

CLINICAL REPORT

Mycosis Fungoides in Childhood: Description and Study of Two Siblings

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Primary cutaneous T-cell lymphomas are exceedingly rare in children and adolescents. However, mycosis fungoides (MF) is the most frequent primary cutaneous lymphoma diagnosed in childhood. Two cases of MF in siblings (a 14-year-old boy and his 10-year-old sister) are reported. On the basis of clinical features (histopathological and immunophenotypical findings) a diagnosis of MF patch lesions was made in both siblings. Since recent data in the literature have underlined a high frequency of the HLA-DQB1*03 allele in patients with familial MF (including child patients), the HLA profile of the patients was analysed, indicating the presence of a haplotype (HLA-DQB1*03,*03 in the girl, HLA-DQB1*02,*03 in the boy) corresponding with that described in recent literature. Two rare and exceptional cases of MF in siblings are reported, highlighting the presence of a peculiar haplotype. Key words: sibling; mycosis fungoides; HLA; UV-B-NB.

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Although the occurrence of primary cutaneous T-cell lymphoma in children is rare (0.5–5%), mycosis fungoides (MF) is the most frequent lymphoma diagnosed in childhood (1).

The presentation, course and prognosis of MF in children have not yet been completely elucidated. In most cases, the clinical presentation of this disease in children is similar to that in adults. MF in children is clinically characterized by lesional monomorphism (erythematous patches) and hypopigmentation (20% of cases), the latest variant is more frequently found in dark-skinned children (2, 3).

In an extensive literature review, Quaglino et al. (4) found that the most frequent clinical manifestation of MF in childhood is the patch lesion, usually multiple; a minority of patients presented plaque lesions. Only 4 out of 49 cases had nodular-presenting disease.

If MF in childhood is rare, MF in relatives is exceptional. Familial MF, in fact, has been found in only eight families (5–10), including two pairs of monozygotic twins (11, 12).

We report here two cases of MF in childhood in siblings, discussing clinical characteristics, histopathological and immunophenotypical findings and evaluating the HLA profile of the two patients.

CASE REPORTS

Case 1

A 10-year-old girl presented with a 2-year-history of multiple erythematous, yellowish and mildly pruritic patches, with fine desquamation and irregular margins, localized on the right flank and abdomen (Fig. 1A). The larger patch measured approximately 12×7 cm. The lesions have been treated previously with topical steroids, with little response and with complete relapse after withdrawal of therapy. A new, mildly erythematous lesion on the left flank appeared recently.

Routine laboratory tests, including blood smear, leukocyte count, biochemistry, T-helper/T-suppressor ratio, serology for human T-lymphotropic virus type (HTLV1) proved negative or in the normal range. Atopy investigations proved negative. There was no family history of allergy, psoriasis and cutaneous or systemic lymphomas.

After obtaining the informed consensus of the parents, a 4-mm punch biopsy on a patch of the patient's right flank was performed under local anaesthesia. The histopathological findings were characterized by a lichenoid and psoriasiform pattern, with a band-like infiltrate composed of lymphocytes, which partially obscured the dermo-epidermal junction (Fig. 1B). Epidermotropism of single lymphocyte, without Pautrier abscesses, was observed. Few lymphocytes had hyperchromatic nuclei. All the lymphocytes had a T-phenotype and were positive for CD2+/-, CD3+, CD5+, CD7+, CD8+, TIA- and CD56-. Other cytotoxic markers were negative. Rare CD30+ cells and B lymphocytes (CD20+ and CD79a+) and scattered CD68+ histiocytes were found. Clonal TCR- γ rearrangements were absent.

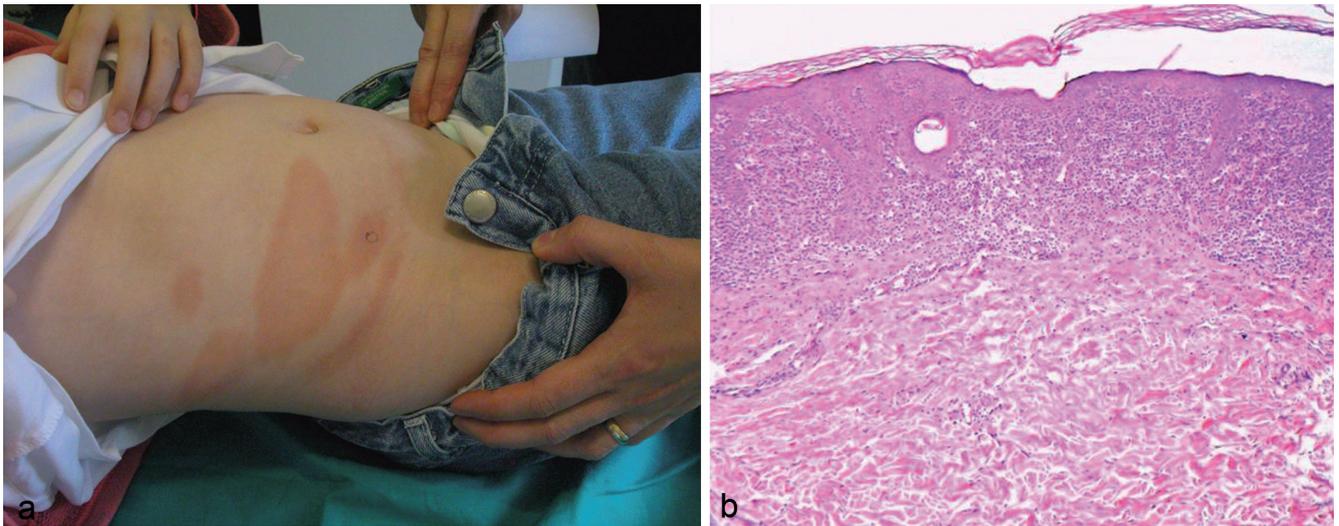


Fig. 1. (A) Erythematous, mildly scaling, multiple patches on the right flank of a 10-year-old girl. (B) The histopathological findings from a patch were characterized by an epidermotropic band-like infiltrate made of small lymphocytes, which showed CD8+ T cells by immunohistochemical staining.

On the basis of the cytotoxic phenotype, a differential diagnosis between epidermotropic T-cell lymphoma CD8+ and juvenile MF with CD8+ phenotype was considered. The patient was treated with ultraviolet (UV)-B-narrowband (NB) as monotherapy using a Waldman Lichttechnik unit as the light source for UV-B-NB, containing a bank of eight fluorescent tubes (Philips TL-01) with an emission spectrum of 310–315 nm, and a maximum wavelength of 311 nm. UVB-NB phototherapy was given 4 times a week for one month, and then 3 times a week for 3 months, with complete remission after 5 months of therapy. The starting dose was 180 mJ/cm²; the dose has been increased by 50 mJ/cm² each treatment. When she complained of erythema or pruritus, the irradiation dose had been held constant until resolution of the symptoms. The total number of treatments was 49, with a total of 42.77 J/cm². After

4 months, new erythematous patches in the same area appeared. A new UVB-NB treatment was given, with, again, a starting dose of 180 mJ/cm², 2 times a week. A complete remission was obtained after 3 months. The presentation and clinical course of the disease favoured a diagnosis of CD8-positive MF. HLA class II genomic typing (HLA Laboratory; Immunohematology and Transfusion Center, IRCCS Policlinico S. Matteo, Pavia, Italy), was performed with PCR-SSP technique on DNA extracted from peripheral lymphocytes. Typing was: HLA-DRB1*0103, *11; DQB1*03, *03.

Case 2

While his sister was under UVB-NB treatment, a 14-year-old boy, presented with a unique, large, slightly erythematous and mildly pruriginous patch localized

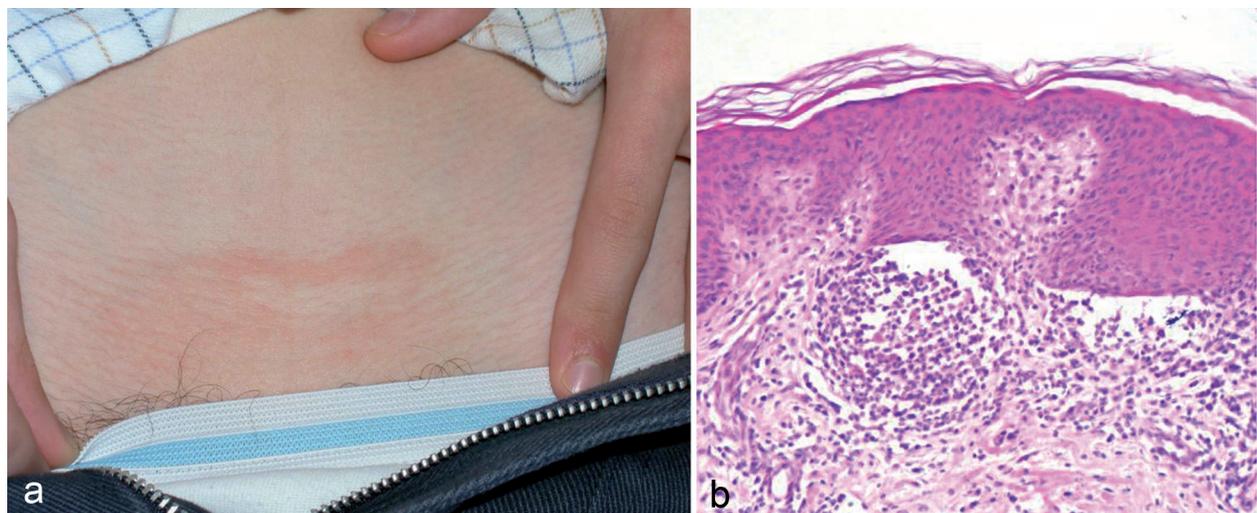


Fig. 2. (A) The 14-year-old brother presented two patches on the trunk: one localized on the pubic area. (B) Histopathological findings from the pubic patch were characterized by a less dense infiltrate, but with conspicuous epidermotropism, especially on the tip of rete ridges.

on the pubic area (Fig. 2A). The lesion lasted for 7 months. Afterwards he developed an erythematous patch on the upper thorax, particularly on the left areola. Suspecting MF, a cutaneous biopsy under local anaesthesia was made after obtaining the informed consent of the parents. Atopy investigations proved negative. The histopathological findings were characterized by a dense lymphocytic infiltrate in the upper dermis, with "patchy"/band-like distribution, and focal epidermotropism localized on inter-papillary crests (lymphocytes in micro-aggregates, absence of true Pautrier micro-abscesses) (Fig. 2B). The infiltrate was composed of small lymphocytes, with slightly irregular nuclei. The lymphocytes presented a CD2+, CD3+, CD5+, CD7+, CD8+, TIA-, CD56-phenotype. Few B CD20+ lymphocytes were also observed. Molecular biology investigations could not demonstrate monoclonal rearrangements for TCR- γ . The histopathological and immunophenotypical findings favoured a diagnosis of CD8-positive MF. The patient has been treated with UVB-NB as monotherapy, using the same Waldman Lichttechnik unit as his sister, 3 times a week for 2 months, until remission. The starting dose was 200 mJ/cm²; the dose has been increased by 50 mJ/cm² each treatment. When he complained of erythema or pruritus, the irradiation dose was held constant until resolution of the symptoms. The total number of treatments was 22, with a total of 26.13 J/cm². HLA class II typing was performed with PCR-SSP molecular technique. The genotype was HLA-DRB1*03, *11; DQB1*02, *03.

DISCUSSION

Few studies have reviewed MF in young patients, and none has been large enough to assess prognosis and outcome (13, 14). In their epidemiological study on long-term outcome of 525 patients with MF and Sèzary syndrome, Kim et al. (15) demonstrated that age of onset is an important demographic favourable predictive factor. The predictive value of age at presentation, however, is greater in the early stages (stage I–III) and becomes less valuable in patients with extracutaneous disease (stage IV) (15). An early diagnosis in young patients could be difficult: MF may clinically and histologically simulate benign inflammatory disorders, in particular atopic dermatitis or vitiligo (16). However, clinical features characterized by fixed erythematous patches without any sign or symptoms of atopic diseases (history of flexural involvement and dry skin, personal/familial history of atopic dermatitis/asthma/conjunctivitis/rhinitis, history of a pruritic skin condition, visible flexural dermatitis with intense pruritus, positive allergic tests) and chronic course address to a correct diagnosis, that should be confirmed by the histopathological and immunophenotypical findings. In MF, a CD8+ phenotype only rarely occurs and it is

especially described in hypopigmented MF, predominantly in children and adolescents (17). It is debated whether the CD8+ infiltrate represents an inflammatory component or is true CD8+ MF (18). In their article, El-Shabrawi-Caelen et al. (18) described the clinical and pathological aspects of 15 patients with hypopigmented patches as the initial manifestation of MF, characterized by the presence of CD8+ epidermotropic lymphocytes, unlike the mature CD4+ T-helper cell phenotype usually encountered in MF. This study could demonstrate that the malignant population derives from CD8+ lymphocytes through isolating intra-epidermal CD8+ T cells via microdissection and analysing the TCR- γ chain gene.

In our case, the presence of CD8+, but not of TIA+, lymphocytes and the clinical course of the disease suggest that it could represent a CD8+ variant of MF, such as the one described by Whittam et al. (19). These authors studied the immunohistochemical and genotypic profiles of six patients and concluded that this kind of cytotoxic T-cell MF can pursue an indolent course and that cases of CD8-positive MF may be over-represented in childhood. On the basis of their experience and review of the literature, Ben-Amitai and co-workers (20) also suggested that CD8+ phenotype is over-represented in juvenile disease (21).

The genetic background of MF seems to be heterogeneous and is largely unknown. There is evidence that chromosomal aberrations may appear during the disease progression but, also in early-stage disease, tumour subclones of MF can be detected, suggesting a multi-lineage progression (22–24).

Although the polymorphism of HLA class II is judged important in the development of other lymphoproliferative diseases, like the lymphoma of Hodgkin, few HLA studies in patients affected by MF have been carried out. The results of studies on HLA class I associations have proved inconsistent, while two studies showed that certain HLA class II alleles were significantly increased among North American Caucasian patients with MF: HLA-DRB1*11 and DQB1*03 (25).

In this study, we describe a family in which MF, patch stage, occurred in two young siblings who shared the HLA-DRB1*11, DQB1*03 haplotype. A similar finding, i.e. familial MF with early onset, has also been described by Hodak et al. (26). These authors report six families comprising 12 Jewish patients (9 male and 3 female) affected by MF, in particular 5 families with two affected siblings and one family with a parent–child pair. The allele frequency of HLA DQB1*03 was found to be significantly greater among the patients than in the control group, indicating an association of this allele with familial MF. In all but one family, the age of onset, clinical features and response to therapy were similar to those in sporadic MF. Also in the study made by Jackow et al. (27) an association between DQB1*03

allele and patients with familial MF has been observed. HLA-DQB1*03 seems to represent a marker of higher susceptibility to the onset of the MF in the familial type.

The presence of HLA-DQB1*03 should be investigated in a larger group of patients belonging to different ethnic populations, especially in children or familial MF, to strengthen the hypothesis of the involvement of this allele in susceptibility to familial MF.

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