Received: 30 January 2020 | Revised: 18 March 2020 | Accepted: 25 March 2020

DOI: 10.1002/ajh.25801

IMAGES IN HEMATOLOGY

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

Paul G. Kemps[1,2] | Arjen H. G. Cleven[3] | Tom van Wezel[3] | Ronald van Eijk[3] | Freek J. Bot[4] | Hendrik Veelken[5] | Peter van Balen[5] | Jean-Louis H. Kerkhoffs[1]

[1]Department of Hematology, HagaZiekenhuis, The Hague, The Netherlands

[2]Leiden University Medical Center, Leiden, The Netherlands

[3]Department of Pathology, Leiden University Medical Center, Leiden, The Netherlands

[4]Department of Pathology, HagaZiekenhuis, The Hague, The Netherlands

[5]Department of Hematology, Leiden University Medical Center, Leiden, The Netherlands

Correspondence
Paul G. Kemps, Leiden University Medical Center, Room P3-40, PO Box 9600, 2300 RC Leiden, The Netherlands.
Email: p.g.kemps@lumc.nl

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, nontender, 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 fluordeoxyglucose—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

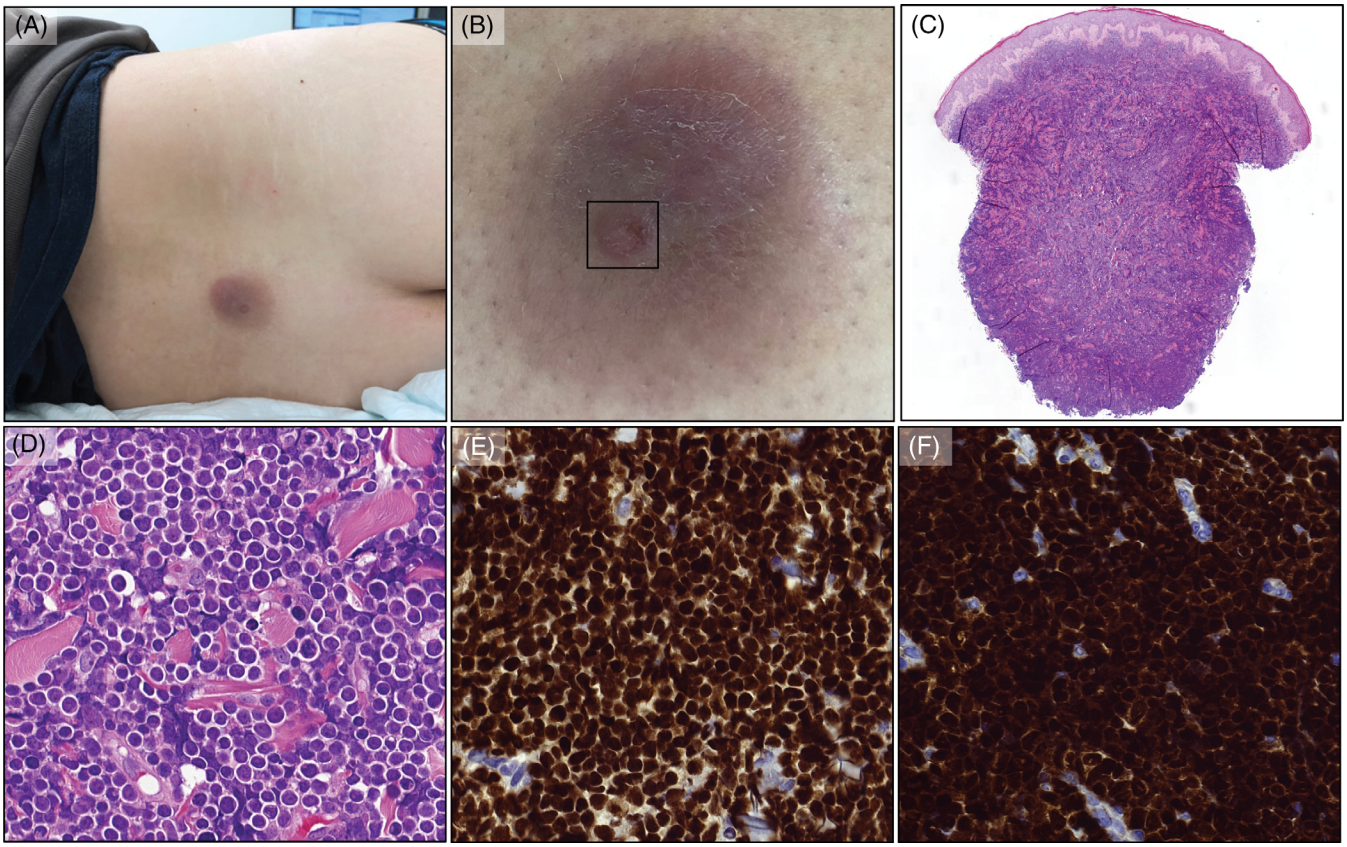

IMAGE 1 Clinical and histopathological findings at diagnosis. A, B, The solitary skin lesion on the lower back. The location of the biopsy is framed in panel B. C, D, Photomicrographs of the hematoxylin–eosin stained skin biopsy at 2.5× (C) and 50× (D) magnification, showing diffuse sheets of monotonous, small, round tumor cells with clear nucleoli and scant cytoplasm in the dermis. E, F, Photomicrographs of the PAX5 (E) and TdT (F) stained skin biopsy at 50x magnification

(Figure S5) and received post-remission treatment according to protocol. 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.[1] 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.[4,5] 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.[3] 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.[3] They are associated with worse prognosis in all types of ALL in infancy,[6] 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.[2] Although subtle differences may exist at the molecular level,[1] 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.[1]

ACKNOWLEDGEMENTS

We thank Karin Kleiverda for performing FISH experiments.

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.

FUNDING SOURCES

None disclosed.

PATIENT CONSENT

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

ORCID

Paul G. Kemps https://orcid.org/0000-0001-9793-7032
Arjen H. G. Cleven https://orcid.org/0000-0002-3672-4348
Tom van Wezel https://orcid.org/0000-0001-5773-7730
Ronald van Eijk https://orcid.org/0000-0001-7955-6295
Hendrik Veelken https://orcid.org/0000-0002-9108-3125
Jean-Louis H. Kerkhoffs https://orcid.org/0000-0001-5107-047X

REFERENCES

1. Burkhardt B, Hermiston ML. Lymphoblastic lymphoma in children and adolescents: review of current challenges and future opportunities. *Br J Haematol*. 2019;185:1158-1170.
2. Swerdlow SH, Campo E, Pileri SA, et al. The 2016 revision of the World Health Organization classification of lymphoid neoplasms. *Blood*. 2016;127:2375-2390.
3. Winters AC, Bernt KM. MLL-rearranged Leukemias—An update on science and clinical approaches. *Front Pediatr*. 2017;5:4.
4. Choi JE, Ahn HH, Kye YC, Kim SN. Precursor B-cell lymphoblastic lymphoma presenting as solitary infiltrative plaque in a child. *Acta Derm Venereol*. 2008;88:282-284.
5. Song H, Todd P, Chiarle R, Billett AL, Gellis S. Primary cutaneous B-cell lymphoblastic lymphoma arising from a long-standing lesion in a child and review of the literature. *Pediatr Dermatol*. 2017;34:e182-e186.
6. Pieters R, Schrappe M, De Lorenzo P, et al. A treatment protocol for infants younger than 1 year with acute lymphoblastic leukaemia (Interfant-99): an observational study and a multicentre randomised trial. *Lancet*. 2007;370:240-250.

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

How to cite this article: Kemps PG, Cleven AHG, van Wezel T, et al. B-cell lymphoblastic lymphoma with cutaneous involvement and a *KMT2A* gene rearrangement. *Am J Hematol*. 2020;95:1427–1429. https://doi.org/10.1002/ajh.25801