

WHEN YOU CANNOT BEAT BACK THE MOULD: CHRONIC MUCOCUTANEOUS CANDIDIASIS

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ABSTRACT

Candida spp are normal human commensal fungi that have co-evolved with human beings over millennia. Normal host immunity with a delicate balance of pro- and anti-inflammatory signals maintains a stable host–fungus relationship. T-cells, particularly intact T-helper 17 cell, neutrophils and the type-1 interferon cytokine networks are non-redundant for preventing invasive fungal disease. Self-limiting and/or easily treated mucosal infections to candida occur in immunocompetent hosts, usually associated with altered mucosal-barrier integrity. In contrast, severe, persistent and recurrent mucosal-candida infections – known as ‘chronic mucocutaneous candidiasis’ (CMC) – suggest an underlying immunodeficiency and warrant investigation. To date, more than ten gene defects have been associated with CMC, either alone or in combination with other syndromic features and/or infections. In this review, we present the first South African CMC family with a confirmed gain-of-function (GOF) STAT1 mutation. We discuss host fungal immunity to candida, describing the known gene defects and then outline a clinical approach to the diagnosis, highlighting specific management of issues in the care of patients with CMC.

CASE PRESENTATION

Our index case is a 37-year-old Caucasian female from non-consanguineous parents. She was born at term with an unremarkable neonatal period. However, from an early age she recalls having severe and multiple fungal nail infections. She received prolonged, predominantly azole, antifungal therapy, but despite this, lost many nails. While at high school she was hospitalised for severe oesophageal candidiasis. Most recently, recurrent oesophageal candidiasis – complicated by an early stricture – prompted referral from a local infectious-disease specialist. She did not have a history of:

- recurrent upper or lower respiratory-tract infections;
- atopic disease;
- skeletal abnormalities, or
- autoimmunity.

Interestingly, apart from candida infections and related complications, her only severe illness was peritoneal tuberculosis with a confirmed diagnosis on biopsy; she responded to standard therapy and has had no recurrence. Examination was unremarkable, given her recent in-patient antifungal therapy. Investigations excluded secondary immunosuppression; organ function was normal, including a normal TSH and fT4, but antithyroid globulin and antithyroid peroxidase autoantibodies were elevated.

The family history supported an autosomal dominant pattern of inheritance. She is an only child. Her father (deceased at age 62) also suffered from severe candida infections. These were complicated by a severe oesophageal stricture and required repeated stenting. She has two children and her son – aged eight – is also has CMC. The features were consistent with either isolated CMC or the recently described GOF mutation in STAT1. The family received genetic counselling, and DNA from the patient and her son was sent to the National Institutes of Health (NIH) in Maryland, the United States, for amplification and sequencing of coding exons and flanking splice sites of STAT1. Analysis of the sequencing reads demonstrated a single base transition, c.821G>A causing the substitution of glutamine for arginine at amino acid 274 (p.R274Q). This is diagnostic of heterozygous STAT1 mutation c.821G>A; p.R274Q consistent with AD STAT1 deficiency.

INTRODUCTION

Fungi are ubiquitous in the environment and human beings are exposed to them continuously. Commensal fungi, such as *Candida albicans* have co-evolved with human beings over millions of years, leading to complex mechanisms of immune surveillance and host control, antagonised by fungal evasion strategies. Disruption of host–fungal homeostasis can lead to disease; in the case of candida

infection in immunocompetent hosts a self-limiting or easily treated mucosal disease ensues, e.g. vulvovaginal candidiasis. However, in certain individuals, either with secondary immunodeficiency such as chemotherapy-associated neutropaenia or primary immunodeficiencies, invasive or severe, persistent and/or recurrent mucosal disease can occur. In this review, we discuss anti-fungal immunity highlighting the relevant pathways of the known immune-gene defects associated with CMC. Thereafter, for the treating clinician, we contextualise CMC from other self-limiting or easily treatable mucosal candida infections. We outline an approach to the clinical care of CMC, while considering diagnosis, associated conditions and complications, and finally treatments.

NORMAL FUNGAL IMMUNITY TO CANDIDA

The host's immune response to candida and other fungal infections involves both resistance (the ability to limit fungal burden) and tolerance (the ability to limit host damage caused by the immune response or other mechanisms).¹ Innate and adaptive immune responses are required to manage the dynamic states of fungi. Figure 1 below provides an overview of the host's immune response to candida, showing the key immune cells and cytokines. The crosstalk between antigen-presenting cells, activated by pattern-recognition receptors (PRRs) and the T-lymphocyte, is highlighted to show molecules where known gene defects lead to CMC.

The first line of defence to candida is the mechanical barrier provided by the epithelium. Epithelial cells can produce β -defensins with direct anti-candida activity and cytokines that recruit phagocytic-immune cells. Candida can invade the tissue by inducing endocytosis or actively penetrating the epithelial cells. On invasion of tissues, candida encounters tissue-resident macrophages which phagocytose and clear candida; neutrophils are recruited and kill by the production of reactive oxygen species (ROS) and the formation of neutrophil extracellular traps. These innate host cells express PRRs such as Toll-like receptors (TLRs), C-type lectin receptors (CLRs) and the galectin family proteins, which sense and recognise evolutionarily conserved fungal pathogen-associated molecular patterns (PAMPs).^{2,3} PRR recognition of pathogens and uptake of pathogen by dendritic cells (DC) lead to the differentiation of naïve T-cells into effector T-helper (Th) cell subtypes.¹ Owing to their central role in fungal recognition and initiation of effective innate and adaptive immune responses, individuals with certain genetic deficiencies of the PRRs – e.g. CARD9 and Dectin-1 – are highly susceptible to candida infections.^{1,4}

Adaptive fungal immunity centres on the balance between Th-17, Th-2 and Th-1 effectors, driven by the DC responses to TLR and CLR signals provided by the fungus. Inflammatory DCs initiate antifungal Th-17 and Th-2 cell responses, whereas tolerogenic DCs activate

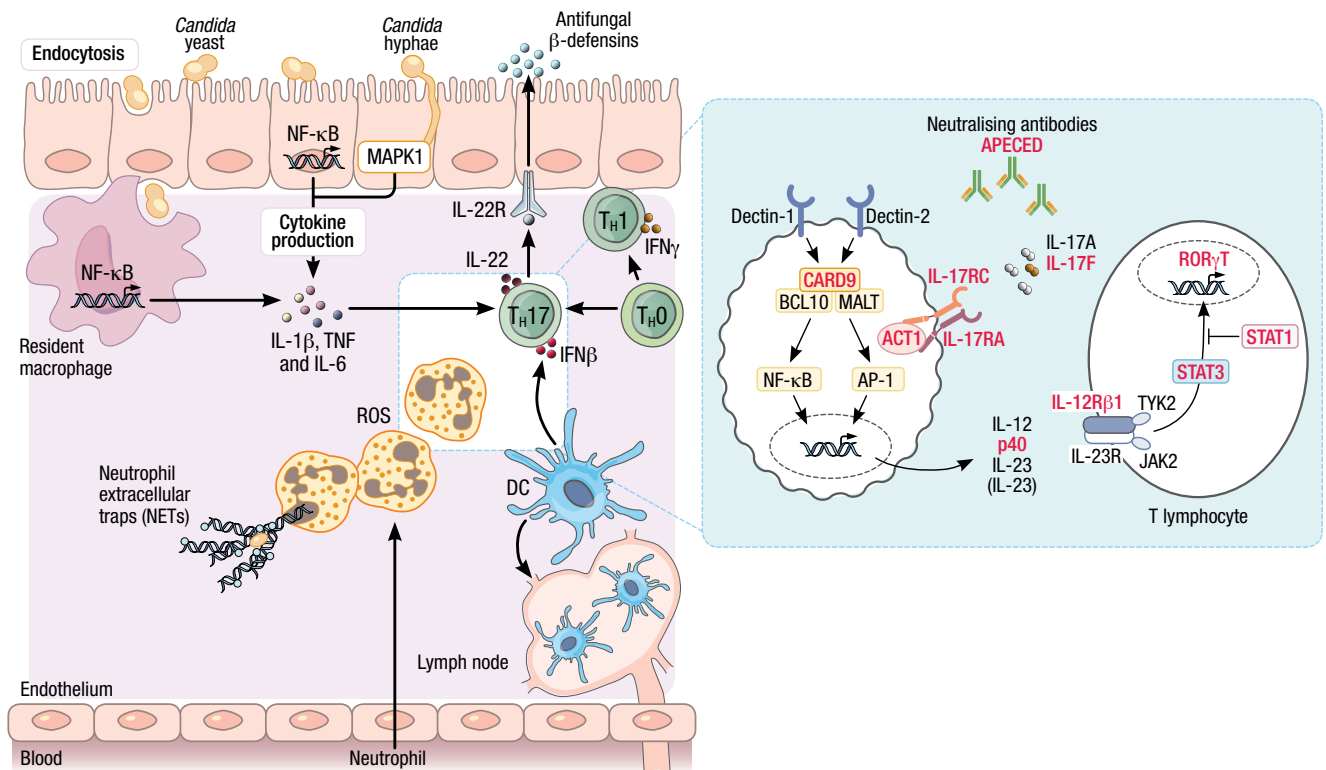


Figure 1: Main players in normal host candida immunity highlighting known molecular defects

Abbreviations: ROS: reactive oxygen species; DC: dendritic cells; APECED: autoimmune polyendocrinopathy candida and ectodermal dysplasia

TABLE I: SPECTRUM OF CANDIDA PATHOLOGY, ASSOCIATED SECONDARY CO-MORBIDITIES AND GENETIC SUSCEPTIBILITIES

CLINICAL PATHOLOGY	SECONDARY IMMUNODEFICIENCY	GENETIC SUSCEPTIBILITY
Intermittent and isolated - oral thrush - VVC - intertrigo - Fungal sinusitis	DM VVC – associated with antibiotic use, COC, HRT and pregnancy	SNPs in IL-4, MBL2, NLRP3 Uncertain effect size of SNPs compared with environmental factors (e.g. antibiotic drug use)
Recurrent and persistent	DM, AIDs, HIV	CMC disorders (see Table II) SNPs IL-4, MBL2 and NLRP3
Severe/organ-invasive - meningitis - sepsis - invasive organ disease	HIV Solid tumor HSCT Immunosuppressive Rx Major organ failure	Severe combined immunodeficiencies (SCID)
Unusual species (e.g. <i>Candida auris</i> ; <i>C. haemulonii</i>)	DM, solid tumor, HSCT, steroid therapy	Unknown

Abbreviations: DM: diabetes mellitus; SNPs: short nucleotide polymorphisms; VVC: vulvovaginal candidiasis; COCs: combined oral contraceptives; HRT: hormone-replacement therapy; MBL: mannan-binding lectin; NLRP3: NLR family pyrin domain containing 3; HIV: human immunodeficiency virus; HSCT: hematopoietic stem-cell transplant; CMC: chronic mucocutaneous candidiasis

Th-1 and regulatory T-cell differentiation. Furthermore, signal transducer and activator of transcription 3 (STAT3) contributes to DC plasticity and functional specialisation. A dominant Th-1 response correlates with strong immunity against fungal infections. Activated Th-1 cells then produce effector cytokines, e.g. IFN-gamma and induces B-cell production of opsonising antibodies. In contrast, Th-2 responses favour fungal infections, fungus-associated allergic responses and disease relapse. Th-17 cells are regulatory in fungal immunity by promoting Th-1 responses and restraining Th-2 responses. These cells form part of the fungus-specific repertoire of memory cells. In the absence of Th-1 and Th-17 cells, then IL-22 (part of the AHR-IL-22 pathway) provides protection against candida at mucosal sites. IL-22 is produced by numerous both activated innate lymphoid cells and Th-1 and Th-17 cells. This protection is particularly prominent against candida overgrowth in the intestinal mucosa.^{4–7}

SPECTRUM OF CANDIDA INFECTIONS: WHEN NOT TO WORRY

The majority of candida infections are self-limiting or easily treatable (see Table I). Oral thrush and vulvovaginal candidiasis (VVC) are most commonly encountered in routine clinical practice. Oral thrush presents as creamy white lesions usually on the tongue or on the inner cheeks. Sometimes, this spreads to the roof of the mouth, palate and pharynx. This may be asymptomatic or cause altered taste sensation, pain, difficulty in chewing and swallowing and, sometimes, bleeding.⁸ Common risk factors for oral thrush include the use of inhaled corticosteroids (e.g. in asthmatics), diabetes, wearing dentures and multiple other causes of secondary immunosuppression: e.g. HIV or cancer and/or chemotherapy.⁹

In people with a competent immune system, oral thrush is often self-limiting, but risk factors need to be eliminated or reduced. Therapy often involves regional antifungals,

e.g. nystatin oral drops, with resolution usually in a few days.¹⁰ Many South African clinicians will have seen severe, persistent or recurrent oral thrush in the context of HIV/AIDs, often progressing to esophageal involvement, causing dysphagia and hyponutrition.^{10,11}

The other common mucosal presentation of candida is VVC.¹² This causes irritation, intense itching and whitish discharge. Associated dysuria, dyspareunia and, rarely, bleeding may be present. Common risk factors for VVC include antibiotic use, especially broad-spectrum antibiotics.¹³ Increased estrogen levels, usually seen in pregnancy or in women taking combined estrogen contraceptives or HRT, also increase the risk.¹⁴ Infections are usually self-limiting, but may need local treatment. Recurrent and/or more extensive VVC should prompt investigations to improve the vaginal microbiota as well as exclusion of secondary immunosuppression.¹⁵

Increasingly, patients investigated for intestinal dysbiosis indicate that they have received treatment – either traditional or alternative – for gastrointestinal candida overgrowth. Prolonged or recurrent use of broad-spectrum antibiotics is often identified as a risk factor, causing alteration in the microbial milieu and prompting candida overgrowth as in VVC.¹⁶ There are mouse models of colitis with knock-out of TLR1 and TLR2, associated with increased intestinal inflammation and the overgrowth of *C. albicans* and *E. coli* populations. These models suggest the involvement of TLR1 and TLR2 in epithelial homeostasis and a role of TLR6 in increasing intestinal inflammation in response to pathogen-sensing.¹⁷ This is now one aspect of therapies used by functional nutritionalists who use dietary manipulation to alter the intestinal microbiota, aiming to limit fungal growth and, secondarily, inflammation. Although no robust data are available to link these changes to improved patient symptomatology in large prospective trials, the ability of dietary manipulation to alter the intestinal microbiome and attendant endomucosal inflammation is well established.¹⁸

TABLE II: KEY GENETIC DEFECTS IN CMC (ADAPTED FROM OKADA 2016²⁰)

DISEASES*	% CMC	OTHER INFECTIONS	ASSOCIATED FEATURES	IMMUNOLOGICAL PHENOTYPE	GENE	INHERITANCE
SYNDROMIC CMC						
Hyper IgE	85	<i>Staphylococcus</i> , <i>Aspergillus</i>	Eczema, scoliosis, pneumatocele, hyperextensibility, dysmorphic facial features, retention of primary teeth	Increased serum IgE, eosinophilia, decreased IL-17-producing T-cells	STAT3	AD
STAT1 GOF	98	Bacteria, viruses, fungi, mycobacteria	Aneurysm, autoimmune diseases, endocrine diseases	Decreased IL-17-producing T-cells, decreased switched memory B-cells	STAT1	AD
APECED	70–98		Ectodermal dysplasia, autoimmune dysfunction of parathyroid and adrenal glands, alopecia	Neutralising antibodies against IL-17A, IL-17F and/or IL-22	AIRE	AR
CARD9 deficiency	35–86		Dermatophytes, candida, brain abscess	Decreased IL-17-producing T-cells, impairment of C albicans killing by neutrophils	CARD9	AR
IL-12Rβ1 and IL-12p40	6–25	Mycobacterium, Salmonella		Decreased IL-17-producing T- cells, impaired IL-12 signalling	IL12RB1 IL12B	AR
ISOLATED CMC DISEASE						
IL-17RA deficiency	3/3 (100)	<i>Staphylococcus</i>		No response to IL-17A, IL-17E and IL-17F	IL17RA	AR

*All individual disorders are uncommon. Additional gene defects causing isolated CMC disease, but described in fewer than ten patients, include: RORYT deficiency, IL-17RC and IL-17F deficiency and ACT1 deficiency are not included.

Abbreviations: CMC: chronic mucocutaneous candidiasis; STAT: signal transducer and activator of transcription; AD: autosomal dominant; AR: autosomal recessive; AIRE: autoimmune regulator; APECED: autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy; IL: interleukin; CARD: caspase recruitment domain-containing protein

Patients that have persistent, severe and recurrent mucosal-candida infections need to be investigated for an underlying immunodeficiency. Likewise, dissemination of candida to major organ systems (e.g. lungs, liver, heart valves, GI tract and CNS) always occurs in the context of severe underlying immunosuppression, requiring diagnosis and treatment.¹⁹ While this deals with the underlying immune deficiency, such patients need systemic antifungal therapy, often for several weeks, with a subsequent need for secondary prophylaxis.¹⁹

SPECIFIC GENE DEFECTS ASSOCIATED WITH SUSCEPTIBILITY TO CANDIDA

In South Africa, the majority of severe and recurrent mucosal candidiasis occurs in the context of persons living with HIV/AIDS. Oesophageal candidiasis is the most common. Other secondary immunosuppressive conditions that should be considered have been highlighted in the previous section and in Table I above. Once these secondary conditions have been excluded and especially where there is a family history of CMC – as in our case presentation – a genetic diagnosis should be pursued.

Table II, adapted from an excellent review article by Okada et al,²⁰ shows the key known gene defects resulting in CMC. Perhaps the most important are the associated clinical features that can aid diagnosis and target gene sequencing. Most CMC cases occur in the context of gene defects with other clinical features. Two of the most common gene defects causing syndromic CMC result from two very different defects

in signal transducer and activator of transcription (STAT) second messenger molecules – STAT3 and STAT1 (see Figure 1). Patients with autosomal dominant (AD) hyper IgE develop CMC and staphylococcal infections associated with other characteristic manifestations and elevated IgE; this is a dominant-negative mutation impairing STAT3-dependent signalling that limits the downstream production of IL-6, IL-21 and/or IL-23. Deficiency in these cytokines leads to a severe decrease in circulating IL-17A-producing and IL-22-producing T-cells with a consequent increased fungal susceptibility. In contrast, in AD gain-of-function (GOF) STAT1 mutations, now thought to be responsible for half of all CMC cases globally the mutations impair the dephosphorylation of STAT1, leading to a persistent 'on' switch after stimulation with IFN-γ, IFN-α/β, and IL-27 and IL-27. This, in turn, inhibits TH-17 cells and IL-17A, IL-17F and IL-22 production and leads to increased fungal susceptibility. GOF mutations are preferentially identified in the coiled-coiled and DNA-binding domains of STAT1. Partial or complete autosomal recessive mutations in other regions of the STAT1 gene are also described; they cause primary immunodeficiencies, but result in increased susceptibility to viral and intracellular pathogens – an excellent illustration of the complexity of monogenic primary immunodeficiency.²⁰

CMC is the major manifestation of GOF STAT1 mutations, but some patients develop fungal infections other than candidiasis, or bacterial and viral infections, mycobacterial infections and autoimmune disorders which can be severe. Toubiana et al report the largest cohort of patients with GOF-STAT1 mutations, describing 274 cases from 167

TABLE III: MAJOR ANTIFUNGAL DRUG CLASSES, MECHANISMS OF ACTION AND SPECIFIC DRUGS USED IN THE TREATMENT OF CMC

ANTIFUNGAL DRUG CLASS	MECHANISM OF ACTION	DRUG NAMES
Azoles	Ergosterol synthesis inhibitors (cell membrane)	Ketoconazole, fluconazole, itraconazole, voriconazole, posaconazole, ravuconazole
Polyenes	Fungal membrane-disrupting agents (e.g. pores in membrane)	Amphotericin B, nystatin
Allylamines	Ergosterol synthesis inhibitors	Terbinafine, butenafine
Echinocandins	Glucan synthesis inhibitors (cell wall)	Caspofungin, anidulafungin, micafungin
Other	Anti-mitotic (spindle disruption)	Griseofulvin

kindreds. The median age of onset of CMC was one year. Many patients also suffered bacterial infections (74%), mainly *S aureus* (36%) and viral infections (37%) typically caused by herpes viruses. Mycobacterial disease – as in our index case – is reported in 6% only. Autoimmunity occurred in 37%, with hypothyroidism in 23%.²¹ Isolated CMC disease, outside of GOF-STAT1 mutations, is extremely rare, having been described in only a few kindreds globally.²⁰

CLINICAL PRACTICE POINTS IN THE CARE OF PATIENTS WITH CMC

DIAGNOSIS

The clinical presentation of mucosal candidiasis is usually straightforward. However, diagnostic confirmation, especially in cases of recurrence is useful to guide thinking and, more importantly, in patients with established CMC, to attain samples for speciation and drug-susceptibility testing. Scrapings or smears obtained from skin, nails or oral or vaginal mucosa are examined as a wet prep under the microscope using a potassium-hydroxide smear, Gram stain or methylene blue for direct demonstration of fungal cells with a light microscope. In cases where oesophageal mucosal involvement is suspected, endoscopy with biopsy with or without culture is necessary. Species identification requires fungal cultures using various assays. Antifungal drug-susceptibility testing using dilution assays and PCR are key to aiding in the proper selection of targeted therapy. In disseminated candidiasis, blood cultures can be performed but yield positive results in only 50–60% of cases.^{22–24} The only available biomarker identifies *systemic* fungal infections – serum 1, 3 β -D-glucan measures the level of β -glucan (a fungal cell-wall component); it is useful in monitoring the development of systemic or invasive fungal infections in patients with advanced immunosuppression. If the diagnosis of CMC is suspected, further detailed immunological tests of cell-mediated immunity (e.g. TH-17 cell number) or autoantibody measurement (e.g. anti-IL-17F) may help define the phenotype, allowing for targeted genetic approaches.²⁵

If a familiar form of CMC is suspected, genetic diagnosis is required. Targeted gene sequencing is the most cost- and time-efficient method. The index case had the results of testing available in under six weeks, and given the interest of the NIH in STAT1 mutations, the only patient costs incurred were for DNA extraction and shipping. Similarly, targeted sequencing can be accessed for the STAT3 and autoimmune

regulator (AIRE) gene responsible for Hyper IgE and APECED syndromes respectively. If the clinical phenotype is not as clearly defined, the options include: first, PID gene panels covering the common CMC genes or, secondly, whole exome/genome sequencing. This is decreasing in cost each year and becoming more accessible locally.

COMPLICATIONS AND ASSOCIATED CONDITIONS

The long-term management of patients with CMC should be two-pronged. First, where possible, genetic diagnosis should be sought. The main reason for this is that the majority of PID genes associated with CMC are syndromic and therefore have associated conditions (see Table II). Knowledge allows for targeted monitoring and follow-up. For instance, APECED patients require close endocrine follow-up as endocrinopathies can develop with unpredictable sequence and timing, becoming life-threatening. Similarly, GOF-STAT1 patients also develop autoimmunity and endocrinopathy (see the list of additional clinical features); additional testing for our index patient was based on the known genotype–phenotype associations and the results suggest that close monitoring is required.

Other benefits of genetic diagnoses include counselling about the mode of inheritance and screening for asymptomatic patients. The second focus in the long-term management of CMC patients is drug susceptibility and the sequelae of severe and recurrent candidiasis, particularly oesophageal. They are at high risk of drug resistance, especially to the azoles. This has particularly been described with the use of intermittent regimens or sub-optimal dosages. Oesophageal and/or laryngeal involvement may lead to hoarseness, dysphagia and hemoptysis. Several cases have been reported of symptomatic stricture formation and pseudodiverticulosis, with such patients needing periodic endoscopic dilatation or placements of stents.

Furthermore, CMC of the oral cavity has been linked to malignant transformation into squamous cell carcinoma of the oral cavity and/or oesophagus, especially in those with APECED syndrome.²⁶ Complications related to specific genetic defects, e.g. STAT1 GOF, have been described.

TREATMENT OPTIONS

CMC requires treatment with topical and/or systemic antifungals. Fortunately, the armamentarium of antifungal drugs has been growing. Table III outlines the major antifungal drug

classes, mechanism of actions and the drugs in each class. Azoles remain the most used and usual first-line therapy for CMC; the other classes such as polyenes (amphotericin B – standard and liposomal, nystatin), griseofulvin, allylamines and the newest agents – echinocandins – may also be required during the course of the illness. In CMC these agents are used for both treatment and prophylaxis. The choice of agent, its usage and the duration of treatment must be guided by sound antifungal stewardship programmes. Ideally, a multidisciplinary team of general specialist, immunologist, microbiologist and infectious-disease specialist should manage these cases in close contact with the patient so that the burden of disease and complications can be minimised through appropriate admissions for intravenous or intramuscular therapies. Where appropriate, patients with certain syndromic CMC (e.g. GOF STAT1) may also need antibiotic prophylaxis to prevent staphylococcal infections; sulfamethoxazole-trimethoprim is the usual choice.

Patients with GOF-STAT1 mutations may develop autoimmunity, as outlined above; target disease-appropriate immunosuppressive treatment may be required. Interestingly, the Janus kinase inhibitor, ruxolitinib, has been trialled in two patients, which has led to improvements in both CMC and autoimmune syndrome, without adverse effects.²⁰ In patients with syndromic CMC and severe clinical phenotypes – e.g. recurrent severe

viral and/or bacterial infections – haematopoietic stem-cell transplantation (HSCT) might be considered as a treatment option. Examples of HSCT being curative for CMC are available in the published literature.²⁰

CONCLUSION

Candida and human beings are intertwined, with fungi and host living in a delicate homeostatic impasse. Disruption of this fine balance can cause disease, which in immunocompetent individuals is restricted to a self-limiting or easily treated mucosal disease. However, in certain individuals, either those with secondary immunodeficiency or those with a small but growing list of primary immunodeficiencies, invasive or severe, persistent and/or recurrent mucosal disease secondary to candida can occur. A good history and examination suggestive of CMC should prompt the pursuit of a genetic diagnosis wherever possible. In addition, a number of associated conditions and complications can be anticipated. Optimal antifungal therapy and long-term care can be provided by teams comprising general specialists, immunologists, microbiologists and infectious-disease specialists.

DECLARATION OF CONFLICT OF INTEREST

The authors declare no conflict of interest.

This article has been peer reviewed.

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