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Case Report

Common Acute Lymphoblastic Leukemia Ph+ Following Langerhans Cell Histiocytosis in a Multi-Malformed Child with INV (9) (p12; q13) (mat): Case Report

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The occurrence of Langerhans cell histiocytosis (LCH) and another malignancy in the same patient is infrequent but has been recognized. The genetic changes that could be responsible for LCH and/or concomitant leukemia development are obscure. To the best of our knowledge, this is the first description of constitutional maternally derived inv (9) (p12; q13) in an LCH patient, and also of the development of common ALL Ph+ after LCH diagnosis and therapy. The potential significance of these findings [inv (9) + LCH + ALL Ph+] and their mutual relationship are unknown. Therefore, cooperative studies of large numbers of patients are needed to identify the common risk factors, if any.

Key words: acute lymphoblastic leukemia, genetic changes, langerhans cell histiocytosis

Langerhans cell histiocytosis (LCH) is both the result of clonal proliferation of Langerhans cells (LC) and the immunologic consequence of increased cellular activation. It may be associated with acute lymphoblastic leukemia, malignant lymphoma or other malignant solid tumors. Malignancy can occur before, after, or concurrently with the diagnosis of LCH. The LCH-Malignancy Study Group initiated the registry of patients in whom this association occurred synchronously or asynchronously. Haupt and coworkers reported that by May 2002, 92 patients were registered, and of 71 pediatric LCH patients, 27 suffered from solid tumors, 21 from AnLL, 17 from ALL and 6 from lymphoma. In 20 patients, malignancy occurred between 7 months and 10 years after LCH.

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Case Report

The genetic changes that could be responsible for LCH and/or concomitant leukemia development are obscure. Here, we describe a 4-year-old boy who developed acute lymphoblastic leukemia (ALL) with Ph+ cells in the bone marrow 2 months after systemic LCH went into remission due to treatment with etoposide (VP-16). The boy was seen at our clinic at the age of 9 months because he suffered from intermittent fever. Clinical check-up showed leukocytosis with 78×10^9/L WBC, liver and spleen enlargement, migrating joint pain and swelling, enlargement of lymph nodes and migrating skin rash. Bone marrow smears demonstrated LC histiocytic infiltration.

Electron microscope analysis confirmed the presence of Birbeck granules. The boy was karyotyped because of his unusual phenotype, predominantly of the face, and his anamnesis of 2 operations, one at the age of 2 years for bilateral inguinal hernia and the other at the age of 3 years for Ductus Bottali persistens. He presented phenotypically with microcephaly, hypertelorism, bilateral epicanthal folds, low set ears, low bridged nose, upward slanted palpebral fissures, high palate, low set umbilicus, 4 finger line on both hands, dysplastic toes, and bilateral cryptorchidism. His karyotype was: 46, XY, inv (9) (p12; q13) (mat). His mother was a carrier of 46, XX, inv (9) (p12; q13).

The boy was treated with etoposide (VP-16) at 200 mg/m^2 for 3 consecutive days (one cycle) for 15 cycles with intervals of 3 weeks between cycles, followed by maintenance therapy with interferon, after which he achieved complete remission. However, ALL occurred 2 months after LCH remission (2 years and 2 months after the first etoposide treatment), and it was treated as high-risk leukemia with the standard BFM protocol. The malignant disease was confirmed by immunophenotyping and by cytological analysis of bone marrow. The karyotype displayed the Philadelphia translocation 9; 22 (q34; q11.2) on one chromosome 9 and inv (9) (p12; q13) (mat) on the other. The latter is a constitutional variation inherited from the subject's mother (Fig. 1).

However, it turned out that ALL was resistant to the BFM treatment, and the boy died in the first early relapse. In the mother's next pregnancy, prenatal diagnosis was performed, and a healthy boy without per inv (9) was born. Both parents gave their consent to release patient/maternal medical information.

Discussion

The reasons that the malignancy occurs in patients with LCH are still unknown. Two main possibilities exist. Either the therapy for LCH on one side or a genetic predisposition or a susceptibility to the facilitated development of pathogenic molecular abnormalities on the other side promotes tumor development. Regarding the first possibility, it should be noted that the therapy for LCH patients is still controversial. Therefore, the question arises as to whether etoposide may induce the development of malignancy. So far, only a few studies have suggested that LCH

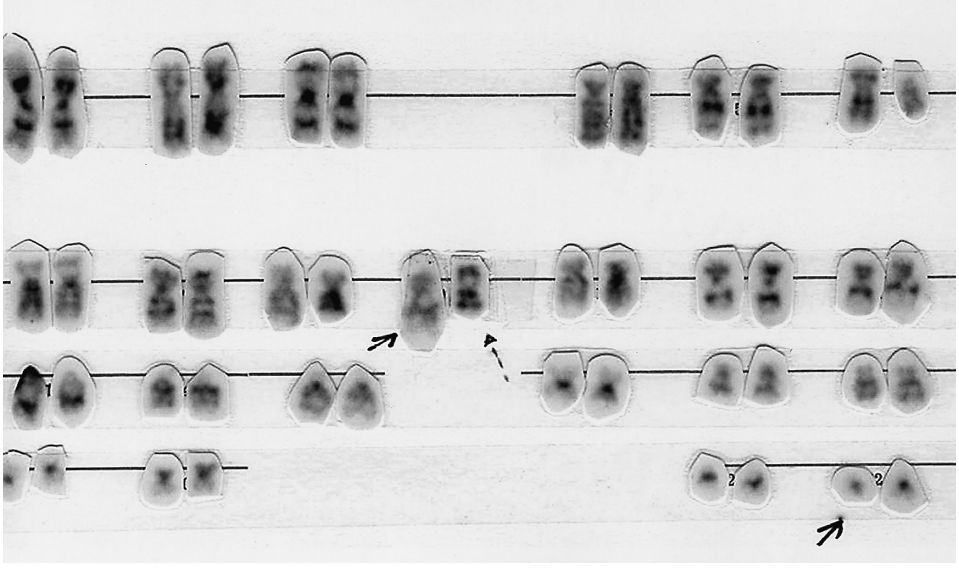

Fig. 1 Karyotype 46, XY, inv (9) (11p; 13q), t (9; 22) (q34; q11) Ph+ of a boy in which acute lymphoblastic leukemia developed 2 months after systemic Langerhans cell histiocytosis (LCH) reached remission. The karyotype displays Philadelphia translocation 9; 22 (q43; q11.2) on one chromosome 9 (left chromosome of the 9th pair — short arrow), and inv (9) (p12; q13) (mat) (right chromosome of the 9th pair — dashed arrow) on the other. The latter is a constitutional variation inherited from the mother.
Chromosome pairs 1, 2, 3, 4, 5 and XY (first row); 6, 7, 8, 9, 10, 11, 12 (second row); 13, 14, 15, 16, 17, 18 (third row); and 19, 20, 21, 22 (fourth row). The small arrow on chromosome pair 22 indicates a deletion in 22q11 [t (9; 22) (q34; q11) Ph+].

therapy can induce tumor development, and most of them involved only a small number of patients [1–4]. Although it seems to us that the first possible reason for malignancy development, *i.e.* the therapy for LCH on one side, may explain the ALL development in our patient, some other observations should also be kept in mind. In all papers describing tumor development after LCH treatment, a much longer period (*i.e.*, longer than in our case) was needed for the tumor development to occur [1]. In addition, there have been only sporadic observations that ALL develops secondary to LCH [5]; it is usually observed to precede LCH [6, 7]. The most common secondary malignancy described in the literature is myeloid leukemia, whose development is usually ascribed to medical treatment for LCH [2–4].

The second possibility (genetic predisposition or the susceptibility to facilitated development of pathogenic molecular abnormalities) might also be operative in our case. The inherited pericentric inversion of the heterochromatic region of chromosome 9 inv (9) (p12; q13) has been regarded as a normal constitutional karyotype variant with no clinically significant consequences. However, some reports have shown an association between inherited inv (9) and a predisposition to develop solid tumors, acute lymphoblastic leukemia and myeloblastic leukemias [8–11]. Moreover, even acquired inv (9), although rare, could also be associated with the development of acute myeloid leukemia and essential thrombocythemia [12, 13]. Therefore, it is possible that inv (9) individuals have either latent impaired hematopoiesis or that the inherited derangement of chromosome 9 [inv (9)] contributes to the genetic change in the second allele 9 [(9; 22)] translocation.

In sum, we have identified, for the first time, an inherited inv (9) (p12; q13) in an LCH patient as well as the development of acute lymphoblastic leukemia after LCH diagnosis and therapy. The potential significance of these findings [inv (9)/LCH/ALL] and their mutual relationship is unknown to us. Therefore, this is a call to all clinicians who manage LCH patients to also perform cytogenetic studies so that the incidence of inherited inv (9) can be accurately estimated and eventually related more precisely to the development of LCH with accompanying leukemia.

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