Aspergillus terreus pulmonary infection in a patient with late-onset combined immunodeficiency: a case report with literature review

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Abstract: Common variable immunodeficiency (CVID) is the most common humoral immune deficiency in adults, characterized by recurrent sinopulmonary bacterial infections. Invasive fungal infections are rarely associated with CVID. Late-onset combined immunodeficiency (LOCID) is a recently recognized variant of CVID with low CD4 counts and immunoglobulins deficiency. The current study reveals the first documented case of invasive pulmonary aspergillosis (*Aspergillus terreus*) in a patient with LOCID. A 52-year-old female with a recurrent history of sinopulmonary infections presented with acute onset fever and shortness of breath. Blood culture and bronchoalveolar lavage culture grew *A. terreus*. Further evaluation revealed low immunoglobulins (IgG, IgM and IgA). Moreover, she also had low CD4 counts (<200 cells/µL). The patient was successfully treated with voriconazole and immunoglobulin therapy. Finally, the study discusses LOCID as a potential risk factor for invasive fungal infections, which can be easily overlooked and cause poor outcomes.

Keywords: aspergillosis, common variable immunodeficiency, immunoglobulins

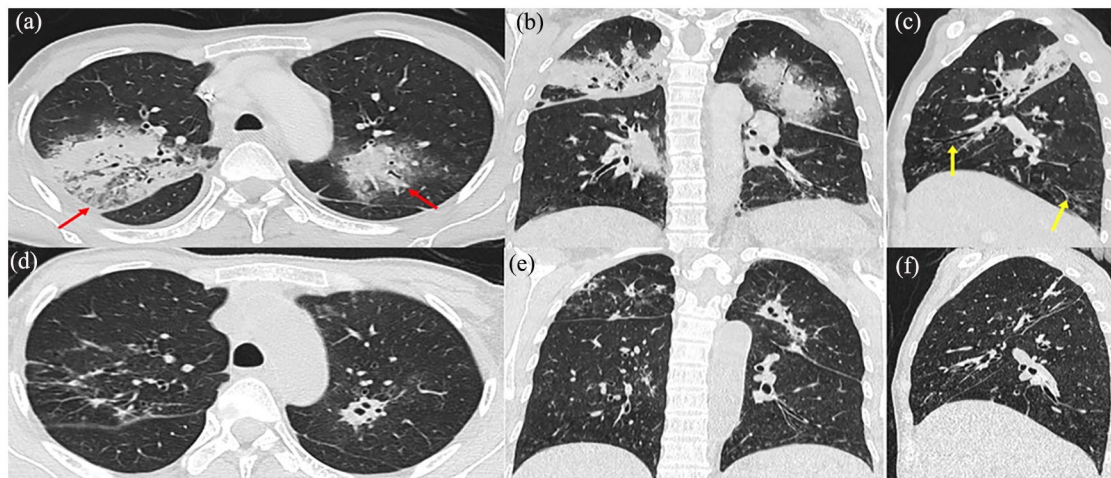Received: 28 March 2024; revised manuscript accepted: 12 June 2024.

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Introduction

B-cell (antibody-mediated) immunodeficiency is the most common immunodeficiency disorder, which comprises X-linked agammaglobulinaemia, common variable immunodeficiency (CVID) and selective IgA deficiency. CVID is characterized by defective B-cell differentiation with impaired immunoglobulin secretion.[1] CVID has a prevalence of ~1 in 30,000 and typically manifests after puberty.[2] Late-onset combined immunodeficiency (LOCID) is a subset of CVID characterized by T-cell defect and CD4 counts <200 cells/µL.[3] Frequent sinopulmonary infections are characteristic clinical presentation in many patients with CVID. Moreover, in nearly one-third of patients, infections could be the only presenting manifestation.[4] Pneumonia is the most common infection in CVID, with encapsulated bacteria like *Streptococcus pneumoniae* and

Haemophilus influenzae are the most frequent causative microorganisms.[5] Invasive pulmonary aspergillosis is usually associated with immunodeficiency syndrome like chronic granulomatous diseases, Hyper-IgE syndrome with recurrent infection (Job syndrome), and sometimes with primary T-cell deficiencies.[6] To date, only two cases of aspergillosis (hepatic and pulmonary) have been reported with CVID,[7,8] none with the LOCID subtype. We herein discuss the first report of invasive pulmonary aspergillosis (*Aspergillus terreus*) in a patient with underlying LOCID.

Case presentation

A 52-year-old female presented to emergency with complaints of high-grade fever, shortness of breath and cough with expectoration for 5 days. She has a history of multiple hospital admissions

Figure 1. CT chest of a 52-year-old lady. (a–c) CT at the time of admission. (a) Axial, (b) coronal, (c) sagittal images showing multifocal areas of consolidation with surrounding halo of ground glass attenuation (red arrows). Focal bronchiolectasis is also evident in lingular and posterior basal segments (yellow arrows) due to previous infections. (d–f) CT after 14 days of voriconazole therapy. Significant resolution of consolidations is seen with small areas of cavitation in left upper lobe.
CT, computed tomography.

in view of lower respiratory and gastrointestinal tract infections. She had received several antibiotics during previous hospital admissions (two admissions in preceding year, last admission was 4 months back). General physical examination was unremarkable except for mild pallor. On respiratory examination, bilateral diffuse crepitations were present (left > right). Chest X-ray showed bilateral heterogeneous opacities (left > right) and bilateral lower lobe bronchiectasis changes. On laboratory investigations, the patient had low haemoglobin (Hb: 9.8 g/dL, normal: 12–15.5, total leukocyte counts: 9500, normal: 4000–11,000, platelet counts: 145,000, normal: 150,000–450,000) and elevated inflammatory markers (high sensitivity C-reactive protein of 80.4 mg/dL, normal < 1, procalcitonin of 10.52 ng/mL, normal < 0.04). The liver function test revealed a low total protein with low albumin and globulin levels (total protein 3.38 g/dL, serum albumin 2.3 g/dL, globulin 1.08 g/dL). In the evaluation of hypoalbuminaemia, both urine microscopy and 24-hour urinary protein did not reveal proteinuria. Ultrasound whole abdomen was unremarkable except for splenomegaly. No evidence of portal hypertension was present. Thus, hypoalbuminaemia was attributed to a chronic inflammatory state. Contrast-enhanced computed tomography (CT) thorax showed multiple patchy areas of consolidation with surrounding ground glass opacities (Figure

1(a)–(c)). Bacterial, fungal and tuberculosis were considered possible differential aetiology for a lung infection. Paired sets of bacterial and fungal blood cultures, sputum for bacterial and fungal culture and serum galactomannan were sent. The patient was initiated on a broad-spectrum antibiotic (i.v. piperacillin-tazobactam); however, she did not show improvement in fever and respiratory symptoms. Sputum culture didn't reveal any growth. Sputum Gene X-pert, a Catridge based nucleic acid amplification test (CBNAAT) for tuberculosis was also negative. The blood culture did not reveal bacterial growth.

On day 5, serum galactomannan came positive (2.75, normal < 0.5, enzyme immune assay, Platelia Aspergillus; Bio-Rad, Marnes-la-Coquette, France). We also ruled out the possibility of false positive galactomannan (no contributory factors were present). The patient received i.v. voriconazole (400 mg on day 1, followed by 200 mg once a day) in view of invasive pulmonary aspergillosis. Furthermore, the raised beta-D-glucan levels (177 pg/mL, normal < 60, also supported the diagnosis of invasive fungal infection). On day 10, the blood fungal culture (two samples) grew *A. terreus* (Figure 2(a) and (b)). Thus, piperacillin-tazobactam was stopped, with the continuation of voriconazole. Bronchoalveolar lavage (BAL) showed similar growth of *A. terreus*. Negative AFB stain, Gene
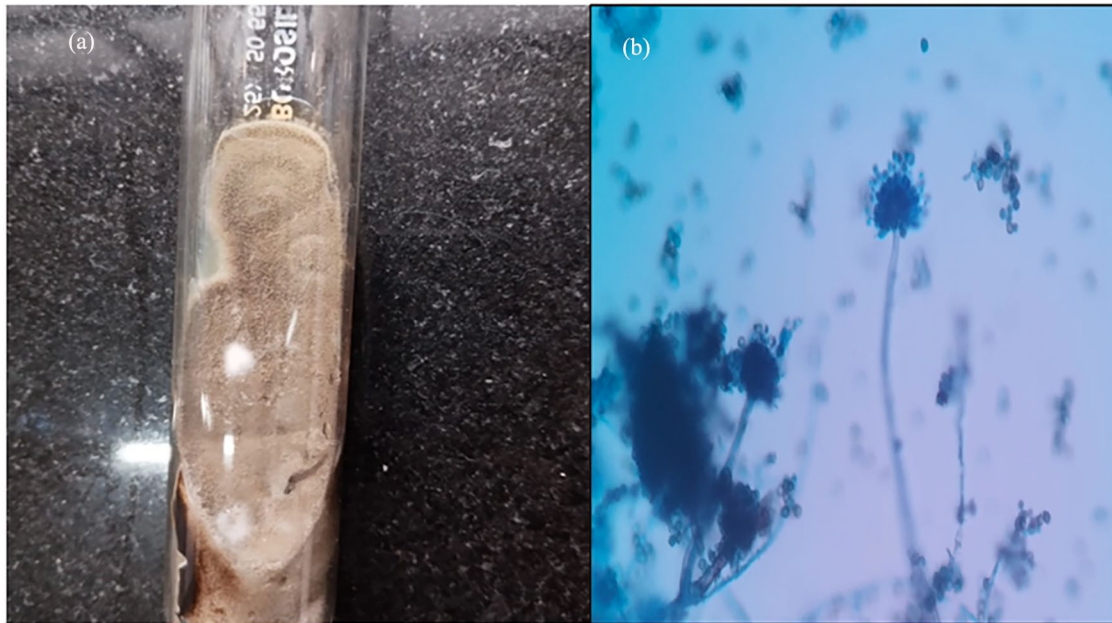
Figure 2. (a) Showing the velvety cinnamon brown colonies of *Aspergillus terreus* complex over the SDA agar slope after an incubation period of 10 days. (b) Showing the LPCB (Lactophenol Cotton Blue) mount with thin hyaline septate hyphae with biseriate and densely columnar conidia.

X-pert and mycobacterium cultures from the BAL and sputum samples obviate the possibility of tuberculosis. In view of hypogammaglobulinaemia (contrary to an infective state where polyclonal hypergammaglobulinaemia is present), an immunoglobulin panel was sent which showed marked reduction in IgG levels (<41 mg/dL, normal range: 700–1600 mg/dL), IgA levels (10 mg/dL normal range: 70–400 mg/dL) and IgM levels (6.40 mg/dL, normal range: 40–230). Peripheral blood smear, bone marrow aspiration and trephine biopsy analysis were unremarkable. All alternative causes for hypogammaglobulinaemia were ruled out (no evidence of protein-losing enteropathy with normal alpha-1 antitrypsin levels, no evidence of lymphoproliferative disorders with normal blood counts, peripheral smear and bone marrow, no evidence of multiple myeloma with normal bone marrow and no history suggestive of drug-induced hypogammaglobulinaemia). Her autoimmune profile was also negative [negative Anti-nuclear antibody (ANA), negative ANA reflex panel]. The antigenic response could not be assessed due to significantly low IgG levels. To further elucidate the immunodeficiency disorder, a CD4 count was sent, which was found to be low (174 cells/µL, normal 500–1500). The diagnosis of late-onset combined variable immunodeficiency (LOCID phenotype) was made based on CVID features (age > 4 years, low immunoglobulins and absence of other causes) and underlying CD4 cell deficiency.

On voriconazole therapy, she showed significant clinical improvement with a marked reduction in inflammatory markers. Repeat imaging (after 14 days of voriconazole treatment) showed a significant resolution in consolidation and ground glass opacities (Figure 1(d)–(f)). Repeat serum galactomannan levels were negative at the end of 2 weeks. She was given intravenous immunoglobulin (IVIG; 500 mg/kg/day). She was discharged on voriconazole 200 mg, azithromycin (in view of underlying bronchiectasis and recurrent infections), trimethoprim/sulfamethoxazole (*Pneumocystis jirovecii* prophylaxis in view of low CD4 count). The patient came on a follow-up visit 1 month later with significant improvement and no episode of fever. IgG levels improved from the previous visit. However, IgA and IgM levels were still very low. She was given IVIG again and continued with the remaining medication on discharge. At 3 months of follow-up, she was doing well with no further infective exacerbation. Voriconazole was continued though optimal duration was uncertain in this case. In further follow-up, we also performed the flow cytometry to document the B-cell subtype dysfunction, which also came positive and suggested B-cell

Table 1. Flow cytometry for primary immunodeficiency panel (B-cell, T-cell and NK cell subtypes).

Test name	Result	Normal interval
Absolute lymphocyte count	1080 cells/µL	1100–4800
B-cell subsets		
CD19 positive (absolute CD19)	84 cells/µL	92–515
Pre-germinal centre CD27⁻ B cells	96%	44–84%
Post-germinal centre CD27⁺ B cells	3.2%	3.7–26%
Switched post-germinal centre IgM⁻ IgD⁻	5%	5–35%
T-cell subsets		
T cells (absolute CD3 positive)	935 cells/µL	800–2300
CD3⁺ CD8⁺	623 cells/µL	131–825
CD3⁺ CD4⁺	258 cells/µL	
Absolute CD4 counts	95 cells/µL	663–1477
Absolute CD3 counts	935 cells/µL	1000–1900
Naïve CD8 positive absolute count	30 cells/µL	400–1400
CD4⁻ CD8⁻ absolute count of all T cells	11 cells/µL	23–157
NK (Natural Killer) cells (CD16⁺ 56 positive)	41 cells/µL (3.7%)	61–607 (5–15%)

dysfunction. Moreover, her CD4 counts remain low even after 4 months which excludes the possibility of low CD4 counts as a result of acute phase marker (complete T-cell and B-cell subtype flow cytometry results are depicted in Table 1).

Discussion

The global burden of invasive aspergillosis is >2.1 million cases/year.[9] Immunosuppressants, transplant recipients, haematological malignancy, intensive care unit admission and chronic obstructive pulmonary disease are the usual predisposing factors for invasive aspergillosis.[9] The epidemiology and clinical spectrum of aspergillosis is evolving; the evaluation should not stop after ruling out the conventional risk factors. In this report, we highlight CVID as a probable risk factor for invasive pulmonary aspergillosis. We could not find any evidence of immunosuppressant use, neutropenia, haematological malignancy, prolonged ICU stay or HIV which might predispose to aspergillosis. Invasive fungal infections are widely reported in patients with underlying phagocytic, cellular or combined immunodeficiency disorders. CVID is a complex clinical syndrome that encompasses around 100 different entities with immunodeficiency disorders. Unlike cellular immunodeficiency syndrome, humoral immune dysregulation rarely predisposes the patient to invasive fungal infections. Our understanding of CVID is evolving with a recent report of abnormalities in T-cell phenotype and function, which is recognized in a subset of the population with CVID.[10] This results in defective cytokine release [interleukin (IL)-2, IL-4, IL-6] and T-cell receptor signalling. It could explain the occurrence of invasive fungal infections in these subgroups, which is otherwise not possible to explain with CVID.

LOCID is a subset of CVID, first described in 2009 and characterized by association of T-cell defects, occurrence of opportunistic infections (OIs) and CVID.[3] A study by Malphettes et al. in 2009 isolated 28 patients of CVID who had recurrent OIs and low CD4 counts (<200 cells/µL). These patients were clinically and

immunologically distinct from other CVID patients (poor prognosis even with comparable immunoglobulins levels as other CVID). No other cause of CD4 deficiency was found in these patients. Furthermore, it is the deficiency of naïve CD4 cells reflected in the late onset of OIs in these patients.[3] In our case, CVID alone could not explain the occurrence of invasive aspergillosis, which prompted us to evaluate for CD4 counts, which were found low. Like the previous cohort,[3] in this case, it was a late-onset OI in the form of *A. terreus*. She had recurrent sinopulmonary infections, which were probably bacterial and relieved with antibiotic therapy. The first report of pulmonary aspergillosis in CVID was described in 1987 in a young girl.[7] The second case of invasive aspergillosis (*A. terreus* hepatic abscess) was reported in 2001 in a young male who already had a history of candidiasis and received itraconazole prophylaxis.[8] However, no investigation for T-cell dysfunction was performed in either case. Notwithstanding, idiopathic CD4 lymphocytopenia (ICL) is postulated as an important differential for CVID/LOCID. Patients with ICL also have mild immunoglobulin deficiency (IgA and IgG). However, in the current case, the patient had a history of recurrent long-standing sinopulmonary infections, which is a characteristic of humoral immunodeficiency. Furthermore, the patient had significantly low immunoglobulin levels, which is unlikely to be seen in ICL. In this patient, bronchiectasis is also a contributory factor for aspergillosis. Usually, it predisposes the patients to allergic bronchopulmonary aspergillosis and aspergilloma; however, in cases with coexisting immunodeficiency (current case), invasive pulmonary aspergillosis could be the manifestation.[11]

Conclusion

A. terreus is an emerging OI with lower treatment response (resistance to amphotericin B) and higher mortality compared to non-terreus aspergillus infections.[12] Both LOCID variants of CVID and *A. terreus* pulmonary infections were the major deterrents for the outcome in this patient. Early diagnosis and initiation of voriconazole were pivotal in the current case. However, uncertainty remains about the long-term outcome, relapse rate and secondary prophylaxis for invasive aspergillosis in CVID patients. Early suspicion and aggressive diagnostic workup for invasive aspergillosis are vital. The absence of conventional host factors should not preclude further evaluation like in the current case. The possibility of CVID/LOCID should be explored in invasive aspergillosis cases. If undiagnosed, this could result in treatment failure and poor outcomes.

Declarations

Author contributions
Naman Lodha: Conceptualization; Formal analysis; Investigation; Methodology; Resources; Validation; Writing – original draft; Writing – review & editing.

Durga Shankar Meena: Conceptualization; Formal analysis; Investigation; Resources; Supervision; Validation; Writing – original draft; Writing – review & editing.

Pyrus Bhellum: Conceptualization; Investigation; Resources; Writing – original draft; Writing – review & editing.

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Sadiya F. C.: Data curation; Investigation; Methodology; Resources; Supervision; Writing – original draft.

Yash Khatod: Data curation; Formal analysis; Investigation; Resources; Validation; Writing – original draft; Writing – review & editing.

Vidhi Jain: Data curation; Investigation; Methodology; Resources; Supervision; Writing – original draft; Writing – review & editing.

Deepak Kumar: Conceptualization; Investigation; Resources; Supervision; Validation; Writing – original draft.

Taruna Yadav: Conceptualization; Investigation; Resources; Supervision; Validation; Writing – original draft; Writing – review & editing.

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