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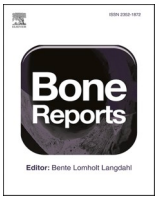

Case Report

Mazabraud's syndrome: A case report supported by molecular studies and review of the literature

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ABSTRACT

Mazabraud's syndrome represents rare benign disorder characterized by simultaneous occurrence of fibrous dysplasia of bone and intramuscular myxomas within surrounding soft tissue. Mutations of *GNAS1* gene were proven to be causative for this condition. Here, we present a case report of a patient with unusual manifestation of this disease, who developed a pathological fracture of the femur in the setting of monostotic fibrous dysplasia. The intramuscular myxoma of the thigh was discovered during the following orthopedic operation, where the intraoperative diagnosis became a pitfall of the case, as the intramuscular myxoma was initially diagnosed as a low-grade sarcoma from the frozen section. Apart from clinical findings, the diagnosis of Mazabraud's syndrome was further proven by histopathological evaluation and molecular studies of *GNAS1* gene. This case raises awareness of such condition as it can easily become a diagnostic pitfall.

1. Introduction

Mazabraud's syndrome (MS) is a rare benign disorder characterized by fibrous dysplasia (FD) of the bone in association with intramuscular myxomas (IM), usually contained within surrounding soft tissue (Vescini et al., 2018; Hagelstein-Rotman et al., 2022). Awareness of MS may help clinicians and pathologists to properly manage incidentally discovered soft tissue tumors in patients with FD. IMs can be mistaken for other myxoid soft tissue lesions, especially low-grade sarcomas which can lead to inappropriate therapeutic approach (Jalan and Jain, 2019).

FD, defined as benign fibro-osseous lesion replacing healthy bone, may be manifested as either monostotic or polyostotic form. Monostotic form tends to be more common, covering 75 % of cases (Riddle and Bui, 2013). The most common sites of involvement are lower limbs, ribs and skull including facial bones. However, practically any bone can be affected. It can be asymptomatic or present with symptoms such as pain, bone deformity or spontaneous fracture. Sarcomas can develop in the terrain of FD as it has rare, but clear potential for malignant transformation. Most common malignancies that can arise from FD are osteosarcoma (70 %) followed by fibrosarcoma (20 %) and chondrosarcoma (10 %) (Riddle and Bui, 2013).

IMs represent benign soft tissue neoplasms. They usually appear as painless, soft, ovoid shaped and slowly growing mass, typically contained within large muscle groups of the lower limbs, especially in the quadriceps muscle. If IM develops as a part of MS, it is most often located in the vicinity of bone lesions (Munksgaard et al., 2013). It is well established that malignant transformation of IM does not occur. Because IM is a rare condition (with incidence of 1:1000000), it can be challenging to distinguish this lesion clinically and radiologically from other myxoid tumors, including low grade sarcomas (Baltu et al., 2017).

Activating mutation of *GNAS1* gene was described as a causative mutation in cases of FD and it is thought to be involved in pathogenesis of MS as well (Vescini et al., 2018). Cases of MS with proven *GNAS1* mutations were sparsely reported in the literature (Majoor et al., 2019).

Here, we present a patient with monostotic FD of the left proximal femur and a solitary IM of left vastus lateralis. Our case is noteworthy because the presence of IM was unknown prior to surgery and the patient was indicated for operation because of the pathological fracture in

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the setting of FD. Usually, the soft tissue lump tends to be detected prior to osseous lesion in MS (Majoor et al., 2019). The lesion was initially misdiagnosed as a malignant neoplasm in frozen section, but detailed histopathological examination and molecular analysis led to the correct diagnosis.

2. Case

A 41-year-old man with chronic pain of the lumbosacral region and irradiation into the left lower limb, without any peripheral neurological deficiency, was admitted to the orthopedic department. His symptoms worsened, i.e. the pain in his left hip increased, causing impairment of ability to walk. His previous medical history was unremarkable. A fracture of his left femoral neck as well as radiolucent lesion of the left proximal femur was detected using X-ray (Fig. 1). However, the patient did not recall any prior trauma nor any other event that could cause the fracture. X-ray finding combined with patient's symptoms led to the clinical diagnosis of monostotic form of FD. Next, the patient was recommended a surgical treatment, i.e., excochleation and plombage of the lesion followed by augmentation with proximal femoral nail. During the operation, the surgeon incidentally discovered a soft tissue tumor within lateral vastus muscle, which he enucleated and sent both, the tumor and samples of the bone lesion, to the intraoperative histopathological examination.

The tumor was macroscopically 45x42x20 mm large with ovoid shape. Grossly it had a pale whitish color and residual skeletal muscle fibers visible at the edges and myxoid appearance on cut surfaces. In the frozen section, it was histopathologically considered as a mesenchymal neoplasm with irregular borders resembling invasive growth into regressively changed surrounding skeletal muscle. Concluded diagnosis from the intraoperative biopsy was low-grade sarcoma. After the operation, the patient was admitted to the oncology department where the initial staging CT scan was performed, which did not reveal any metastatic spread nor any other lesions of FD at other skeletal sites. Further follow-up was to be planned.

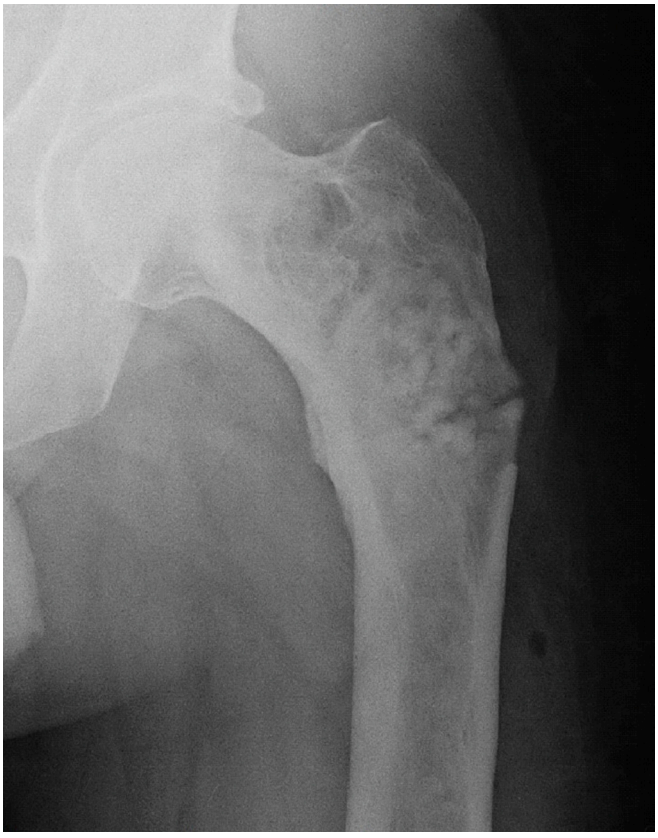

Fig. 1. X-ray: frontal radiograph of the left proximal femur. Well defined radiolucent lesion in intertrochanteric region of proximal femoral epiphysis. Fine radiolucent line in subtrochanteric lesion.

In the final histopathological examination, the bone lesion was composed of bland fibroblasts and numerous bone trabeculae of irregular shapes sometimes resembling the letters “C” or “O” without osteoblastic rims. There were no signs of malignancy detected (mitoses, cytological atypia or necrosis) (Fig. 2). The diagnosis of FD was therefore established.

The soft tissue tumor was hypocellular with abundant myxoid stroma and consisted of bland spindle to stellate cells. The tumor was focally pseudo-cystically changed. There were no cytological atypia nor mitotic activity detectable (Fig. 2). Immunohistochemically, the stellate cells were diffusely positive for marker CD34, focally positive for EMA and smooth muscle actin (Fig. 2); Ki-67 was positive in 2 % of cells. Desmin, S-100 and CK AE1/AE3 were all negative. Clear resection margins were established. These findings changed the diagnosis from low-grade sarcoma to the intramuscular myxoma and suspicion of Mazabraud's syndrome was raised. For confirmation of such diagnosis, samples of both lesions were subject to NGS examination using Variant Plex HS Solid Tumor kit for possible gene mutations including *GNAS1* gene.

The DNA NGS VariantPlex HS Solid Tumor kit (Archer) (For more information, see Supplements) was used following manufacturer's instructions. DNA was extracted from FFPE sections followed by library preparation. Anchored Multiplex polymerase chain reaction amplicons were sequenced on Illumina MiSeq and the data were analyzed using the Archer software. The DNA NGS assay identified pathogenic variant of the *GNAS* gene (NM_000516.4: c.602G>A); R201H, which is a mutation in the *GNAS* gene that is specific for IM associated with MS.

With the diagnosis of MS confirmed by molecular studies, the patient was withdrawn from planned oncologic follow-up. The patient recovered well and currently nine months of follow-up is without any residual disease.

3. Discussion

According to the literature, there has been a little over 100 cases of MS reported to this date (Vescini et al., 2018). MS affects females (68 %) more than males (32 %) and the mean age of diagnosis is 40 years. Polyostotic form tends to be more common than monostotic form (3:1 ratio) (Majoor et al., 2019). Lower limbs were involved in 83 % of cases and upper limbs in 41 % of cases. Development of FD usually precedes the development of IM by 6.5 years (Vescini et al., 2018). Multiple IMs were seen in 70 % of cases with the rest having only single IM (Zoccali et al., 2009). Other conditions, which accompanied these reported cases, such an association with McCune-Albright syndrome, are café-au-lait spots, precocious puberty and thyroid disease (Vescini et al., 2018; Zoccali et al., 2009; Hagelstein-Rotman et al., 2022). FD as a part of MS presents clinically at a later time than isolated FD, which has peak incidence in late childhood and adolescence (Majoor et al., 2019; Riddle and Bui, 2013). FD in MS also has higher potential for malignant transformation into osteosarcoma (Jalan and Jain, 2019).

Mazabraud's syndrome and the closely related McCune-Albright syndrome [OMIM 174800] are caused by activating missense mutations in codon 201 of the *GNAS* gene (Bekers et al., 2019). Cases with proven *GNAS1* mutations in MS were sparsely reported in literature. *GNAS*-activating R201 mutations were first described in sporadic GH-secreting pituitary adenomas (Landis et al., 1989). As for its function, one of the transcriptional products of *GNAS1* gene is the alpha subunit, which is a part of stimulatory GS protein. This alpha subunit has a GTPase activity, which inactivates the downstream receptor signaling by hydrolysis of GTP to GDP. Mutation, most commonly missense at the R201 position, causes a loss of this function and results in constitutive downstream signaling activation (Cox et al., 2017). It was proven that missense mutation, which causes the substitution of arginine on position

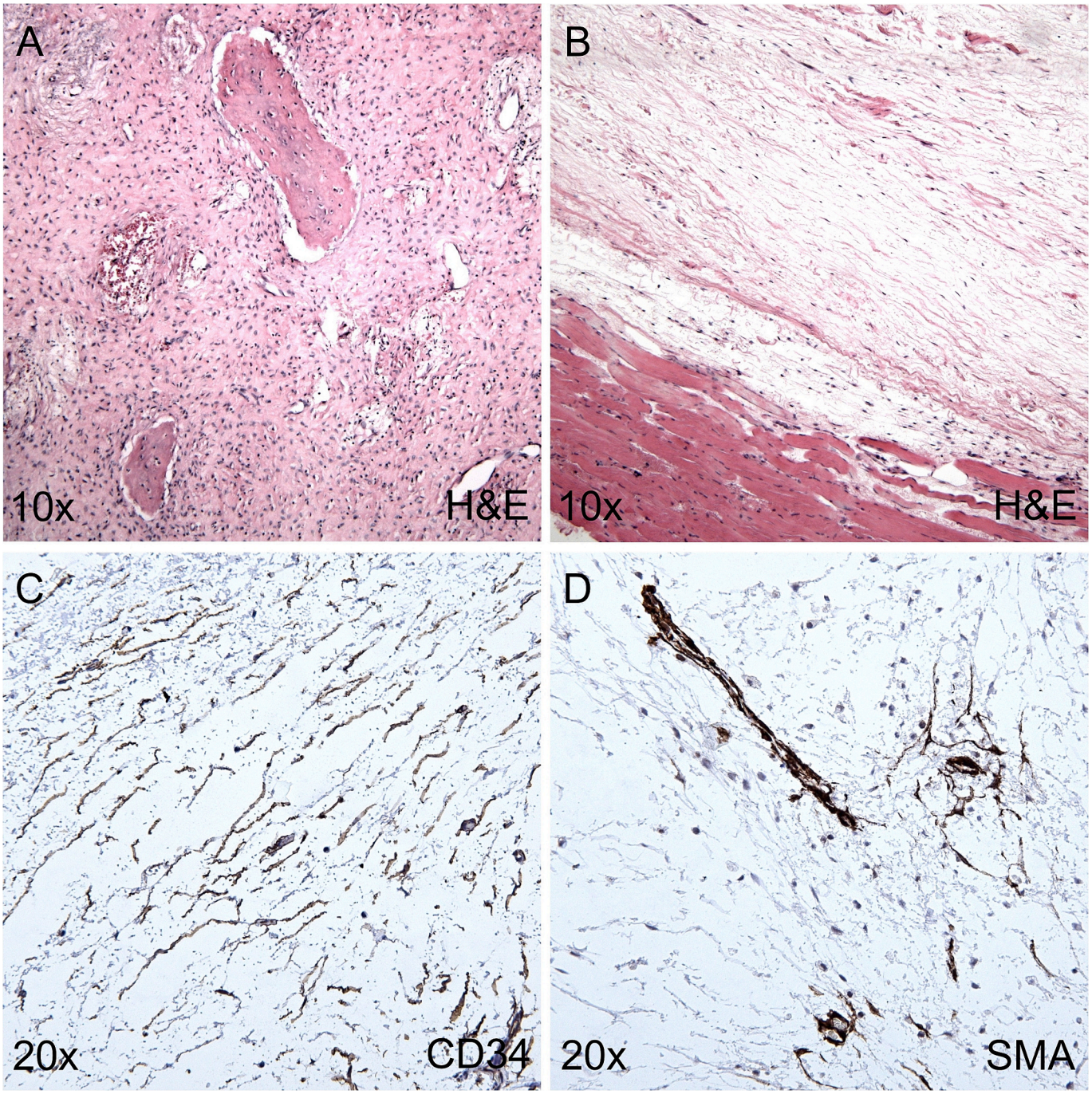

Fig. 2. Microscopic image of the soft tissue tumor and bone lesion. A. Bone lesions - bone trabeculae of irregular shapes without osteoblastic rims are embedded within fibrotic stroma with bland fibroblasts (H&E stain, 100×). B. Soft tissue tumor - bland spindle and stellate cells within abundant myxoid stroma (H&E stain, 100×). C. Diffuse cytoplasmic positivity of CD34 (immunohistochemistry, CD34 staining, 200×). D. Focal cytoplasmic positivity of SMA (immunohistochemistry, SMA staining, 200×).

201 of the *GNAS* gene product with either cysteine or histidine, substantially decreases its intrinsic GTPase activity which leads to higher cAMP levels (Weinstein et al., 1991).

Although MS represents a rare and benign neoplasm, our case demonstrates the importance of awareness of this diagnosis for both the orthopedic surgeon and the pathologist. In most of the reported cases, the patient was admitted to hospital with soft tissue swelling and during initial work-up, mainly with MRI, the bone lesion was discovered. The soft tissue tumor was usually verified to be IM by needle biopsy and the diagnosis of MS was made (Vescini et al., 2019; Jalan and Jain, 2019; Majoor et al., 2019). Our case differs by the fact that there was no soft tissue lesion recognized upon the admission, and the main concern was the patient's pathological fracture in the terrain of the FD. Therefore, no other imaging technique than X-ray was indicated at that time. It came as a surprise when the soft tissue tumor was discovered during the operation itself. If MS – an association of FD and IM – would have been considered during the initial differential diagnosis, it could have helped with identifying the correct diagnosis of IM instead of low-grade sarcoma and it could have prevented patient's administration to the oncology department. Our case also further emphasizes the role of NGS in diagnosis of MS. In our case the results from NGS confirmed that the soft tissue tumor was an IM as a part of MS and that the initial

intraoperative diagnosis of low-grade sarcoma was wrong.

CRediT authorship contribution statement

Ludvík Kašpar: Conceptualization, Data curation, Formal analysis, Writing – original draft, Writing – review & editing. **Jan Balko:** Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Writing – original draft, Writing – review & editing. **Martina Strnadová:** Data curation, Investigation, Methodology. **Lenka Krsková:** Data curation, Formal analysis, Methodology, Supervision, Writing – review & editing, Funding acquisition. **David Máška:** Data curation. **Josef Zámečník:** Conceptualization, Formal analysis, Supervision, Validation, Writing – review & editing, Funding acquisition.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

Data will be made available on request.

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Authors are thankful to the patient for his cooperation. Written informed consent was obtained from the patient.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bonr.2023.101685.

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