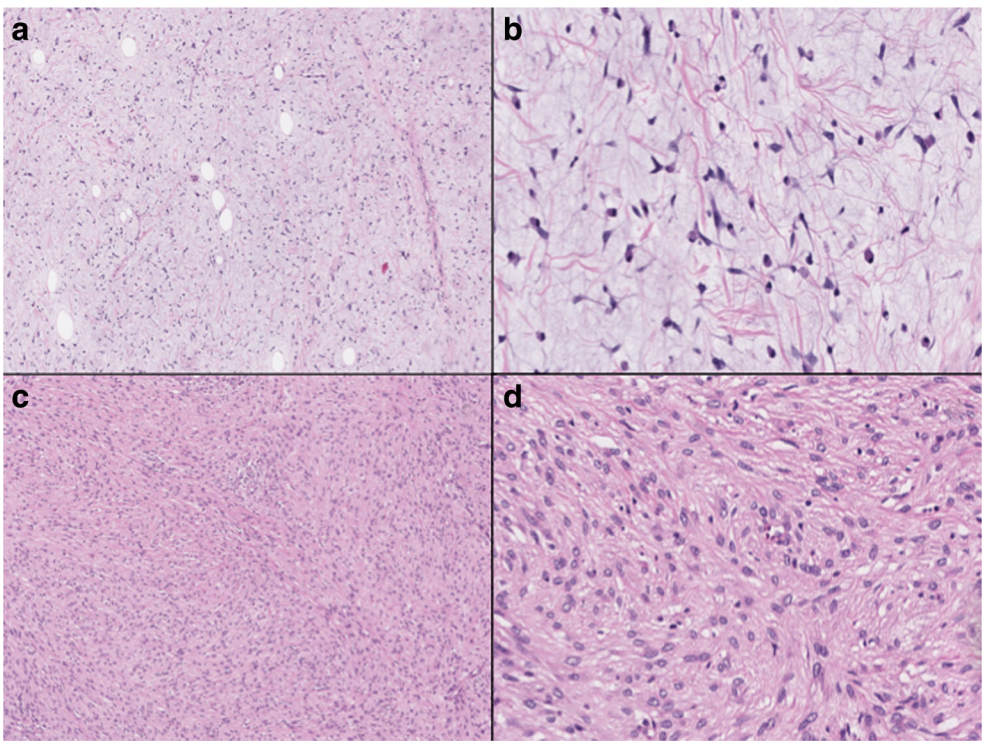

Fig. 4 Myxoid stroma was present in areas, and contained bland spindled and stellate cells (**a**, 100× and **b**, 400×). A more cellular focus was present, consisting of spindled cells with mild cytological atypia (**c**, 100×). There was no evidence of mitotic activity, nuclear pleomorphism, or necrosis (**d**, 200×)

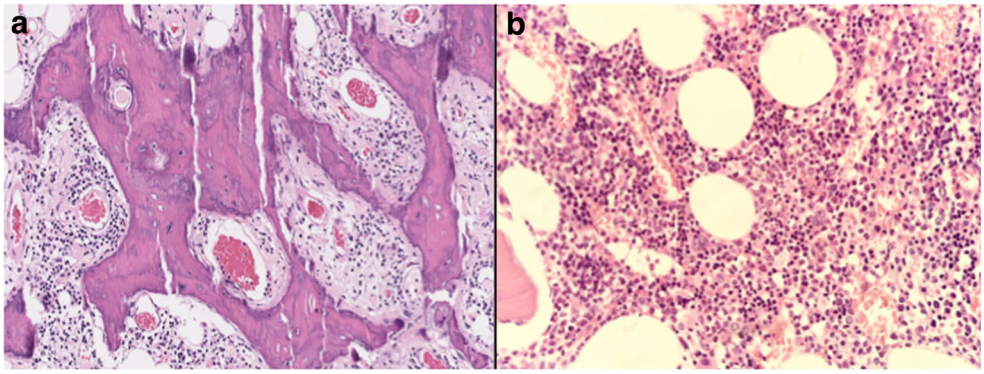

Fig. 5 Osseous metaplasia, comprising benign, metaplastic bone, with trilineage hematopoiesis, was seen focally (**a**, 100×; **b**, 200×)

cells with hyperchromatic nuclei that are indented or sharply scalloped due to lipid-rich mono- or multi-vacuolated cytoplasmic droplets. They may or may not be present in WDLs, and this is reflected in the current World Health Organization (WHO) diagnostic criteria for ALT/WDL, whereby lipoblasts are considered a helpful clue, but not a prerequisite, for the diagnosis [15]. Graham and colleagues reported that the morphological features of esophageal WDLs typically seem to be less impressive than those of their soft tissue and retroperitoneal counterparts, usually lacking markedly pleomorphic, hyperchromatic stromal cells, and instead showing an increased number of slightly enlarged stromal cells with irregular, hyperchromatic nuclei [5].

ALT-WDLs are characterized by supernumerary ring chromosomes or giant marker chromosomes that demonstrate amplifications in the chromosomal region 12q13-15 [16]; these amplifications constantly affect *MDM2* (100%), and frequently *CDK4* (90%), and *HMGA2* genes. As such, ALT/WDLs demonstrate MDM2 and CDK4 overexpression by immunohistochemistry. Amplifications of *MDM2* and *CDK4* can be detected using FISH, which is currently the criterion standard method [17, 18]. $p16^{Ink4A}$ (p16) is a transcript of the cyclin-dependent kinase inhibitor 2A (*CDKN2A*) gene and it inhibits cell cycle progression by binding to CDK4 [19]. p16 has been proposed as a diagnostic marker for ALT/WDL as it has been shown to be over-expressed in these tumors by both quantitative reverse-transcription polymerase chain reaction and immunohistochemistry [20]. Nuclear Rb expression is typically intact in ALT/WDLs.

DDL is a "non-lipogenic sarcoma" arising in association with a well-differentiated liposarcoma/an atypical lipomatous tumor. Up to 90% of DDLs present as de novo neoplasms and

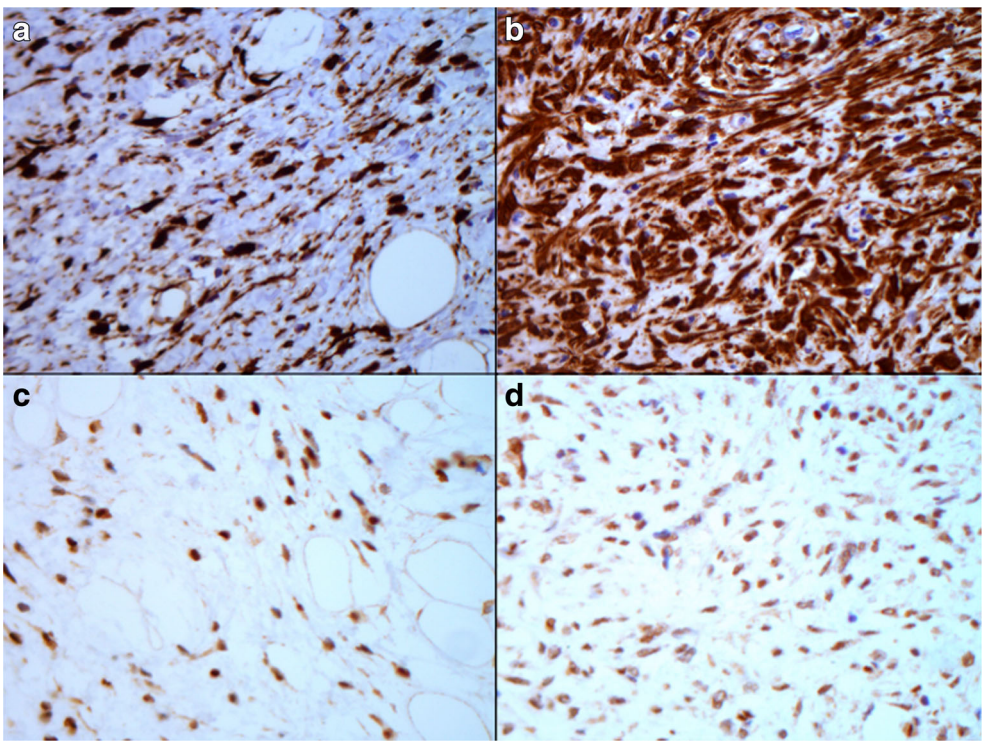

Fig. 6 Immunohistochemistry with p16 (**a** and **b**, both 400×) and with retinoblastoma protein (pRb) (**c** and **d**, both 400×) showed strong and diffuse nuclear staining in the well-differentiated (**a** and **c**) and in the dedifferentiated (**b** and **d**) components of the tumor

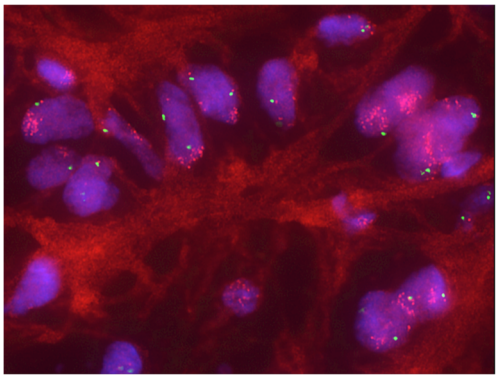

Fig. 7 Fluorescence in situ hybridization (FISH) showed amplification of *MDM2* in the well-differentiated adipocytic component (demonstrated in this image) as well as in the more cellular dedifferentiated spindle cell component (not shown). The green probe represents the centromere of chromosome 12 and the pink probe represents the *MDM2* gene

the remaining DDLs occur as a recurrence of a pre-existing ALT/WDL, after an average interval of 7.7 years [21]. Dedifferentiation can occur in up to 10% of ALT/WDLs at any site [22], with the risk being greater in tumors that are deep-seated, particularly those in the retroperitoneum, where this risk is approx. 28% [22–24]. Primary esophageal DDLs are extremely rare [5].

DDLs can show a spectrum of morphological appearances. The majority shows features of undifferentiated pleomorphic sarcoma or spindle cell sarcoma not otherwise specified [22], characterized by high to moderate cellularity, comprising cells disposed in loose fascicles, patternless distributions, or sometimes with a storiform architecture, within variably fibrous stroma. Nuclear pleomorphism, with moderate to marked cytological atypia is seen, the mitotic index is variable and necrosis can also be seen [25, 26]. Prominent myxoid stroma can be a feature of DDLs. When present, atypical spindle or ovoid cells with a myxofibrosarcoma-like morphology are seen within the myxoid stroma. Metaplastic bone, meningothelial-like whorls, and metaplastic cartilage may be seen rarely [27–29]. DDLs may exhibit heterologous differentiation toward other mesenchymal lineages, including chondroid, osteoid, myoid (rhabdomyosarcomatous or leiomyosarcomatous elements), or smooth muscle [21, 30, 31]. Rarely, angiosarcomatous differentiation has been described [32].

A minority of DDLs are of low cellularity and low grade, comprising only histologically "low-grade" areas resembling fibromatosis or low-grade fibromyxoid sarcoma [21, 33, 34]. Low cellularity DDLs are composed of sparsely to moderately cellular proliferations comprising loose fascicles or patternless distributions of fibroblast-like spindle cells with mild nuclear atypia and low mitotic activity [22].

Graham et al. described three cases of esophageal DDLs, which comprised significant zones of mitotically active, variably pleomorphic, non-lipogenic spindle cell sarcoma, with one case showing a whorled, "perineurioma-like" growth pattern [5].

DDLs can show variable expression of CD34, with focal positivity for smooth muscle actin and desmin, while S100 protein is absent in non-lipogenic areas of DDLs [22]. A recent paper details the results of whole-exome sequencing performed on 50 DDLs, all of which were defined by 12q13-15 amplifications, including highly recurrent copy number gains or amplification of *MDM2* (100% of samples), *CDK4* (92%), and *HMGA2* (76%) [35]. There is strong correlation between expression of MDM2 and CDK4 immunohistochemical stains and their gene amplification status [36]. In addition, the assessment of *MDM2* gene amplification by FISH is a highly useful adjunctive diagnostic tool for the diagnosis of DDL [37]. p16 has been shown to be the most sensitive and specific marker for detecting DDLs [38], and the combination of p16 with CDK4 and MDM2 is a useful immunohistochemical panel in distinguishing DDLs from other adipocytic neoplasms in the differential diagnosis.

Spindle cell adipocytic tumors of the esophagus can be challenging and accurate histological classification is essential. The distinction between esophageal WDLs and benign adipocytic tumors, such as benign lipomas, both of conventional and spindle cell/pleomorphic types [5], is crucial because of differences in both prognosis and treatment. Difficulties diagnosing WDL may be encountered when the atypical stromal cells are poorly represented or absent and when lipoblasts are not seen. In lipomas, fibrosis, necrosis, inflammatory cells, and pseudo-lipoblasts may be present, leading pathologists to consider a diagnosis of WDL. *MDM2* gene amplification by FISH is an essential adjunct to prevent both under- and over-diagnosis of WDL [39].

The diverse histological patterns of DDL can lead to difficulty in distinguishing it from other sarcomas, particularly in tumors in which a component of WDL is lacking [22]. The diagnosis of DDL is prognostically significant, as it has a lower tendency toward local recurrence and metastasis, when compared with morphologically similar pleomorphic sarcomas such as leiomyosarcomas or undifferentiated pleomorphic sarcomas [26]. Morphological clues to identify DDLs are the presence of an abrupt transition from a well-differentiated adipocytic component into non-lipogenic spindle cell areas, and/or the presence of higher-grade areas, widespread atypia, and varied morphology or nuclear pleomorphism [22]. Essentially, all neoplasms in the differential diagnosis of DDL will lack any adjacent WDL, and will tend to lack expression of p16, CDK4, and MDM2 by immunohistochemistry and evidence of *MDM2* amplification by FISH [22].

The prognosis of spindle cell adipocytic tumors of the esophagus varies widely. Most cases reported as esophageal GFP had a benign clinical course, and the rare deaths described were caused by asphyxia after regurgitation of the polyp and obstruction of the upper airway. While WDL has no metastatic potential, Graham and colleagues state that the

natural history of esophageal WDL appears to be similar to that of their more common somatic soft tissue counterparts, with potential for local recurrence and dedifferentiation (in up to 10% of ALT/WDLs) [14, 22]. DDLs behave in a more aggressive manner than WDLs, with a greater propensity for local recurrence and the capacity to metastasize, but they tend to behave less aggressively than other pleomorphic sarcomas [21, 22, 26]. Graham et al. report in their recent review that esophageal DDLs have a relatively high risk of metastases [5]. Macroscopic tumor clearance at any site has been shown to be significantly associated with reduced local recurrence and improved survival [40]. Histologically, low-grade DDLs have been shown to have the capacity to metastasize and to behave like traditional DDLs, rather than like WDLs [21, 41].

Given the typically large size of theses lesions, the question of the representivity of lesions' pre-/intra-operative (either FNA and/or biopsy) diagnosis arises. As seen with the pre-operative attempt at ascertaining the diagnosis in our case, it can be difficult to obtain enough tissue to render an accurate diagnosis. In addition, multiple sections of our excised lesion had to be examined histologically because of its complex appearance, being composed of spindle cells, fat and vessels, the deceptively bland cytology, and the heavy reliance of ancillary tests, in this case, immunohistochemistry and the diagnostic application of FISH for *MDM2* amplification.

Conclusion

We report a case of a 21 cm atypical lipomatous tumor/well-differentiated liposarcoma of the esophagus, with a focus of well-differentiated dedifferentiation. Fluorescence in situ hybridization analysis demonstrated the presence of *MDM2* amplification in both the well-differentiated liposarcoma component and the dedifferentiated component.

Primary esophageal WDLs are extremely rare, and the presence of a low-grade dedifferentiated focus within a primary esophageal WDL is exceptionally rare.

As highlighted by this case, the classification of spindle cell adipocytic tumors of the esophagus can be a significant challenge to pathologists. Morphologically, giant fibrovascular polyp of the esophagus may be indistinguishable from WDL and DDL. Ancillary tests are required to make this important distinction.

When faced with spindle cell adipocytic tumors of the esophagus, clinical, histopathological, immunohistochemical, and molecular approaches must be combined to overcome diagnostic challenges and render an accurate diagnosis.

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

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