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Langerhans' cell histiocytosis in an adult with acute myelogenous leukaemia

Received: 10 December 2003 / Accepted: 26 February 2004 / Published online: 22 April 2004
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Sir,

We have had the opportunity to study a case of localised Langerhans' cell histiocytosis (LCH) in a patient with a 10-year history of acute myelogenous leukaemia (AML). To the best of our knowledge, there is no other similar case in the literature.

The patient was a 57-year-old woman who consulted her primary care physician to complain of acute upper airway ache and a constitutional syndrome in October 1991. Her blood test revealed a leukocyte count of $9.5 \times 10^9/l$ with 81% of blast cells, 8.3 g/dl of haemoglobin and a $115 \times 10^9/l$ platelet count. Bone marrow biopsy and aspirate contained 85% blast cells with no significant maturation (Fig. 1). The blast cells occasionally exhibited Auer rods (Fig. 1) and were oxidase positive, chloroacetate esterase and non-specific esterases were negative and cytogenetic studies revealed no abnormalities. A diagnosis of AML-M1 was given. A later immunohistochemical study revealed the neoplastic cells to be strongly positive for myeloperoxidase (polyclonal, dilution 1/5000) and weakly positive for CD68 (monoclonal, clone KP1, 1/100) and lysozyme (polyclonal, 1/4); immunostaining for CD3 (monoclonal, 1/50), CD79 α (monoclonal, 1/100), CD10 (monoclonal, 1/20), terminal deoxynucleotidyl transferase (polyclonal, 1/30), CD34 (monoclonal, 1/50), CD68 (monoclo-

nal, clone PG-M1, 1/50), CD61 (monoclonal, 1/50), factor VIII (polyclonal, 1/500), factor XIIIa (polyclonal, 1/2000) and CD1a (monoclonal, predilute) were all negative (CD10 was manufactured by Novocastra, Newcastle, UK, lysozyme by Biomedica, Foster City, USA, factor XIIIa by Berhing, Marburg, GFR, CD1a by Master

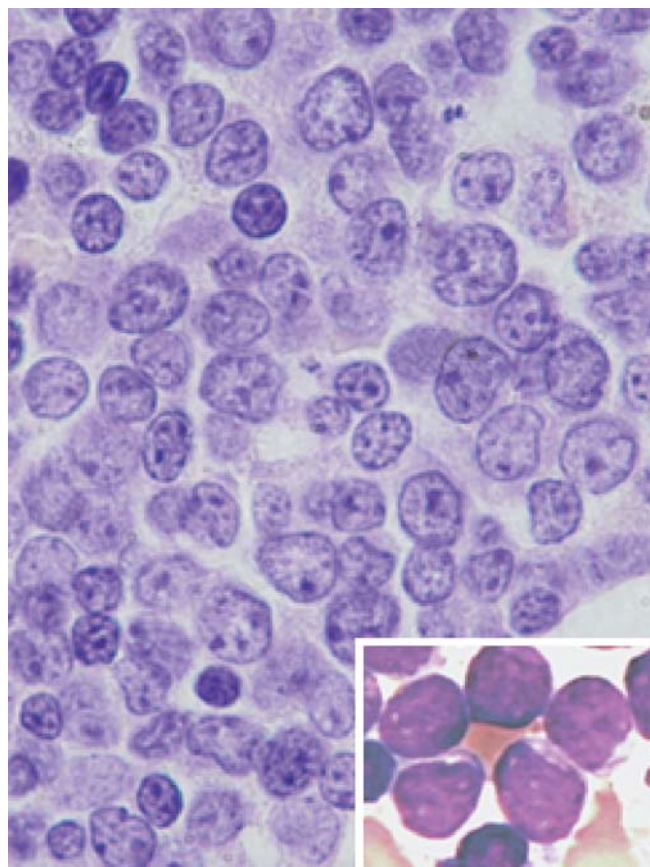


Fig. 1 Initial bone-marrow biopsy showing diffuse blast involvement. Haematoxylin and eosin $\times 1000$. *Inset* Detail of the initial aspirate demonstrating medium size cells; one Auer rod may be seen. May-Grünwald-Giemsa $\times 1000$

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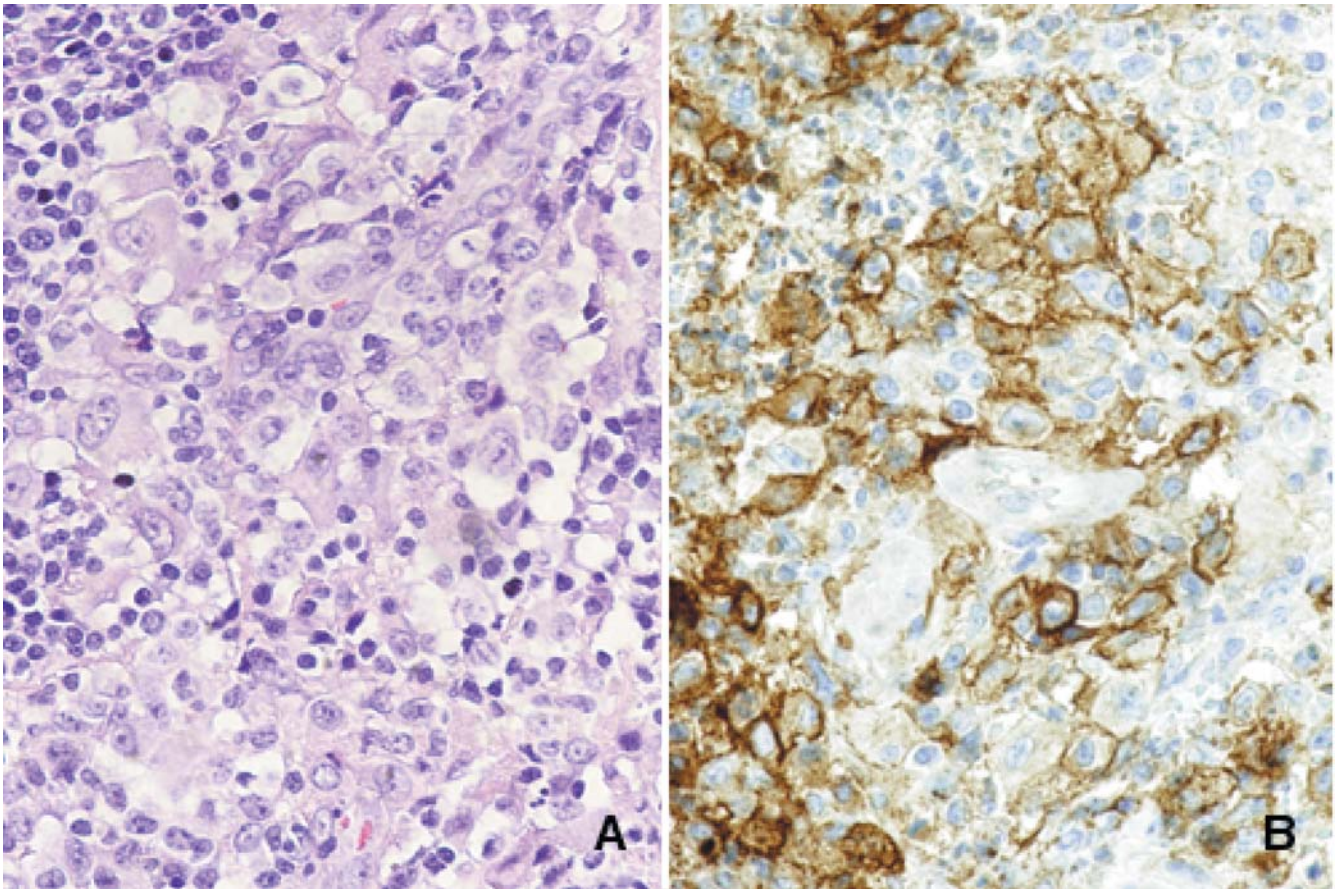


Fig. 2 A Detail of the lymph-node biopsy showing large cells with ample cytoplasm and irregular nuclei. Haematoxylin and eosin $\times 400$. B Infiltrating cells were CD1a positive. Immunoperoxidase $\times 1000$

Diagnostic, Granada, Spain and the remaining antisera by Dako, Glostrup, Denmark). A regimen of daunorubicin and cytosine arabinoside (ara-c) (3+7) obtained complete clinicocytological remission; consolidation treatment was based on high doses of daunorubicin and ara-c.

A recurrence was treated with idarubicin and ara-c (3+7), and the new remission was consolidated with medium doses of idarubicin and ara-c 5 years after the initial diagnosis. While in the second complete remission, the patient underwent an autologous bone marrow transplant in April 1997; her blood count was acceptable on day 21 post-transplant.

In October 2001, the patient presented with a hard, deep-tissue-adhering, 3 \times 2-cm nodule in her left supraclavicular fossa. Histological study identified the nodule as a lymph node that was focally affected by an infiltrating proliferation of large cells with ample cytoplasm and convoluted nuclei with deep indentations and disperse chromatin (Fig. 2). These cells were positive for CD1a, S-100 protein (dilution 1/2000, Dako) and CD68 (clone KP1). The rest of the node showed preserved architecture, and neither haematoxylin eosin histological examination nor myeloperoxidase immunostaining revealed atypical cells. A diagnosis of LCH was made. At that time, there

were no signs of recurrence of the leukaemia, and a staging study found no other sites of involvement.

The patient suffered a new recurrence of the leukaemia 1 year after the diagnosis of the LCH, and she died from acute respiratory insufficiency before any treatment could be initiated. Necropsy was not performed.

LCH is a rare condition, most commonly occurring in children under 5 years old. The clinical picture is variable, with localised, multifocal and disseminated forms. The aetiology is uncertain, but most cases studied have proved to be clonal proliferations. LCH has been reported in association with a large variety of lesions, including neonatal infection, solvent exposures, lack of vaccination in children and thyroid diseases [5], as well as a large number of tumours, including solid tumours, lymphomas and chronic as well as acute leukaemias [1, 3, 5].

The lymph nodes may be involved in both the disseminated and localised variants of LCH. Nodal involvement may be "primary" or associated with tumours, primarily Hodgkin's lymphoma. In contrast to "primary" nodal LCH, lymph-node involvement in tumour-associated LCH is focal with an infiltrating margin and a necrotic eosinophilic central core, rather than sinusoidal and expansive [5].

LCH and acute leukaemia occurring in the same patient is unusual, and most cases have been described in paediatric patients, with two major clinical patterns: first, acute lymphoblastic leukaemia may precede LCH, which may be either localised or disseminated and may persist after the treatment of the leukaemia; the cause of this association remains uncertain. Second, AML may appear months or years after etoposide treatment of LCH, and, in these cases, leukaemic proliferation is attributed to the leukaemogenic effect of the drug.

In our case, the patient developed a localised nodal LCH 10 years after the initial diagnosis of AML-M1, which was treated with daunorubicin, ara-c, idarubicin and autologous bone marrow transplant. To explain this association, we suggest three possibilities.

First, we could hypothesise that both LCH and AML have their origin in a common progenitor. The reports of *in vitro* differentiation of human myeloid leukaemia-derived cell lines to Langerhans' cells, acute monocytic leukaemias expressing CD1a [4] and chronic myelomonocytic leukaemia associated with Langerhans' cell proliferation [3] all suggest a common origin for monocytic cells and Langerhans' cells. However, in our case, the hypothesis of a common origin for AML and LCH is improbable, since the retrospective CD1a staining of the leukaemic cells was negative, LCH was localised, and the Langerhans' cell proliferation she developed did not appear in the setting of a recurrence of her leukaemia.

Second, LCH could have resulted from an immunological surveillance deficiency, as has been suggested in some Langerhans' cell proliferations [1]. Although, at the time of the diagnosis of LCH, our patient did not show features of being immunodepressed, we must admit that in an aggressively treated patient, immune dysregulation could be, at least, another factor in the pathogenesis of LCH.

Finally, a third and more attractive hypothesis is that LCH could be the result of anomalous cytokine produc-

tion. The World Health Organization's Committee on Histiocytic/Reticulum Cell Proliferations [2] believes that tobacco-associated pulmonary Langerhans' cell proliferation is probably a cytokine-mediated reactive lesion. Although there are no clonality studies, the same committee classifies tumour-associated LCH under the heading of Secondary Dendritic Processes, suggesting that it would also correspond to a reactive lesion. In our patient, the fact that the lesion involved only one lymph node and was cured by surgical resection alone with no other treatment also suggests a reactive process.

In summary, we present the case of an adult woman who suffered from a localised nodal LCH after a 10-year history of recurrent AML-M1 treated with anti-neoplastic antibiotics, ara-c and autologous bone marrow transplant. To the best of our knowledge, this association has not been reported before and it should be kept in mind in the differential diagnosis of lumps arising in the course of AML.

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