An unusual acute myeloid leukemia associated with hyper IgE: another case of AML-M5c?

Although a large number of histiocytic diseases have been described, their classification remains controversial[1,2] and only a few cases of primary histiocytic disorders presenting with or evolving into an overt leukemic phase - AML-M5c – have been reported.[3,9] We describe a leukemia with unusual clinical and laboratory features whose diagnosis is compatible with AML-M5c.

A 50-year old white male was studied because of anemia and thrombocytopenia. Clinically, only anemia-related symptoms were found and the physical examination yielded negative results. Blood counts were: hemoglobin (Hb) 5.9 g/dL, platelets (PLT) 48×10^9/L, white blood cells (WBC) 6.8×10^9/L (neutrophils 63%, eosinophils 1%, lymphocytes 27%, monocytes 9%). Biochemical tests were normal except for increased serum lactic dehydrogenase (744 U/L; normal range 225-450 U/L), ferritin (523 ng/mL; normal range 12-200 ng/mL) and lysozyme (15 µg/mL; normal values < 12 µg/mL). There was a polyclonal hyper IgE (2,198 IU × 2/mL, normal values < 100 IU × 2/mL), without any clinical or laboratory evidence of parasitosis or atopic conditions. The bone marrow (BM) film showed 24% blasts, 44% granulocytic cells, 2% monocytes, 16% lymphocytes, 3% plasma cells and 11% erythroid precursors. Blasts were markedly polymorphic and hemophagocytosed other blood cells; a few mature-looking histiocytes were also found (Figure 1A). The BM biopsy showed a hypercellular and disorganized marrow with excess of blasts (Figure 1B). The megakaryocytic and erythroid lineages showed dystrophic elements while granulocytic cells matured normally. Ultrastructural studies did not shown Birbeck granules or ferritin deposits (Figure 1C). BM cells had a normal

Table 1. Blast cell cytochemical, immunophenotypic and immunohistochemical studies.

	Positive	*Negative*	
Cytochemistry	*Acid phosphatase* *α-naphthyl butyrate esterase** *α-naphthyl acetate esterase** *Periodic acid schiff*	*Naphthol AS-D chloroacetate esterase* *Myeloperoxidase* *Sudan Black*	
Immunophenotyping	CD4	CD1a	CD41
	CD11a	CD2	CD45RO
	CD11c	CD3	CD56
	CD13	CD5	CD57
	CD15	CD7	CD61
	CD16	CD8	CD64
	CD29	CD10	CDw65
	CD33	CD11b	CD66b
	CD35	CD14	Glycophorin A
	CD38	CD19	HLA-DR
	CD42	CD20	Ig heavy chains
	CD45	CD22	Ig light chains
	CD45RA	CD25	TCRαβ
	CD54	CD54	TCRγδ
	CD117	CD34	
Immunohistochemistry	CD68	CD20	CD61
	Lysozyme	CD45RO	VWF

*Ig, Immunoglobulins; TCR, T-cell receptor; vWF, von Willebrand Factor; *Inhibited by sodium fluoride.*

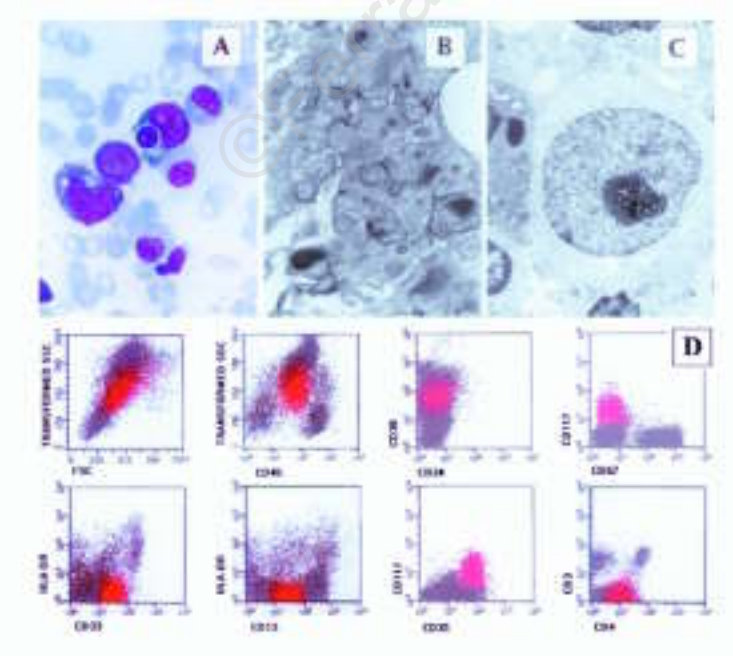

Figure 1. Bone marrow film (Leishmann´s stain) showing polymorphic medium to large sized blast cells, one of which is hemophagocytosing an erythroblast (panel A); blast cells had a relatively abundant cytoplasm with moderate to strong basophilia, sometimes with scattered vacuoles and fine granules. The nucleus was usually round, sometimes eccentric and had reticulated chromatin, usually with one or more well defined nucleoli. Some mature-looking histiocytes with hemophagocytic features were also found. As shown in panel B, bone marrow trephine biopsy revealed a hypercellular disorganized marrow with CD68+ blast cells. Ultrastructural microscopy studies illustrated in panel C showed blast cells with round or oval, sometimes irregularly shaped nuclei, with a marked predominance of euchromatin and large nucleoli: the cytoplasm was rich in cytoplasmic organelles. Birbeck´s granules, azurophilic granules or other specific granules were not found, neither were ferritin deposits. Occasionally, hemophagocytic features were observed. Representative dot plots illustrating some of the immunophenotyping features of the blast cells are displayed in panel D.

chromosomal constitution. Blast cell cytochemical, immunophenotypic and immunohistochemical features are illustrated in Table 1 and Figure 1D. Blasts expressed a low intensity of CD45 and myeloid associated markers such as CD13, CD15, CD33 and CD117. In spite of the negativity for CD14 and CD11b, they were positive for other markers that are usually found on monocyte-macrophage cells such as surface CD4, CD11c, CD16, CD29, CD35, CD38, CD54, cytoplasmic CD68 and lysozyme. However, the disease did not fulfill criteria for conventional AML-M4 and AML-M5 and AML-M5 with erythrophagocytosis was also excluded due to the lack of t(8;16) in conventional cytogenetics, no cells being available for molecular studies. The diagnosis of an AML-M6 was excluded based on FAB criteria, negativity for glycophorin A and absence of ferritin granules. The possibility of an AML-M7 appeared very unlikely because blasts were positive only for CD42b, a marker that may also be expressed on monocytes and macrophages. Taken together, these results suggest that the proliferating cell was an immature cell potentially committed to the monocyte-macrophage lineage. Putative causes for a secondary histiocytic proliferation were exhaustively ruled out, as was the possibility of a histiocytic lymphoma. In fact, there was no clinical or laboratory evidence of infectious diseases or other neoplasms, no organomegaly, adenomegaly, cutaneous lesions or bone alterations. The diagnosis of a disease of Langerhans-dendritic cells was excluded based on the negativity for CD1a and the absence of Birbeck granules. The patient became dependent on blood transfusions for 4 months. By that time he had fever and petechiae, Hb 8.6 g/dL, PLT 16×10^9/L, WBC 7×10^9/L with 16% of circulating blasts and LDH 4,505 U/L. Chemotherapy was then proposed but the patient died before treatment due to a cerebral hemorrhage. Although at diagnosis the disease was reminiscent of a myelodysplastic syndrome with excess of blasts it rapidly evolved into an overt acute leukemia and the data support the hypothesis that this was one of the very uncommon cases of histiocytic leukemia previously referred to as AML-M5c. The significance of the associated hyper IgE remains an open question. As IgE synthesis is selectively promoted by interleukin 4, which is produced by T-cells and stimulates various macrophage functions,[10] we speculate that hyper IgE is related to the immune disturbance associated with the malignant histiocytic proliferation.

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