Case Report
Olgu Sunumu

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Juvenile unilesional folliculotropic mycosis fungoides: Two siblings with HLA-DRB1*04 and HLA-DQB1*03 alleles

*Juvenil unilezyonel folikülotropik mikozis fungoides: HLA-DRB1*04 ve HLA-DQB1*03 allelleri ile iki kardeş*

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Abstract

The pathogenesis of mycosis fungoides (MF) is poorly understood, and an immunogenetic mechanism has been suggested to play a role. Human leukocyte antigen (HLA) class II alleles DRB1*11 and DQB1*03 were found to be significantly increased for patients with sporadic and/or familial MF. The juvenile-onset familial MF is extremely rare. Herein, we report two siblings diagnosed with folliculotropic MF, both exhibiting similar morphology of a unilesional presentation on the flexural region of the arms. Both were positive for HLA-DRB1*04 and HLA-DQB1*03 alleles. The HLA-DQB1*03 allele has been described in familial MF in the literature recently, whereas "HLA-DRB1*04" allele has not been reported previously in familial MF cases.
Keywords: Mycosis fungoides, juvenile, familial, unilesional, folliculotropic, HLA alleles

Öz

Mikozis fungoides (MF) patogenezi tam olarak anlaşılamamıştır, immünogenetik mekanizmaların rol oynayabileceği öne sürülmüştür. İnsan lökosit antijeni (HLA) sınıf II allelleri DRB1*11 ve DQB1*03 sporadik ve/veya ailesel MF'si olan hastalarda önemli oranda yüksek bulunmuştur. Juvenil başlangıçlı ailesel MF ise oldukça nadirdir. Burada, her ikisinde de kolların fleksural bölgesinde tek taraflı benzer morfoloji sergileyen ve folikülotropik MF tanısı alan iki kardeşi sunmaktayız. Her iki kardeşde HLA-DRB1*04 ve HLA-DQB1*03 allelleri pozitif bulundu. HLA-DQB1*03 alleli literatürde yakın zamanda ailesel MF'de tanımlanmış olup, "HLA-DRB1*04" alleli daha önce ailesel MF olgularında bildirilmemiştir.
Anahtar Kelimeler: Mikozis fungoides, juvenil, ailesel, unilezyonel, folikülotropik, HLA alelleri

Introduction

Although mycosis fungoides (MF) is the most frequent primary cutaneous T-cell lymphoma diagnosed before the age of 18 years and over, the ratio of pediatric MF ranges up to 5% of all MF cases[1]. The clinicopathological manifestation of pediatric MF can be similar to that of adults. However, the morphology may sometimes be distinct, which presents as hypopigmented, poikilodermatous, and purpuric lesions and folliculotropism. Immunohistochemically, atypical lymphocytes are predominantly CD4 negative and CD8 positive, especially in the hypopigmented variant[2].

The clinical and phenotypic presentations of familial MF are similar to that of sporadic MF. Genetic factors were thought to influence the pathogenesis because specific human leukocyte antigen (HLA) class II alleles were detected in sporadic and familial MF cases[3,4]. Herein, we report two siblings with unilesional folliculotropic MF who had similar HLA alleles (HLA-DRB1*04 and HLADQB1*03).

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Case Reports

Case 1

A 12-year-old boy was diagnosed with MF 6 years ago at our department. He had a solitary lesion that had appeared 2 months before admission. He had been treated at another center with topical corticosteroid creams and demonstrated partial response. Physical examination revealed a sharply demarcated, hypopigmented, slightly scaly plaque with follicular keratotic plugs on his inner left arm (Figure 1a). His past medical history was unremarkable, and his parents were consanguineous. His mother's cousin had been diagnosed with Hodgkin lymphoma at age 8, and the child of his father's cousin was diagnosed with leukemia at age 4. Skin biopsy showed CD8-positive MF characterized by folliculotropism and syringotropism (Figure 2). Multiplex polymerase chain reaction (PCR)-based immunoglobulin (Ig)/T-cell receptor (TCR) clonality showed T-cell clonality. Results of lymph node ultrasonography, blood flow cytometry, and peripheral blood smear were normal. Bexarotene gel treatment was initiated following the inadequate response to topical steroids. The therapy was well tolerated with minimal local irritation, and within 3 months, a complete response was achieved. During follow-up, narrow-band ultraviolet B was added for 6 months because of frequent unilesional recurrences on the previous lesion and the patient was refractory to topical treatments (i.e., bexarotene gel and clobetasol propionate). The patient has been followed up without further recurrence for the last 3 years.

Case 2

The sibling of the first case, aged 2.5 years, was admitted to our outpatient clinic for an erythematous rash on her arm. The parents noticed the lesion 2 weeks previously (Figure 1b). Physical examination revealed an erythematous scaly macular lesion that was 2.5 cm in diameter, with follicular keratotic plugs on her right inner arm. A skin biopsy was performed because of similarities with her brother's presentation, as described above (case 1). Histopathological and immunohistochemical examinations of a punch biopsy showed CD4-positive MF characterized by folliculotropism (Figure 3). Multiplex PCR-based Ig/TCR clonality showed T-cell clonality. Results of lymph node ultrasonography, peripheral blood smear, and flow cytometry examination were normal. Complete remission was achieved after 6 months with the intermittent application of mometasone furoate cream 0.1% twice daily. The patient is currently in remission without any further treatment for 17 months.

For further evaluation of the possible role of genetic factors in the pathogenesis of our familial MF cases, we analyzed the HLA system, specifically HLA subtype class II alleles with the PCR-sequence-specific oligonucleotide low-resolution method in all family members. The genotype was HLA-DRB1*04, *11; DQB1*03 for case 1 and HLA-DRB1*04, *08; DQB1*03, *04 for case 2. HLA-DRB1*04 and HLA-DQB1*03 alleles were detected in two siblings (Supplementary Table 1).

Since it is a retrospective study, patient consent is not obliged. So it was not obtained.

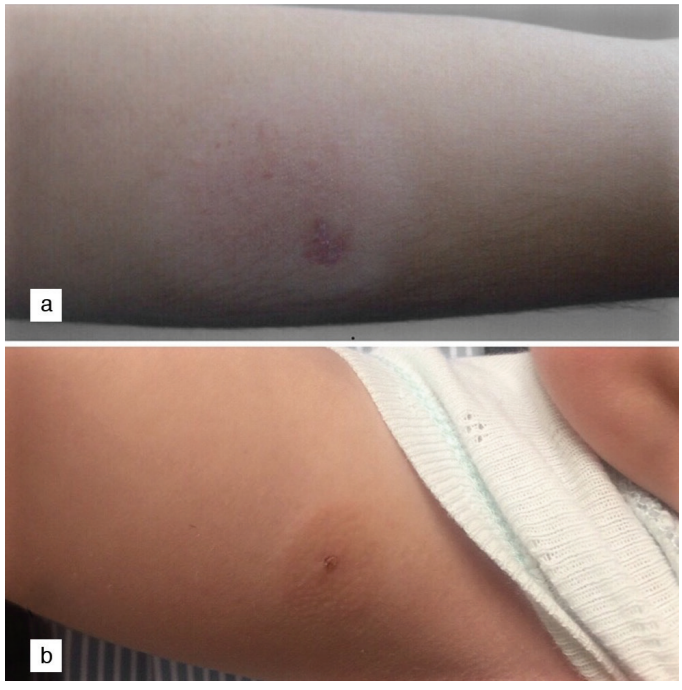

Figure 1. (a) A sharply demarcated, hypopigmented, slightly scaly plaque on the inner left arm of case 1 (boy). **(b)** An erythematous scaly macular lesion, 2.5 cm in diameter with follicular keratotic plugs on the inner right arm of case 2 (girl)

Discussion

MF is rare during childhood. The incidence of MF in children ranged from 10% and 39% of all cutaneous lymphomas, and the mean age at diagnosis is 10[5]. Similar to adults, children may have an indolent clinical course with slow progression over time. Yazganoglu et al.[6] reported 20 Turkish children with MF that did not progress to the advanced stage. Pediatric MF generally manifests with an overrepresentation of atypical variants, specifically hypopigmented, folliculotropic, and poikilodermatous lesions[7]. One case series of 34 children with MF reported poikiloderma in 26% of children, a higher percentage than reported in adult patients[8]. In contrast to adult folliculotropic MF, comedo-like follicular plugs, fistula, abscess, and pruritus are not observed in pediatric folliculotropic MF, which generally presents with follicular papular lesions on the upper extremities[9]. Unilesional MF is a rare but well-documented presentation of MF with an excellent prognosis. The majority of the reported cases are adults; however, few pediatric cases are reported in the literature. The reported cases of unilesional MF presented with either classical or eczematoid, psoriasiform, hypopigmented, or poikilodermatous features[10]. In our cases, the solitary plaques were located on the upper extremities, and histopathologically, folliculotropism was demonstrated. Histopathological findings of juvenile MF are similar to those of adults; however, cytotoxic immunophenotype with CD8 positivity has been described in up to 39% of cases of juvenile MF compared with less than 5% for adult MF[2]. A study reported that juvenile-onset CD8-positive MF appears to have a similar course to CD-4 positive cases[8]. In the present report, the elder sibling was diagnosed with CD8-positive folliculotropic MF without loss of CD5 expressions.

The etiopathogenesis of MF is remains unknown; however, persistent antigenic cell stimulations due to infectious agents, chemicals, and environmental factors have been suggested as possible pathogenic

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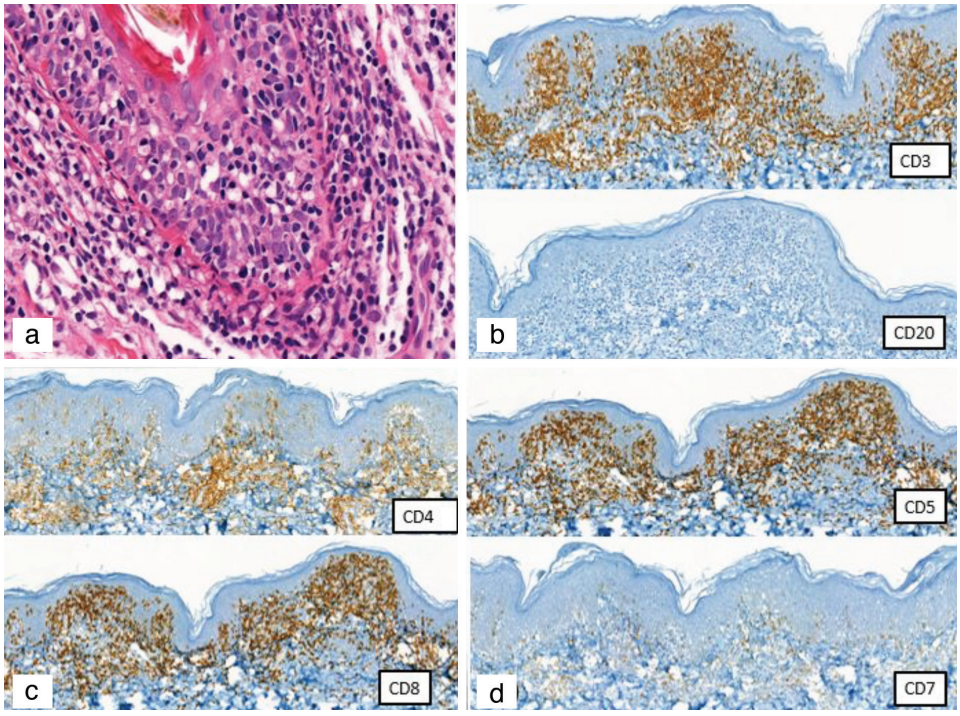

Figure 2. Dermatopathology images. **(a)** Medium-sized atypical lymphoid cells with irregular nuclei characterized by epidermotropism in the epidermis (hematoxylin-eosin staining, original magnification x21. **(b)** CD3 (+), CD20 (-) atypical T-lymphoid cells with epidermotropism (original magnification CD3 x 9.2, CD20 x 11.2). **(c)** T-lymphoid cells characterized by epidermotropism have CD8 (+), CD4 (-) phenotype (original magnification CD4 x 10, CD8 x 8). (**d)** Expression of CD5 and lack of expression with CD7 on T-lymphocytes (original magnification CD5 x 10.5, CD7 x 0.6)

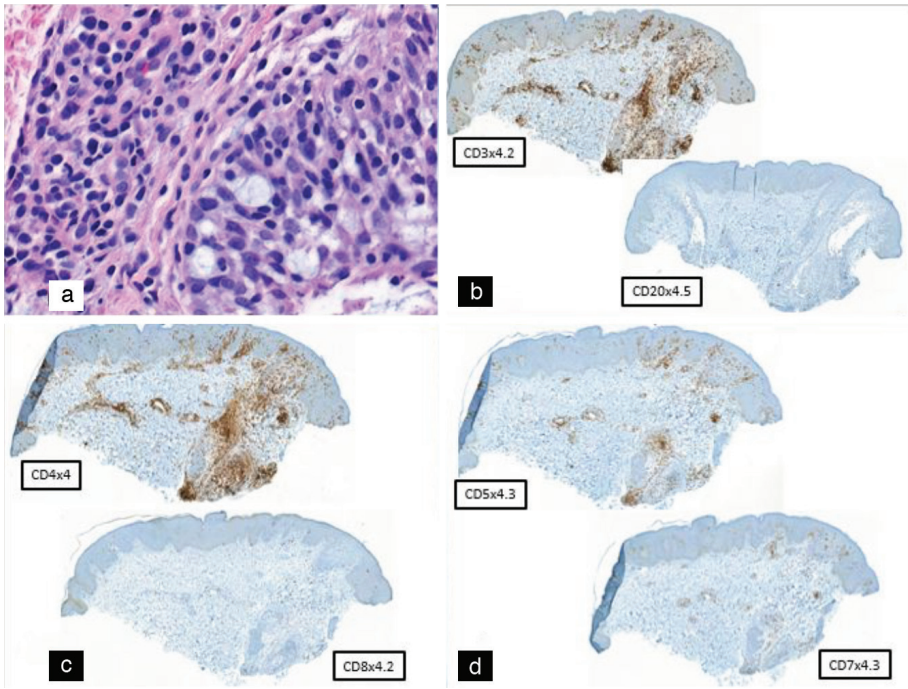

Figure 3. Dermatopathology images. **(a)** Perifollicular lymphoid infiltration; a few of them show foliculotropism. Atypical lymphocytes with cerebriform hyperchromatic irregular nuclei are also observed. Mucinous degeneration of the follicular epithelium is also noted (hematoxylin-eosin staining, original magnification x 7.1). **(b)** CD3 (+), CD20 (-) T-lymphoid cells in the epithelium of hair follicles, around the hair follicles, and in the epidermis (original magnifications, CD3 x 4.2, CD20 x 4.5). **(c)** Lymphoid cells showing epidermotropism and folliculotropism are CD4 (+), CD8 (-) (original magnifications, CD4 x 4, CD8 x 4.2). **(d)** Expression of CD5 and lack of expression with CD7 on T-lymphocytes (original magnifications, CD5 x 4.3, CD7 x 4.3)

factors. The importance of the HLA locus in the pathogenesis of lymphoproliferative malignancies, mainly non-Hodgkin lymphoma, Hodgkin lymphoma, and chronic lymphocytic leukemia, is well established. The familial occurrence of MF among first-degree relatives is rare, and only 15 such families have been reported[11]. Baykal et al.[12] reported Turkish familial MF cases, in which a 37-year-old woman and her son presented with early-stage MF. Familial clustering of MF, together with the detection of certain HLA class II alleles in both sporadic and familial cases, suggests the possible role of genetic factors in MF.

The HLA-DQB1*03 allele is associated with familial MF, whereas the HLA-DRB1*11 allele tends to be associated with sporadic MF[3,4,11]. Despite the few studies showing an association between sporadic MF and various HLA class I antigens/alleles in some populations, the majority failed to confirm any HLA class I associations. To further evaluate the role of genetic factors in the pathogenesis of our familial MF cases, we examined the HLA system in the present cases and found that HLA-DRB1*04 and HLA-DQB1*03 alleles were positive in both siblings. As for HLA-DR, in association with the previous reports, in which HLA-DRB1*11 was found to be significantly increased in patients with sporadic MF, the HLA-DRB1*11 allele was detected in case 1. Our data support the association between HLA-DQB1*03 allele and familial MF. HLA-DRB1*04 allele was significantly higher in Turkish children with acute lymphoblastic leukemia than in controls[13]. Hodak et al.[4] reported that a family history of malignancy among first-degree relatives was positive for one family, in which a 38-year-old male sibling died of acute myelomonocytic leukemia. The relationship between the HLA-DRB1*04 allele and MF has not been reported previously. However, in both cases, the presence of this allele and their family history of leukemia might reflect a genetic predisposition to leukemia and lymphoproliferative disorders.

We described cases of two siblings who presented with solitary lesions that were located on similar sites of opposite arms, suggesting a genetic role with the possibility of genetic background. A family history of chronic lymphoproliferative neoplasms in two relatives of our cases supports a genetic role in such high-risk families. The determination of HLA-DQB1*03 and HLA-DRB1*04 alleles in these siblings supports the assertion that HLA alleles can influence the pathogenesis of familial MF as previously reported.

Ethics

Informed Consent: Since it is a retrospective study, patient consent is not obliged. So it was not obtained.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: H.Ş., İ.K.Y., B.N.A., C.A., A.O.H., Concept: H.Ş., İ.K.Y., B.N.A., C.A., A.O.H., Design: H.Ş., B.N.A., A.O.H., Data Collection or Processing: H.Ş., İ.K.Y., C.A., Analysis or Interpretation: H.Ş., İ.K.Y., C.A., Literature Search: İ.K.Y., C.A., Writing: H.Ş., İ.K.Y., C.A.

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References

1. Reiter O, Ben Amitai D, Amitay-Laish I, Israeli M, Pavlovsky L, Hodak E: Pediatric mycosis fungoides: a study of the human leukocyte antigen system among Israeli Jewish patients. Arch Dermatol Res 2017;309:851-6.
2. Boulos S, Vaid R, Aladily TN, Ivan DS, Talpur R, Duvic M: Clinical presentation, immunopathology, and treatment of juvenile-onset mycosis fungoides: a case series of 34 patients. J Am Acad Dermatol 2014;71:1117-26.
3. Hodak E, Lapidoth M, Kohn K, et al.: Mycosis fungoides: HLA class II associations among Ashkenazi and non-Ashkenazi Jewish patients. Br J Dermatol 2001;145:974-80.
4. Hodak E, Klein T, Gabay B, et al.: Familial mycosis fungoides: report of 6 kindreds and a study of the HLA system. J Am Acad Dermatol 2005;52:393-402.
5. Ceppi F, Pope E, Ngan B, Abla O: Primary cutaneous lymphomas in children and adolescents. Pediatr Blood Cancer 2016;63:1886-94.
6. Yazganoglu KD, Topkarci Z, Buyukbabani N, Baykal C: Childhood mycosis fungoides: A report of 20 cases from Turkey. J Eur Acad Dermatol Venereol 2013;27:295-300.
7. Wu JH, Cohen BA, Sweren RJ: Mycosis fungoides in pediatric patients: Clinical features, diagnostic challenges, and advances in therapeutic management. Pediatr Dermatol 2020;37:18-28.
8. Wain EM, Orchard GE, Whittaker SJ, Spittle MSMF, Russell-Jones R: Outcome in 34 patients with juvenile-onset mycosis fungoides: a clinical, immunophenotypic, and molecular study. Cancer 2003;98:2282-90.
9. Hodak E, Amitay-Laish I, Feinmesser M, et al.: Juvenile mycosis fungoides: Cutaneous T-cell lymphoma with frequent follicular involvement. J Am Acad Dermatol 2014;70:993-1001.
10. Alsaleh QA, Nanda A, Baker H, Al-Sabah H, Calonje E: Unilesional (segmental) mycosis fungoides presenting in childhood. Pediatr Dermatol 2004;21:558-60.
11. Hodak E, Friedman E: Familial mycosis fungoides: model of genetic susceptibility. Clin Lymphoma Myeloma Leuk 2010;10(Suppl 2):S67-9.
12. Baykal C, Büyükbabani N, Kaymaz R: Familial mycosis fungoides. Br J Dermatol 2002;146:1108-10.
13. Ozdilli K, Oguz FS, Anak S, Kekik C, Carin M, Gedikoglu G: The frequency of HLA class I and II alleles in Turkish childhood acute leukaemia patients. J Int Med Res 2010;38:1835-44.

Supplementary Table 1. HLA class II genotypes of case 1, case 2, and their parents

	HLA-DRB1	HLA-DQB1
Case 1	DRB1*04 DRB1*11	DQB1*03
Case 2	DRB1*04 DRB1*08	DQB1*03 DQB1*04
Mother	DRB1*08 DRB1*11	DQB1*03 DQB1*04
Father	DRB1*04	DQB1*03

HLA: Human leukocyte antigen