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Case Report OMICS International

Treatment of Chronic Mucocutaneous Candidiasis, an Unsolved Issue. Case Report and Literature Review

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Introduction

Chronic mucocutaneous candidiasis (CMC) is a rare and heterogeneous group of disorders that may appear as an isolated disease or as a part of a complex syndrome (hyper-IgE syndrome or autoimmune polyendocrine syndrome-1 with ectodermal dystrophy). CMC can be transmitted as an autosomal-recessive (AR) or autosomal-dominant (AD) form, with common features including recurrent or persistent noninvasive Candida infections of the skin, nails, oral and genital mucosae, and associated autoimmune manifestations (most commonly endocrinopathies). It is caused by genetic faults in the immune system, through quantitative or qualitative, acquired or inherited T-cell deficiencies [1-4].

Case Report-Guided Issue

We present a female patient, now 51 years old, who has suffered from recurrent Candida infections, involving oral, vulvar and vaginal mucosae, for more than 9 years.

Neither endocrine disorders nor family history of recurrent mucocutaneous infections by Candida have been displayed. Multiple laboratory studies to rule out other causes or primary and secondary immune deficiencies showed normal results, except a weak IgG1 deficiency (333 mg/dl; reference range 402-715 mg/dl). Analyses of autoimmunity, organ specific (anti-parathyroid, adrenal and ovary) and celiac disease antibodies, neoplasia screening and viral serologies (including HIV infection), were negative. A blood test revealed anemia of chronic disease: low serum iron level, with 27 µg/dl, (reference range 50-170), transferrin saturation 7% (reference range 15-50), ferritine 81 ng/ml (reference range 10-291) and hemoglobin 10.9 g/dl (reference range 11.7-16). The endoscopic studies of the digestive tract were normal. Search for mutations by next generation sequencing NGS (SOLID 5500XL) of the entire coding regions and flanking intronic regions of *STAT 1* (signal transducer and activator of transcription 1), *STAT3*, *IL17A* (interleukin 17 A), *CLEC7A* (C-type lectin domain family 7 member A/Dectin) and *CARD9* (caspase recruitment domain-containing protein 9) genes reported to be critical pieces in controlling infection by *C. albicans*, was negative [5,6].

Due to recurrent oropharingeal pain, neurologists suggested to rule out an underlying burning mouth syndrome or trigeminal neuralgia. A brain magnetic resonance imaging showed supratentorial white matter hyperintensities compatible with small foci of non-inflammatory demyelination (non-specific lesions suggestive of leukoaraiosis).

Along the course of the disease, the patient developed an interstitial lung pattern without microbiological documentation. A thoracic CT scan showed bilateral ground glass pattern, right paratracheal mediastinal, prevascular and aortopulmonary lymphadenopathy, the larger 1.5 X 0.9 cm, locating on the back of left upper lobe, as well as subpleural nodule of approximately 8 mm. Bronchoscopy was performed, without endoscopic findings; bronchoalveolar aspirate and lavage revealed normal T4 and T8 cell counts and no malignant cells. The pathologic examination of a lung biopsy showed respiratory bronchiolitis with areas of desquamated pneumocytes and emphysematous changes. These findings could be explained by smoking habit in the past. No lung pattern changes were seen in following imaging studies.

The patient received many antifungal drugs (IV amphotericin lipid complex, oral azoles, IV echinocandins) unsuccessfully, with persistent painful oral and vulvovaginal lesions and isolation of fungi identified as *Candida albicans*, *Candida glabrata* and less often *Candida guilliermondii*. Antifungal susceptibility tests demonstrated sensitivity to all agents. Currently, she is receiving chronic suppressive treatment with an IV echinocandin (caspofungin 50 mg daily) to prevent recurrences, through central venous catheter.

A recent report [7] has shown clinical benefit of granulocyte-colony stimulating factor (G-CSF, filgrastim) treatment in a patient with AD form of isolated CMC with *STAT1* gain-of-function (GOF) mutation who showed a decrease in Th17 cells and IL-17 secretion. Based on this study, we considered the possibility to assess the Th17 function in our patient, as well as the role of G-CSF to achieve a potential therapeutic benefit.

Investigations: Material and Methods/Results

The level of IL-17 was measured using the IL-17A ELISA kit (Diaclone, lower limit of detection 1.6 pg/ml) in untreated plasma samples. Furthermore Th17 function was evaluated in supernatants of cultured Ficoll-Hypaque purified patient's peripheral blood mononuclear cells (PBMC) upon stimulation or not with phorbol

myristate acetate (PMA) 10 ng/ml and ionomycin 1 µg/ml. PBMC from a healthy individual was run in parallel. Stimulated and unstimulated cells were cultured for 48 hours. Figure 1 shows that patient's PBMC produced about 30 time's smaller amounts of IL-17 than the control subject. In contrast, the plasma IL-17 levels were 16.2 and 10.3 pg/ml for case and control samples respectively. Both values fell in the normality range, assuming in healthy subjects a mean level of IL-17 of 27.1+/-30.1 pg/ml [8]. Treatment with subcutaneous G-CSF was started, at a dose of 60 MU (5 µg/Kg) twice a week during two months, keeping white blood cell counts below 15,000/mm^3 (the leukocyte count was increased during the treatment, and returned to reference range when C-GSF was stopped), following the safety cutoff established by Wildbaum G. et al. [7]. A second measurement of IL-17 in plasma and PBMC was performed after two months on treatment with G-CSF. No major changes in plasma levels were noticed, IL-17 levels were 20.6 and 9.5 pg/ml for case and control samples respectively (both in the normal range). Importantly, no improvement in the production of IL-17 by Th17 lymphocytes was observed either in unstimulated or stimulated cultured PBMC (Figure 1B). Consistently, clinical remission was not achieved and the patient remained with painful oral lesions (and isolation of *Candida* sp.) during the treatment.

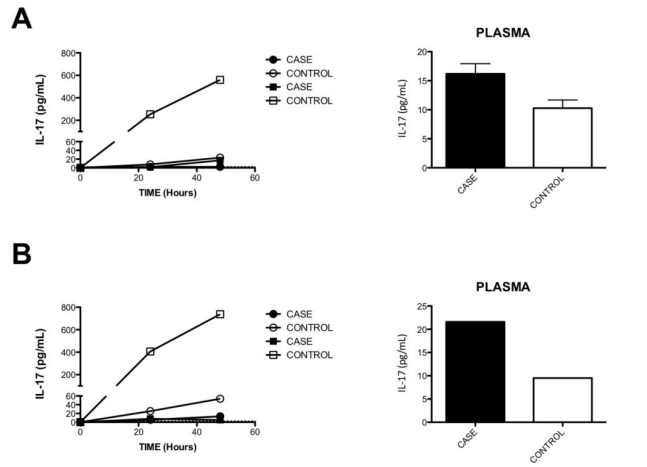

Figure 1. Th17 function and plasma levels of IL 17 in case and control samples. Production of IL-17 by PMA7 Ionomycin stimulated (squares) or unstimulated PBMC (circles). Purified PBMCs from the Case (filled symbols) and a control sample (empty symbols) were cultured for 24 or 48 hours. Supernatants were collected and assayed for IL-17 by ELISA. In parallel plasma levels of IL-17 were determined by ELISA in the case and control samples. Panel A shows determinations at baseline, before GMCSF treatment. Panel B shows determinations alter during treatment.

Therefore, based on all laboratory findings (normal *STAT1*, *STAT3*, *IL17A*, *CLEC7A* and *CARD9* genes, normal plasma IL-17 levels, and a severe deficit in IL-17 production by the patient's PBMCs upon stimulation), the patient was diagnosed of a defect in IL-17 production by lymphocytes Th17, as the underlying mechanism for development of recurrent isolated CMC. No clinical or *ex vivo* response was seen with G-CSF therapy.

Discussion

Th17 cell development is directed by multiple cytokines, including IL-23 (as well as *IL-12β* and *IL12-Rβ1* gene products) [4], produced by antigen-presenting cells stimulated through pathogen-recognition receptors (including Dectin-1), in response to pathogen-associated molecular patterns (b-glucans, lipoproteins, peptidoglycan). The later are found within the cell walls of fungi and bacteria and activate the signal transducer and activator of transcription *STAT3*, *STAT1* and *CARD 9*. Exposure of naïve T cells to this cytokines induces their differentiation into Th17 cells which produce IL-17 with essential effector functions for adequate response of the immune system against Candida infections of oral and vaginal mucosae, skin and nails [9].

Patients with genetic defects in Th17 immunity suffer from recurrent infections by *Candida* species, involving mucosae or skin. Most cases are sporadic, but both, isolated or syndromic, with AD or AR inheritance, have been described [10].

Recent findings show low IL-17 production and/or plasma levels in patients with AD hyper-IgE syndrome and subjects bearing heterozygous *STAT3* mutations, susceptible to CMC and staphylococcal diseases, as well as in a family with AR *CARD9* deficiency, prone to CMC and other fungal infections [7]. High levels of autoantibodies against IL-17 were documented in patients with AR autoimmune polyendocrine syndrome type 1 presenting with CMC, and in AD form of isolated CMC with *STAT1* GOF mutation [7].

Physiopathology findings in patients with CMC and potential mechanisms involved

The first reported genetic etiologies of CMC, impairing IL-17-producing T cell development, were: *AR IL-17RA* (IL-17 receptor alpha) and *AD IL-17F* deficiencies [10] and *STAT1* GOF mutation.

Some genetic etiologies of CMC have been well-described, mutations in some genes like: AIRE, STAT1, STAT3 (2,4,11,12,13,14,15,16,17) Other genetic syndromes are associated with far smaller numbers of cases, such as those due to mutations of *IL-17RA*, *ACT1*, *IL-17F*, *PTPN22*, *CLEC7A*, *TLR3*, *CARD 9* (5,6,10,11,12,19,20,21,22, 23). There are distinct forms of CMC for which the genetic defects have not yet identified (24).

The diagnosis of CMC is based upon clinical features of the skin and mucous membranes lesions, demonstrably caused for Candida, of chronic recurrent evolution. It is necessary to rule out other causes of immune deficiency (primary and secondary) that affect T cell function, including combined immune deficiencies, usually refractory to antifungal treatments.

The treatment includes antifungal therapy and treatment of associated endocrine and autoimmune abnormalities, as appropriate. There are two reports of successful hematopoietic cell transplantation [25,26] and one report of long-term clinical remission in a patient with a *STAT1* mutation treated with G-CSF [7].

We have done a therapeutic trial with G-CSF. However, our patient did not show any clinical benefit or a restoration in the production of IL-17 *ex vivo* by lymphocytes Th17. The patient did not have the previously reported *STAT1* GOF mutation [7], and no other genetic defect has been found so far (Table 1).

Biochemistry	Full blood count	T-cell and NK count	Autoantibody levels and other biomarkers	Hormonal axis	Iron profile and vitamin B12	Immunoglobulins and complement	Organ specific antibodies	Viral serologies
Normal renal function	Hemoglobin 10,9 g/dl (11.7-16).	CD4 normal	ANA, ANCA, anti-DNA, anti-ENAs, Antiphospholipid antibodies, negative	TSH: 1,08 µUI/dl (0.35-5,5)	Serum iron level: 27 µg/dl, (50-170),	Ig A, M, G, E and IgG subclasses normal	Anti-parathyroid antibodies negative	HCV, HBV, HAV, negative
Normal hepatic function	Hematocrit 35,5 % (36-48)	CD8 normal	Antibodies against myositis antigens negative	T4 0,9 ng/dl (0,9-1,8)	Transferrin saturation 7% (15-50),	Complement normal	Anti-adrenal antibodies negative	HIV negative
Normal ions and low 25-hidroxi-vitamin D	Medium corpuscular volume 92 fL (80-100)	CD4/CD8 ratio normal	Rheumatoid factors and antibodies to cyclic citrullinated peptidenegative	Cortisol, ACTH normal	Ferritine 81 ng/ml (10-291)	Serum electrophoresis without monoclonal peak	Anti-ovary antibodies negative	
	ESR normal	NK normal	Angiotensi-converting enzyme negative		Vit B12 normal			

Table 1. Laboratory results and screening tests.

Conclusions

Many causes of CMC, either isolated or associated with other autoimmune or endocrinopathic manifestations have been elucidated. The recent works on IL-17 and Th17 cells have led to an expanded understanding of the mechanisms underlying the host defense from *Candida* sp. on mucosal surfaces. This pathway is regulated by multiple receptors and signal transductors, requiring normal function from all of them, to achieve an adequate fungal immune response. Whether some of these pathways might be modulated by G-CSF, others appear to be unresponsive.

Further studies should determine the most effective treatment for each of the molecular and clinical manifestations experienced by these patients.

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