Cardiovascular Pathology 30 (2017) 1–5

Contents lists available at ScienceDirect

Cardiovascular Pathology

Case Report

Primary inferior vena cava smooth muscle tumor with diffuse bizarre giant nuclei and low mitotic rate: a nomenclatural conundrum

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ARTICLE INFO

Article history:
Received 11 May 2017
Received in revised form 30 May 2017
Accepted 31 May 2017
Available online xxxx

Keywords:
Leiomyosarcoma
Leiomyoma
Symplastic
Bizarre nuclei
Inferior vena cava

ABSTRACT

A male patient with obstructive jaundice was found to have an incidental nodule within the inferior vena cava (IVC), below the level of the renal vein, on abdominal imaging. At the time of the Whipple's procedure for pancreatic adenocarcinoma, the IVC mass measuring 3.4×2.7×2.2 cm was also removed.
Histologically, the lesion was well circumscribed, composed focally of spindle-shaped cells with cigar-shaped nuclei reminiscent of smooth muscle and a dominant pervasive, pleomorphic, bizarre giant cell component. Two mitoses per 10 high-power fields were identified in the most mitotically active area of the entire tumor, with the vast majority of the tumor being mitotically inert. Additionally, no evidence of coagulative necrosis was noted. The bizarre giant cells had multi- and polylobated configurations, and several were replete with nuclear pseudoinclusions. Both the spindle cell and pleomorphic components displayed strong immunoreactivity for all smooth muscle markers.
This lesion conformed morphologically to a smooth muscle tumor with bizarre nuclei or so-called symplastic/bizarre leiomyoma, as encountered in the uterus.
However, current thinking based on location in the IVC and the presence of any mitotic activity with cellular atypia makes this lesion a leiomyosarcoma. Perhaps more pragmatic terminology would be smooth muscle tumor with bizarre nuclei and low malignant potential since the limited number of cases described thus far appear to have a more indolent course.

1. Introduction

Primary sarcomas of the great vessels are rare, occurring primarily in the pulmonary arteries, aorta, and inferior vena cava (IVC). The vast majority of sarcomas are constituted by leiomyosarcomas, angiosarcomas, and so-called undifferentiated (intimal) sarcoma [1]. Sporadic cases of rhabdomyosarcoma and synovial sarcoma have also been documented [2]. Benign mesenchymal tumors within vessels usually occur in women with a history of uterine leiomyomas, suggesting intravenous extension or the entity of intravenous leiomyomatosis. Benign smooth muscle tumors arising within the IVC are limited to just two case reports of bizarre or symplastic leiomyoma [3,4].

Leiomyomas are monoclonal benign tumors, and 40% harbor karyotypic abnormalities such as deletions in chromosome 7, trisomy of chromosome 12, and rearrangements involving the *high mobility group AT-hook* (*HMGA*) *1* (located on chromosome 6p21) and *HMGA2* (on chromosome 12q14) genes [5]. Recently, heterozygous somatic mutations in the *mediator complex subunit 12* (*MED12*) were identified in approximately 70%–80% of uterine leiomyomas [6]. The incidence of mutations in extrauterine smooth muscle tumors, on the other hand, ranges from zero to 16% [7,8].

The purpose of this brief report is to highlight the occurrence of a primary smooth muscle tumor of the IVC that was rich in cells with bizarre giant nuclei, low mitotic rate, and pervasive degenerative change invoking a differential diagnosis of symplastic/bizarre leiomyoma versus leiomyosarcoma.

2. Materials and methods, results

2.1. Case report

A 73-year old man presented with obstructive jaundice and was found to have a 2.3-cm mass in the head of the pancreas on computed tomographic (CT) scan of the abdomen. An incidental well-defined, slightly enhancing mass was identified in the IVC, just below the right

Compliance with ethical standards: funding, none; conflict of interest, none.
The authors declare that they have no conflict of interest.
Funding: none.

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http://dx.doi.org/10.1016/j.carpath.2017.05.007
1054-8807/

renal vein. Located mainly within the wall, the lesion also had a nonocclusive intraluminal component. At the time of the Whipple's procedure, the IVC mass was also removed. The patient had an uneventful recovery from the surgery and has been followed up for the last 10 months. There was no recurrence of the pancreatic tumor or the IVC lesion.

2.2. Pathology and immunohistochemistry

An adenocarcinoma of the head of the pancreas was confirmed, and the separately submitted IVC mass consisted of a well-circumscribed, pale firm tumor measuring 3.4×2.7×2.2 cm. On cut section, it appeared uniform with no obvious foci of necrosis or hemorrhage. The entire specimen was sampled for microscopic evaluation.

Microscopic examination revealed a well-circumscribed, spindle cell lesion characterized by numerous large, pleomorphic bizarre cells (Fig. 1a). The spindle cells were arranged in interlacing fascicles and had typical cigar-shaped nuclei (Fig. 1b). Liberally interspersed and admixed with the spindle cells were the bizarre, giant cells. They ranged from uninucleate to polylobated multinucleated forms (Fig. 1c). Several contained one to three eosinophilic intranuclear pseudoinclusions, coarse nuclear chromatin which imparted a hyperchromatic appearance to the nuclei (Fig. 1d). Additionally, several large hyperchromatic spindle cells are also noted. Assiduous search for mitoses yielded a maximum count of 2 mitoses per 10 high-power fields in the most mitotically active area. Indeed, the vast majority of the lesion was devoid of mitotic activity. Mitoses were distinguished from karyorrhectic nuclei by use of anti-phosphohistone H3 immunostain which showed occasional large cells to be positive (Fig. 2a). No mitotic activity was noted in the blander spindle cell component (Fig. 2b). In addition, an MIB-1 stain showed the proliferation index of the tumor to be approximately 3%. Spindle cells and bizarre giant cells displayed both nuclear staining as well as being negative (Fig. 2c and d).

Another striking histologic feature was the presence of degenerative stromal change within the tumor. These took the form of edematous, hemorrhagic foci (Fig. 3a); areas of stromal hyalinization; cystic degeneration (Fig. 3b); and several vessels demonstrating fibrinous degeneration of walls (Fig. 3c) and hyalinization. These stromal degenerative changes are reminiscent of the changes seen in an ancient schwannoma.

No evidence of coagulative tumor necrosis was seen.

The smooth muscle lineage of the tumor was established by strong desmin (Fig. 3d), smooth muscle actin, and caldesmon immunoreactivity. The spindle cells showed the most intense staining for the muscle markers; occasional pleomorphic bizarre cells were negative.

This constellation of findings raised a diagnostic conundrum of leiomyosarcoma or a symplastic or bizarre leiomyoma of the IVC.

2.3. MED12 mutation screening

MED12 mutation screening was performed by Sanger sequencing. Genomic DNA was extracted from the formalin-fixed paraffin-embedded (FFPE) tissue sample with GeneRead DNA FFPE Kit (Qiagen, Hilden, Germany). Oligonucleotide primer sequences in the 5′ to 3′ direction are CCCCTTTTCGGCTCCCTC (forward) and GTCAGTGCCTCCTC CTAGG (reverse) for *MED12* exon 1, and GCCCTTTCACCTTGTTCCTT (forward) and AAGCTGACGTTCTTGGCACT (reverse) for exon 2. Polymerase chain reactions (PCRs) were performed in duplicate to ensure accuracy. PCR products were sequenced using Big Dye Terminator v.3.1 Kit (Applied Biosystems, Foster City, CA, USA) on an ABI3730 Automatic DNA Sequencer. Sequences were analyzed both manually and with the Mutation Surveyor software (Softgenetics, State College, PA, USA). No *MED12* hotspot mutations were detected in the IVC tumor.

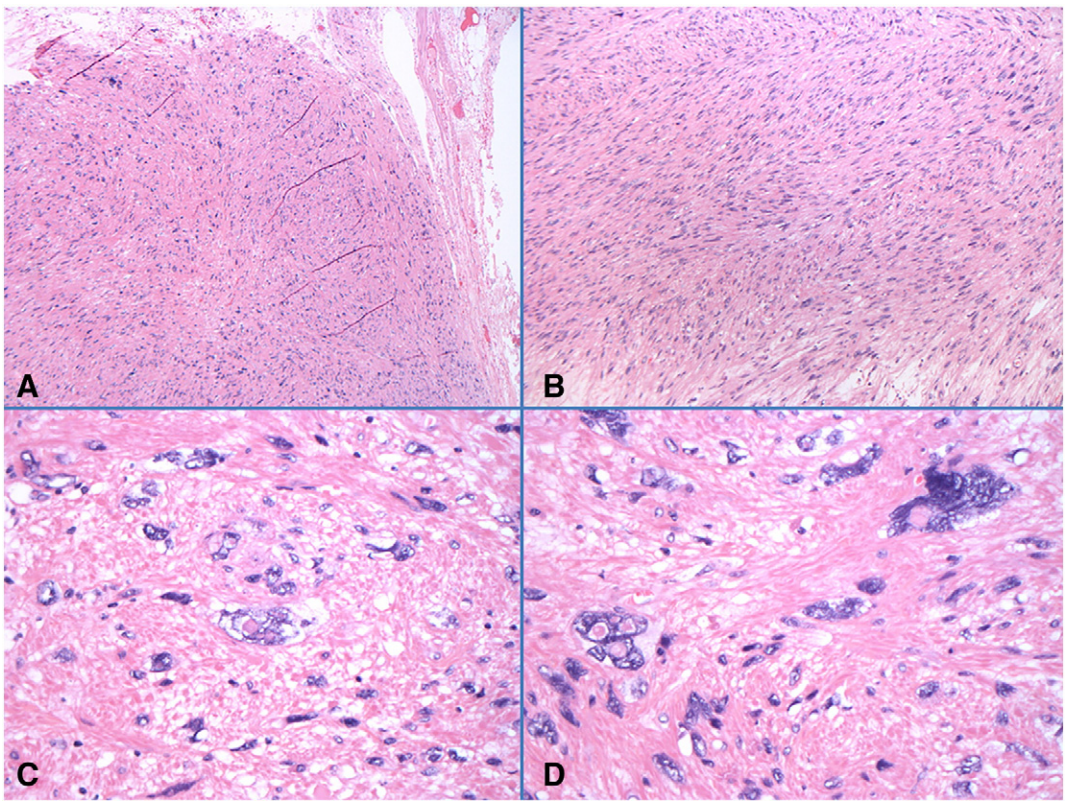

Fig. 1. The lesion was a discrete, well-circumscribed nodule composed of bizarre cells (a) (×200) as well as spindle cells more reminiscent of a typical leiomyoma (b) (×200). The bizarre cells were typical pleomorphic appearing with multi- and polylobation and intranuclear pseudoinclusions (c & d) (×400).