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Case report

Singular case of osteolytic lesions revealing transformation of myeloproliferative syndrome to acute leukemia

Guillaume Duval[a,1], Hélène Meytadier[a,1], Béatrice Bouvard[b,c,*]

[a] Service de gériatrie, CHU d'Angers, 4, rue Larrey, 49933 Angers cedex 9, France
[b] Service de rhumatologie, CHU d'Angers, 4, rue Larrey, 49933 Angers cedex 9, France
[c] Groupe d'Eudes Remodelage Osseux et bioMatériaux LHEA UPRES EA 4658, CHU d'Angers, 4, rue Larrey, 49933 Angers cedex 9, France

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ABSTRACT

Hematological malignancies can cause bone lesions, of which the most common are the punched-out foci of osteolysis seen in multiple myeloma. However, osteosclerotic lesions are more common in myeloproliferative disorders. We report the unusual case of a patient with myeloproliferative syndrome in whom the development of osteolytic lesions revealed transformation to acute leukemia. In 2007, this 82-year-old man with essential thrombocythemia since 1994 developed primary polycythemia with the *JAK2* mutation V617F. In July 2017, he was evaluated for an osteolytic lesion in the right humerus with incipient fracturing. Bone marrow smear results provided only limited information, due to the myelofibrosis, showing 7% of blast cells with no plasmacytosis. No solid malignancies were identified by imaging studies. Examination of a right humeral biopsy specimen taken during internal fixation showed myeloproliferative syndrome with osteosclerosis and grade-3 myelofibrosis, as well as a malignant proliferation of large cells carrying the leukocyte cluster of differentiation antigens CD45, CD 43, CD4, and CD34. The diagnosis was transformation of the myeloproliferative syndrome to acute myeloid leukemia. The development of an osteolytic lesion during the course of myeloproliferative syndrome is an exceedingly rare event that should suggest acute leukemic transformation.

1. Introduction

Hematological malignancies can be responsible for bone lesions, of which the most common are the punched-out foci of osteolysis seen in multiple myeloma. Whereas osteolytic lesions may develop also in some of the lymphoid hematological malignancies such as acute lymphoblastic leukemia, HTLV1-related non-Hodgkin lymphoma, Waldenström macroglobulinemia, and chronic lymphocytic leukemia, they are less common in myeloid malignancies [1]. Myeloproliferative syndromes are a group of chronic diseases characterized by the malignant clonal proliferation of one or more myeloid cell lines with terminal cell differentiation. The bone lesions seen in myeloproliferative syndromes are generally sclerotic. Blastic transformation of myeloproliferative neoplasms is a complication of poor prognosis whose frequency is 5% to 15% in primary polycythemia, 5% to 20% in primary myelofibrosis, and less than 5% in primary polycythemia [2]. Acute myeloid leukemia is responsible for pancytopenia, which manifests as a decline in general health, infection, and/or bleeding. Bone lesions are rare [3,4].

Here, we describe a patient with myeloproliferative syndrome in whom the development of osteolytic lesions revealed transformation to acute leukemia.

2. Case-report

In 2007, an 82-year-old male receiving follow-up since 1994 for primary thrombocythemia and IgG monoclonal gammopathy of undetermined significance was given a diagnosis of primary polycythemia with a *JAK2* V617 mutation. His initial treatment with hydroxyurea was responsible for oral ulcers and he was switched to pipobroman. In 2015, he was found to have splenomegaly and his peripheral blood tests showed anemia (hemoglobin, 8 g/dL), dacryocytes, 7% myelemia, and 0.7% blasts. The findings from a bone marrow biopsy of grade III myelofibrosis with osteosclerosis led to a diagnosis of primary myelofibrosis. Due to the development of cognitive impairments, no specific treatment was given. In July 2016, he was admitted for a decline in general health and

* Corresponding author at: Service de rhumatologie, CHU d'Angers, 4, rue Larrey, 49933 Angers cedex 9, France.
E-mail address: bebouvard@chu-angers.fr (B. Béatrice).
[1] Guillaume Duval and Hélène Meytadier equally contributed to this article.

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pain in the right shoulder. A humeral osteolytic lesion with an incipient fracture was visible on the radiographs of the right shoulder and humerus (Fig. 1). An orthopedic surgical procedure was planned to prevent fracturing. Before the procedure, however, the patient fell, fracturing his right humerus at the site of the osteolytic lesion. Internal fixation was therefore performed. As myelofibrosis is usually responsible for osteosclerotic lesions, the first diagnoses considered to explain the osteolysis were multiple myeloma and metastases from an unknown primary.

Diffuse infiltration of the vertebral bone marrow without epidural involvement was seen by magnetic resonance imaging of the spine. Positron emission tomography showed splenomegaly and moderately to markedly increased uptake by osteolytic lesions in the entire axial skeleton and some parts of the appendicular skeleton, with no evidence of a solid malignancy (Fig. 2). Blood test results were as follows: hemoglobin, 9.1 g/dL; corrected calcium level, 2.08 mmol/L; lactic dehydrogenase, 1597 IU/L; and creatinine, 77 μmol/L. Serum protein electrophoresis identified a stable monoclonal IgG-lambda peak (3.7 g/L). Serum levels of kappa and lambda light chains were 51.17 mg/L and 37.43 mg/L, respectively, yielding a kappa/lambda ratio of 1.53. The percentage of blasts in circulating blood was 2.5%. The serum 25(OH)D level was abnormally low at 14 nmol/L. The bone marrow biopsy provided limited information due to the myelofibrosis; there were 7% of blasts with no plasmacytosis. Examination of a biopsy from the right humeral lesion, collected during internal fixation, showed a myeloproliferative syndrome with osteosclerosis and grade III myelofibrosis, as well as a malignant proliferation of large cells that carried the leukocyte cluster of differentiation antigens CD45, CD43, CD4, and CD34. Efforts to formally identify this this cell population failed.

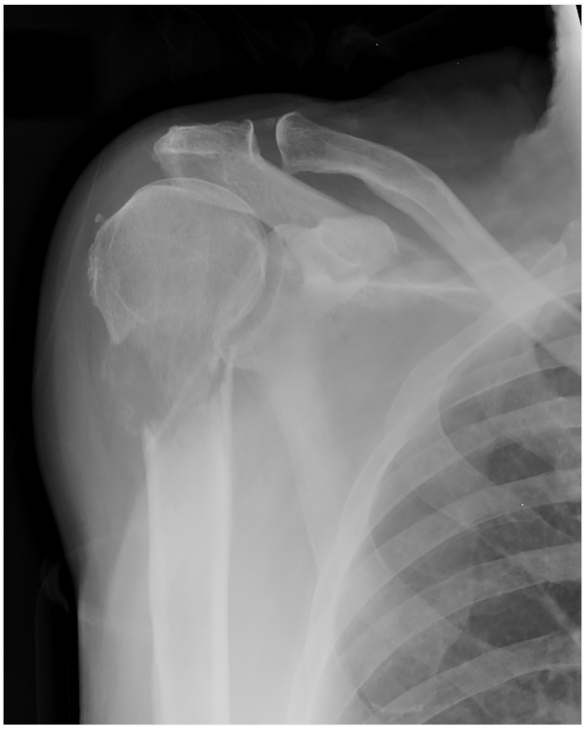

Fig. 1. Radiograph showing the osteolytic lesion in the right humerus.

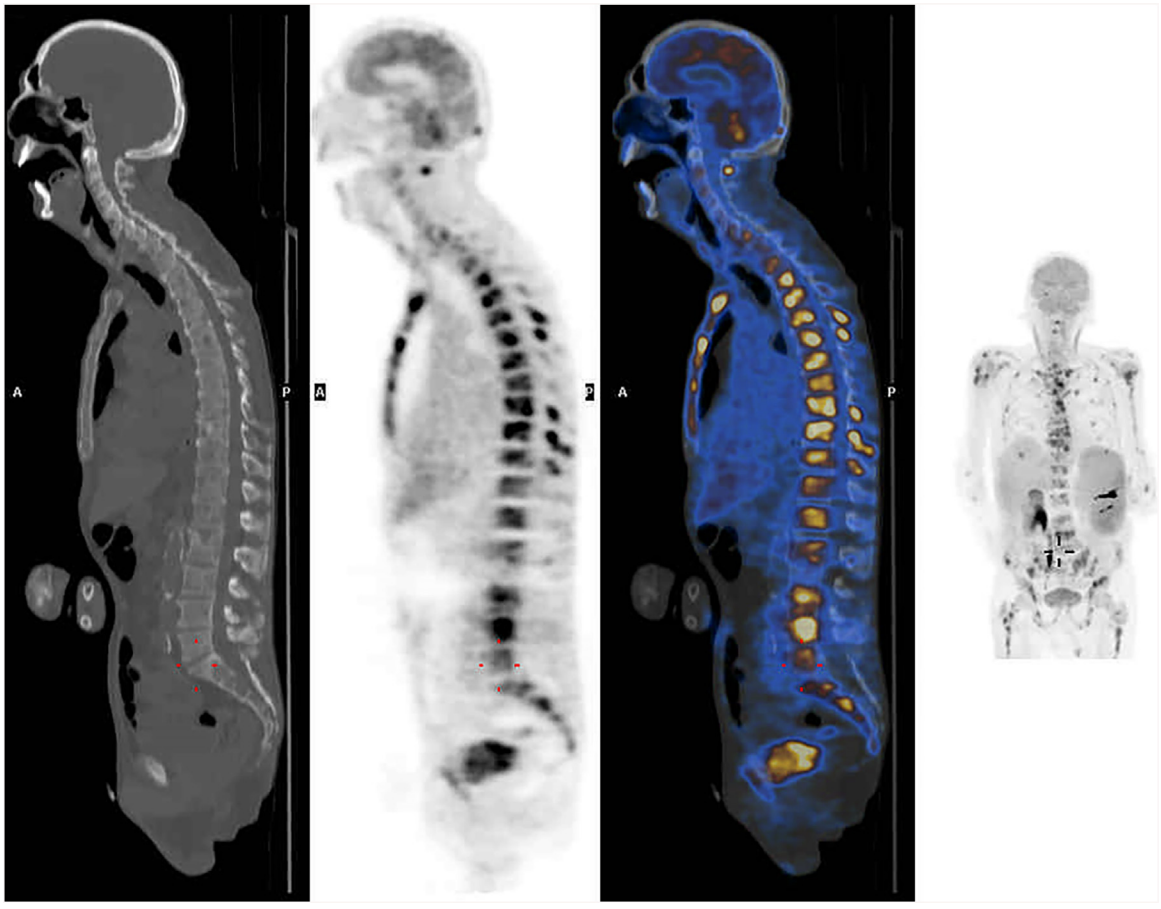

Fig. 2. Positron emission tomography: increased uptake by the osteolytic lesions.

A second bone marrow biopsy performed 3 weeks after the first showed 13% of blasts. The patient was given a diagnosis of acute myeloid leukemia transformation of myeloproliferative syndrome.

The patient's advanced age and poor general health precluded curative treatment. Transfusions of several red blood cell packs were given to correct the anemia. Palliative care was initiated. The patient died 2 months after admission to our department.

3. Discussion

We describe a rare instance in which osteolytic lesions developing in a patient with primary myelofibrosis revealed transformation to acute myeloid leukemia. This case is atypical, since osteolytic lesions are uncommon in hematological malignancies other than multiple myeloma. Although a few cases of acute myeloid leukemia with osteolytic lesions have been reported, they occurred in young patients with de novo leukemia [3–5]. The most common bone lesion in primary myelofibrosis is osteosclerosis, which is found in 40% to 70% of cases [6], whereas osteolysis is exceedingly rare. Two patients who developed osteolytic lesions during end-stage primary myelofibrosis complicating primary polycythemia have been reported. One of these patients experienced accelerated progression of the myelofibrosis without acute leukemic transformation [7]. Splenectomy was effective in relieving the bone pain. In the more recently reported patient, the osteolytic lesions involved the skull and a single vertebra and revealed acute myeloid leukemia [8].

The pathophysiology of these osteolytic lesions in patients with myelofibrosis is unclear. Conceivably, excessive fibrosis may lead to bone tissue atrophy and destruction [7]. In a patient who experienced transformation of primary myelofibrosis to M4 acute myeloid leukemia with osteolytic lesions of the pelvis, long limb bones, and vertebral bodies [9], serum levels of tumor necrosis factor alpha were elevated, suggesting a role for this cytokine in the bone destruction. Our patient transitioned from primary thrombocytopenia to primary polycythemia with the V616F *JAK2* mutation and, subsequently, to primary myelofibrosis. This sequence, which is not uncommon, illustrates the fluidity of the boundaries between the various BCR/ABL-negative myeloproliferative syndromes, which can occur in succession in the same patient [10]. The histological examination of the humeral biopsy was crucial to the diagnosis and ruled out the other conditions usually responsible for osteolytic lesions, i.e., multiple myeloma and metastases from solid malignancies. However, the characteristics of the leukemia remained unknown as the population of blasts in the biopsy could not be accurately identified.

Disclosure of interest

The authors declare that they have no competing interest.

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