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ORIGINAL ARTICLE

Successful Allogenic Stem Cell Transplantation in Patients with Inherited CARD9 Deficiency

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Abstract

Autosomal recessive (AR) CARD9 (caspase recruitment domain-containing protein 9) deficiency underlies invasive infections by fungi of the ascomycete phylum in previously healthy individuals at almost any age. Although CARD9 is expressed mostly by myeloid cells, the cellular basis of fungal infections in patients with inherited CARD9 deficiency is unclear. Therapy for fungal infections is challenging, with at least 20% premature mortality. We report two unrelated patients from Brazil and Morocco with AR CARD9 deficiency, both successfully treated with hematopoietic stem cell transplantation (HSCT). From childhood onward, the patients had invasive dermatophytic disease, which persisted or recurred despite multiple courses of antifungal treatment. Sanger sequencing identified homozygous missense CARD9 variants at the same residue, *c.302G>T* (p.R101L) in the Brazilian patient and *c.301C>T* (p.R101C) in the Moroccan patient. At the ages of 25 and 44 years, respectively, they received a HSCT. The first patient received a HLA-matched HSCT from his CARD9-mutated heterozygous sister. There was 100% donor chimerism at D + 100. The other patient received a T cell–depleted haploidentical HSCT from his CARD9-mutated heterozygous brother. A second HSCT from the same donor was performed due to severe amegakaryocytic thrombocytopenia despite achieving full donor chimerism (100%). At last follow-up, more than 3 years after HSCT, both patients have achieved complete clinical remission and stopped antifungal therapy. HSCT might be a life-saving therapeutic option in patients with AR CARD9 deficiency. This observation strongly suggests that the pathogenesis of fungal infections in these patients is largely due to the disruption of leukocyte-mediated CARD9 immunity.

Keywords CARD9 · primary immunodeficiency · deep dermatophytosis · hematopoietic stem cell transplantation · invasive dermatophytic disease

Introduction

Autosomal recessive (AR) CARD9 deficiency predisposes to chronic superficial and invasive fungal infections. CARD9 is an essential adaptor molecule, which forms a complex with B cell lymphoma 10 (BCL10) and mucosa-associated lymphoid tissue lymphoma translocation gene 1 (MALT1) and mediates intracellular signaling during antifungal immunity [1]. This complex engages CARD9 in the canonical NF-κB and MAPK (mitogen-activated protein kinase) pathways, enhancing the production of pro-inflammatory cytokines and chemokines [2]. CARD9 is primarily expressed in myeloid cells, especially neutrophils, macrophages, and dendritic cells [3, 4]. In patients with CARD9 deficiency, phagocytes probably play a key role in invasive infections, as suggested by the impaired cytokine and chemokine production by macrophages, peripheral blood mononuclear cells (PBMCs), or dendritic cells (DCs) [2]. Defects of fungal killing by neutrophils and impaired neutrophil recruitment to the site of infection have been found in vitro or in vivo, in both humans and mice [5–9]. The cellular basis of invasive fungal disease (IFD) in CARD9-deficient patients, however, remains unclear. The contribution of non-hematopoietic cells cannot be excluded.

Key Points
- Allogenic stem cell transplantation is a therapeutic option for CARD9 deficient patients.
- Our observation supports the role of hematopoietic cells in the pathogenesis of fungal infections in patients with CARD9 deficiency.

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In addition, CARD9 probably influences Th17 cell differentiation, possibly by inducing the production of pro-Th17 cytokines (e.g., IL-6, IL-23) by myeloid cells upon fungal recognition. CARD9 deficiency therefore apparently also underlies defects of Th17 functions [2].

The spectrum of IFD in CARD-9-deficient patients has progressively expanded, with the description of patients with extensive/deep dermatophytosis [7, 10, 11], invasive *Candida* spp. diseases [12–14], subcutaneous and invasive phaeohyphomycosis [15], extrapulmonary invasive aspergillosis [8], or more recently, cutaneous mucormysosis [16]. A striking feature is that all causal fungi belong to the ascomycete phylum [2], except *Mucorales* which belongs to the zygomycota phylum [16]. The risk of invasive candidiasis of the central nervous system seems to be increased in CARD9-deficient patients [8, 17, 18]. Several case reports describe recurrence of symptoms after multiple and/or combined antifungal therapies [10, 16, 17, 19–21]. A review of 58 patients with CARD9 deficiency showed that 52 (89.7%) had IFD and 19 (32.8%) patients displayed disseminated disease, as defined by affecting two or more organs although no persistent fungemia was found (proven positive blood culture) [2, 11, 18, 22]. In evaluating the result of antifungal therapy, approximately 2/3 of the patients relapsed after treatment cessation and almost 1/5 died from active disease at the mean age of 23 years [2]. Considering the severe clinical course and high mortality rate of deep dermatophytosis associated with inherited CARD9 deficiency, we performed HSCT in two patients, whose genetic and clinical features have been previously reported [10, 16].

Case Reports

Case 1

A 3-year-old male Brazilian patient born to non-consanguineous parents presented with erythematous scaly cutaneous lesions in the mandibular area and thrush. At that time, he was treated with topical nystatin and oral ketoconazole, and symptoms were controlled. During the following years, hair loss was observed without fungal identification, and lesions progressively disseminated to other skin areas, including the scalp. At the age of 12 years, an ulcerative lesion appeared in the inferior lip with rapid involvement of the mandibular area. Biopsy showed a deep fungal infection and *Trichophyton mentagrophytes* was identified. Itraconazole (200 mg/day) was given for 3 years, followed by 4 years of terbinafine (250–500 mg/day), and 3 years of posaconazole (400–800 mg/day). Combined antifungal treatment (specify here the treatment) and granulocyte-colony stimulating factor (G-CSF) were also used with poor or transient response [7]. At the age of 23 years, the patient was found to be homozygous for a novel variant *c.302G>T* in exon 3 of *CARD9* (p.R101L) [7]. One month before admission for HSCT, the patient presented with an ulcerative lesion on the back region of 30 × 15 cm and smaller lesions on the shoulder (Fig. 2, left panel). He received 3 weeks of therapy with amphotericin B lipid complex (3 mg/kg/day) and voriconazole (400 mg/day), with mild improvement of the ulcers before transplantation. When he was admitted, he presented with disseminated scaly and ulcerative lesions and a supraclavicular lymphadenopathy of 6 cm in diameter. A lymph node aspirate revealed several septated hyaline hyphae and culture identified *T. mentagrophytes* complex. The molecular identification was performed by sequencing the internal transcribed spacer regions of rDNA, as described previously, and was found 100% similar to *T. interdigitale* [20–22]. A classic immunophenotyping was performed and showed normal lymphocyte counts, with normal T cell subpopulation proportions, an increased eosinophil count (1368 cells/mm3); Immunoglobulin (Ig)G, IgM, and IgA were within normal ranges, while IgE was increased (> 2000 UI/mL), and proliferative T cell responses were impaired in response to *Candida* spp. (Table 1). Neutrophils showed impaired *Candida* spp. opsonophagocytosis. At the age of 25 years, the patient received a HSCT from his HLA-matched (8/8) 32-year-old healthy sister, heterozygous for the CARD9 variant. She was CMV and EBV seropositive, Toxoplasma seronegative, and ABO compatible. The conditioning regimen consisted of fludarabine 180 mg/m^2 (total dose, divided in 5 days); oral busulfan 12 mg/kg (total dose, divided in 4 days); and rabbit antithymocyte globulin (r-ATG) 7.5 mg/kg (total dose, divided in 3 days). Seven days after the beginning of the conditioning, a non-T cell–depleted bone marrow transplant was infused to the patient with a total nucleated cell dose of 4.76×10^8/kg and CD34$^+$ of 1.73×10^6/kg. GVHD immunoprophylaxis consisting of cyclosporine beginning one day before HSCT (d-1) and oral mycophenolate mofetil from day 1 (d + 1) to day 35 (d + 35) post-HSCT was given to the patient. The transplant course was complicated by mucositis grade 3 and febrile neutropenia that was treated with meropenen 1 g (3 times/day) and vancomicin 1 g (twice/day) for 14 days. He also received liposomal amphotericin B, 3 mg/kg/day, and oral terbinafine, 250 mg/day, for the treatment of fungal lesions. During the neutropenic phase, new erythematous scaly lesions emerged on the face, chest, and legs. A skin biopsy was performed showing hyaline-septated hyphae positive for *T. interdigitale* in culture. Granulocyte transfusions were performed from healthy volunteers, on days + 6, + 10, and + 11. The patient showed neutrophil engraftment on d + 16 and platelet engraftment on d + 35. He was discharged on d + 26 without any signs of acute GVHD, while receiving oral cyclosporine and mycophenolate mofetil, liposomal AMB and terbinafine. Total peripheral blood chimerism analysis on d + 30 showed only donor cells.

Table 1 Immunological evaluation of the two CARD9 deficient patients before and after hematopietic stem cell transplantation

	Before BMT	D + 30	D + 100	D + 180	D + 365	Normal range
Case 1						
IgG (mg/dL)	2110	nd	1950	1867	1808	540–1822
IgA (mg/dL)	101	nd	131	118	166	63–484
IgM (mg/dL)	65	nd	78	81	79	22–240
CD3+ (cells/mm3)	3739	–	–	–	–	1500–2300
CD4+ (cells/μL)	1854	18%	488	302	609	880–1500
CD8+ (cells/μL)	1353	38.3%	1151	668	1265	570–1010
CD4/CD8	1.37	0.47	0.42	0.45	0.49	1.5
B cells (cells/μL)	448	< 0.1%	16	144	401	230–950
NK cells (cells/μL)	82–760	10.3%	333	117	362	82–760
Global chimerism (%)	–	100 donor	100 donor	100 donor	100 donor	
Case 2						
IgG (mg/dL)	1240	nd	1870	632	1370	751–1560
IgA (mg/dL)	364	nd	27	11	107	82–453
IgM (mg/dL)	47	nd	12	9	67	46–304
CD3+ (cells/mm3)	2481	nd	881	2368	2109	798–2823
CD4+ (cells/μL)	1463	nd	210	378	306	455–1885
CD8+ (cells/μL)	940	nd	667	1965	1763	219–1124
CD4/CD8	1.54	nd	0.31	0.19	0.17	0.8–3.5
B cells (cells/μL)	336	nd	nd	nd	113	82–476
NK cells (cells/μL)	202	nd	nd	nd	226	66–745
Global chimerism (%)	–	100 donor	100 donor	100 donor	100 donor	

nd not done

On d + 40, the patient had a CMV reactivation and was treated for 14 days with gancyclovir 10 mg/kg/day. After engraftment, the size of the supraclavicular lymph node drastically reduced, the skin lesions rapidly improved, and a new skin biopsy on d + 70 showed no fungal involvement. On d + 80, he presented with an erythematous rash over 50% of his body surface diagnosed as GvHD and graded as acute GvhD grade II according to Glucksberg criteria. Metylprednisolone was started with an excellent and rapid response. Steroids were tapered and stopped by d + 100 and cyclosporine was stopped 8 months post-HSCT. After discharge from the HSCT Unit, he had no reactivation of the fungal lesions, and liposomal amphotericin B was stopped at d + 45 and terbinafine at d + 100. Immune recovery was also rapid and effective, as described below. Immunoglobulin levels (evaluated from d + 100 to d + 365) were normal and chimerism (evaluated from d + 30 to d + 365) showed 100% of donor cells for all lineages (Table 1; Fig. 1). The patient was doing well with scarring of all cutaneous lesions until d + 800 (Fig. 2, middle and right panels). At d + 900, a supraclavicular lymphadenopathy was noticed and biopsied. The excised lesion contained a purulent fluid with several hyaline hyphae on direct examination. Stained histologic sections also depicted fungal elements with granulomatous reaction, acute and chronic inflammation, and cellular debris. Tissue fragments and lymph node secretions were both negative for fungal culture after 1 month incubation in Sabouraud dextrose agar. He is now on d + 1320 without any symptoms. Whole blood chimerism was evaluated every year (2017 and 2018) and was complete.

Case 2

The second patient is a 44-year-old Moroccan male from consanguineous parents. During childhood, he presented with recurrent thrush and *tinea pedis*. At age 16, the patient developed hyperkeratotic skin lesions, initially limited to the left foot. Progressively, at the age of 35 years, these lesions extended to other body parts, became ulcerative, and were associated with severe lymphadenopathy. Radiological examination confirmed osteomyelitis of the first and second toe of the left foot. Histopathological examination of a deep skin biopsy was performed and revealed an inflammatory infiltrate with numerous granulomas and infiltrating eosinophils, plasma cells, and lymphocytes. These granulomas consisted of multinuclear cells containing PAS-positive intracellular conidia and hyphae; fungal culture and molecular analysis confirmed the presence of *Trichophyton rubrum*. The patient was subsequently diagnosed with deep dermatophytosis. At the age of

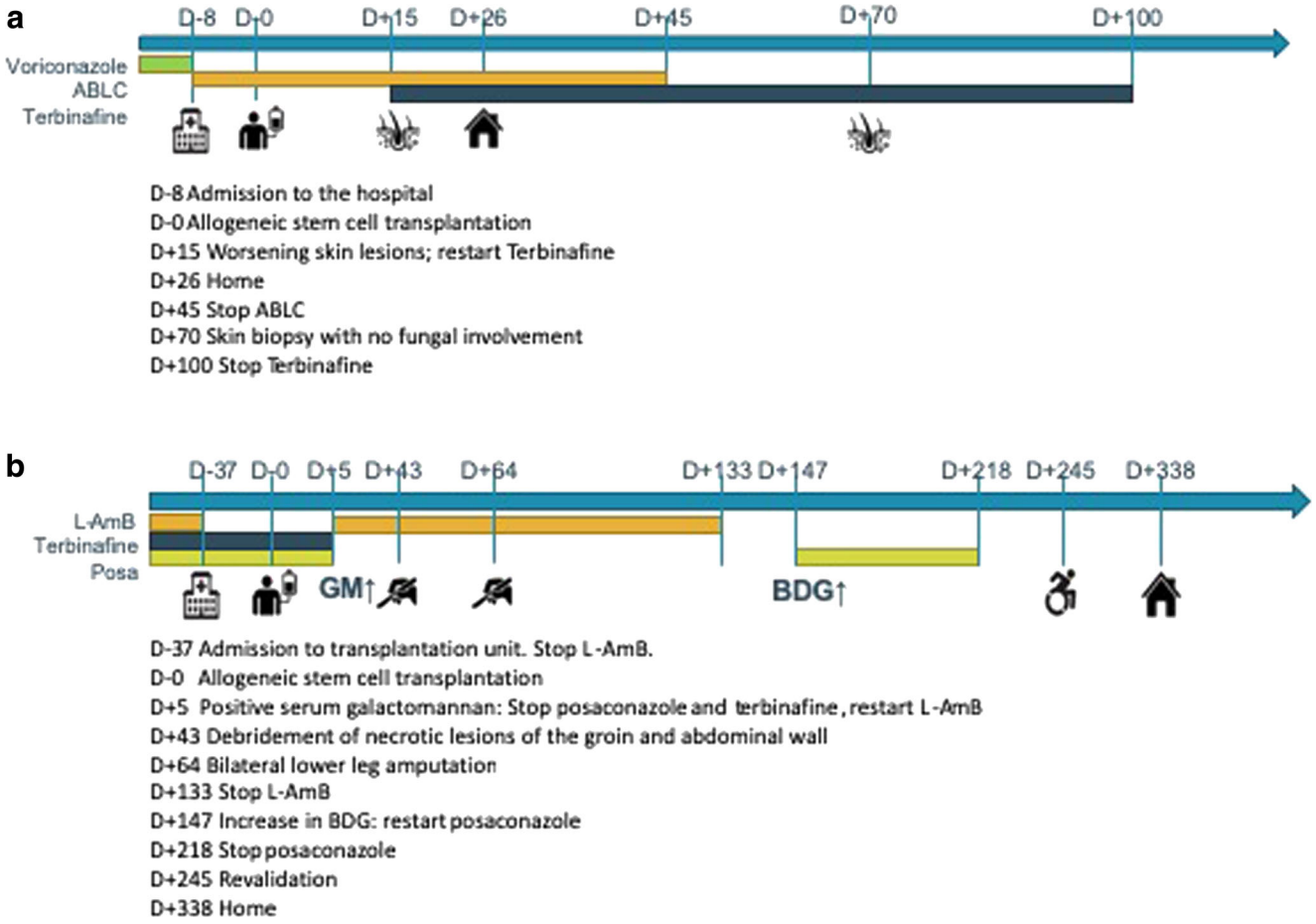

Fig. 1 Timelines of cases 1 (**a**) and 2 (**b**) showing the main interventions performed during the follow up. GM galactomannan, BDG beta-D-glucan, L-AmB liposomal amphotericin B, D day relative to day of allogeneic stem cell transplantation, ABLC amphotericin B lipid complex

40 years, a homozygous variation *c.301C>T* in *CARD9* (p.R101C) was reported [7]. His skin lesions slowly progressed, despite sequential antifungal treatment with terbinafine, voriconazole, posaconazole, and liposomal amphotericin B, as well as the combined use of anti-fungals and interferon-gamma (IFN-γ) for more than 10 years. Finally, the second toe of the left foot needed to be amputated, and the patient was referred for HSCT. On admission, the

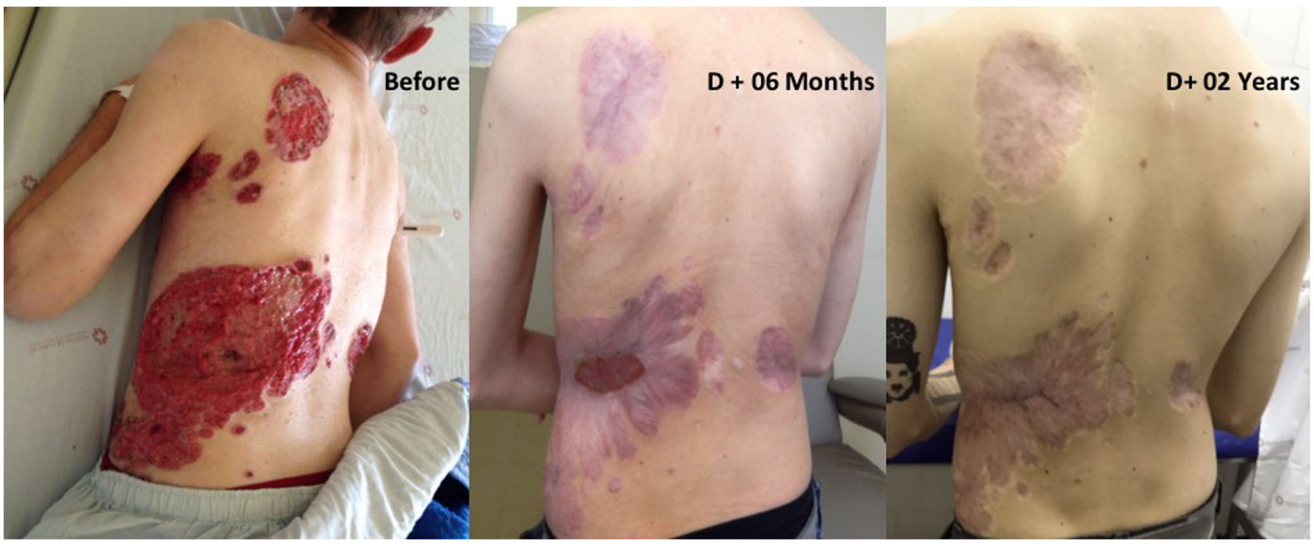

Fig. 2 Left: Lesions due to *Trichophyton interdigitale* in case 1 (at 25 years), middle and right: lesions after 6 months and 2 years post-HSCT

patient, severely weakened, presented with biopsy- and culture-proven ulcerative and necrotic fungal lesions, and superinfected by multi-resistant *Pseudomonas aeruginosa* of the abdominal wall, left groin, and both feet. His antifungal treatment consisted of posaconazole gastro-resistant tablets (300 mg per day), liposomal amphotericin B (250 mg, three times weekly), and terbinafine (250 mg per day). Serum beta-D-glucan was extremely elevated (103,000 pg/mL; threshold for positivity ≥ 80 pg/mL). A PET-CT scan revealed extensive PET avidity of the lesions of the abdominal wall and the left groin (Fig. 3). At first evaluation, the patient had normal B cell, NK-cell, and CD4+ and CD8+ T cell counts, with high IgE levels (1741 kIU/mL) and hypereosinophilia. Levels of IgA, IgG, and IgM were within normal ranges. The lymphocyte activation test (LTT) was normal after stimulation with *Candida* spp., tetanus toxoid, *Herpes simplex virus*, or phytohaemagglutinin (PHA). Th17 cell count was decreased. Interleukin (IL)-6 and IL-17 responses were diminished after stimulation with *Candida albicans* and zymosan (a protein-carbohydrate complex prepared from the cell wall of *Saccharomyces cerevisiae*), but normal after stimulation with PHA.

A T cell–repleted haploidentical peripheral blood cell transplantation was performed from his healthy brother, heterozygous for the CARD9 variant. The conditioning regimen consisted of fludarabine (30 mg/m^2 on d-6 until d-2), cyclophosphamide (14.5 mg/kg on d-6 and d-5), and total body irradiation (2 Gy) on d-1, followed by post-transplant cyclophosphamide (50 mg/kg) on d + 3 and d + 4 and cyclosporine from d + 5 onwards. A T cell–repleted haploidentical peripheral blood cell transplantation was performed from his healthy brother, heterozygous for the CARD9 variant. The conditioning regimen consisted of fludarabine 150 mg/m^2, cyclophosphamide 29 mg/kg, and total body irradiation (2 Gy), followed by post-transplant cyclophosphamide (50 mg/kg) on d + 3 and d + 4 and cyclosporine and mycophenolae mofetil from d + 5 onwards. Neutrophil engraftment occurred at d + 18, after which the fungal lesions became clearly demarcated, followed by spontaneous release from the underlying tissue.

Neutrophil engraftment occurred at d + 18, after which the fungal lesions became clearly demarcated, followed by spontaneous release from the underlying tissue. Following multidisciplinary consultation, it was decided to perform a bilateral below-the-knee amputation, as well as a debridement of the necrotic lesions of the groin and abdominal wall. Pathological examination of these debrided tissues confirmed the presence of fungal hyphae. Three months after transplantation, the patient successfully received a second donation of CD34$^+$-selected cells from the same donor because of severe amegakaryocytic thrombopenia in the setting of full donor chimerism. Other major post-transplant complications included *Enterococcus faecium* bacteremia during neutropenia, septic shock due to multi-resistant *Pseudomonas aeruginosa*, *Klebsiella pneumoniae* pneumonia, relapsing *Clostridium difficile* colitis, disseminated adenovirus infection (with bilateral pneumothorax), and multiple cytomegalovirus reactivations. A single episode of grade II acute GVHD, according to Glucksberg criteria, was successfully treated with corticosteroids (1 mg/kg). Immunosuppressive therapy was

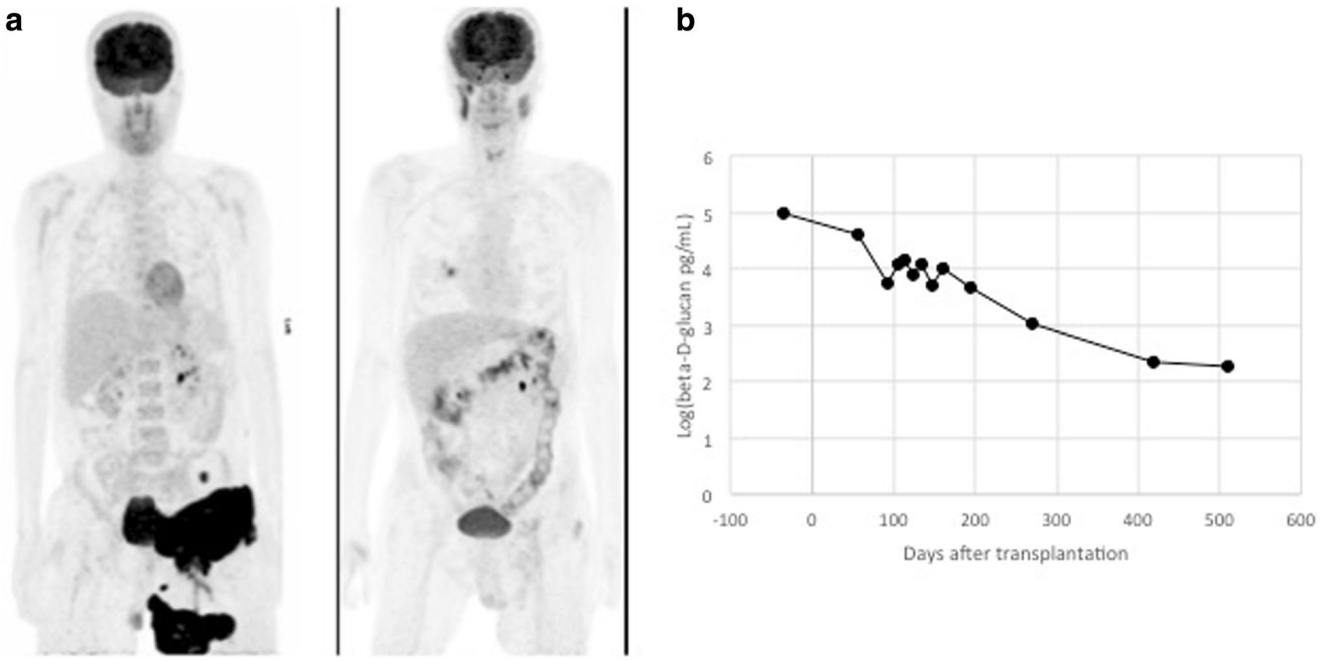

Fig. 3 **a** PET-CTs revealing extensive PET avidity of the lesions in the abdominal wall and the left groin before HSCT (left panel) and 1 year post-HSCT (right panel). **b** Evolution of the serum beta-D-glucan since admission

tapered and stopped completely on d + 138. All antifungal treatments were successfully stopped on d + 218 (Fig. 1). Thirty-six months after transplantation, full donor chimerism was still maintained. An immunological assessment showed a normalization of the eosinophil counts and of the IgE levels. PET-CT scan imaging showed no signs of residual inflammation, and serum beta-D-glucan had decreased to 223 pg/mL (Fig. 3a, b). The patient now carries a bilateral lower leg prosthesis and follows an extensive rehabilitation program. His most recent Karnofsky performance score was of 90%.

Both patients gave written informed consent for these reports.

Discussion

We present the first report of successful HSCT for CARD9 deficiency in two unrelated patients with deep/invasive dermatophytosis [7, 10]. This therapy was previously attempted in a 12-year-old CARD9-deficient patient with intra-abdominal aspergillosis refractory to multiple antifungal therapies. However, the patient died from a fatal diffuse alveolar hemorrhage after two consecutive HSCTs [11]. Multiple antifungal therapies were used in both patients before HSCT, G-CSF was also concomitantly given as previously recommended [23, 24], without any clinical improvement. Beside extensive cutaneous fungal infection, the second case had bacterial infections and osteomyelitis was diagnosed. Both patients had severe disease and poor quality of life.

Impaired opsonophagocytosis of *Candida albicans* in the first patient led us to the hypothesis that myeloid cells could be responsible for fungal susceptibility in CARD9 deficiency. HSCT was discussed as an option for both patients to improve their clinical situation [25]. In both cases, the donors were healthy, but heterozygous carriers of the CARD9 variant, however in the present cases, the outcome was successful. Performing allogeneic stem cell transplant from a healthy heterozygous carrier may not be perfect, however, in the present cases, such donors appeared as the best matches for the patients.

Low-toxicity regimens with busulphan or low-toxicity myelo-ablative regimens using treosulphan in combination with fludarabine have demonstrated excellent engraftment, and survival rates of 90%, even in older patients with significant pre-existing comorbidities [26]. The second case received low dose of total body irradiation and developed GVHD, which has been well controlled. Clinical improvement was clear and full donor chimerism developed in both cases, with fast hematological engraftment (d + 16 and d + 18 for neutrophils for cases 1 and 2, respectively). In case 1, follow-up showed several hyaline hyphae on a direct exam of lymph nodes biopsy at day + 800, but no viable fungus could be evidenced. This was interpreted as a late form of immune reconstitution inflammatory syndrome (IRIS).

Both cases represent the first report of definitive therapy for inherited CARD9 deficiency with HSCT. Although beta-D-glucan levels remained positive for a prolonged time in case 2, the progressive logaritmic decline indicates an ongoing clearance of the extremely high initial levels of beta-D-glucan. This is in accordance with the slow decline of beta-D-glucan seen in other fungal infections [27]. Both cases have now been followed for more than 3 years. This result provides an approach to improve the currently poor clinical outcome of patients with CARD9 deficiency [2, 28–30], in particular, those with severe invasive dermatophytosis. Finally, our observation incriminates hematopoietic cells in the pathogenesis of fungal infections in patients with CARD9 deficiency.

Authorship Contributions FQT and ASG were involved in all steps of the report; TM, JM, RMNCS, RS, FH, JFM, PFH, GLC, JBF, and NARF were involved in the patients' care and immunologic evaluation before and after HSCT; TM, JM, CBSS, and CB were responsible for HSCT; FH, JFM, and PFH performed the microbiologic and molecular identification of the isolates; OL, FL, JLC, and AP were responsible for critical revision and previous discussion about the directions for therapy. All the authors revised the manuscript and agreed before submitting to the journal.

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflicts of interest.

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