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LETTER TO THE EDITOR

Getting away with phase transition: NPM1-mutated bone myeloid sarcoma mimicking Ewing sarcoma

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Dear Editor,

A 20-year-old female presented with an atraumatic intolerable pain in the left knee, at first managed with leg rest, ice pack and analgesics. The left knee MRI revealed an abnormal diffuse signal pattern of the distal femur and proximal tibia, without a soft tissue mass clearly identifiable. The whole-body scintigraphy with 99-mTC showed an elevated uptake within the same segment and moderate accumulation of the radio-drug in few other skeletal sites (i.e. bilateral iliac crests, manubrium of the sternum) (Fig. 1). Blood counts were normal, but acute-phase proteins, lactate dehydrogenase and alkaline phosphatase were markedly elevated. To rule out a primary bone tumour, a bone biopsy was performed. Unexpectedly, the bioptic specimen was infiltrated by monoblastic looking cells (Fig. 2a) that at immunohistochemistry (IHC) were positive for the macrophage marker (CD68, PGM1), negative for CD34 and displayed aberrant cytoplasmic nucleophosmin (NPMc+), predictive of the leukaemia-associated NPM1 gene mutation (Fig. 2b). The latter is consistent with the diagnosis of NPMc+ bone myeloid sarcoma (MS). The scarcity of the specimen did not allow for any molecular analysis. A bone marrow (BM) evaluation was performed to investigate acute myeloid leukaemia (AML) occurrence. Morphology and immunophenotyping of BM aspirates were negative for leukemic infiltrates (not shown). Also, peripheral blood appeared not involved. Accordingly, karyotype showed no abnormalities, and molecular analysis did not show any known leukaemia-associated gene alterations. Strikingly, BM biopsy allowed detection of a minimal patchy infiltration by NPMc+ monoblasts at IHC (Fig. 2c–d). Standard chemotherapy induction was started leading to resolution of bone pain symptoms and achievement of a complete response (CR) at IHC BM evaluation. Thus, two consolidation chemotherapy courses were performed. However, an extramedullary (EMD) relapse occurred early (at 3 months since CR) upon the end of therapy. At that time, NPM1 gene mutation could be molecularly confirmed firstly on EMD specimen and later on BM aspirate. Despite salvage intensive chemotherapy and allogeneic bone marrow transplantation, the patient died shortly after. According to the WHO 2016 classification of lympho-haemopoietic neoplasms, MS is a tumour mass consisting of myeloblasts with or without maturation occurring at an anatomical site other than bone marrow. Patients carrying NPM1 mutation have a relatively higher incidence, especially in the skin. Distal femur and proximal tibia localizations are extremely infrequent and can be confused with primary bone tumours (i.e. Ewing sarcoma, osteosarcoma), bone involvement by haematological malignancies (e.g. multiple myeloma, non-Hodgkin lymphoma, hystiocytosis) and metastatic carcinoma. Differential diagnosis is based on the immunohistochemical detection of a number of lineage-specific markers. Due to the frequently small size of the samples (e.g. punch biopsy), molecular characterisation of MS is challenging. Immunohistochemical detection of cytoplasmic nucleophosmin in tissue paraffin sections may serve as surrogate marker for the presence of NPM1 mutations that are important in the molecular work-up of AML patients and have a potential prognostic value.

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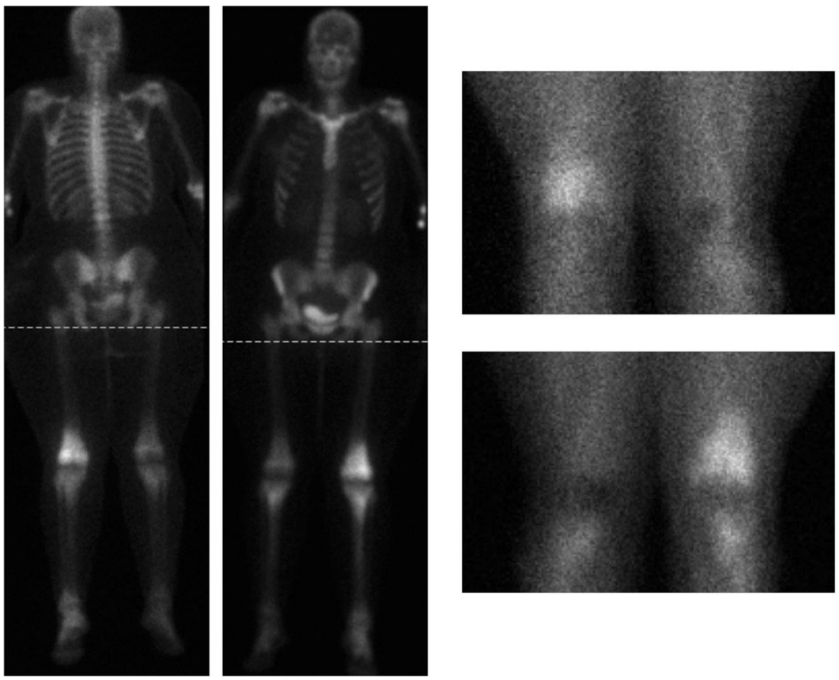

Fig. 1. Whole-body scintigraphy with 99-mTC depicting an elevated uptake of the left distal femur and proximal tibia

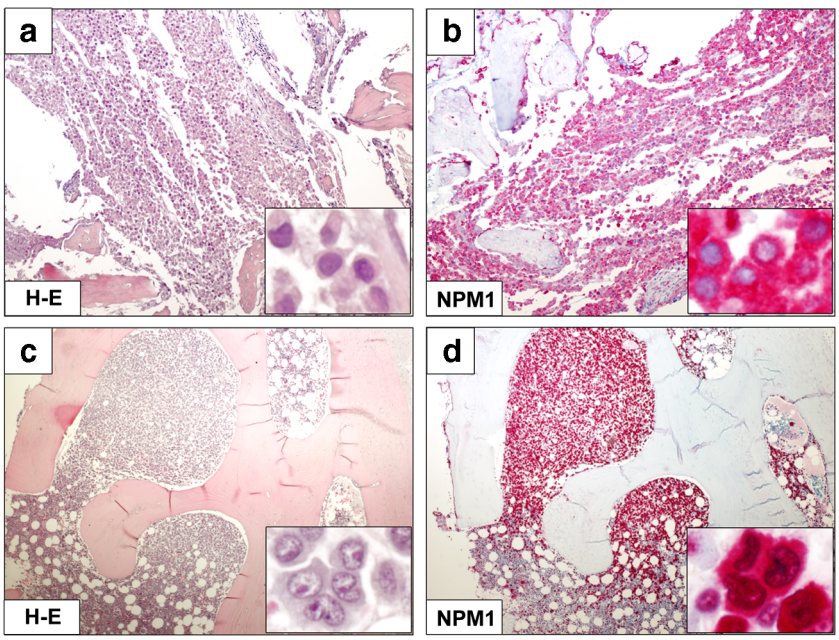

Fig. 2. **a**–**b** Hematoxylin-eosin and NPM1 immunostaining of the bone bioptic specimen showing monoblastic-looking cells with aberrant cytoplasmic NPM1. **c**–**d** Hematoxylin-eosin and NPM1 immunostaining of the bone marrow highlighting a patchy leukemic infiltration

manuscript. All authors were involved in the care of the patient. All authors approved the final manuscript.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Consent to publication Written informed consent to publication was obtained.

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