

Dedifferentiated Liposarcoma of the Gastroesophageal Junction

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ABSTRACT

Liposarcoma is one of the most common sarcomas in adults, but very rarely presents as a primary in the upper gastrointestinal system. Herein, we present a 71-year-old male patient who underwent wedge excision biopsy twice and then fine needle aspiration and total gastrectomy for a recurrent gastroesophageal junction mass. In microscopic sections, both well-differentiated and dedifferentiated components were seen. Tumor cells were positive for MDM2, CDK4 and negative for CD117, DOG1, CD34, SMA, Desmin, S-100, HMB45, SOX10, AE1/AE3, CAM5.2, CK18. Fluorescence in situ hybridization (FISH) was performed and MDM2 gene (12q15) amplification was detected. According to these findings, a diagnosis of dedifferentiated liposarcoma was supported. We believe this is the first reported case of dedifferentiated liposarcoma of the gastroesophageal junction.

Key Words: Gastrointestinal neoplasms, Gastroesophageal junction, Dedifferentiated liposarcoma

INTRODUCTION

Liposarcoma is one of the most common malignant soft tissue tumors in adults. Current World Health Organization (WHO) divides liposarcomas into four subtypes (1,2). The atypical lipomatous tumor/well differentiated liposarcoma (WDLPS) is the most common subtype and, along with dedifferentiated liposarcoma (DDLPS), commonly occurs in the retroperitoneum (3, 4), whereas the myxoid, and pleomorphic types typically present in the extremities (5).

In general, liposarcomas are extremely uncommon in the gastrointestinal tract (6-13), especially at the gastroesophageal junction. We describe herein the first case of DDLPS of the gastroesophageal junction. The diagnosis was based on morphology, MDM2 and CDK4 immunoreexpression and fluorescence in situ hybridization analysis.

CASE REPORT

A 71-year-old male with a history of long-term dysphagia underwent a wedge excision in 1996 for presumed benign gastroesophageal junction mass, as per history from the patient. In 2006, repeat endoscopy revealed a recurrent lesion and another partial excision was performed. Pathology materials of these excisions were not available for our evaluation.

The patient was regularly followed up and a 3-4 cm mass with ulceration was found in the cardia at upper endoscopy, performed in 2013. Biopsies were non-diagnostic. Endoscopic ultrasound revealed a 2.2 cm hypoechoic mass with superficial erosions at the gastroesophageal

junction. It was thought to be arising from the mucosa and likely invading the superficial submucosa. The muscularis propria was intact. Fine needle aspiration (FNA) biopsy/cell block revealed a spindle cell neoplasm with nuclear pleomorphism and hyperchromasia. The neoplastic cells were positive for CD34 while negative for CD117 and DOG1, SMA, S100, and pan-cytokeratin. The morphological and immunophenotypic findings were not sufficient for a definitive diagnosis but sarcoma was favored. Axial oral-IV contrast enhanced computerized tomography (CT) revealed a solid mass in the gastroesophageal junction protruding into the lumen (Figure 1). There was no definitive evidence of metastatic disease.

The resection specimen consisted of total gastrectomy material with distal esophagus. There was a relatively well-circumscribed, submucosal lesion at the gastroesophageal junction measuring 3 cm in length, 2.5 cm in width and 1.1 cm in depth. Sectioning revealed a tan-white, solid cut surface. The overlying mucosa was eroded but the adjacent mucosa was unremarkable.

Microscopic sections revealed a multinodular neoplasm at the gastroesophageal junction, predominantly located within the submucosa and focally extending to the surface epithelium (Figure 2). The tumor was cellular and was predominantly composed of pleomorphic and spindle cells (Figure 3), associated with a polymorphic inflammatory infiltrate including neutrophils, eosinophils, lymphocytes, and plasma cells. Some of the cells had cytoplasmic vacuoles/bubbly cytoplasm. The mitotic count was up to 15/50 HPF.

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The differential diagnosis included gastrointestinal stromal tumor (GIST), leiomyosarcoma, schwannoma, malignant melanoma, and less likely sarcomatoid carcinoma. Performed immunohistochemical stains revealed that the tumor cells were negative for CD117, DOG1, CD34, SMA, Desmin, S-100, HMB45, SOX10 as well as AE1/AE3, CAM5.2, and CK18, arguing against these differential diagnoses. At this point additional sampling was done and revealed a small component composed of adipose tissue with fibrous septae containing atypical hyperchromatic stromal cells and scattered lipoblasts (Figure 4), suggesting DDLPS as the likely diagnosis. Second round immunohistochemical stains revealed that the tumor cells were indeed positive for

MDM2 (Figure 5A), and CDK4, supporting the diagnosis of DDLPS. In order to confirm the diagnosis, fluorescence in situ hybridization (FISH) was performed and MDM2 gene (12q15) amplification was detected (Figure 5B).

The patient was alive with no evidence of disease 4 months after the resection.

DISCUSSION

Per its first description by Evans (14), dedifferentiated liposarcoma (DDLPS) is defined as a combination of atypical lipomatous tumor/well-differentiated liposarcoma (WDLPS) and a high-grade non-lipogenic sarcoma-

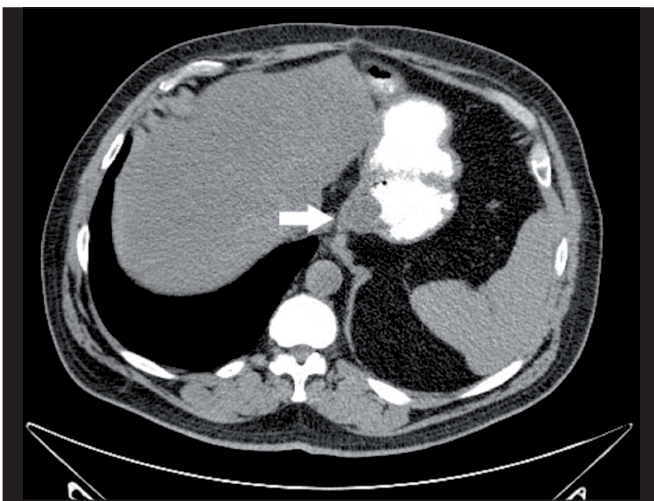


Figure 1: Axial oral-IV contrast enhanced CT images showing a solid mass (arrow) in the gastroesophageal junction protruding into the lumen.

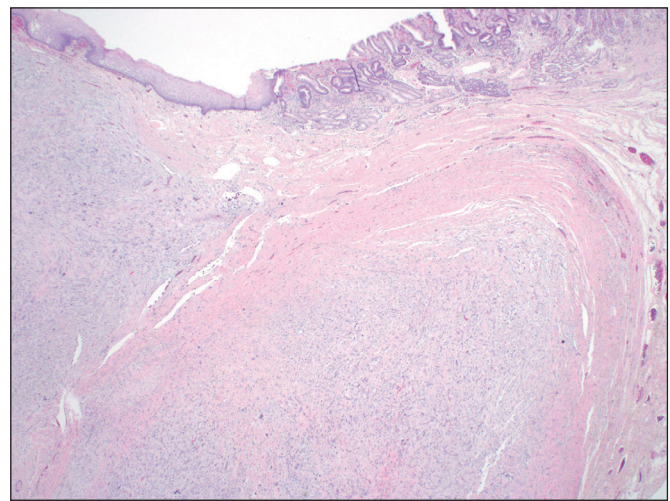


Figure 2: A multinodular spindle cell tumor at the gastroesophageal junction (H&E; x40).

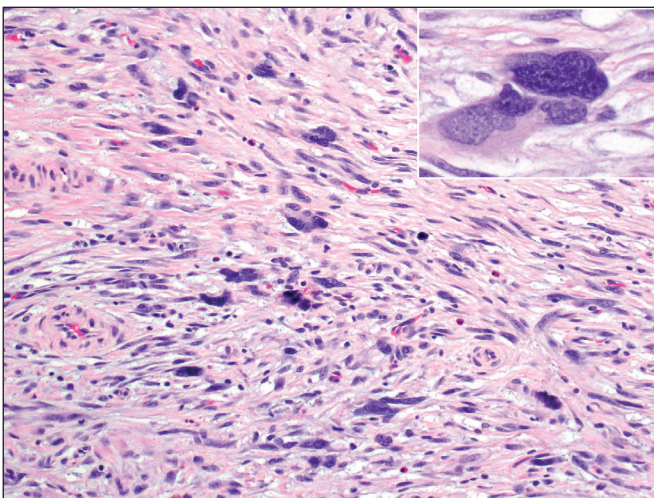


Figure 3: The dedifferentiated component is predominantly composed of highly pleomorphic spindle cells with nuclear hyperchromasia (H&E; x100).

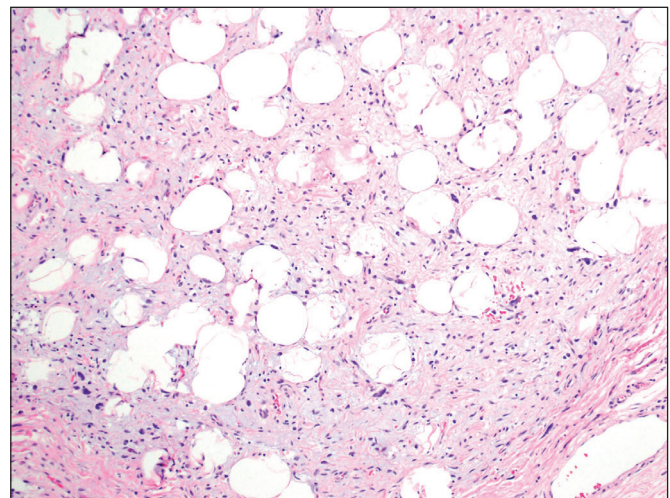


Figure 4: Atypical lipomatous tumor/well differentiated liposarcoma component is characterized by adipose tissue with fibrous septae containing atypical hyperchromatic stromal cells (H&E; x400).

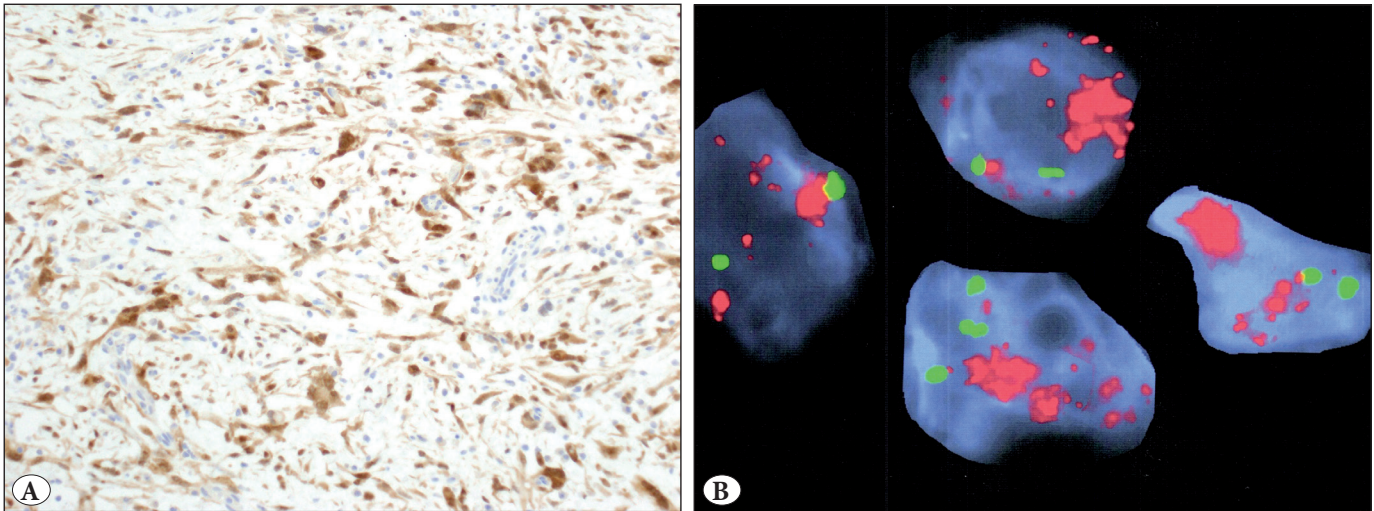


Figure 5: **A)** Tumor cells show diffuse nuclear labeling with MDM2 antibody (MDM2; x200), **B)** Fluorescence in situ hybridization analysis show amplification of the MDM2 gene (Green - CEP 12 and red - MDM2).

like component, such as undifferentiated high-grade pleomorphic sarcoma (i.e. malignant fibrous histiocytoma), fibrosarcoma, or myxofibrosarcoma. It occurs in late adult life (sixth to seventh decades) with an equal distribution between males and females (1). The most common location is the retroperitoneum.

DDLPS can occur *de novo* (90%) while about 10% occur as recurrence from a preexisting WDLPS (10%) (15). If it arises from a preexisting WDLPS, dedifferentiation develops in 20% of the first local recurrences and 44% of the second local recurrences (5). Although we could not evaluate the previous pathology materials, the history of recurrent lesions at the gastroesophageal junction suggests preexisting WDLPS in our patient.

CT imaging have been described as the best way to confirm the adipose component in these tumors (16, 17) and FNA/tru-cut biopsy seems to be the best way to confirm the diagnosis of sarcoma (18), and the tissue obtained by biopsy may even be used for molecular tests.

The histological diagnosis is usually based on the identification of WDLPS areas, which was very limited in our case. In such cases, immunopositivity for CDK4 and MDM2 and detection of amplification of the MDM2 and CDK4 genes are diagnostically helpful. Although MDM2 and CDK4 immunohistochemical staining alone is sufficient for the accurate diagnosis in the appropriate context (19, 20), they are not 100% specific and sensitive. Therefore, FISH, quantitative polymerase chain reaction (PCR), and/or comparative genomic hybridization (CGH) may be essential in cases with diagnostic difficulties (21, 22).

To our knowledge, this is the first DDLPS of the gastroesophageal junction and only two primary DDLPS cases of the esophagus have been reported in the English literature (23, 24). Both patients were elderly males who presented with progressive dysphagia, weight loss, and large masses measuring up to 10 cm, one protruding into the lumen. In one of these cases, the tumor was also predominantly located in the mucosa and submucosa, as seen in our case.

DDLPS appears to have a better prognosis (especially in terms of metastatic potential) than other high-grade sarcomas. However, careful long-term follow-up is recommended as approximately 40% of DDLPS cases will recur locally, 17% will metastasize and 28% of patients will ultimately die of disease (1). Surgery is still the best choice of treatment for DDLPS and it is important to remove the tumor entirely (4). Targeted chemotherapeutic agents and radiation therapy are being investigated (25).

DDLPS of the upper gastrointestinal system is rare but should be considered in the differential diagnosis of any poorly or undifferentiated sarcoma, and extensive sampling may be required for accurate diagnosis. We believe that our case represents the first report of DDLPS of the gastroesophageal junction with both well-differentiated liposarcoma and dedifferentiated sarcoma components, as well as confirmation with molecular analysis.

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