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Case Report

A family with interleukin-17 receptor A deficiency: a case report and review of the literature

Mehmet Kılıç[1], Mehmet Hazar Özcan[2], Erdal Taşkın[3], Aşkın Şen[4]

Divisions of [1]Allergy and Immunology and [3]Neonatology, [2]Department of Pediatrics, [4]Department of Medical Genetics, Fırat University Faculty of Medicine, Elazığ, Türkiye.

ABSTRACT

Background. Chronic mucocutaneous candidiasis (CMC) is characterized by recurrent or persistent infections of the skin, nail, oral, and genital mucosa with Candida species, mainly *Candida albicans*. In a single patient, the first genetic etiology of isolated CMC autosomal recessive interleukin-17 receptor A (IL-17RA) deficiency was reported in 2011.

Case. We report four patients with CMC who displayed autosomal recessive IL-17RA deficiency. The patients were from the same family, and their ages were 11, 13, 36, and 37 years. They all had their first CMC episode by six months of age. All patients manifested staphylococcal skin disease. We documented high IgG levels in the patients. In addition, we found the coexistence of hiatal hernia, hyperthyroidism, and asthma in our patients.

Conclusions. Recent studies have provided new information on the heredity, clinical course, and prognosis of IL-17RA deficiency. However, further studies are needed to reveal the full picture of this congenital disorder.

Key words: chronic mucocutaneous candidiasis, interleukin-17 receptor A (IL-17RA), staphylococcal infection, family.

In human beings, fungi of the genus Candida are found in the normal flora of the skin and mucous membranes of the gastrointestinal, genitourinary, and respiratory systems. *Candida albicans* (*C. albicans*) does not cause chronic disease in healthy individuals. Chronic mucocutaneous candidiasis (CMC) is a selective cellular immune deficiency characterized by persistent candida infection of the mucosa, skin, scalp, and nails. CMC usually does not have a systemic spread and is a heterogeneous disorder. It is thought that the insufficiency causes the primary defect in the proliferative response of T lymphocytes against the candida antigen and the production of cytokines.[1]

Chronic mucocutaneous candidiasis is divided into two groups; syndromic and isolated CMC. Patients with a predisposition to infectious agents other than Candida and staphylococcus or autoimmune clinical signs are defined as syndromic CMC. Syndromic CMC manifestations include STAT1 gain-of-function (GOF), STAT3 loss-of-function (LOF), AIRE, DOCK8, CARD9, IL-12p40, IL-12Rβ1, ROR-γ/γT, and Dectin-1 mutations.[2-6] Interleukin-17 receptor A (IL-17RA), IL-17RC, IL-17F and ACT1 (TRAF3IP2) mutations cause isolated CMC disease.[2,7-9] In isolated CMC patients, symptoms usually begin early in infancy, and staphylococcal skin infections are also seen in some patients. In addition, patients with primary immunodeficiencies affecting T cells, including severe combined immunodeficiency and combined immunodeficiencies, are also prone to CMC.[10]

IL-17RA deficiency shows autosomal recessive inheritance and causes isolated CMC disease. IL-17RA deficiency is the second most common cause of CMC after STAT1 GOF.[5,11] Among clinical findings of IL-17RA deficiency,

✉ Mehmet Kılıç
drmkilic@gmail.com

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candidiasis in the anogenital area, skin, scalp, nails, oral mucosa, pustules, folliculitis, furunculosis, and skin abscess formation, seborrheic dermatitis, scaly pustule formation on the scalp can be counted. Other clinical findings of IL-17RA deficiency are; conjunctivitis, development of tuberculosis (pulmonary tuberculosis, tuberculous meningitis), eczema, sinusitis, otitis, lobar pneumonia, and bronchitis.[11]

In this study, in light of the literature, we reviewed IL-17RA deficiency in a family (father, two daughters, and father's sister) with a history of recurrent mucocutaneous candidiasis and diagnosed with homozygous IL 17 RA mutation in the genetic analysis.

Case Report

Case 1

A thirteen-year-old female patient was admitted to our clinic at three years of age. The patient had complaints of dandruff on the scalp and white plaque in the mouth that started from birth and recurred. In addition, the patient had a history of acne-like rashes that started at the age of eight months and was more common on the anterior and posterior parts of the chest. Although the patient was intermittently using oral nystatin drops and oral antibiotic treatment, her complaints were constantly recurring. There was no pathological finding in her prenatal and natal history. It was learned that the patient's father and aunt had similar recurrent complaints and that the frequency and severity of the complaints decreased when they reached adulthood. The pedigree of the patient's family is given in Fig. 1.

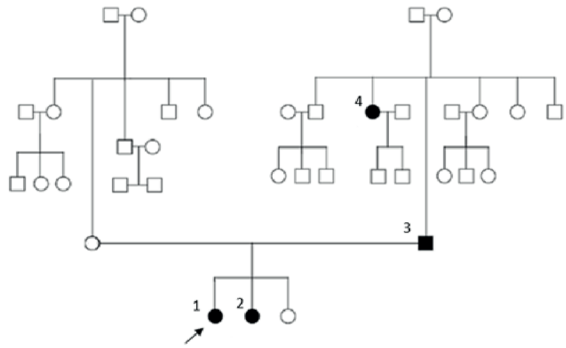

Fig. 1. Pedigree of the patients diagnosed with IL-17RA deficiency (the index patient is shown with arrow).

The patient's vital signs were normal. There were widespread papular rashes all over her body (Fig. 2a). There were white plaques on the tongue and in the mouth (Fig. 2b). Microbiological examination of the white plaque lesions was performed, and yeast and pseudohyphae

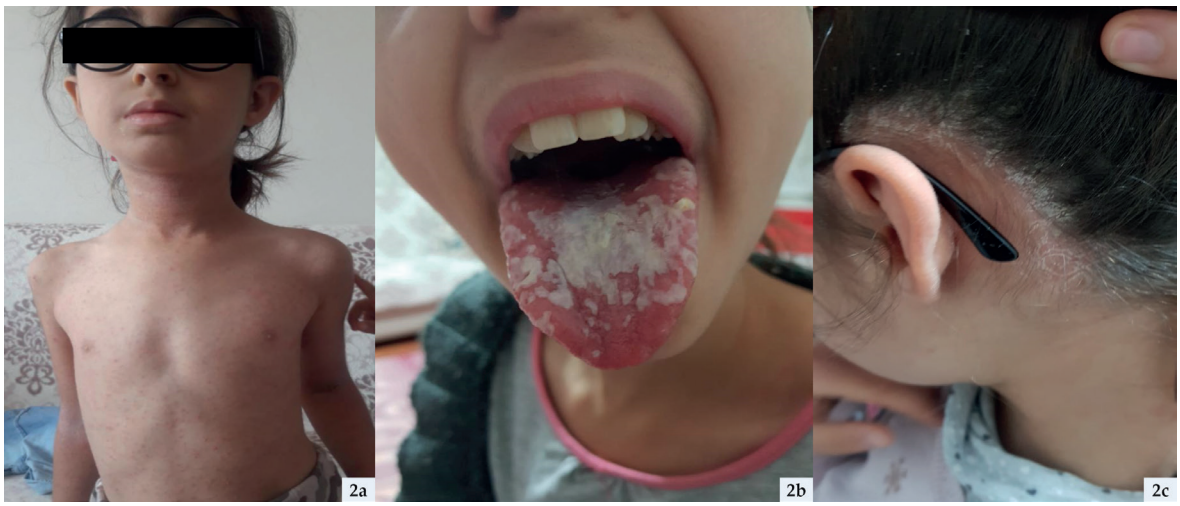

Fig. 2. 2a: Diffuse erythematous papular rashes on the patient's chest, 2b: Diffuse candida plaques on the patient's tongue, 2c: White scalings detected on the patient's scalp.

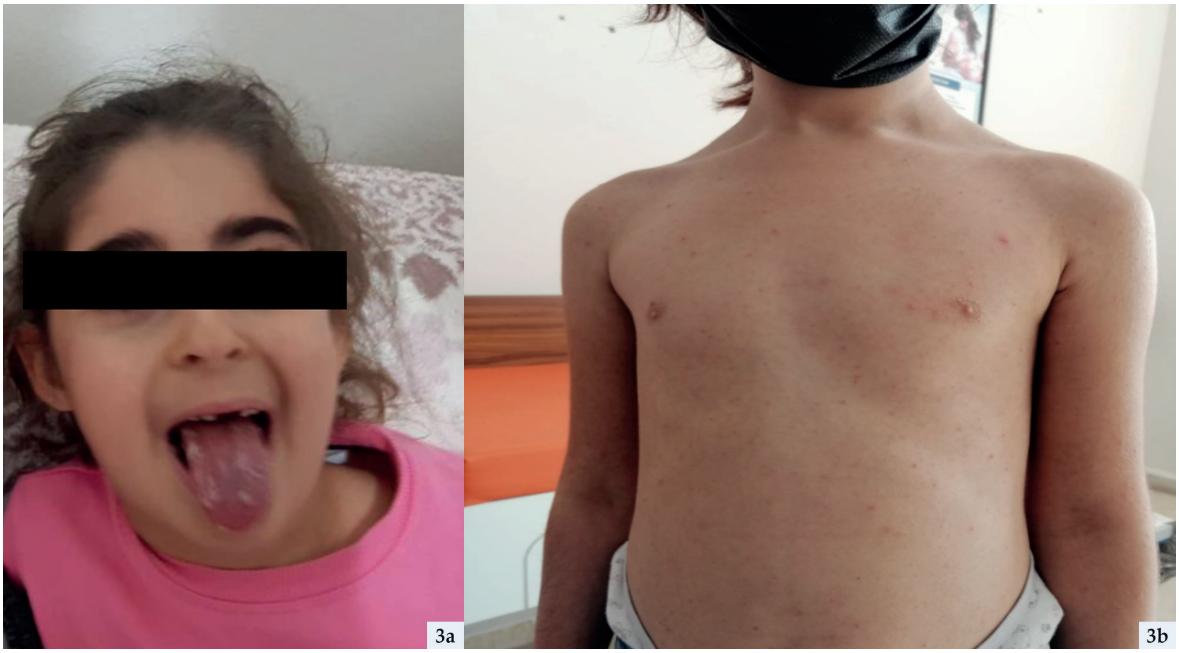

Fig. 3. 3a: Candida plaques on the patient's tongue, 3b: Diffuse erythematous papular rashes on the patient's chest.

were seen on Gram staining. Gram-positive cocci were grown in the wound swab culture taken from the skin lesions. In addition, there were white scales on the occipitotemporal region of the scalp (Fig. 2c). In the laboratory examination, the results of the biochemical tests were within normal limits. Other laboratory findings of the patient are given in Table I. We used an investigation based on whole-exome sequencing for CMC in the patients.[11] Genetic analysis revealed a homozygous mutation of c.1159G>A (p.Asp387Asn) in the *IL17RA* gene. With the current clinical and laboratory findings, we considered the diagnosis of CMC due to *IL17RA* mutation. Therefore, oral prophylactic fluconazole and trimethoprim-sulfamethoxazole treatment was started.

Case 2

An eleven-year-old female patient applied to our clinic when she was six months old. The patient's history revealed the presence of white plaque in the mouth that started when she was two months old. She also had acne-like rashes on her trunk that started when she was five months old. Oral nystatin treatment was given to the patient to treat her oral lesions, but the patient's complaints did not regress. There was no pathological finding in her prenatal and natal history. The patient's older sister, father, and aunt had similar complaints in the family history.

Her vital signs were within normal limits. In her physical examination, there were white plaques on the tongue and in the mouth (Fig. 3a) and diffuse papular eruptions, which were more intense on the anterior and posterior parts of the chest, and all over the body. (Fig. 3b). Microbiological examination of the samples taken from the white plaque lesions was performed, and yeast and pseudohyphae were seen on Gram staining. Gram-positive cocci were grown in the wound swab culture taken from the skin lesions. In the laboratory examination, biochemical test results were within normal ranges. Other laboratory findings of the patient are given in Table I. In the patient follow-up, complaints of recurrent cough, shortness of breath, and wheezing emerged. At the age of seven, prolonged expiration, wheezing, and rhonchi were detected on physical examination.

Table I. Laboratory findings of the cases.

Laboratory findings	Case 1	Case 2	Case 3	Case 4
Hb (g/dL)	13.8	13.2	14.4	12.4
Hct (%)	43.8	40.2	44.4	40.5
MCV (fL)	86.4	79.8	87.2	79.3
MCHC (g/dL)	31.5	32.8	32.5	30.6
RDW (%)	12.1	12.7	13.1	14
RBC (10^6 /mm^3)	5.08	5.04	5.09	5.11
WBC (/mm^3)	7700	8050	7090	7420
PLT (/mm^3)	283000	409000	291.000	337.000
ANC (/mm^3)	3620	3440	3860	4490
ALC (/mm^3)	3270	3740	2560	2330
Eosinophils (/mm^3)	200	350	120	90
CRP (mg/dL)	3.4	4.2	0.14	8.2
ESR (mm/h)	11	14	8	41
C3 (g/dL)	1.15 (0.9-1.8)	1.43 (0.9-1.8)	1.08 (0.9-1.8)	1.45 (0.9-1.8)
C4 (g/dL)	0.15 (0.1-0.4)	0.25(0.1- 0.4)	0.21 (0.1- 0.4)	0.23 (0.1- 0.4)
CH50 (%)	88.8 (51-150)	86.9 (51-150)	85.7 (51-150)	93 (51-150)
IgG (mg/dL)	2140 (441-1135)	821 (215-704)	1590 (700-1600)	1460 (700-1600)
IgA (mg/dL)	66.5 (22-159)	34 (8.1-68)	203 (70-400)	408 (70-400)
IgM (mg/dL)	90.5 (47-200)	60 (35-102)	91 (40-230)	240 (40-230)
IgE (IU/mL)	16.4 (0.19-16.9)	14.0 (0.44-16.3)	121 (1.53-114)	46.4 (1.53-114)
IgG1 (mg/dL)	1432 (280-1120)	705.5 (230-710)	1380 (280-1020)	917 (280-1020)
IgG2 (mg/dL)	334.6 (30-630)	204.4 (30-170)	340 (60-790)	480 (60-790)
IgG3 (mg/dL)	74.4 (40-250)	55.4 (11-98)	119 (14-240)	49 (14-240)
IgG4 (mg/dL)	50.5 (11-620)	30.3 (4-43)	70 (11-330)	32 (11-330)
CD45RO+ (%)	32 (14-44)	30 (14-44)	32 (14-44)	34 (14-44)
CD3+ (%)	64.1 (43-76)	57.8 (50-75)	59 (52-78)	61 (52-78)
CD4+ (%)	35.5 (23-48)	33.8 (33-58)	36 (28-57)	33 (28-57)
CD8+ (%)	27.5 (12-30)	26.1 (13-26)	28 (10-39)	29 (10-39)
CD19+ (%)	21.6 (11-31)	23 (14-41)	23 (10-30)	21 (10-30)
CD20+ (%)	21 (11-29)	22 (13-40)	22 (9-28)	19 (9-28)
CD16+/56+ (%)	14 (5-28)	15 (5-23)	15 (8-30)	15 (8-30)
Blood group	0 Rh (+)	0 Rh (+)	0 Rh (+)	B Rh (+)
Anti-A titer	1/32	1/32	1/16	1/16
Anti-B titer	1/32	1/32	1/16	1/16
Anti rubella IgG	+	+	-	+
Anti mumps IgG	+	-	-	+
Anti measles IgG	+	+	-	+
Anti-HBs IgG	-	+	-	-
Anti tetanus IgG	-	-	-	-
Genetic result	c.1159G>A (p.Asp387Asn)	c.1159G>A (p.Asp387Asn)	c.1159G>A (p.Asp387Asn)	c.1159G>A (p.Asp387Asn)

ALC: absolute lymphocyte count, ANC: absolute neutrophil count, C: complement, CD: cluster of differentiation, CRP: C-reactive protein, ESR: Erythrocyte sedimentation rate, fL: femtoliter, Hb: hemoglobin, Hct: hematocrit, Ig: Immunoglobulin, MCHC : mean corpuscular hemoglobin concentration, MCV: mean corpuscular volume, PLT: platelet count, RBC: red blood cell, RDW: red cell distribution width , WBC: white blood cell count.

Increased aeration in the patient's chest X-rays and early reversibility in the pulmonary function tests were detected. No sensitization was detected in the skin prick test performed with inhaled allergens. The results of a child food panel-specific IgE (fx5) and phadiatop test were negative. The patient was diagnosed with asthma based on the current history, physical examination, laboratory test results, and treatment with 5 mg oral montelukast and inhaled fluticasone propionate in two doses of 250 mcg/day was started. To prevent developing oral candidiasis due to fluticasone propionate treatment, we recommended that the patient administer the drug through the chamber spacer and gargled with plenty of water after each application.

We had previously diagnosed CMC in the patient's sister due to *IL17RA* mutation, and documented a homozygous mutation of c.1159G>A (p.Asp387Asn) in the *IL17RA* gene So, this sibling also got the diagnosis of IL-17RA deficiency. In addition to asthma treatment, oral prophylactic fluconazole and trimethoprim-sulfamethoxazole were started.

Case 3

It was learned that a 36-year-old male patient had complaints of white plaques in the mouth and acne-like rashes on the body, which started in childhood. During this period, although the doctors prescribed the patient with a bicarbonate mouthwash and topical skin creams containing fusidic acid, the patient's complaints constantly recurred. However, the frequency and severity of the patient's complaints decreased after adolescence. Later, at the age of 23, the patient complained of a sour or bitter taste in his mouth, belching, and abdominal pain that aroused him from sleep. Because of these complaints, the patient was diagnosed with a hiatal hernia and gastroesophageal reflux. The case was operated on twice for the hiatal hernia. Additionally, endoscopic findings consistent with esophageal candidiasis were detected. Furthermore, when the patient was 32 years old, complaints of diarrhea that continued intermittently for six months emerged. Abundant Candida was detected in stool microscopy. After using oral fluconazole treatment, the patient's diarrhea resolved.

The patient's vital signs were within normal limits. His physical examination was unremarkable except for scars due to previous operations on the abdomen. In the laboratory examination, the results of biochemical tests were within normal limits. Other laboratory findings of the patient are given in Table I. A homozygous mutation of c.1159G>A (p.Asp387Asn) in the *IL17RA* gene was detected, and a diagnosis of IL-17RA deficiency was made.

Case 4

It was learned that a 37-year-old female patient developed complaints of white plaque in the mouth and acne-like rashes on the body, which started in childhood. During this period, although the doctors gave the patient oral care with bicarbonate mouthwash and topical skin creams containing fusidic acid, the patient's complaints were constantly recurring. However, the frequency and severity of these complaints decreased after adolescence. Later, the patient was diagnosed with hyperthyroidism at the age of 33 because of irritability, palpitations, sweating, and weight loss, and propylthiouracil treatment was started.

The patient was admitted to our clinic because of the detection of *IL17RA* mutation in his brother and two nieces. The patient's vital signs were normal. There was no pathology in the physical examination of the patient. Her biochemical test results were within normal limits. Other laboratory findings of the patient are given in Table I. A homozygous mutation of c.1159G>A (p.Asp387Asn) in the *IL17RA* gene was detected, and a diagnosis of IL-17RA deficiency was made. We obtained consent from his family to publish this report and to include their photographs.

Discussion

Approximately 50 years ago, CMC was defined as a primary immunodeficiency.[12] In recent years, many genetic mutations that cause CMC have been described. Most of these mutations are directly or indirectly related to defects in IL-17. IL-17 is mainly produced by Th17 cells. IL-17 belongs to the six-membered cytokine family (IL-17A, IL-17B, IL-17C, IL-17D, IL-17E, IL-17F).[13-15] Unlike IL-17, the IL-17 receptor (IL-17R) is expressed in all body cells. Therefore, many different cells are the target of IL-17.[14,16,17] Five receptors for IL-17 have been identified so far; IL-17RA, IL-17RB, IL-17RC, IL-17RD, and IL-17RE. IL-17RA and IL-17RC have been shown to bind IL-17A and IL-17F. However, IL-17RA primarily binds to IL-17A with high affinity, while it has a lower binding affinity for IL-17F.[16-18] The binding of IL-17A and IL-17F to their receptors induces various signaling pathways and causes the secretion of some cytokines and chemokines. These cytokines and chemokines recruit and activate polymorphonuclear neutrophils in that area and provide protection against various infectious agents in the environment.[19] In IL-17RA deficiency, the functions of epithelial cells, fibroblasts, mononuclear cells, and phagocytes are affected. The IL-17RA signaling pathway is essential for mucocutaneous immunity against *C. albicans* and *Staphylococcus aureus* (*S. aureus*). It has also been reported that the IL-17RA-dependent signaling pathway is important for protective immunity against various bacteria in the respiratory tract.[11]

IL-17RA deficiency was first described in a Moroccan boy. The patient developed recurrent CMC infection resistant to local antifungal therapy since the first month of his life. In this case, *C. albicans* dermatitis developed in the newborn period and *S. aureus* dermatitis at five months. In addition, the development of recurrent folliculitis and abscess in his hip caused by *S. aureus* was also reported.[7] In the literature, in addition to mucocutaneous candidiasis and skin infections caused by *S. aureus* in CMC patients, concomitant recurrent lower and upper respiratory tract bacterial infections, tuberculosis, conjunctivitis, and eczema have been reported.[11] The pathogenesis of staphylococcal disease in CMC patients has not been clarified yet. Staphylococcal skin disease is frequently seen in patients with ACT1 and IL-17RA deficiencies but not reported in patients with IL-17F and IL-17RC deficiencies. This observation suggests that staphylococcal disease may be due to a disorder in the cytokine responses of IL-17E (IL-25), which requires ACT1 and IL-17RA.[11] In general, clinical findings of IL-17RA deficiency include candidiasis on the anogenital region, scalp, nails, and oral mucosa, skin pustules, folliculitis, furunculosis, skin abscess, seborrheic dermatitis, and crusty pustular lesions on the scalp. In all our cases, there was a history of oral candidiasis that started in early childhood and skin infection caused by S. *aureus*. However, it was learned that the frequency and severity of these infections decreased after adolescence in the children's father and aunt. This improvement in symptoms may be due to the development of the adaptive immune system with age. In addition, when the immunological examinations of the patients were evaluated, we found elevated IgG in 3/4 of the patients. IgG elevation may be due to chronic *C. albicans* and *S. aureus* infections. In chronic mucocutaneous candidiasis, there is a predisposition to many microorganisms together with a candida infection. Therefore, in patients with CMC as a major finding, the differential diagnosis should be primarily made between isolated (IL-17RA, IL-17RC, IL-17F, ACT1) and syndromic CMC (STAT1 GOF, STAT3 LOF, AIRE, CARD9, IL-12p40, IL-12Rβ1, ROR-γ) /γT).[2-9] IL-17RA, ACT1, and IL-17RC deficiencies are autosomal recessive, while IL-17F deficiencies are autosomal dominant disorders. It has been reported that patients with IL-17F or IL-17RC deficiency have a relatively mild, while patients with ACT1 or IL-17RA deficiency have a more severe phenotype.[7-9,20] In contrast to IL-17RA and ACT1 deficiencies, recurrent staphylococcal infections and severe or recurrent bacterial infections are

not seen in patients with IL-17RC deficiency.[8] In ACT1 deficiency, attacks of recurrent folliculitis caused by *S. aureus* and bilateral blepharitis are seen together with CMC.[9]

CARD9 deficiency is associated with chronic candidiasis, deep dermatophytosis, invasive exophiala dermatitis, subcutaneous phaeohyphomycosis, candida meningoencephalitis, and colitis.[2,21] In patients with STAT3 LOF deficiency characteristic facial features, high palate, retention of primary teeth, chronic candidiasis, scoliosis, osteoporosis and hyperextensibility of joints, eczema, eosinophilia, IgE elevation, severe skin, and pulmonary infections due to staphylococcus have been reported.[3] Also, in APECED (APS-1) syndrome signs of autoimmune polyendocrinopathy such as Addison's disease, hypoparathyroidism, and hypogonadism are seen.[2,4] In addition, fungal infections other than candidiasis, viral infections, mycobacterial infections, autoimmune symptoms (hypothyroidism, type 1 diabetes, and cytopenias), and IPEX-like clinical picture are seen in STAT1 GOF deficiency.[5] In IL-12Rβ1 and IL-12p40 deficiencies, Mendelian susceptibility to mycobacterial disease and recurrent salmonella infections[2,6], and RORγT deficiency, severe mycobacterial infections are observed.[2] In our cases, there was no history of infection due to microorganisms other than mucocutaneous candida infection and folliculitis caused by *S. aureus*. The 36-year-old male patient (Case 3) had a hiatal hernia and gastro-oesophageal reflux, the 37-year-old female patient (Case 4) had hyperthyroidism, and we diagnosed the eleven-year-old girl (Case 2) with asthma.

Most cases of CMC are treated with topical or systemic antifungal agents. As a topical treatment, nystatin can be used, but cases are often refractory to this treatment. Fluconazole is the first choice for oral therapy, followed by itraconazole, posaconazole, or voriconazole.[2] Flucytosine is also among the treatment options. These treatments can be used continuously or intermittently. In cases where oral antifungal therapy is ineffective, intravenous fluconazole or miconazole may be administered. As a second alternative, amphotericin B can be used. Surgical removal of the nails is also recommended along with, oral antifungals for onychomycosis.[2,7] In severe cases, candida-specific transfer factors may be effective when given antifungal treatments. In addition, leukocyte transfusions provide temporary relief of symptoms. Staphylococcal infections develop in addition to CMC in IL-17RA and ACT1 deficiency patients. Antibiotic prophylaxis with trimethoprim-sulfamethoxazole may effectively treat these patients.[7,9] It has been reported that an H2 receptor antagonist (cimetidine) can stimulate the cellular immune system in some cases with CMC. Hematopoietic stem cell transplantation appears to be an effective treatment for CMC. However, large case studies are needed to implement hematopoietic stem cell transplantation in all individuals with CMC.[22] In our patients, we started oral prophylactic fluconazole and trimethoprim-sulfamethoxazole treatment for both of the female patients (Cases 1 and 2). After starting the treatments, we were able to control the complaints of folliculitis and mucocutaneous candidiasis.

In conclusion, the genetic etiologies of syndromic and isolated CMC cases have been defined recently, revealing that IL-17 has an important role in mucocutaneous immunity against *Candida spp.* and *S. aureus*. These discoveries have provided new information about the inheritance, clinical course, and prognosis of CMC manifestations, including IL-17RA deficiency. However, further studies are needed to reveal the full picture of this congenital disorder.

Ethical approval

We obtained consent from the family to publish this report and to include their photographs.

Author contribution

The authors confirm contribution to the paper as follows: study conception and design: MK, ET, MHÖ; data collection: MK, MHÖ; analysis and interpretation of results: MK, ET, MHÖ, AŞ; draft manuscript preparation: MK, ET, MHÖ, AŞ. All authors reviewed the results and approved the final version of the manuscript.

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Conflict of interest

The authors declare that there is no conflict of interest.

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