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Review

New clinical phenotypes of fungal infections in special hosts

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ABSTRACT

Incidence of invasive fungal infections increases over time with the rise in at-risk populations; in particular, patients with acquired immunodeficiencies due to immunosuppressive therapies such as anti-tumour necrosis factor-α (TNF-α) treatment, cirrhosis or burns. Some primary immunodeficiencies (PID) can also predispose selectively to invasive fungal diseases. Conversely, some atypical fungal diseases can reveal new PID. Deep dermatophytosis, *Candida* central nervous system infections or gastrointestinal disease, or disseminated phaeohyphomycosis-revealed CARD9 deficiency. Most patients with inherited chronic mucocutaneous candidiasis were found to carry *STAT1* gain-of-function mutations. The spectrum of fungal susceptibility and clinical presentation varies according to the PID. Among acquired immunodeficiencies, immunosuppressive treatments such as TNF-α blocker therapy, which has revolutionized autoimmune disorder treatment, may be complicated by endemic mycosis, aspergillosis, pneumocystosis or cryptococcosis. Burn patients with damaged skin barrier protection are susceptible to severe *Candida* infections and filamentous fungal infections (such as *Aspergillus* spp., *Mucorales*). Moreover, patients with cirrhosis are at increased risk of fungal infections. Therefore, physicians should think of any potential underlying acquired or inherited immunodeficiency in a patient developing an atypical fungal infection, or of a potential fungal disease in the context of an atypical presentation in specific hosts. **CMI 2016;22:681**

Introduction

Over the past decades, fungal infection incidence has increased dramatically [1]. The number of patients with haematological malignancies, allogeneic haematopoietic stem cell transplantation, solid organ transplant, immunosuppressive therapies, including anti-tumour necrosis factor-α (TNF-α) therapy has increased over time, explaining the rise of candidaemia, invasive aspergillosis and mucormycosis [1]. Invasive fungal diseases (IFD) occur in patients with host factors such as primary or acquired immunodeficiency or can be due to environmental factors. The development of genetic tools, such as next generation sequencing, led to the identification of new primary immunodeficiencies (PID) predisposing to specific forms of invasive fungal infections. Better survival of patients with severe conditions due to acquired immunodeficiencies such as cirrhosis or with extensive burns led to the description of IFD in these settings. We review IFD presentation in special hosts including new phenotypic fungal disease revealing new innate immunity defects and IFD in selected groups of patients with impaired immunity (Table 1).

Fungal Diseases in Primary Immunodeficiencies

New phenotypic fungal disease revealing 'new' innate immunity defects

Invasive fungal infections associated with autosomal recessive CARD9 deficiency

Caspase recruitment domain family, member 9 (CARD9) is a major component of the anti-fungal innate immune response, involved in the signalling downstream of C-type lectin receptors, such as Dectin-1, Dectin-2 and Mincle [2], and the production of pro-inflammatory cytokines after fungal recognition [3].

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Table 1
Immune deficiency and fungal infections presentation

Immune defect	Fungal infection	Clinical phenotype
Primary immunodeficiency		
CARD9 deficiency	Deep dermatophytosis [5–11]	Severe or recurrent tinea capitis (84.2%) Recurrent tinea corporis (63.1%) Onychomycosis (42.1%) Papules, nodules, extensive and infiltrative lesions resistant to antifungal treatment Lymph node involvement (52.6%) Organ (bones, central nervous system, digestive tract) extension (15.7%)
	Central nervous system candidiasis [12–18]	Cerebral abscess Meningitis Meningo-encephalitis
	Candida colitis [17]	–
	Phaeohyphomycosis [20–22]	Subcutaneous infection *Phialophora verrucosa* *Corynespora cassiicola* Disseminated infections *Exophiala dermatitidis* (cholangitis, cerebral abscesses), *Exophiala spinifera* (bone, lung)
STAT1 gain-of-function	Chronic mucocutanous candidiasis [28–31]	Chronic mucocutaneous candidiasis (*Candida albicans*) Oral candidiasis (73%) Aphtous stomatitis (69%) Onychomycosis (64%)
	Invasive fungal infection [19]	Cryptococcosis, Mucormycosis, Dimorphic fungal infections
Chronic granulomatous disease	Aspergillosis [32–35]	Pneumonia (*Aspergillus fumigatus*, *Aspergillus nidulans*) Loco-regional extension (*A. nidulans* > *A. fumigatus*) Osteomyelitis (*A. fumigatus*, *A. nidulans*)
Autosomal dominant hyper-IgE syndrome (STAT3 deficiency)	Fungal cutaneous infection [40]	Chronic mucocutaneous candidiasis (85%) (*C. albicans*) Oral candidiasis (63%) Chronic onychomycosis (57%) Genital candidiasis (18%) Cutaneous candidiasis (16%) Oesophageal candidiasis (8%)
	Fungal pulmonary infection [40,41]	Always on bronchiectasis or pneumatocoeles (*Aspergillus* spp., *Scedosporium apiospermum* complex, *Histoplasma capsulatum*)
Acquired immunodeficiencies		
Tumour necrosis factor blocker therapy	Histoplasmosis [44,45]	Pneumonia Miliary or reticulonodular infiltrates Progressive disseminated histoplasmosis Hepatosplenomegaly (30%–40%) Gastrointestinal obstructions (12%–13%) Extra-pulmonary lymphadenopathy (7%–8%) Skins lesions (3%–4%)
	Coccidioidomycosis [48]	Pneumonia (100%) Disseminated infections (30.8%)
Liver disease (cirrhosis)	Spontaneous fungal peritonitis [51,52]	Spontaneous fungal peritonitis (3.5%) (*C. albicans*, *C. neoformans*)
Burn patients	Cutaneous mold fungal infection [55,56]	Cutaneous infections (*Aspergillus* spp., *Fusarium* spp., Mucorales)

Furthermore, CARD9 was recently shown to play a major role in neutrophil trafficking into the central nervous system (CNS) [4].

Deep dermatophytosis

Dermatophytes are cosmopolitan filamentous fungi usually responsible for benign infections (tinea capitis, tinea corporis and/or onychomycosis) but in rare cases, such as in patients with acquired immunosuppression [5], they can invade the dermis and be responsible for deep dermatophytosis (Fig. 1). In North Africa, severe forms of dermatophytosis, in patients without known immunodeficiencies were described by physicians as '*Maladie dermatophytique*' [6]. Such patients, otherwise healthy, were reported as suffering from severe, extensive, deep dermatophytosis, affecting lymph nodes, bones, digestive tract or CNS, and resistant to antifungal treatments [7]. Skin histological examination revealed granulomatous dermatitis with dermal extension, frequent necrosis and eosinophilia (Fig. 2). Hyphae were present in the granuloma and sometimes in the cytoplasm of giant cells. Presence of hyphae in the dermis defines a diagnosis of deep dermatophytosis if the culture grows dermatophytes. The genetic study of patients from North Africa with deep dermatophytosis revealed that autosomal recessive CARD9 deficiency was responsible for all the so far reported cases of deep dermatophytosis [8–11]. Overall, 21 patients have now been reported with deep dermatophytosis and autosomal recessive CARD9 deficiency [8–11]. Based on published studies, median age at first symptoms was 8 years (range 6–11.25 years). The first symptoms were severe or recurrent tinea capitis for 84.2% patients, severe or recurrent tinea corporis for 63.1% and onychomycosis for 42.1%. Patients developed skin-invasive dermatophytic infection as well as lymph node (52.6%) or organ (15.7%) extension in young adulthood [8–10]. In deep dermatophytosis, skin lesions appear as plaques or infiltrative and/or ulcerative nodules and papules sometimes associated with itching, pain and discharge. Deep dermatophytosis in autosomal recessive