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B-cell lymphoblastic lymphoma with cutaneous involvement and a KMT2A gene rearrangement

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Lymphoblastic lymphoma (LBL) is an aggressive neoplasia of immature lymphoid progenitor cells. Debate still exists about whether LBL and acute lymphoblastic leukemia (ALL) are distinct entities or the same disease at a molecular level with a different clinical presentation.1 According to the WHO classification,2 LBL is distinguished from ALL by a bone marrow blast count of less than 20% of nucleated cells. The majority of lymphoblastic lymphomas originate from the T-cell lineage and occur in children.1 Yet, here we report a 30-year-old male with a B-cell lymphoblastic lymphoma (B-LBL) with typical cutaneous involvement and a KMT2A gene rearrangement that is common in (B-)ALL.3

The patient was referred to the internal medicine clinic with a 4-month history of a painless skin lesion on the lower back and left inguinal lymphadenopathy of five weeks duration. The left groin was painful for two days. The patient’s medical history was unremarkable, and he reported no other (B) symptoms. On physical examination, a solitary, non-tender, purple-red plaque was observed on the back about midline in the lumbar region (Image 1A,B). Multiple firm-elastic, tender enlarged lymph nodes were palpable in the left groin, and a painful erythematous rash was revealed on the left upper thigh (Figure S1). Routine laboratory evaluation demonstrated a normal complete blood count and leukocyte differentiation. A biopsy of the skin lesion was taken. Before the pathology result was available, the patient presented to the emergency department with severe worsening of the pain in the left groin after alcohol consumption. A left inguinal lymph node was dissected, whereupon the pain greatly diminished. The biopsy of the skin lesion (Image 1C) and the dissected left inguinal lymph node both showed diffuse sheets of small, round tumor cells (Image 1D) with a Ki67 proliferation index of more than 90% (Figure S2). The tumor cells stained strongly positive for PAX5 and TdT (Image 1E and F, respectively). A KMT2A (previously termed MLL) gene rearrangement was identified using fluorescence in situ hybridization (FISH). Targeted RNA-sequencing using the commercial Archer FusionPlex Lymphoma Kit revealed a KMT2A-MLLT1 (MLL-ENL) gene fusion and a WT1 frameshift mutation (supplementary methods). Only a very small population (<5%) of PAX5 and TdT positive cells was observed in a bone marrow biopsy (Figure S3). Moreover, no leukemic involvement was detected in the peripheral blood, bone marrow aspirate and liquor by morphological analysis and flow cytometry (Figure S4), and a diagnosis of B-LBL was made. KMT2A FISH and targeted RNA-sequencing did not detect the KMT2A gene fusion in the bone marrow. Apart from the solitary skin lesion and left inguinal lymph node involvement, positron emission tomography-computed tomography (PET-CT) showed fluorodeoxyglucose—avid right inguinal, para-iliac, para-aortic and left supraclavicular lymphadenopathy (Figure S5). Induction chemotherapy with vincristine, daunorubicin, methotrexate, PEG-L-asparaginase and corticosteroids was initiated according to the HOVON-100 ALL regimen (EudraCT 2008-005798-36). PET-CT after induction chemotherapy showed partial remission (Figure S5), and chemotherapeutic therapy was continued including high-dose methotrexate and cytarabine. The patient obtained complete remission by PET-CT.
This consisted of intensification chemotherapy followed by myeloablative allogeneic hematopoietic stem cell transplantation (HSCT) from a matched sibling donor. At 11 months after HSCT, the patient remains in complete remission.

Cutaneous involvement occurs in approximately one-quarter of patients with B-LBL. We noticed many similarities in the (almost asymptomatic) clinical presentation and appearance of the solitary skin lesion between our case and two previously reported children with B-LBL. This suggests that these features may be typical for cutaneous presentation of B-LBL. Awareness of these matters may reduce diagnostic delay in patients with cutaneous presentation of B-LBL. Furthermore, our patient adds to the small number of six children and one adult patient that have been reported with a KMT2A-rearranged B-LBL to date (Table S1). It is the first reported case of a KMT2A-MLLT1 (MLL-ENL) gene fusion in B-LBL, specifically. KMT2A gene rearrangements are present in approximately 10% of all acute leukemias. There is a bimodal distribution of affected patients, with KMT2A gene rearrangements being particularly common in infants and slightly more frequent in older children or adults with acute leukemia. They are associated with worse prognosis in all types of ALL in infancy, and several cooperative groups, including the Children's Oncology Group, also consider non-infant KMT2A-rearranged B-ALL (very) high risk and recommend intensified therapy. Together, these B-LBL cases with ALL-associated KMT2A gene rearrangements support the interpretation of B-LBL and B-ALL as a spectrum of the same disease by the WHO classification. Although subtle differences may exist at the molecular level, their molecular drivers appear very similar. Notably, the prognosis of LBL also dramatically improved with the use of ALL-based treatment regimens. More research efforts aimed at evaluating the frequency of KMT2A gene rearrangements in B-LBL and investigating whether this genetic alteration can be used for risk stratification in B-LBL as in B-ALL are warranted.

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CONFLICT OF INTEREST
All authors state that they have nothing to disclose.

AUTHOR CONTRIBUTIONS
P.G.K., H.V., P.B., and J.L.H.K. cared for the patient and collected the clinical data. A.H.G.C. and F.J.B. performed the histopathological analyses.
R.E. and T.W. performed the molecular testing. P.G.K. wrote the first draft of the manuscript. All authors contributed to the final version of the manuscript.

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**PATIENT CONSENT**

Written informed consent for publication of this manuscript was obtained from the patient.

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**REFERENCES**


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