CASE REPORT

Dedifferentiated adamantinoma associated with fibrous dysplasia

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Summary  A 21-year-old patient presented with an aggressive lesion of the left tibia associated to lymph nodes and lung metastasis. Histological examination revealed a high grade spindle cell sarcoma involving some areas of cytokeratine positive cells. Ultrastructural examination showed the presence of epithelial features in the sarcomatoid cells. The diagnosis of dedifferentiated spindle-celled adamantinoma was established. A second lesion of the right tibia was diagnosed as fibrous dysplasia. The patient had a leg amputation. He died 2 years later with multiple lung and bone metastases. The diagnosis of dedifferentiated adamantinoma should be considered when a clinician is confronted with a tibial biopsy of a ”keratin-positive sarcoma”. The association with fibrous dysplasia in this case is discussed.

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Introduction

Adamantinoma is a rare primary low grade malignant bone tumor involving the tibia in the majority of cases. It remains a perplexing tumor for its histology as well as for its histogenesis. Four patterns of growth have been described: tubular, basaloid, squamous and spindle cell. In its appropriate clinico-radiologic setting, the clear epithelial differentiation of cell groups embedded in fibrous tissue does not even necessitate immunohistochemestrical analysis for diagnosis. However, this epithelial component can be easily overlooked in other cases especially in the spindle-cell pattern. The latter variant, often seen in local recurrences and metastasising cases can be undistinguishable from spindle cell soft tissue sarcoma. Hazelbag et al. [1] described this morphologic pattern characterised by the loss of epithelial differentiation of tumor cells as a “dedifferentiated” adamantinoma.

The possible relationship of adamantinoma with osteofibrous dysplasia (OFD) is the subject of conflicting discussions. Despite the fact that there is ample clinical, radiological and pathological evidence that OFD and

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Figure 1  a and b: X-ray of the left leg antero-posterior (AP) and lateral views. Osteolytic lesion of the middle shaft of the tibia with cortical interruption and soft tissue extension.

adamantinoma are related lesions, the exact relation between them is not well established yet.

We report an exceptional case of dedifferentiated adamantinoma of the tibia associated with fibrous dysplasia (FD). The particular histological pattern of this case and its association with FD are discussed.

Case report

A 21-year-old patient was referred to our institution for a bone tumour of the left tibia. At the age of 17, a biopsy was performed in another hospital and revealed a high-grade spindle cell sarcoma diagnosed as fibrosarcoma. At that time, CT scan of the chest revealed multiple lung metastases. The patient had chemotherapy subsequently below the knee amputation was proposed. The patient refused further therapy and was lost of view.

Four years later, he sought again medical attention because the tumor continued to progress. Physical examination showed a 10-cm soft tissue mass developed at the antero-medial side of the leg associated with painful inguinal lymph nodes. Conventional radiographs revealed a multi-lobulated osteolytic lesion in the middle shaft of tibia, with a "mouth eaten" appearance destroying the cortex and expanding widely to soft tissues (Fig. 1a and b). CT scan and MRI confirmed the aggressive pattern of this lesion and the extension to soft tissues. They also showed a second lesion distally in the metaphysis and another well circumscribed intramedullary lesion in the right tibia (Fig. 2 et 3 a, b, c). Pulmonary CT showed multiple lung metastases.

Open biopsies were performed in different sites: both lesions of the left tibia, lymph node and lesion of the right tibia.

In the three first sites, histological examination showed a highly cellular tumor composed of spindle-shaped cells arranged in bundles (Fig. 4a). The nuclei were large irregular and hyperchromatic and contained prominent nucleoli. Mitotic figures were observed at the rate of 10 per high power fields (Fig. 4b). No epithelial cells, neither isolated nor in nesting pattern, were recognized with hematoxylin and eosin stain. This spindle-shaped proliferation was admixed with scattered trabecular bone. The trabeculae consisted mainly of woven bone; which was frequently covered with active osteoblasts.

The microscopic aspects of high-grade sarcomatoid tumor were not very helpful and did not orient us to any specific diagnosis. Therefore, we used a panel of markers for immunohistochimistry and ultrastructural studies.

Antibodies against vimentin, S100 protein, Bcl2, CD99, smooth muscle actin, desmin and cytokeratin were used. All the tumor cells were positive for vimentin. Fewer cells were positive for cytokeratin (Fig. 5). Staining for S100 protein, Bcl2, CD99, desmin and smooth muscle actin were negative.

Ultrastructural study was done with classic technique: fresh tumor tissue was immediately fixed in a 3% glutaraldehyde solution (buffered pH 7,4) and postfixed in 2% osmium tetroxide. Following hydration, the tissue blocks were embedded in Epon 812. An ultrathin section was stained with uranyl acetate and lead citrate and examined with a JEM 1010 electronic microscope. The tumor spindle-shaped cells contained intracytoplasmic tonofilbrils, There were several desmosomes between the cells and basal lamina around them (Fig. 6).

The diagnosis of sarcomatoid dedifferentiated adamantinoma was done because of the sarcomatoid morphology, keratin positivity and epithelial features seen ultrastructurally.

The histologic examination of the right tibial lesion showed both moderately cellular fibrous tissue and
immature woven bone trabeculae. The fibrous part was composed of spindle-shaped, fibroblast like cells. These spindle cells lacked pleomorphism or mitosis and were negative to cytokeratine. The bone trabeculae were small and disconnected, bizarrely contorned, and resemble to “Chinese writing” pattern. There was a lack of osteoblastic rimming surrounding the dysplastic trabeculae. The diagnosis of fibrous dysplasia was made (Fig. 7).

Subsequently, leg amputation was performed. Macroscopic examination of the specimen revealed a solid tumor of 12 × 7 × 6 cm, white and lobulated, occupying the marrow and destroying the cortex, with invasion of the surrounding periosteum and soft tissue. There were areas of necrosis and bleeding. Histological examination of the entire specimen didn’t identify any area of FD nor classic adamantinoma.

The patient died within 2 years by multiple metastases (Fig. 8).


**Figure 6** Electron microscopy: the tumor cells are interconnected by desmosomes (triangle) and exhibited numerous bundles of tonofilaments (arrow).

**Figure 7** Photograph of the open biopsy of the controlateral lesion: hypocellular spindle cell proliferation with C shaped bony spicules, corresponding to the diagnosis of fibrous dysplasia HES × 200.

**Figure 8** Bone scan showing multiple bone metastases.

spindle-cell soft tissue sarcoma [6]. In these tumours, the epithelial keratine positive spindle cells often merge gradually with mesenchymal keratine-negative ones. Based on histologic features only, it would be impossible to recognize the

Epithelial nature of the tumor, and the diagnosis of adamantinoma can be mistaken with soft tissue sarcomas especially fibrosarcoma or synovial sarcoma [2,7,8]. The present tumour showed positivity to keratine. This is incompatible with the diagnosis of fibrosarcoma, which is vimentine positive but keratine negative. Also, the negative immunostaining to Bcl 2 and CD99 made the diagnosis of synovial sarcoma improbable.

In such cases, ultrastrutural study can be very helpful in differential diagnosis in order to recognize the epithelial nature of the tumour when it shows tonofibrils, desmosomes and basal lamina [1,2,7].

This particular pattern characterised by the loss of classic epithelial differentiation, accompanied with the increase nuclear pleomorphism and mitotic count is uncommon in adamantinomas. Hazelbag et al. [1] reported in 2003 three cases of adamantinoma with sarcomatoid transformation of the epithelial component: one in a primary tumor and two after local recurrence. The tumors showed loss of the original characteristic epithelial differentiation with transition to fields of highly pleomorphic cells without epithelial features, high mitotic count and deposition of ostoid and chondroid matrix. These areas showed pankeratin positivity. Based on the observation of sarcomatoid transformation of the epithelial component in these cases and the results of some studies which provided strong arguments that the epithelial components of adamantinoma directly derive from mesenchymal tissue [9—12], Hazelbag et al. [1] stated that the originally mesenchymal derived tumour cells have retained phenotypic properties of that cell lineage. He was the first to introduce the term of "dedifferentiated" adamantinoma to describe this new morphologic variant of adamantinoma.

**Discussion**

Adamantinoma is a rare primary low-grade malignant bone tumor, slightly prevailing in the male sex and affecting any age from adolescent to the elderly [2]. The distinct histological subtypes of adamantinoma were extensively discussed in earlier reports [3—6]. In classic adamantinomas four growth patterns have been described: tubular, basaioidal, squamous and spindle cell. This latter variant, often seen in local recurrences and metastasising cases — as observed in this report — in its pure form can be undistinguishable from
More recently, Izquierdo et al. [8] reported a case of an adamantinoma of the distal third of the tibia with a sarcomatoid transformation that showed a complete loss of epithelial differentiation. They believe that it represents an extreme case of the spectrum of epithelial-to-mesenchymal transformation.

Adamantinoma metastasizes in about 15 to 30% of cases by both hematogenous and lymphatic routes to other parts of the body, usually to the lungs or lymph nodes; bone and abdominal viscera make up a minority [5,6,9,13]. In another study, Hazelbag et al. [4] reported among 28 patients followed with a mean duration of 10 years and 2 months, eight metastasising cases (29%), six of which to the lung. All eight patients with metastases died of disease. The mean survival after diagnosis of the first metastasis was 4 years and 3 months.

Unlike Jain et al. [5] who didn’t find any correlation between histology and clinical course, we think that spindle cell subtype and especially dedifferentiated adamantinoma is associated with a high rate metastasis. As mentioned by Hazelbag et al. [1], we believe that this sarcomatoid dedifferentiation is associated with tumor progression and invasive metastatic properties. Theros and Ishak [14] reported that the more malignant the lesion is, the less distinctive the histological pattern. Metastatic classic adamantinomas have not proven to be sensitive to chemotherapy or radiotherapy [1] neither dedifferentiated subtype as seen in our case. However, prognosis of metastases of an adamantinoma is probably better than in other bone sarcomas, but data available in the literature are scarce. A rough approximation of the 5-year survival rate of disseminated adamantinoma appears to be in the range of 50 to 60% [6,13,15].

The association of adamantinoma with undifferentiated spindle cell pattern and FD observed in this case is very interesting. It creates much speculation about the relationship between the two entities. Association between adamantinoma and OFD was widely debated in literature [1,14–17]. A recent study suggested that OFD and adamantinoma are likely related entities in the spectrum of osteofibrous neoplasms showing epithelial differentiation [15]. Nevertheless, evolution of OFD to adamantinoma (or vice versa) has not been convincingly documented. To our knowledge, this case is unique since it described FD and adamantinoma in the same patient. We think that adamantinoma in our case could result from a malignant transformation of FD for many reasons:

- firstly, malignant transformation of FD is well established. It has been estimated that only 0.4% of all cases of FD undergo malignant change, but degeneration seems to occur more likely in polyostotic form [1,17];
- secondly, Yabut et al. [18] reported an interesting observation of a malignant transformation of FD in the tibia. In his report he described the lesion as follows: “biopsy study of the lytic lesion showed a malignant spindle-cell sarcoma, without evidence of recognisable pattern of histologic differentiation”. Unfortunately, in his report no more investigations were done to recognize the exact nature of that sarcoma. Thirdly, in the same study, Yabut [18] reported 83 cases of malignant transformation of FD from the literature. Fibrosarcoma and “spindle-cell sarcomas” were the second histological subtype of malignant transformation in FD. We can speculate that some of these lesions could be unrecognized dedifferentiated adamantinomas.

In summary, the diagnosis of dedifferentiated adamantinoma should be considered when a clinician is challenged with a tibial biopsy of a “keratin-positive sarcoma”. This epithelial to sarcomatoid transformation is associated with malignant progression. Otherwise, this report highlights the importance of the multidisciplinary management of bone tumors.

Disclosure of interest

The authors declare that they have no conflicts of interest concerning this article.

References

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