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LETTER TO THE EDITOR

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Aggressive natural killer cell leukaemia with a complex karyotype: a case report

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Dear Editor,

We report a case of aggressive natural killer (NK) cell leukaemia characterised by hepatitis C virus (HCV) and Epstein–Barr virus (EBV) infection and multiple karyotype abnormalities in a patient previously treated with radio-chemotherapy for non-haematological cancer.

NK cell malignancies are rare haematopoietic tumours usually associated with EBV infection [1, 2], and aggressive NK cell leukaemia is an even rarer disease with a grim prognosis [3–5]. It typically shows multi-organ involvement leading to multi-organ failure and has an aggressive course that responds poorly to chemotherapy [6, 7].

A 76-year-old white woman came to our hospital in April 2003 complaining of fatigue, dyspnea and fever. Her medical history included HCV-related liver cirrhosis and ovarian cancer, which had been diagnosed 2 years earlier and treated by means of surgery and radio-chemotherapy with alkylating agents and topoisomerase II inhibitors.

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Physical examination revealed multiple superficial lymphadenomegalies and liver and spleen enlargement. Laboratory examinations showed hyperleucocytosis (WBC 162×10^9/l), mild thrombocytopenia (PLT 89×10^9/l) and high LDH levels (1,486 U/l). Clotting tests showed increased XDP (8,900 mg/dl) and a prolonged prothrombin time (ratio 1.63). A peripheral blood smear revealed large undifferentiated blasts with abundant and slightly granular cytoplasm. A three-colour immunofluorescence assay of peripheral blood (FACScalibur, Becton Dickinson, Boston, MA, USA) showed the expression of CD1a, CD2, CD4, CD16, CD43, CD30, CD56, CD11c and CD38, but there was no detectable presence of CD33, CD13, CD19 or surface or cytoplasmic CD3. She had a hypertriploid karyotype with trisomy of all chromosomes and tetrasomy of chromosomes 2, 10, 12 and 16. Furthermore, some structural abnormalities were also detected, including the long arm deletion of chromosome 6 and an additional long arm of chromosome 17.

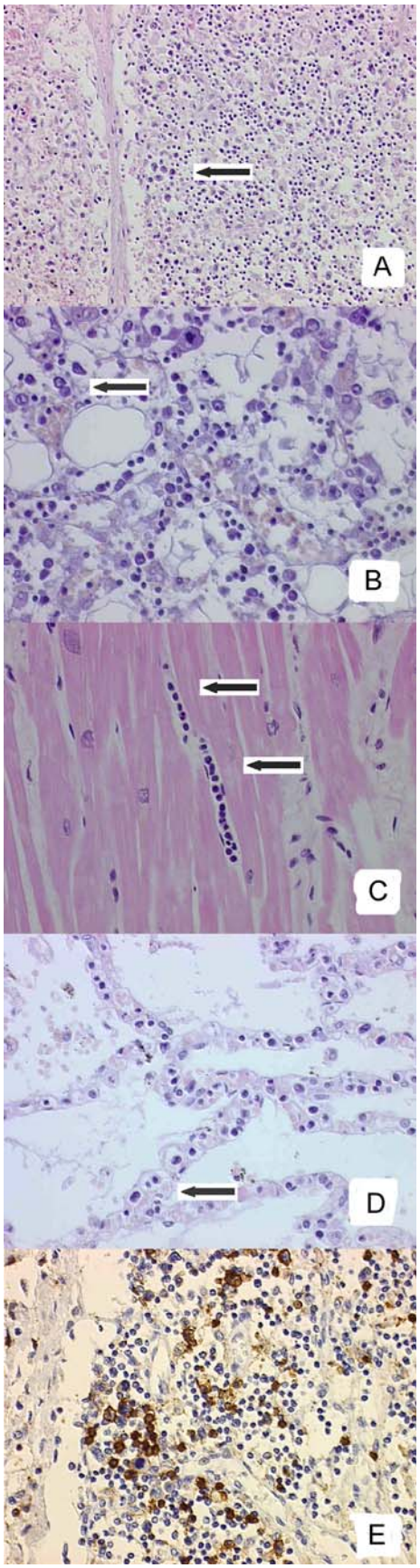
PCR analysis revealed a germ line configuration of T-cell receptor genes and identified EBV genome in the leukaemic cells.

A diagnosis of aggressive NK cell leukaemia was made and, given the patient's poor performance status, she was prescribed non-intensive treatment with cyclophosphamide (500 mg/day i.v. for 3 days), vincristine (2 mg i.v) and 6-methyl-prednisolone (60 mg/day i.v. for 3 days), which partially reduced the hyperleucocytosis (WBC $240\rightarrow74\times10^9$/l).

However, the disease pursued a fulminant course: disseminated intravascular coagulation and multi-organ failure ensued, and the patient died 30 days after being diagnosed.

Autopsy revealed adult respiratory distress syndrome and NK cell infiltration of the bone marrow, spleen, liver, lymph nodes, lungs and heart by medium- to large-sized haematopoietic blasts (Fig. 1). No skin involvement was detected.

NK cell tumours constitute a group of highly heterogeneous lymphoproliferative disorders that have an aggressive course and typical extra-nodal involvement. In our



◀ **Fig. 1** Large to giant blastic lymphoid cells in **a** the marginal sinus of an abdominal lymph node (*arrows*), **b** the bone marrow sinusoids (*arrows*) and **c**, **d** the capillary vessels of the myocardium and alveolar septa. **e** The neoplastic cells expressed the CD45Ro (UCHL1) antigen. No angio-invasive or angio-destructive pattern was detected

case, the NK cell origin was demonstrated by the expression of CD16 and CD56, the lack of CD3 expression and a germ line T-cell receptor configuration.

The absence of skin involvement and the aberrant CD4 expression are unusual findings in NK cell leukaemia, but the main peculiarity of this case is the association of previous intensive chemotherapy and HCV-related cirrhosis. No case of chemotherapy-related NK disorders has so far been described, whereas the association between acute leukaemias and radio-chemotherapy is well-known [8].

Karyotype abnormalities have been reported in aggressive NK leukaemia [9], although there are no published descriptions of such an aberrant cytogenetic pattern. Some of these abnormalities may represent non-random markers of NK tumours, but it is not known whether specific genes regulating NK development are located in these chromosomes. This karyotype may in fact have been the expression of multiple genotoxic factors: radio-chemotherapy and HCV and EBV infection. Chronic HCV and EBV stimulation of the immune system may have induced NK oligoclonal proliferation and allowed a further neoplastic evolution. The role of HCV infection in the pathogenesis of NK tumours is unknown: it may induce an increase in liver NK cells [10, 11], but their function seems to be inhibited [12]. EBV infection stimulates NK cell proliferation, especially through IFN-γ production by EBV-infected T lymphocytes [2].

In conclusion, this may have been a case of secondary NK cell leukaemia, whose prognosis was made even worse as a result of the associated HCV-related liver cirrhosis and previous radio-chemotherapy for ovarian cancer and which contributed to the multiple cytogenetic abnormalities.

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