Letter to the Editor: Secondary Acute Promyelocytic Leukemia After Treatment With Etoposide for Langerhans Cell Histiocytosis (LCH)

To the Editor: We here describe a 3-year-old-boy who was treated for LCH using vinblastine, etoposide and prednisone according to the International Langerhans Cell Histiocytosis Study I. The patient was admitted in March 1993 with multiple bone lesions, diabetes insipidus and biopsy confirmed LCH. He was treated with vinblastine and prednisone for 6 months. In October 1995 he relapsed with multiple bone lesions and severe pain. Treatment was resumed with weekly etoposide and prednisone for 3 months and then etoposide every 3 weeks for 3 more months. His treatment was irregular because of social-economic family problems. From March 1996 to October 1997 he was in remission without treatment when he was admitted to our unit with fever and sinusitis. Laboratory investigations showed a leukocyte count of 4.800 mm^3 with 63% of blasts. A bone marrow aspirate confirmed a French-American-British (FAB) M3 with CD33 89% positive, CD13 90% positive, MPO 70% positive, CD15 60% positive, CD19 no markers. Cytogenetic studies of the bone marrow showed 46XY with t(1,3)(p36;q21); del 17p, del 18p, iso16q. No clinical signs of active LCH were observed. Treatment was started with all-trans retinoic acid (ATRA) for 20 days and interrupted because of side effects (lung and splenic infarction). Treatment was continued with thioguanine, doxorubicin and cytarabine with hematologic remission. He is receiving maintenance according to BFM-83 protocol.

LCH in association with malignancy has been described and appears more frequently than previously recognized [1]. It can be concurrent, preceding or after treatment for LCH [2]. LCH has been described in association with a variety of solid tumors, including lung carcinoma and it has been suggested that it could be a reactive focal Langerhans cell proliferation [1,3]. Chemotherapy and radiation therapy used in the treatment of LCH may increase the risk of secondary leukemia or solid tumors [1,4,5]. Acute lymphoblastic leukemia (ALL) usually precedes the diagnosis of LCH while acute myeloid leukemia (AML) develops thereafter [2]. Epipodophyllotoxin therapy is considered to be a possible cause of secondary AML [4–6] so the Italian and Austrian-German cancer registries evaluated LCH patients who had been treated with etoposide. In contrast to previous descriptions of epipodophyllotoxin-related leukemia that are mostly FAB M4 or M5, these leukemias showed typical FAB M3 features. All these patients had received >4,000 mg/m^2 of etoposide. This study suggests that high doses of the drug appear to increase the risk of s-AML in LCH patients. All the leukemias described in the Italian LCH cohort were promyelocytic. This and the other evidence of a higher incidence of promyelocytic leukemia among Italians and Latinos suggest that high doses of etoposide* in subjects of Mediterranean or Latino origin may lead to alterations of chromosomes 15 and 17 [7]. We have previously described 3 patients with a malignancy associated with LCH in our institution; this one is the fourth [8] and appears to be another epipodophyllotoxin-related FAB M3-secondary leukemia. As a general principle, we therefore try to avoid etoposide in LCH patients, but this child had relapsed and there was no response to vinblastine and prednisone.

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*Our patients received only 1560 mg/m^2 of etoposide and that, irregularly.