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SUPPLEMENT ARTICLE

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IL-17 serum level in patients with chronic mucocutaneous candidiasis disease

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Abstract

Chronic mucocutaneous candidiasis (CMC) is defined by recurrent or persistent superficial infections involving nails, skin, and/or oral and genital mucosae. IL-17 promotes the recruitment, chemotaxis, and expansion of neutrophils and acts directly on keratinocytes and epithelial cells, driving the production of antimicrobial peptides, essential for the immune response against Candida.

To evaluate the serum level of IL-17 in a family affected by CMC restricted to the nails of the hands and feet.

Serum IL-17 was assayed on 16 patients (aged 21 ± 3.1 years) suffering from persistent onychomycosis caused by Candida and 18 healthy controls (aged 19 ± 2.7 years). Comparisons between groups were performed by Student's unpaired *t*-test. The level of significance was set at 0.05.

The mean serum IL-17 level in patients was 74 ± 1.42 pg/ml, whereas the control group showed a significantly lower level of 25.6 ± 6.7 pg/ml ($p < 0.05$).

We showed a potential defect in the IL-17 signaling pathway in a family affected by CMC restricted to the nails of the hands and feet. Further research is needed to clarify the immunological mechanisms and the genetic etiology at the basis of the unusual clinical presentation in this family.

KEYWORDS

Candida, chronic mucocutaneous candidiasis, IL-17

1 | INTRODUCTION

Candida species constitute the major components of the human microbiome in healthy subjects. However, this fungus has a pathogenic potential linked to the environmental changes promoted either by alterations in local conditions or the host immune system. Within the spectrum of Candida spp.–related diseases, chronic mucocutaneous candidiasis (CMC) is defined by recurrent or persistent superficial infections involving nails, skin, and/or oral and genital mucosae. IL-17 promotes recruitment, chemotaxis, and expansion of neutrophils and drives the production of antimicrobial peptides, essential for the immune response against Candida.

The present study aimed to evaluate the serum level of IL-17 in a family affected by CMC restricted to the nails of the hands and feet.

Roberto Chimenz and Angelo Tropeano equally contributed as co-first authors.

2 | PATIENTS AND METHODS

The family originates from a rural village in Sicily and includes (24 patients) affected subjects in eight generations. A complete clinical description and a genotyping study of the family have been previously reported.[1,2] Sixteen patients (10 males and 6 females, aged 21 ± 3.1 years), suffering from persistent onychomycosis caused by Candida since the first years of age, were admitted to our Pediatric Emergency Outpatient Clinic at the University of Messina. The patients enrolled presented nail dystrophy with hyperkeratosis involving all the nails of hands and feet. None of the patients had a personal history of other opportunistic infections. Nail specimens from the lesional sites were obtained by scarifying and cutting the nail matrix. Oral and vaginal swabs were also collected. The laboratory workup included complete blood count (CBC), liver and renal function, glycemia, glycosuria, serum immunoglobulin, autoantibody profile, and a complete endocrinological panel, including thyroid and parathyroid and adrenal function. Serum IL-17 was assayed on the patients and 18 healthy controls (9 males and nine females, aged 19 ± 2.7 years) using an ELISA Kit according to the manufacturer's instructions. These control subjects were recruited according to the following inclusion criteria: no personal history of candidiasis and autoimmune diseases; normal hormonal and immunological function at enrollment. The subjects with any hormonal and/or immunological defects were excluded. Results are expressed as mean ± SD or median and range values. Comparisons between groups were performed by Student's unpaired *t*-test. The level of significance was set at 0.05.

3 | RESULTS

Except for the nail dystrophy, the patients were relatively healthy and, as previously reported in other family members, routine, endocrine, and autoimmune tests resulted negative or within the normal range.[2] All the patients had a nail specimen positive for *Candida albicans* or *parapsilosis*, while oral and genital swabs were negative. The mean serum IL-17 level in patients was 74 ± 1.42 pg/ml, whereas the control group showed a significative lower level that was 25.6 ± 6.7 pg/ml ($p < 0.05$).

4 | DISCUSSION

Candida species constitute the major components of the human mycobiome in healthy subjects. Under physiological conditions, they colonize several niches, including skin, oral cavity, gastrointestinal, and urogenital tracts. However, the fungus has a pathogenic potential linked to the environmental changes promoted either by alterations in local conditions (eg, dysbiotic microbiota, changing pH, or nutrients) or in the host immune system.[3] Consequently, under the conditions mentioned above, Candida species can overgrow, cross the epithelial barriers, and cause infections.[3,4] In clinical practice, the most frequent risk factors for candidiasis are acquired and include broad-spectrum antibiotics, chemotherapy, and steroid treatment. Conversely, some inhered or acquired T-cell deficiencies impairing the immunological response against the fungus predispose the host to persistent or chronic Candida infections.

Key Message

The immunological response against Candida spp. is highly complex. The comprehension of the exact mechanism at the basis of host defense might guarantee future therapeutic prospective for the patient with chronic and/or persistent infections.

From an immunological point of view, the immunity to Candida represents the best example of anatomical compartmentalization of the effector response. This peculiarity explains the following clinical pictures: Most HIV + individuals experience frequent episodes of thrush, whereas disseminated candidemia is not common; similarly, patients with congenital immunodeficiencies are more susceptible to superficial candidiasis but not to systemic infections.[5] Murine models showed a significant role of Th1 cells against systemic but not cutaneous C. Albicans reinfection, whereas Th17 cells were more protective against cutaneous than systemic reinfection.[6] The mechanism of this compartmentalized protection might derive from the different tissue homing, persistence, and/or function of the distinct T helper subsets. In particular, IL-17 is a potent regulator of neutrophil response leading to enhancement of intercellular adhesion molecule 1 (ICAM-1), IL-8, C-X-C Motif Chemokine Ligand 1 (CXCL1), CXCL5, CXCL2, and granulocyte-colony stimulating factor (G-CSF), which promoted recruitment, chemotaxis, and expansion of neutrophils. IL-17 acts directly on keratinocytes and epithelial cells, driving the production of antimicrobial peptides (including B-defensins and S100 proteins), essential for superficial immune response.[5,6]

Within the spectrum of Candida spp.–related diseases, CMC is defined by recurrent or persistent superficial infections involving nails, skin, and/or oral and genital mucosae.[7] Considering the clinical phenotype of CMC, two main groups of disease are distinguishable: syndromic CMC, in which the superficial candidiasis is associated with other clinical and infectious manifestations (eg, hyper IgE syndrome [HIES], polyendocrinopathy-candidiasis-ectodermal dystrophy [APECED], caspase recruitment domain-containing protein 9 [CARD9] deficiency) and CMC disease, defined as CMC without any other prominent clinical signs.[7] The immunological defects of CMC diseases include mainly an impaired response or function to IL-17.

In light of the current knowledge on immunological response against Candida spp., we have evaluated the serum concentration of IL-17 in a family affected by CMC disease. Previous clinical studies on affected family members reported a low serum concentration of ICAM-1 and a disease locus to a 19 cM pericentromeric region on

chromosome 11 (OMIM ID: 607644).[1,2] The pedigree pattern in the family was consistent with either autosomal recessive inheritance of autosomal dominant inheritance with incomplete penetrance.[1] Considering the recurrent superficial candidiasis in the absence of other clinical manifestations, we expected pathological IL-17 serum levels in the patients' group. Our results demonstrated a paradoxically increased level of IL-17 in affected subjects when compared to healthy controls. Probably a defect in the IL-17 signaling pathway may explain this finding even if without a precise mechanism. Recent research showed a complex regulation of Th17 cells, with an autocrine loop triggered by binding of IL-17A, which represses Th17 cytokines via the induction of IL-24; consequently, an IL-17A deficiency led to increased production of other Th17-lineage cytokines.[8] A similar regulative mechanism may probably justify our results.

The present study has two main limitations. First, we had not differentiated between the members of the IL-17 family, which is composed of six cytokines (IL-17A-IL-17F). Second, we had not performed next-generation sequencing (NGS) genetic testing, a powerful and modern diagnostic tool to clarify the genetic etiology and the cytokine profile evaluated.

5 | CONCLUSIONS

Here, we showed a potential defect in the IL-17 signaling pathway in a family affected by CMC restricted to the nails of the hands and feet. Further research is needed to clarify the immunological mechanisms and the genetic etiology at the basis of the unusual clinical presentation in this family. However, any physician-treating recurrent candidiasis should consider the possibility of a defect in the host immunological response and start an initial screen with a complete laboratory workup.

CONFLICT OF INTEREST

The authors declare that they have no competing interests.

AUTHOR CONTRIBUTIONS

Roberto Chimenz: Writing-review and editing (equal). **Angelo Tropeano**: Writing-review and editing (equal). **Valeria Chirico**: Writing-review and editing (equal). **Giorgia Ceravolo**: Writing-review and editing (equal). **Carmalo Salpietro**: Supervision (lead); Writing-review and editing (equal). **Caterina Cuppari**: Supervision (lead); Writing-review and editing (equal).

ETHICAL APPROVAL

All procedures performed in the study were in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki declaration.

INFORMED CONSENT

Informed consent for participation in the study was obtained for patients, and the Hospital Ethical Research Committee authorized the study.

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