

Detection of GM-CSF in the sera of children with Langerhans' cell histiocytosis

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GM-CSF induces proliferation and activation of Langerhans' cells *in vitro*. The density of Langerhans' cells in human tumours is correlated to the *in situ* density of GM-CSF, and intradermal injection of GM-CSF induces local accumulation of Langerhans' cells. Therefore, we investigated the presence of GM-CSF in the sera of children with Langerhans' cell histiocytosis (LCH). We detected GM-CSF in the sera of all children with disseminated and active LCH, but not in the sera of patients with localized (i.e. bone) LCH. These results suggest that GM-CSF level is related to extent and the activity of LCH.

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Langerhans' cell histiocytosis (LCH) embraces several previous eponyms, including histiocytosis X, Letterer-Siwe disease, Hand-Schüller-Christian disease, eosinophilic granuloma and Hashimoto-Pritzker syndrome (1). When LCH is localized, it is of good prognosis. When it is disseminated, it may have a fatal outcome. The bone is involved in approximately 80% of cases (2). LCH is characterized by proliferation of Langerhans' cells. Its etiology is unknown. Granulocyte-macrophage colony-stimulating factor (GM-CSF) generates Langerhans' cells from hematopoietic progenitors when associated to TNF α (3). GM-CSF also activates Langerhans' cells *in vitro* (4). Intradermal administration of GM-CSF induces local accumulation of human Langerhans' cells (5). Therefore, we have investigated the presence of GM-CSF in the sera of children with LCH.

Results

Frozen sera of 15 children with LCH were analyzed. Clinical characteristics are shown in Table 1. All patients had a blood count, a complete skeletal radiography and a chest radiography at the time of diagnosis. Lung involvement of Patients 1 and 2 was confirmed by alveolar lavage. Bone marrow involvement of Patient 1 was confirmed by bone marrow

trephine biopsy. Patient 4 was anemic (hemoglobin = 7,7 g/l). Liver involvement of Patient 4 was confirmed by liver biopsy. Skin involvement of Patient 3 was confirmed by skin biopsy. The sera of the children were collected before treatment, except for four of them, and cryopreserved at -20°C . Concentrations in children' sera were assayed by use of a commercially available ELISA (Medgenix, Fleurus, Belgium). The sensitivity of this GM-CSF ELISA is 10 pg/ml.

We detected GM-CSF in the sera of 3 children (Table 1). These three patients had a disseminated LCH. Patients 1 and 2 were not treated at the time of serum collection. Patient 3 had detectable GM-CSF, and was in disease progression on treatment (vinblastine, corticosteroid). Patient 4 had disseminated LCH. At time of serum collection, he was on treatment (vinblastine, corticosteroid), and had no more sign of LCH involvement; he had no detectable GM-CSF. The 11 patients with only bone localization of LCH had no detectable levels of GM-CSF.

Discussion

We detected GM-CSF in the sera of 3 children with disseminated and active Langerhans' cell histiocytosis (LCH). The half-life of the recombinant human

Table 1. Initial clinical characteristics of children with Langerhans' cell histiocytosis, and their serum levels of GM-CSF. Sera were collected at the time of diagnosis except for patients 3, 4, 14 and 15. The values of GM-CSF ELISA are mean of two measures. For patients 1, 2 and 3, values are higher than the lower point of the standard curve (10 pg/ml), but lower than the linear part of this standard curve.

Patient	Age at diagnosis (years)	Initial localization of LCH	Serum level of GM-CSF (pg/ml)
1	2	Bone, lung, bone marrow	20
2	3 months	Bone, lung, skin	52
3*	3 months	Skin, small bowel	25
4**	3	Bone marrow, liver	<10
5	2	Bone	<10
6	16	Bone	<10
7	2	Bone	<10
8	2	Bone	<10
9	11	Bone	<10
10	7,5	Bone	<10
11	6 months	Bone	<10
12	2	Bone	<10
13	4,5	Bone	<10
14***	4,5	Bone	<10
15***	7	Bone	<10

* Patient in disease progression on treatment at the time of serum collection.

** Patient with low performance status, anemia, liver and spleen enlargement at time of diagnosis. This patient was in good condition and had normal blood count, and normal liver and spleen size at time of serum sampling, receiving vinblastine and corticosteroid.

*** The serum of these two patients was collected after treatment achievement (vinblastine, corticosteroid).

GM-CSF varies from 0.3 to 2 h, depending on the state of glycosylation (6). Therefore, GM-CSF is undetectable in normal human serum (7). We detected no GM-CSF in the control sera of two children with anaplastic large cell lymphoma, nor in the sera of two children with neuroblastoma. The 11 children with localized LCH, and the child with good response to the treatment, had no detectable GM-CSF levels in their sera. Therefore the detection of GM-CSF only in the sera of children with disseminated LCH could be related to the extent and the activity of the disease.

In human lung tumour, the density of Langerhans' cells is closely correlated to the *in situ* presence of GM-CSF (8). Intradermal administration of GM-CSF to leprosy patients induces local accumulation of Langerhans' cells (5). We have previously demonstrated the *in situ* presence of GM-CSF in all the LCH tissue samples that we tested (9). We propose that GM-CSF may be a growth factor of LCH. Supporting this hypothesis, transgenic mice for GM-CSF develop a diffuse tissue infiltration by mononu-

clear cells and eosinophils (10–11), which looks like the human LCH.

Our detection of GM-CSF in the sera of children with disseminated LCH confirms that this cytokine is associated to LCH, and suggests that it is related to the extent and the activity of the disease. Further investigations are needed to determine the part of GM-CSF in the pathogenesis of LCH, and the prognostic value of serum GM-CSF level.

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References

1. Writing Group of the Histiocyte Society. Histiocytosis syndromes in childhood. *Lancet* 1987; i: 208–9.
2. BEN-EZRA JM, KOO CH. Langerhans' cell histiocytosis and malignancies of the M-PIRE system. *Am J Clin Pathol* 1993; 99: 464–71.
3. CAUX C, DEZUTTER-DAMBUYANT C, SCHMITT D, BANCHE-REAU J. GM-CSF and TNF α cooperate in the generation of dendritic Langerhans' cells. *Nature* 1992; 360: 258–61.
4. WITMER-PACK MD, OLIVIER W, VALINSKY J, SCHULER G, STEINMAN RM. Granulocyte/macrophage colony-stimulating factor is essential for the viability and function of cultured murine epidermal Langerhans' cells. *J Exp Med* 1987; 166: 1484–98.
5. KAPLAN G, WALSH G, GUIDO LS, et al. Novel responses of human skin to intradermal recombinant granulocyte/macrophage colony-stimulating factor: Langerhans' cell recruitment, keratinocyte growth, and enhanced wound healing. *J Exp Med* 1992; 175: 1717–28.
6. LIESCHKE GJ, BURGESS AW. Granulocyte colony-stimulating factor and granulocyte/macrophage colony-stimulating factor (first of two parts). *N Engl J Med* 1992; 327: 28–35.
7. CEBON J, DEMPSEY P, FOX R, et al. Pharmacokinetics of human Granulocyte-Macrophage Colony-Stimulating Factor using a sensitive immunoassay. *Blood* 1988; 72: 1340–7.
8. TAZI A, BOUCHONNET F, GRANDSAIGNE M, BOUMSELL L, HANCE AJ, SOLER P. Evidence that granulocyte/macrophage colony-stimulating factor regulates the distribution and differentiation state of dendritic cells/Langerhans' cells in human lung and lung cancers. *J Clin Invest* 1993; 91: 566–76.
9. EMILE JF, PEUCHMAUR M, FRAITAG S, BODEMER C, BROUSSE N. Immunohistochemical detection of Granulocyte/Macrophage-Colony Stimulating Factor in Langerhans' cell histiocytosis. *Histopathology* 1993; 23: 327–32.
10. LANG RA, METCALF D, CUTHBERTSON RA, et al. Transgenic mice expressing a hematopoietic growth factor gene (GM-CSF) develop accumulation of macrophages, blindness, and a fatal syndrome of tissue damage. *Cell* 1987; 51: 675–86.
11. METCALF D, MOORE JG. Divergent disease patterns in granulocyte/macrophage colony-stimulating factor transgenic mice associated with different transgene insertion sites. *Proc Natl Acad Sci USA* 1988; 85: 7767–71.