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Early onset post-transplant lymphoproliferative disorder following cutaneous NK/T-cell lymphoma mimicking recurrence

To the Editor,

Nasal-type NK/T-cell lymphoma is an extranodal lymphoma of NK-cell or cytotoxic T-cell lineage, characterised morphologically by angiocentricity and tumour necrosis, and associated with Epstein–Barr virus (EBV).¹ Clinically, it is more prevalent in Asian and Latin American regions and usually affects male adults in their fifth to sixth decades.² The most common involved organs are the upper aerodigestive tract, with the nasal cavity being the prototypical site; other preferential sites may include the skin, gastrointestinal tract

and testes.³ Genetically, three molecular subtypes have been classified, including TSIM [alterations in tumour suppressors (TP53 mutation and del6q21) and immune modulators (JAK-STAT mutations and amp9p24.1/PD-L1/2 locus)], MB [MGA mutations and BRDT loss of heterozygosity (LOH)], and HEA (HDAC9, EP300, and ARID1A mutations).⁴ Nasal type NK/T-cell lymphoma has been considered an aggressive disease but recently the outcome has been improved with the administration of more intensive therapy including radiotherapy and chemotherapy.³ The detection of EBV by *in situ* hybridisation targeting EBV-encoded RNA (EBER) is the gold standard and helps to define disease stage and recurrence.⁵ Here, we report a case of primary cutaneous NK/T-cell lymphoma with multiple recurrences, which received allogeneic peripheral blood stem cell transplantation (PBSCT) and developed early onset post-transplant lymphoproliferative disorder (PTLD) in the liver, mimicking recurrent NK/T-cell lymphoma.

A 48-year-old man presented with nasal type extranodal NK/T cell lymphoma of the leg skin in April 2019 (Fig. 1A). Immunohistochemical examination revealed that the tumour cells were positive for CD45, CD3 (cytoplasmic), granzyme B (focal), CD56 (weak) and TIA-1, and negative for CD20, CD4, CD8, BCL-2, BCL-6, CD10, CD30, CD138, ALK, TCR-beta, and TCR-delta. The tumour cells were also strongly and diffusely positive for EBV detected by EBER *in situ* hybridisation (Fig. 1A, inset). The skin tumour resolved with radiotherapy. In August 2019, the patient received segmental resection of the small intestine due to tumour recurrence in the ileum with perforation. He also underwent chemotherapy for the subsequent development of multiple skin lesions with the regimens of SMILE (dexamethasone, methotrexate, ifosfamide, L-asparaginase, and etoposide) and DeVIC (dexamethasone, etoposide, ifosfamide, and carboplatin). In March 2021, with the intent of cure, the patient received an allogeneic hematopoietic stem cell transplant (SCT) from an HLA-matched unrelated donor (MUD). The preparative regimens (fludarabine, busulfan, and antithymocyte globulin) and graft versus host disease (GVHD) prophylaxis regimens (short course of methotrexate and cyclosporine) were given. The post-SCT short tandem repeat (STR) analysis revealed complete donor chimerism. Unfortunately, 2 months later he was hospitalised due to fever (38°C) and elevated serum liver enzymes (aspartate aminotransferase 378 U/L; alanine aminotransferase 487 U/L; bilirubin (total) 1.7 mg/dL; bilirubin (direct) 1.1 mg/dL; alkaline phosphatase 455 U/L). Computed tomography scans revealed multifocal poorly enhanced lesions in the liver and spleen, and multiple enlarged lymph nodes in the abdomen and neck. A complete blood count showed 21% of leukaemia/lymphoma cells (Fig. 1B). With the suspicion of lymphoma recurrence, he underwent bone marrow and liver biopsies. The bone marrow biopsy specimen revealed nodular infiltrates of atypical lymphoid cells positive for EBV; these nodules were absent in the previous bone marrow before this episode. Assessment of the liver specimen showed dense infiltration by a mixed infiltrate of medium sized and large lymphoid cells (Fig. 1C), that were composed of CD3-positive cells (Fig. 1D) and CD20-positive cells (Fig. 1E). A subset of these cells was positive for EBV detected by *in situ* hybridisation for EBER (Fig. 1F). These atypical lymphocytes were negative for CD56. Double staining with CD3/

Fig. 1 Pathological features of initial NK/T-cell lymphoma and subsequent post-transplant lymphoproliferative disorder. (A) The initial nasal-type NK/T-cell lymphoma of the skin shows dense infiltration of small to medium sized lymphocytes in dermis with occasionally epidermal infiltration (H&E). The tumour cells are positive for EBV detected by EBER *in situ* hybridisation (inset). (B) Two months post-allogeneic hematopoietic stem cell transplant, the peripheral blood examination reveals atypical lymphoid cells with moderate amount of cytoplasm, irregular nuclear contours and several small nucleoli (Liu stain). (C) The liver biopsy shows a dense infiltrate of medium sized to large lymphoid cells (H&E) with scant cytoplasm, hyperchromatic nuclei and inconspicuous nucleoli (inset H&E). (D–F) These atypical lymphocytes are composed of both (D) CD3-positive and (E) CD20-positive cells with part of them positive for EBV detected by *in situ* hybridisation for EBV-encoded RNA (EBER). (G,H) Double staining with (G) CD3/EBER and (H) CD20/EBER highlights EBV infection in B cells, which are consistent with EBV-positive diffuse large B-cell lymphoma of post-transplant lymphoproliferative disorder (PTLD), rather than recurrence of NK/T cell lymphoma.

EBER (Fig. 1G) and CD20/EBER (Fig. 1H) localised EBV in the B cells. In addition, the tumour cells expressed both EBV proteins, latent membrane protein 1 (LMP1) and nuclear antigen 2 (EBNA2) (Fig. 2), consistent with a type III latency program.⁶ Taken together, all the findings supported a diagnosis of a PTLD, EBV-positive diffuse large B-cell lymphoma subtype, rather than recurrence of NK/T-cell lymphoma. The patient was treated with rituximab after cyclosporine was discontinued. He is currently in remission.

Fig. 2 Expression of type III EBV latency program in the tumour cells. (A,B) Immunohistochemically, the tumour cells are positive for (A) EBV protein LMP1, and (B) EBNA2, which are consistent with a type III EBV latency program (EBER+/LMP1+/EBNA2+).

PTLD is a lymphocytic/plasmacytic proliferation that develops as a consequence of immunodeficiency in a recipient of a solid organ or allogeneic stem cell transplant, and is usually associated with EBV. The morphological spectrum of PTLD ranges from polyclonal lymphoplasmacytic hyperplasia to monomorphic lymphomatous proliferations, as they occur in immunocompetent hosts, and are categorised as non-destructive, polymorphic, monomorphic and classic Hodgkin lymphoma PTLDs.¹ The clinical course of PTLD is highly variable. The median time from transplantation to emergence of PTLD ranges from less than 1 year to more than 10 years.⁷ PTLD frequently presents in the first year after transplantation, especially in EBV-negative recipients. The risk of early onset PTLD (within 1 year) is highest in unrelated donors with selective T-cell depletion of donor bone marrow and with usage of anti-thymocyte globulin or anti-CD3 antibodies.⁸ Our case was an EBV-seropositive recipient with a post history of multiple recurrences. The early onset (2 months) of EBV-positive PTLD may closely mimic recurrence of NK/T-cell lymphoma. Since PTLD and NK/T-cell lymphoma are both strongly associated with EBV infection, double staining as well as EBV latency program in this context were appropriate to clarify the nature of the EBV-positive cells and lead to the correct diagnosis.

EBV, also known as human herpesvirus 4 (HHV-4), is a member of the herpesvirus family that infects more than 90% of the population worldwide.⁶ The nature of lymphotropism and the demonstration of monoclonal proliferation of EBV genomes in lymphoma cells suggest its pathogenic role in

lymphomagenesis,^{9,10} especially for nasal-type NK/T-cell lymphoma and PTLDs. Based on the distinct patterns of EBV latency programs: type I (EBER+/LMP1-/EBNA2-), type II (EBER+/LMP1+/EBNA2-) and type III (EBER+/LMP1+/EBNA2+),¹¹ the tumour cells of NK/T-cell lymphoma and PTLT are consistent with type I and type III latency patterns, respectively.⁶ In this regard, in addition to its tumourigenetic role, the expression of EBV latency program may also play a role in the differential diagnosis of NK/T-cell lymphoma (LMP1-/EBNA2-) versus PTLT (LMP1+/EBNA2+) in our case.

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Unique nested formation in a case of large cell transformation of follicular lymphoma mimicking adenocarcinoma

To the Editor,

Follicular lymphoma (FL) is the archetypal indolent lymphoma and the second most common type of non-Hodgkin lymphoma. Histological transformation to an aggressive lymphoma occurs at a rate of 1–2% per year, is associated with accelerated clinical progression and alters the therapeutic paradigm.^{1,2} Transformation causes a loss of follicular architecture with the accumulation of large cells, with features most frequently resembling diffuse large B-cell lymphoma (DLBCL). We report a case of large cell transformation of FL in which nests or foci of cohesive clustering large cells in the bone marrow gave rise to a distinct pseudo-acinar architecture; this initially caused diagnostic confusion as it raised the possibility of metastatic carcinoma infiltrating the marrow.

A 78-year-old man with a history of AL (light chain) amyloidosis and FL Stage II, the latter condition being treated 4 years earlier with radiotherapy only, presented with fatigue, symptomatic splenomegaly and pancytopenia. Positron emission tomography scan confirmed splenomegaly and showed nodal involvement on both sides of the diaphragm with intense fluorodeoxyglucose avidity in the spine and proximal appendicular skeleton suggestive of bone marrow involvement. Core biopsy of a supraclavicular lymph node showed morphological features of low-grade FL only, the limited diagnostic material being insufficient for immunohistochemical studies.

A bone marrow biopsy was performed. The aspirate was aparticle with no specific diagnostic features. The trephine biopsy was markedly hypercellular, with normal haematopoietic tissue being effaced by sheets of small lymphocytes throughout the marrow. Additionally, foci of cohesive clusters of larger cells resembling acini were observed (Fig. 1) with an appearance reminiscent of carcinoma. By immunohistochemistry, the larger cells were negative for AE1/3 and CD30, and had a germinal centre B-cell phenotype, with CD45+, CD20+, CD10+, bcl2+ and bcl6+ (Fig. 2A–E). Immunostaining with CD31 and CD34 for endothelial cells and D2-40 for lymphatics showed that these clusters of cells were not confined within blood or lymphatic vessels. Overall the Ki-67

Fig. 1 Nests or foci of cohesive clustering large cells resembling acini or metastatic carcinoma in the bone marrow (bone marrow trephine, H&E).