

LETTER TO THE EDITOR

Juvenile myelomonocytic leukaemia presentation after preceding juvenile xanthogranuloma harbouring an identical somatic *PTPN11* mutation

To the Editor:

The association of juvenile xanthogranuloma (JXG) and juvenile myelomonocytic leukaemia (JMML) has been described in approximately 20 cases in the literature¹⁻³; however, the pathogenesis underlying the concomitant presentation has never been elucidated in detail. We present the case of a child who developed JXG at the age of 3 months, and 23 months later he was diagnosed with JMML harbouring a somatic *PTPN11* p.E76K mutation. The same mutation was detected in his previous JXG specimen, suggesting a clonal relationship between the two diseases in this case.

A 3-month-old male infant presented with yellowish maculopapular lesions on the skin of the chest, followed by the appearance of similar lesions on the head and extremities at 7 months (Figure 1). The skin biopsy revealed CD68⁺, S100⁻ and CD1a⁻ infiltrating tumour cells in the dermal layer confirming the diagnosis of JXG. The magnetic resonance imaging, bone scintigraphy, ultrasonography and laboratory evaluations revealed no evidence of extracutaneous disease. Subsequently, no alteration was observed on follow-up physical, imaging and laboratory examinations. At month 23, he presented with pansinusitis, significant blood count alterations and minor splenomegaly, however histopathological examination of the bone marrow did not clearly indicate malignancy. As his blood count parameters had deteriorated further with an increased grade of anaemia and thrombocytopenia, a bone marrow biopsy was performed again at month 26. Performing cytogenetic and molecular diagnostics for JMML, a heterozygous, pathogenic c.226G>A *PTPN11* mutation was detected resulting in p.E76K (Figure 1). The germline genetic analysis from hair follicle returned a negative result, and according to the standard treatment protocol the patient received allogeneic haemopoietic stem cell transplantation (HSCT). The cutaneous lesions resolved, and the child is in complete remission 18 months post-HSCT.

Intriguingly, mutation analyses of *PTPN11* in the skin biopsy specimen from month 7, and in the bone marrow biopsy from month 23 detected an identical p.E76K mutation (Figure 1). Next-generation sequencing of 52 genes (Table S1) recurrently harbouring mutations in childhood myeloid malignancies revealed solely the previously identified *PTPN11* mutation with a variant allelic frequency of 30.0% in the JXG sample and 34.0% in the JMML sample, respectively, confirming a common cell of origin for both JXG and JMML.

The pathomechanism underlying the concomitant presentation of JXG and JMML has long been a subject of discussion.²⁻⁷ *PTPN11*

harbours gain-of-function mutations in 35% of the patients with JMML, leading to an increased activation of the RAS-MAPK signalling pathway.^{8,9}

The p.E76K mutation was described exclusively in de novo, non-syndromic JMML conferring a great transforming potential.⁹ Additionally, activating *PTPN11* mutations also play an important role in the development of other haematological and solid malignancies, including acute myeloid leukaemia, lung cancer and melanoma.¹⁰⁻¹² Historically, JXG has been considered a reactive process.^{13,14} Recently, Diamond et al identified somatic mutations targeting the RAS-MAPK pathway in 7/11 (63%) patients with JXG and in the case of a patient with disseminated juvenile xanthogranuloma the activating mutation of *MAPK1* has been described as well, however *PTPN11* mutations were not investigated in these studies.^{15,16}

To date, only a single case has been reported, where clonal association of a haematological malignancy and JXG was described based on identical TCR- γ rearrangement in a 5-year-old child, who developed systemic JXG secondary to T-cell acute lymphoblastic leukaemia.¹⁷ Presumably, in our patient the mutation arising in the haemopoietic stem cell compartment contributed to the aberrant development of the myelomonocytic lineage, first presenting as JXG, and retained the capacity to subsequently transform into JMML.^{13,18}

We report the first case of the sequential presentation of a clonally related JXG and JMML harbouring an identical somatic driver mutation. Further studies will be required to evaluate a possible clonal relationship in similar cases.

Informed consent was obtained from the family of the patient for the publication of pictures and data.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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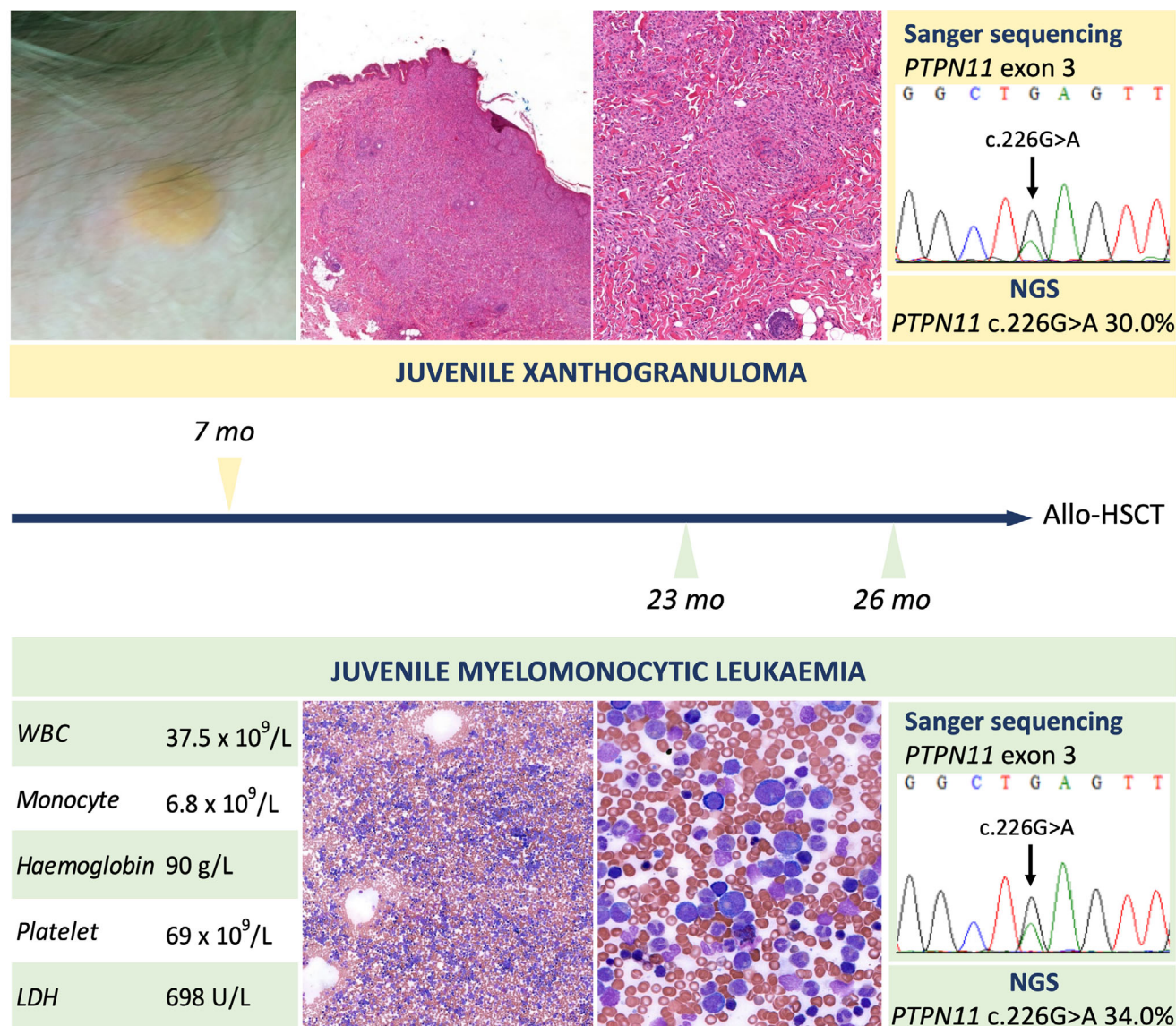


FIGURE 1 Detailed illustration of the clinical, histologic and genetic events underlying the concomitant presentation of juvenile xanthogranuloma (JXG) and juvenile myelomonocytic leukaemia (JMML). The yellow box shows the JXG lesion on the face at the age of 7 months. In the biopsy specimen, the dermal layer is infiltrated by monomorphic tumour cells resembling histiocytes corresponding to JXG (haematoxylin-eosin, 1× and 10×, respectively). Sanger and next-generation sequencing of the JXG sample identified the somatic *PTPN11* mutation previously detected in the bone marrow biopsy from month 23 and 26. The green box shows the blood count and laboratory alterations present at diagnosis of JMML. Bone marrow aspirate from month 26 is dominated by left shift with 5% blasts (haematoxylin-eosin, 10× and 60×, respectively). The representative electropherogram demonstrates the c.226G>A *PTPN11* mutation resulting in p.E76K detected in the bone marrow samples from month 23 and 26. Next-generation sequencing of 52 recurrently mutated genes in childhood myeloid malignancies revealed solely the c.226G>A *PTPN11* mutation

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