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Diagnostic cues for natural killer cell lymphoma: primary nodal presentation and the role of in situ hybridisation for Epstein-Barr virus encoded early small RNA in detecting occult bone marrow involvement

C-S Chim, E S K Ma, F Loong and Y-L Kwong

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CASE REPORT

Diagnostic cues for natural killer cell lymphoma: primary nodal presentation and the role of in situ hybridisation for Epstein-Barr virus encoded early small RNA in detecting occult bone marrow involvement

C S Chim, E S K Ma, F Loong, Y L Kwong

Natural killer (NK) cell lymphomas are rare, and atypical features might lead to diagnostic pitfalls. This report describes an unusual patient in whom lymphoma occurred initially as isolated lymph node involvement, an exceptional presentation of an almost exclusively extranodal disease. Furthermore, during the terminal haemophagocytosis in the bone marrow, lymphoma cells lost the expression of the NK cell marker, CD56, making the histopathological diagnosis of bone marrow involvement difficult. This was resolved by in situ hybridisation for Epstein-Barr virus encoded small RNA, which detected occult bone marrow infiltration.

**CASE REPORT**

A 59 year old man presented with intermittent fever, night sweating, and left submandibular swelling. The submandibular lymph node biopsy showed partial replacement by a polymorphic infiltration of small to medium sized abnormal lymphoid cells with a prominent eosinophilic infiltrate. Focal angioinvasion by the abnormal lymphoid infiltrate was identified (fig 1A, B). The abnormal lymphoid cells were CD2+, surface CD3+, CD3ε+, and CD56+ (fig 1C). EBER was strongly positive on ISH (fig 1D). Polymerase chain reaction for the T cell receptor gene showed a germline configuration. These findings confirmed the diagnosis of NK cell lymphoma. To search for occult nasopharyngeal involvement, endoscopy of the nasopharynx with random biopsies was performed, but lymphoma was not seen. The serum lactate dehydrogenase concentration was increased to 640 U/litre (normal, < 400). Real time quantitative polymerase chain reaction showed circulating plasma EBV DNA to be 1.4 × 10^6 copies/ml at diagnosis. Further investigations showed no involvement of other anatomical sites. The diagnosis was therefore primary nodal NK cell lymphoma, Ann Arbor stage IB. The patient achieved complete remission with three courses of combination chemotherapy, which was consolidated with local radiotherapy. He remained well until two years later when he developed a refractory left leg ulcer associated with enlarged left inguinal lymph nodes. Biopsy of the leg ulcer confirmed recurrent NK cell lymphoma. There was no apparent involvement of other sites. He received cisplatinum, high dose cytosine arabinoside, and dexamethasone, together with local irradiation to the leg ulcer. The response was poor, and despite chemotherapy, he developed persistent fever, hepatosplenomegaly, nodular lesions over the trunk and limbs, and pancytopenia (haemoglobin, 84 g/litre; platelets, 46 × 10^9/litre; and white blood cell count, 1.2 × 10^9/litre). Lactate dehydrogenase was extremely high at 5640 U/litre. Bone marrow aspiration showed scattered atypical lymphoid cells with prominent haemophagocytosis. Immunohistochemical analysis did not reveal CD56+ cells (fig 2A–C), although ISH showed multiple EBER positive lymphoid cells (fig 2D). Computerised tomography of the thorax and abdomen showed mediastinal lymphadenopathy and hepatosplenomegaly. He deteriorated rapidly and died. A postmortem examination was not permitted by the family.

**DISCUSSION**

This case showed some extraordinary features. First, the lymphoma initially presented as the isolated involvement of a lymph node, which is exceptional. In a review of 45 cases of

**Abbreviations:** EBER, Epstein-Barr virus encoded early small RNA; EBV, Epstein-Barr virus; ISH, in situ hybridisation; NK, natural killer
nasal-type (extranasal) CD56 positive lymphomas, only one had primary nodal presentation, but this patient had concurrent bone marrow involvement. In another series of 13 aggressive nodal T and NK/T cell lymphomas, only one had a classic NK cell lymphoma profile (CD2+, CD3-*, CD56+, EBER+). The low copy number of plasma EBV DNA at presentation (1.4 × 10^3 copies/ml, compared with 10^5 to 10^10 copies/ml for nasal and non-nasal NK cell lymphomas).

**Figure 1**  Histopathology of a case of nodal natural killer cell lymphoma. (A) Lymph node biopsy, showing interfollicular areas expanded by abnormal lymphoid cells with angioinvasion (haematoxylin eosin (H&E) stain; original magnification, ×40). (B) The neoplastic lymphoid cells were small to medium in size, with prominent eosinophilic infiltration (H&E stain; original magnification, ×200). (C) Immunostaining for CD56, showing abundant positive lymphoma cells (original magnification, ×200). (D) In situ hybridisation for Epstein-Barr virus encoded early small RNA, showing numerous positive cells (original magnification, ×200).

**Figure 2**  Histopathological features of bone marrow infiltration in relapsed natural killer cell lymphoma. (A) Trephine biopsy showing an interstitial infiltrate of abnormal lymphoid cells. They were large in size, having coarse chromatin texture, 1–3 small nucleoli, and an appreciable amount of cytoplasm (haematoxylin eosin stain; original magnification, ×1000). (B) Immunostaining for CD3, showing positive cells (original magnification, ×1000). (C) Immunostaining for CD56, showing no positive cells (original magnification, ×1000). (D) In situ hybridisation for Epstein-Barr virus encoded early small RNA, showing clusters of positive lymphoma cells.
Take home messages

- We describe an unusual patient in whom natural killer (NK) cell lymphoma occurred initially as isolated lymph node involvement, an exceptional presentation of an almost exclusively extranodal disease.
- During the terminal haemophagocytosis in the bone marrow, lymphoma cells lost the expression of the NK cell marker, CD56, making the histopathological diagnosis of bone marrow involvement difficult.
- This was resolved by in situ hybridisation for Epstein-Barr virus encoded small RNA, which detected occult bone marrow infiltration.

CD56 should not be relied upon alone as a marker of neoplastic natural killer cells.

During the terminal phase of illness, our patient showed peripheral blood pancytopenia with prominent bone marrow haemophagocytosis. From a diagnostic viewpoint, the distinction between haemophagocytosis and lymphomatous infiltration as a cause of the pancytopenia might not be easy. Haemophagocytosis occurs commonly in the liver, spleen, and bone marrow in NK cell lymphomas. It may be reactive, and is itself not necessarily an indicator of infiltration in the involved tissue. Furthermore, NK cell lymphoma infiltration might be patchy and inconspicuous. Immunohistochemical staining for CD56 offers a diagnostic aid to identifying the lymphomatous cells. However, a notable caveat is that the expression of CD56 on the lymphoma cells might occasionally be lost at relapse. This phenomenon was again seen in our patient, highlighting the important point that CD56 should not be relied upon alone as a marker of neoplastic NK cells.

This problem was overcome by the use of EBER-ISH. In fact, EBER-ISH has been shown to be more sensitive than CD56 immunostaining in detecting occult bone marrow infiltration by NK cell lymphoma. Other ancillary markers such as cytotoxic granule associated proteins (granzyme B, TIA-1, and perforin), expressed in NK cell lymphoma but rarely in other lymphomas, might also be helpful, although their use has not been formally compared with EBER-ISH.

In conclusion, our case showed that NK cell lymphoma can present atypically in the lymph node, and that both immunohistochemical staining and EBER-ISH are necessary in the histopathological diagnosis.

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