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Systemic mastocytosis with B-acute lymphoblastic leukaemia: clonal or coincidental?

To the Editor,

Systemic mastocytosis (SM) comprises a clinically diverse set of haematological malignancies characterised by clonal proliferation of abnormal mast cells (MCs) and, in >90% of cases, a gain of function mutation in *C-KIT* (*C-KIT* D816V).¹ An associated haematological neoplasm (SM-AHN) co-occurs in 20–40% of cases and is overwhelmingly of myeloid origin.² Herein, we report a case of SM-AHN with B-acute lymphoblastic leukaemia (B-ALL).

A 67-year-old male was referred for evaluation of fatigue, cytopenias and progressive spinal issues with pain, kyphosis and loss of height. There were no B symptoms, cutaneous symptoms, anaphylaxis or angioedema. Past medical history was significant for hypertension, diverticulosis, gastro-oesophageal reflux disease and a resected adrenal adenoma. Full blood count showed: Hb 102 g/L, MCV 103, platelets 110×10^9 /L, neutrophils 0.7×10^9 /L. There was no eosinophilia or circulating blasts. Computed tomography (CT) of neck/chest/abdomen/pelvis showed multiple vertebral crush fractures and diffuse osteopenia without lymphadenopathy or hepatosplenomegaly.

Bone marrow aspirate and flow cytometry showed 88% B-lymphoblasts with the following immunophenotype: CD19+/CD20–/CD10v/SMIG–/cCD79aw/cCD22–/cIgM–/CD13+/CD33w/CD15v/MPO–/CD34+/HLADR+/TDT+. Although there were aberrant myeloid markers, the criteria for mixed phenotype acute leukaemia were not met. There were occasional hypogranular mast cells and no marrow eosinophilia. Bone marrow trephine was markedly hypercellular (~95%) with a heavy blastoid infiltrate. There were multi-focal clusters of spindle shaped MCs, each containing >15 cells and accounting for 5–10% of total cellularity (Fig. 1). Immunohistochemistry confirmed the flow cytometric immunophenotype of blast population with the addition of CD20+. The MCs were CD117+/tryptase+/CD2+/CD25+ (Fig. 1).

Fluorescent *in situ* hybridisation (FISH) was negative for BCR-ABL1 [t (9; 22)], KMT2A (11q23), FIP1L1-PDGFR (4q12), PDGFRB (5q32), and FGFR1 (8p11) rearrangements. There were insufficient dividing cells for conventional cytogenetics. *C-KIT* D816V mutation was detected by allele-specific-polymerase chain reaction in unselected cells. Serum tryptase was modestly elevated at 17.1 µg/L (normal <13.5 µg/L), but less than the World Health Organization (WHO) specified diagnostic threshold (20 µg/L). Thus, the major and minor (3/4) WHO criteria for SM were met. The integrative diagnosis was SM-AHN with B-ALL.

Although the progressive vertebral crush fractures were suspected to be related to MC infiltrate, B-ALL was felt to be the dominant of the two pathologies and induction chemotherapy was commenced with cyclophosphamide, vincristine, doxorubicin and dexamethasone (hyper-CVAD, A cycle). The disease was refractory to this treatment and alternative treatment options are now being considered.

To the authors' knowledge, this is the third reported case of adult SM-AHN with B-ALL and is unique in several ways.^{3,4}

Firstly, SM-AHN typically involves myeloid malignancies (~90%): especially chronic myelomonocytic leukaemia; myeloproliferative neoplasms (MPN); myelodysplastic syndromes (MDS) and MDS/MPN overlap syndromes.^{1,2} In these cases, SM and AHN are usually clonally related with *C-KIT* mutation demonstrated in both MC and AHN compartments. The developmental stage at which *C-KIT* mutation arises likely determines the phenotype and prognosis of SM, with indolent cases having *C-KIT* mutation only in MC and aggressive cases harbouring *C-KIT* mutation in stem cells and other lineages.^{2,5} Lymphoid malignancies have rarely been reported with SM-AHN including chronic lymphocytic leukemia (CLL), atypical CLL, T-cell lymphoblastic lymphoma, Hodgkin lymphoma, diffuse large B-cell lymphoma and splenic marginal zone lymphoma.^{3,6–8}

Secondly, this case raises questions about the biological relationship between MC and lymphoid malignancies. In

Fig. 1 (A) Trephine — note hypercellularity, blastoid infiltrate and clusters of spindle-shaped mast cells (H&E). (B) CD20 staining of same biopsy — note blastoid B cell infiltrate (immunoperoxidase). Mast cells are (C) CD117, (D) mast cell tryptase, (E) CD25 and (F) CD2 positive (immunoperoxidase).

previously published cases of lymphoid SM-AHN, laser microdissection or flow cytometric cell sorting has been used to demonstrate *C-KIT* mutation in MC but not malignant lymphoid cells, suggesting distinct clonal origins.^{4,6,7} On the other hand, non-malignant lymphocytes in SM patients have been demonstrated to harbour *C-KIT* mutation in ~40% of cases and a trans-genic mouse model of SM resulted in development of a B-ALL like leukaemia in 50% of mice.^{5,9} This provides scientific rationale to the hypothesis that B-ALL and SM may have arisen from the same *C-KIT* D816V mutated stem cell. An alternate hypothesis is that both malignancies are being driven by a currently unidentified, molecular/cytogenetic driver with *C-KIT* mutation in MC as a downstream event. This hypothesis is supported by the recent description of myeloid/lymphoid neoplasms with *PDGFRB/PDGFRB/FGFR1* rearrangements, which can give rise to

lymphoblastic leukaemia/lymphoma, mast cell proliferation and even *C-KIT* D8617V positivity.^{8,10}

Finally, this is the first case of *C-KIT* D8617V mutated SM with B-ALL diagnosed simultaneously. The two other cases were either *C-KIT* wild type³ or the diagnosis of SM predated that of B-ALL.⁴ Important similarities between this case and previously published cases include a relatively low tryptase (both cases)^{3,4} and aberrant expression of myeloid markers on B-lymphoblasts (one of two cases).³

In conclusion, this case adds to a very small body of literature regarding SM-AHN with B-ALL. In the evolving era of *C-KIT* inhibition, identification of this combination may have treatment implications for clinicians.¹ For the pathologist, an awareness of this case may avoid the potential diagnostic pitfall of assuming MC proliferations to be reactive.

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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/