

Langerhans' Cell Histiocytosis: Complete Remission after Oral Isotretinoin Therapy

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We report a 48-year-old male patient with Langerhans' cell histiocytosis, who showed a complete remission of his single-system skin disease after an 8-month therapy with oral isotretinoin (1.5 mg/kg/day) and remained free of recurrence and visceral involvement for 5 years. Key words: retinoids; S-100 protein.

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CASE REPORT

A 48-year-old male patient presented at our department with a 1-year history of pruritic and painless nodules and plaques on the face and the scalp. The lesions had started on the scalp as erythematous and scaly flat "plaques" which had been diagnosed as seborrhoeic dermatitis. Due to the rapid progression of his disease in September 1986, the patient was referred to the Department of Dermatology, University of Athens, where a skin biopsy specimen was interpreted as histiocytosis X. He had been orally treated with systemic steroids (25–100 mg/day prednisolone) over a period of 9 months without any response.

Physical examination of the cushingoid patient subsequent to his admission to our department revealed several large, mostly eroded erythematous nodules and plaques, partly covered by haemorrhagic crusts at the upper lip, right fronto-temporal, temporal and mandibular region and at various sites of the scalp (Figs. 1A and 2A). All results of routine laboratory investigations were within normal limits. Radiological investigations, endocrine tests, computer tomography, skeletal survey and bone marrow investigations showed no abnormalities.

Histological examination of formalin-fixed, paraffin-embedded biopsy specimens obtained from the lesional skin revealed a dense

diffuse cellular infiltrate throughout the entire dermis, predominantly consisting of ovoid histiocytic cells with abundant, clear or slightly eosinophilic cytoplasm and kidney-shaped or lobulated hyperchromatic nucleus (Fig. 3A). Immunohistochemical studies with the avidin-biotin-peroxidase method revealed that the histiocytic cells were positive for CD 68, HLA-DR and S-100 protein (Fig. 3B) but negative for Mac-387 (Dako Diagnostik GmbH, Hamburg).

Electron microscopic investigation of specimens fixed in 2.5% glutaraldehyde, postfixed in OsO₄ and embedded in Epon 812 revealed large numbers of histiocytic cells. In the cytoplasm of these cells Birbeck granules were regularly seen. Thus, the diagnosis of Langerhans' cell histiocytosis (LCH) was definitely confirmed. Considering the immunomodulatory effects of synthetic oral retinoids particularly on Langerhans' cells and their haemopoietic differentiating potential, we decided to start a therapeutic trial with oral isotretinoin (Roaccutan, Roche Hellas S.A., Athens, Greece), the side-effects of which are less severe than those of systemic chemotherapeutic agents. A written consent was obtained from the patient subsequent to a thorough explanation of the possible therapeutic efficacy and toxicity of this retinoid. Then the therapy was started with an oral isotretinoin dose of 1.5 mg/kg/day. About 6 weeks later the first signs of therapeutic response were evident. The inflammatory component of the lesions became less prominent and the size of the nodules and plaques was slightly decreased. The isotretinoin dose was then reduced to 1 mg/kg/day in an attempt to decrease the intensity of the troublesome mucocutaneous side-effects of this compound, which included severe cheilitis and facial dermatitis, intense pruritus, blepharconjunctivitis, dryness of nasal mucosa and frequent epistaxis, xerosis, retinoid dermatitis and palmoplantar desquamation. Apart from an increase in serum triglyceride levels the results of the laboratory investigations were within normal limits. The reduced dosage was administered over a period of 4 weeks, during which the side-effects became less intense and were better tolerated but no evidence of further regression of the skin lesions could be observed. The increase of the daily isotretinoin dose to the initial levels led to a gradual remission of the lesions, which completely disappeared after an 8-month therapy (Figs. 1B and 2B). During therapy, hypertriglyceridemia was the only laboratory abnormality detected. Presently our patient



Fig. 1. (A) Clinical aspect of nodules and plaques at the right temporal region before therapy (B). Complete remission after 8 months of oral isotretinoin treatment.

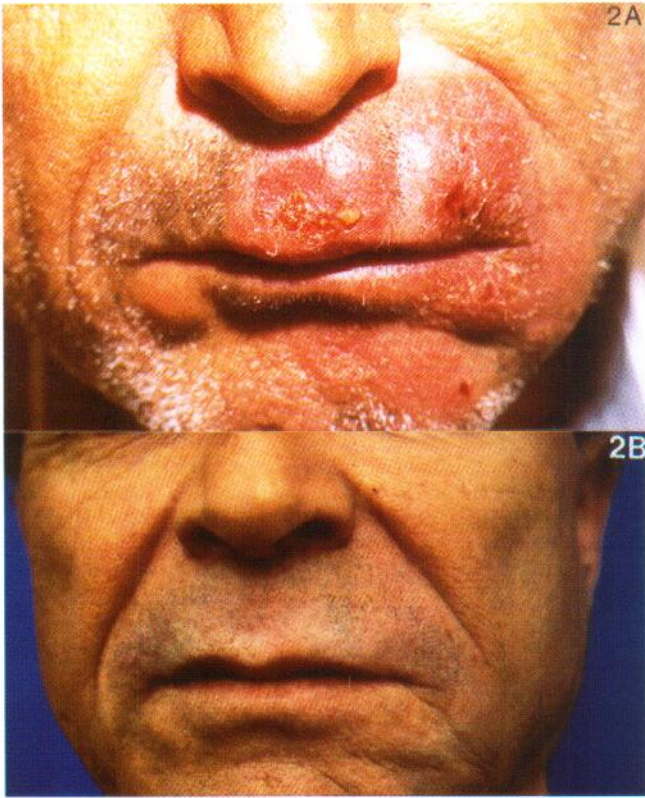


Fig. 2. (A) Clinical aspect of nodules and plaques at the upper lip before therapy. (B) Complete remission after 8 months of oral isotretinoin treatment.

completes a 5-year follow-up and still remains free of recurrence and of visceral involvement.

DISCUSSION

LCH is a heterogeneous group of proliferative disorders of histiocytic cells expressing the Langerhans' cell phenotype (1). LCH includes entities of uncertain etiopathogenesis that were previously known as eosinophilic granuloma, Letterer-Siwe disease and Hand-Schüller-Christian syndrome (2). LCH can

occur at any age but is mostly seen in children and is extremely rare in adults. Its clinical spectrum is variable depending on the number of the affected organ systems and on the extent of their involvement. Cutaneous manifestations are common in LCH occurring in 50% to 80% of the patients (3), and comprise scaly, yellow-brown papules (sometimes with purpura), papulovesicles, papulopustules, nodules and plaques, some of which may become eroded or ulcerated.

Our case fulfills the criteria of the writing group of the Histiocyte (2) Society for classification in the class I of the histiocytosis syndromes (Langerhans' cell histiocytosis). Indeed, definite diagnosis of LCH requires the finding of T-6 antigenic determinants on the surface of lesional cells or of Birbeck granules in their cytoplasm. The latter were demonstrated in the lesional cells of our patient. Our diagnostic considerations included progressive nodular histiocytosis and progressive nodular histiocytoma. In the first condition, however, in contrast to what happens in LCH, the histiocytic cells are negative for S-100 protein and possess no Birbeck granules (4). Also the second condition could be ruled out, since apart from the differences in clinical terms in our case no fibrohistiocytic infiltrate or giant cells were found in the skin biopsy (5). The specific interest in our case is based on the impressive therapeutic response of the cutaneous lesions of LCH to oral isotretinoin which, to the best of our knowledge, is reported for the first time, and on the stability of the complete remission during the 5-year follow-up.

Intralesional and systemic steroids, radiotherapy, topical nitrogen mustard, immunotherapy, PUVA and etoposide are some of the most important therapeutic modalities for the management of the single-system skin disease in LCH (6-8), whereas in multi-system involvement systemic administration of one or more chemotherapeutic agents is indicated (9).

Synthetic retinoids are known to inhibit the proliferation and to promote the differentiation of various cell types (10). Furthermore, they are capable of interacting with Langerhans' cells and other immunocompetent cells (11). On the other hand, the side-effects of these compounds are predictable and in most cases less severe than those of chemotherapeutic agents. Thus, considering the immunomodulatory effects and the haemopoietic dif-

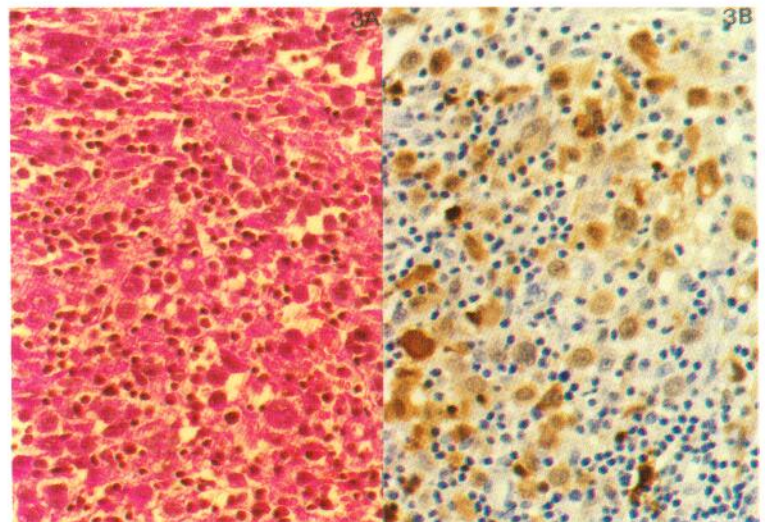


Fig. 3. (A) Large numbers of histiocytic cells in the dermal infiltrate admixed with eosinophils and a few plasma cells (haematoxylin-eosin stain; $\times 130$). (B) Immunohistochemical staining for S-100 protein. Large numbers of positive histiocytic cells ($\times 130$).

ferentiating potential of isotretinoin (12), we decided to apply it in the systemic treatment of our patient with adult LCH, a proliferative disorder of bonemarrow-derived histiocytic cells. The possibility that the complete regression of LCH observed in our patient may represent a spontaneous remission rather than a result of isotretinoin therapy cannot be definitely ruled out. Nevertheless, in view of the clear dose-dependent therapeutic response of this disorder to oral isotretinoin this possibility seems very unlikely. Further studies are now warranted in order to define the mechanisms underlying the therapeutic action of oral isotretinoin and to answer the question as to whether this retinoid may be regarded as an effective alternative therapeutic agent for the management of adult LCH.

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