

**Bone marrow infiltrate by atypical histiocytic cells with cytoplasmic Birbeck granules as initial presentation of an acute monoblastic leukemia**

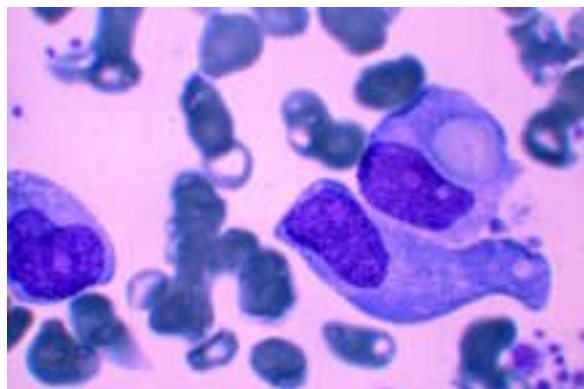
Langerhans cells (LCs) are characterized by the presence of the CD1a complex and cytoplasmic Birbeck granules, and have been identified as the cell that proliferates in Langerhans cell histiocytosis. However, little information is available about the participation of LCs in acute leukemias. We present here a case of a 72-year-old man who presented with and infiltration of the bone marrow with atypically histiocytic large cells that showed cytoplasmic Birbeck granules, preceding the onset of an acute monoblastic leukemia.

Histiocytic disorders represent a very heterogeneous, and sometimes unclear group of diseases.<sup>1</sup> The term *histiocyte* includes both the monocyte/macrophage cell series and the Langerhans cell/dendritic cell (LC/DC) lineage.<sup>1,2</sup> However, although the leukemias affecting the monocyte/macrophage cell series are well described and characterized,<sup>1</sup> very little information about the participation of LCs/DCs in acute leukemia is available.<sup>3-5</sup> We report a case of marrow infiltration by atypical histiocytic cells with cytoplasmic Birbeck granules<sup>3,6</sup> as a presentation of an acute monoblastic leukemia (AMoL).

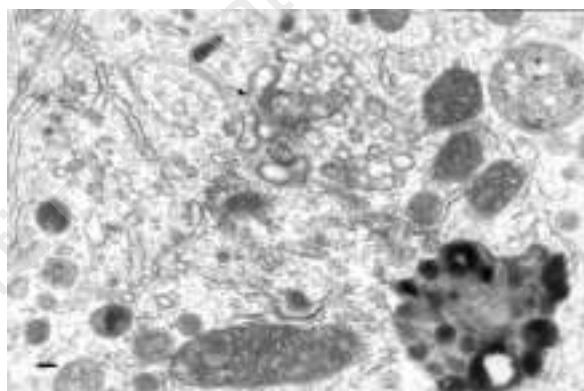
A 72-year-old man was admitted to hospital with a history of anal pain and rectorrhagia. Physical examination revealed an anal abscess with ulceration. Lymphadenopathy, hepatosplenomegaly and skin lesions were absent. A complete blood count showed a white blood cell count of  $1.6 \times 10^9/L$ , with 93% lymphocytes, hemoglobin level of 103 g/L and platelets of  $336 \times 10^9/L$ . Serum biochemistry was normal. The results of a total body computerized axial tomography were normal, and a complete radiological study ruled out bone lesions. The bone marrow aspirate was normocellular, with myeloid precursors nearly absent (1%), 77% of erythroblasts and 5% of undifferentiated blast cells. The most important finding was the presence of an infiltrate (12%) of atypical large cells (50% of the non erythroid cells) with blast appearance, resembling histiocytic cells, with occasional nucleolus, plentiful cytoplasm and frequent hemophagocytosis (Figure 1). These cells were negative for PAS, peroxidase and esterases. Bone marrow biopsy was normocellular and revealed the absence of myeloid precursors, as well as an interstitial infiltrate of cells of histiocytic appearance. Immunophenotyping of these atypical cells, by both flow cytometry and immunohistochemistry, showed positivity for CD45, CD36, CD4, CD38, lysozyme, S-100,  $\alpha$ 1-antitrypsin, and CD68 antigens, and negativity for CD1a, CD14, CD13, CD33, CD34, CD11b, CD11c, cytokeratin, and  $\alpha$ 1-antichymotrypsin. The ultrastructural analysis revealed the presence of Birbeck granules in their cytoplasm (Figure 2). There were no metaphases available for cytogenetic analysis.

The patient became increasingly pancytopenic and a second bone marrow aspiration performed one month later revealed normocellular marrow with normal megakaryocytes and 60% erythroblasts, 3% myeloid cells, 2% lymphocytes and 35% blast cells, which showed a morphology and immunophenotype of monocytic differentiation leading to the diagnosis of AMoL. No response was observed after one course of intensive chemotherapy with citarabine, idarubicine and fludarabine. Eight months later, the patient died due to septic shock.

In this case a bone marrow infiltration by atypical LCs was the initial presentation of an AMoL. Although both monocyte/macrophage and LCs display several common immunological markers, monocyte/macrophage are characterized by a greater expression of CD15, CD54 and CD68, and by the presence of phagocytosis.<sup>1,7</sup> By contrast, LCs are well characterized by displaying the CD1a and by the presence of Birbeck granules.<sup>1,7,8</sup> Interestingly, the cells with histiocytic morphology found



**Figure 1. Bone marrow aspirate. Atypical histiocytic cells with blast appearance, marked nucleolus, plentiful cytoplasm and presence of hemophagocytosis (May-Grünwald-Giemsa; x1200).**



**Figure 2. Two Birbeck granules with an irregular annular shape lying in the cytoplasm of an atypical Langerhans cells, surrounded by vesicles, mitochondria and numerous lysosomal bodies (Bar: 100 nm).**

in our patient had features of both monocyte/macrophage and LC lineages, because they were CD68 positive and presented frequent hemophagocytosis, but were also positive for S-100 and had cytoplasmic Birbeck granules. This last finding, at the ultrastructural level, was the basis for the recognition of these cells as atypical LCs with blast appearance. The explanation for the expression of characteristics of two different cell series in the same cell is unclear. However, a common origin, with a common bone marrow precursor, for both monocyte/macrophage and LC/DC lineages has been previously demonstrated,<sup>9,10</sup> and could explain the rapid evolution of the first bone marrow infiltrate to an AMoL over a short time.

At time, there is very little information about the participation of LC/DC series in acute leukemias, and most of that information is based on culture studies.<sup>4,5</sup> In fact, Santiago-Schwarz *et al.*<sup>5</sup> showed *in vitro* differentiation of the blast cells of a patient with acute myeloblastic leukemia (FAB, M2) along the DC pathway, and they proposed the term myelodendritic leukemia. Moreover, Srivastava *et al.* reported a case of acute leukemia involving progenitors of dendritic LCs.<sup>4</sup> The culture of these leukemic cells resulted in a differentiation to mature LCs.<sup>4</sup> In our case, the presence of a population of histiocytic blast cells

with cytoplasmic Birbeck granules supports the previously reported concept of myelodendritic leukemia by Santiago-Schwarz *et al.*<sup>5</sup> Like in these two previous reports,<sup>4,5</sup> our patient did not achieved remission after treatment with intensive chemotherapy, suggesting a poor prognosis in acute myelogenous leukemias with LC/DC participation.

In conclusion, we report a case of bone marrow infiltration by atypical LCs with blastic appearance, preceding the onset of AMoL. The diagnosis was mainly based on the direct ultrastructural study of these atypical cells, which showed the presence of Birbeck granules. Further studies are needed for a better understanding of our findings.

Federico Gomis, Federico Moscardó, Fernando Mayordomo,\*  
Guillermo Martín, Amparo Sempere, Miguel A. Sanz  
Hematology and Pathology\* Departments,  
Hospital Universitario La Fe, Valencia, Spain

**Key words:** Langerhans cells, Birbeck granules, acute monoblastic leukemia

**Correspondence:** Miguel A. Sanz, Hematology Department, Hospital Universitario La Fe, Av. Campanar 21, 46009 Valencia. Phone & Fax: international +34.96.3868757. E mail: msanz@uv.es

#### References

1. Cline MJ. Histiocytes and histiocytosis. *Blood* 1994; 84:2840-53.
2. Austyn JM. Lymphoid dendritic cells. *Immunology* 1987; 62:161-70.
3. Wright-Brone V, McClain KL, Talpaz M, Ordonez N, Estrov Z. Physiology and pathophysiology of Dendritic cells. *Hum Pathol* 1997; 28:563-79.
4. Srivastava BI, Srivastava A, Srivastava MD. Phenotype, genotype and cytokine production in acute leukemia involving progenitors of dendritic Langerhans cells. *Leuk Res* 1994; 18:499-511.
5. Santiago-Schwarz F, Coppock DL, Hindenburg AA, Kern J. Identification of a malignant counterpart of the monocyte-dendritic cell progenitor in an acute myeloid leukemia. *Blood* 1994; 84:3054-62.
6. Birbeck MS, Breathnach AS, Everall JD. An electron microscopic study of basal melanocyte and high level clear cell (Langerhans cell) in vitiligo. *J Invest Dermatol.* 1961; 37:51-63.
7. Jennings CD, Foon KA. Recent advances in flow cytometry: application to the diagnostic of hematologic malignancy. *Blood.* 1997; 90:2863-92.
8. Chu T, Jaffe R. The normal Langerhans cell and the LCH cell. *Br J Cancer.* 1994; 70(Suppl. XXIII):S4-S10.
9. Caux C, Dezutter-Dambuyant C, Schmitt D, Banchereau J. GM-CSF and TNF- $\alpha$  cooperate in the generation of dendritic Langerhans cells. *Nature* 1992; 360:258-61.
10. Herbst B, Köhler A, Mackensen A, Veelken H, Mertelsmann R, Lindemann A. CD34+ peripheral blood progenitor cell and monocyte derived dendritic cells: a comparative analysis. *Br J Haematol* 1997; 99:490-99.