Case Report

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Candida krusei pneumonia in graft-versus-host disease after allogeneic hematopoietic stem cell transplant for paroxysmal nocturnal hemoglobinuria: a case report

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Introduction and importance: Paroxysmal nocturnal hemoglobinuria (PNH) is a rare disorder caused by a somatic mutation of PIGA (phosphatidylinositol glycan anchor biosynthesis, class A) gene that leads to the destruction of blood cells. Allogeneic haematopoietic stem cell transplant (HSCT) is a treatment option for PHN, but it can cause graft-versus-host disease (GVHD). Long-term immunosuppression as a treatment of GVHD increases the risk for invasive fungal infections such as *Candida krusei* pneumonia.
Case presentation: We present the case of a 22-year-old male with *C. krusei* pneumonia in a known case of chronic GVHD following HSCT for PNH undergoing long-term immunosuppressive therapy. The patient presented with progressive shortness of breath, productive cough, palpitations, and difficulty swallowing. On examination, he had skin rashes and oral lesions, along with signs of severe malnutrition. Diagnosis was made on the basis of radiological imaging and fungal culture.
Discussion: The combination of PNH, GVHD, and HSCT created an immunocompromised state, making the patient susceptible to opportunistic infections, including fungal pneumonia. Early recognition of this condition is challenging due to its non-specific symptoms and potential overlap with other post-transplant complications. Timely diagnosis and appropriate treatment, including antifungal therapy and immunosuppression management, are crucial for optimising patient outcomes.
Conclusion: This case highlights the importance of early recognition and timely treatment of fungal infections in patients with severe conditions such as GVHD following HSCT for PNH. Timely treatment with appropriate antifungals is necessary for optimal outcomes. Additionally, more research with long-term follow-up and monitoring is necessary to address the necessary knowledge gaps in this field.

Keywords: *Candida*, case report, hematopoietic stem cell transplantation, paroxysmal nocturnal hemoglobinuria, pneumonia

Introduction

Paroxysmal nocturnal hemoglobinuria(PNH) is a rare, life-threatening disease condition of the blood caused by the acquired mutation of X-linked PIGA (phosphatidylinositol glycan anchor biosynthesis, class A) gene, which codes for glycosylphosphatidylinositol (GPI) anchored proteins of blood cells[1–3]. The deficiency of GPI-anchored proteins causes complement-mediated destruction of red cells, thromboembolic events, bone marrow dysfunction and cytopenia[4,5]. It has an estimated occurrence of 15.9 individuals per million worldwide[6].

Diagnosis of PNH is made by establishing the history of haemolytic anaemia in conjunction with severe GPI deficient cells on multiple cell lineage by flow cytometry[7,8], with supplementary tests like complete blood profile, cytogenetics, bone marrow aspirates and biopsy[9]. Treatment of PNH is based on the treatment of underlying bone marrow failure syndrome, either by immunosuppressive or an allogenic bone marrow

HIGHLIGHTS

- Fungal infection accounts for a quarter of all infections in GVHD (graft-versus-host disease).
- *Candida krusei* is a rarely encountered species in clinical mycology, known for its inherent resistance to fluconazole.
- Early diagnosis is important, as *C. krusei* rarely causes pneumonia and primarily affects immunocompromised patients with unfavourable outcomes.
- A changing trend in *Candida* infections, with fewer *C. albicans* cases and more infections caused by non-albicans, *Candida* challenges its diagnosis and treatment.
- Lifelong follow-up of HSCT (haematopoietic stem cell transplant) recipients is crucial to monitor and check for other complications, thus improving the outcome.

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transplantation[9]. Allogeneic hematopoietic stem cell transplantation (allo-HSCT) offers a chance to cure PNH, but it can cause graft-versus-host disease (GVHD) in about one-third of patients[10]. It occurs when immunologically competent cells from a donor recognise alloantigens in an immunodeficient recipient[11,12].

Fungal infection accounts for a quarter of all infections in GVHD[13]. *Candida* infection has an incidence of 1.1%, among which non-albicans *Candida* (*C. glabrata and C. krusei*) accounts for 75.8% of the isolates and has the potential to affect multiple organ systems of the body[13]. *C. krusei* is a rarely encountered species in clinical mycology, known for its inherent resistance to fluconazole[14]. Due to advances in medical technologies, invasive medical devices, and a wide range of antibiotics used, the incidence of uncommon organisms is rising[15].

The combination of HSCT, GVHD and PNH creates an immunocompromised state, predisposing the patient to opportunistic infections such as fungal pneumonia. Early recognition is challenging due to its non-specific symptoms and potential to overlap with other post-transplant conditions. Timely diagnosis and treatment are crucial for optimising patient outcomes. This case report has been reported in line with SCARE 2020 Guidelines[16].

Patient details

A 22-year-old male follow-up case of graft versus host reaction post-allo-HSCT in July 2017 for PNH presented with complaints of progressive shortness of breath for the past 5 months, which was insidious in onset, severity of MMRC grade 3, aggravated on mild exertion and relieved upon rest. There was no diurnal variation or variation due to change of posture, no nocturnal awakening and no signs of cyanosis or peripheral oedema. However, there was a subjective feeling of tightness in the chest while sleeping and on rest. Additionally, the patient had productive cough for 5 months, with mucopurulent sputum of less than 100 ml per day, which is yellowish-white in colour. The cough is not associated with chest pain and fever. Furthermore, the patient described difficulty swallowing solid food, which often became lodged in the pharynx and relieved on coughing and drinking water; it was non-progressive with no regurgitation or other associated factors. The patient experienced a significant weight loss, from 55 kg in 2019 to 35 kg in 2023. Pertinent family history of similar diseases in the past was not present. He is on medication with immunosuppressants such as tacrolimus, prednisolone; antimicrobial such as acyclovir, azithromycin, fluconazole; and bronchodilators as foscarnet, inhalational salbutamol and montelukast. The diagnosis of PNH was done on the basis of clinical findings, and investigation such as flow cytometry. However, genetic testing was not performed.

Clinical findings

On admission, the patient presented with stable vitals, with a blood pressure of 110/70 mmHg, a pulse rate of 80 beats per minute, a respiratory rate of 20 per minute, oxygen saturation (SpO_2) of 98%, and a body temperature of 97°F. On general examination, the patient had multiple non-pruritic, polygonal, and violaceous papules, with the largest measuring 1.5 × 2 cm. These lesions were observed over the chest, abdomen, left shoulder, and left scapula. Additionally, there were multiple small whitish patches, a few millimetres in size, located on the palate, tongue and cheeks. These patches could be easily scraped off, and the borders appeared to be hyperaemic. During chest examination, normal vesicular breath sounds were heard, along with right infrascapular crackles. On auscultation, his heart sounds were normal. Furthermore, the patient was identified as severely malnourished with a height of 162 cm, weight of 35 kg and BMI of 13.35 kg/m^2.

Timeline

Figure 1.

Diagnostics assessment and interpretation

On laboratory investigation, CBC (complete blood count) showed total leucocyte count of 12.1×10^3/µl (Ref: 4–11), with neutrophils being 83.3% (Ref: 40–80%), and lymphocytes being 13.8% (Ref: 10–40%). PBS (peripheral blood smear) showed normocytic normochromic red cells without any morphological variation; there are no toxic granules and vacuoles seen in WBC (white blood cells), platelets were adequate in the smear and no atypical cells were seen. The iron profile showed serum iron of 220.61 µg/dl (Ref: 65–175), an unsaturated iron binding capacity of 2.1 µg/dl (Ref: 110–370) and serum ferritin of 1953.2 µg/l (Ref: 10–120). D-dimer is in normal range. Urine R/E (routine examination) is unsuggestive. TFT (thyroid function test) and RFT (renal function test) were nonsuggestive. Blood culture was negative. All the serological tests were negative.

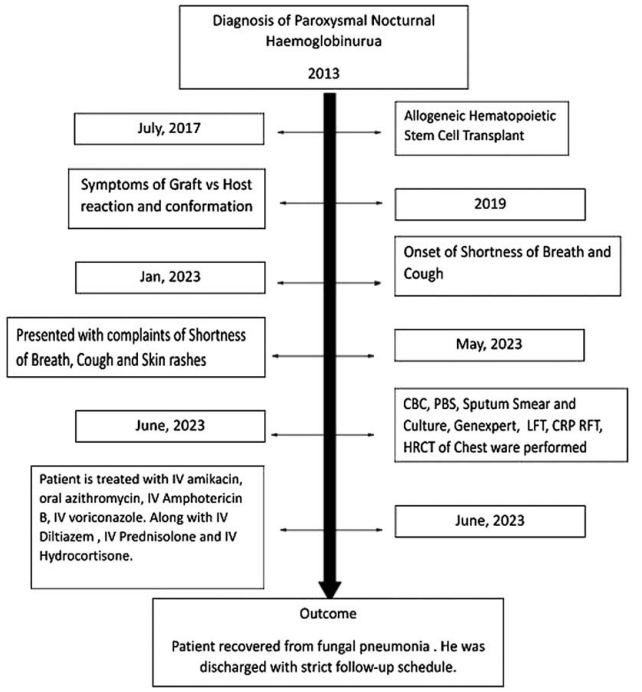

Figure 1. Timeline describing important events in this case. CBC, complete blood count ; CRP, C-reactive protein; HRCT, high-resolution computed tomography; LFT, liver function test; PBS, peripheral blood smear; RFT, renal function test.

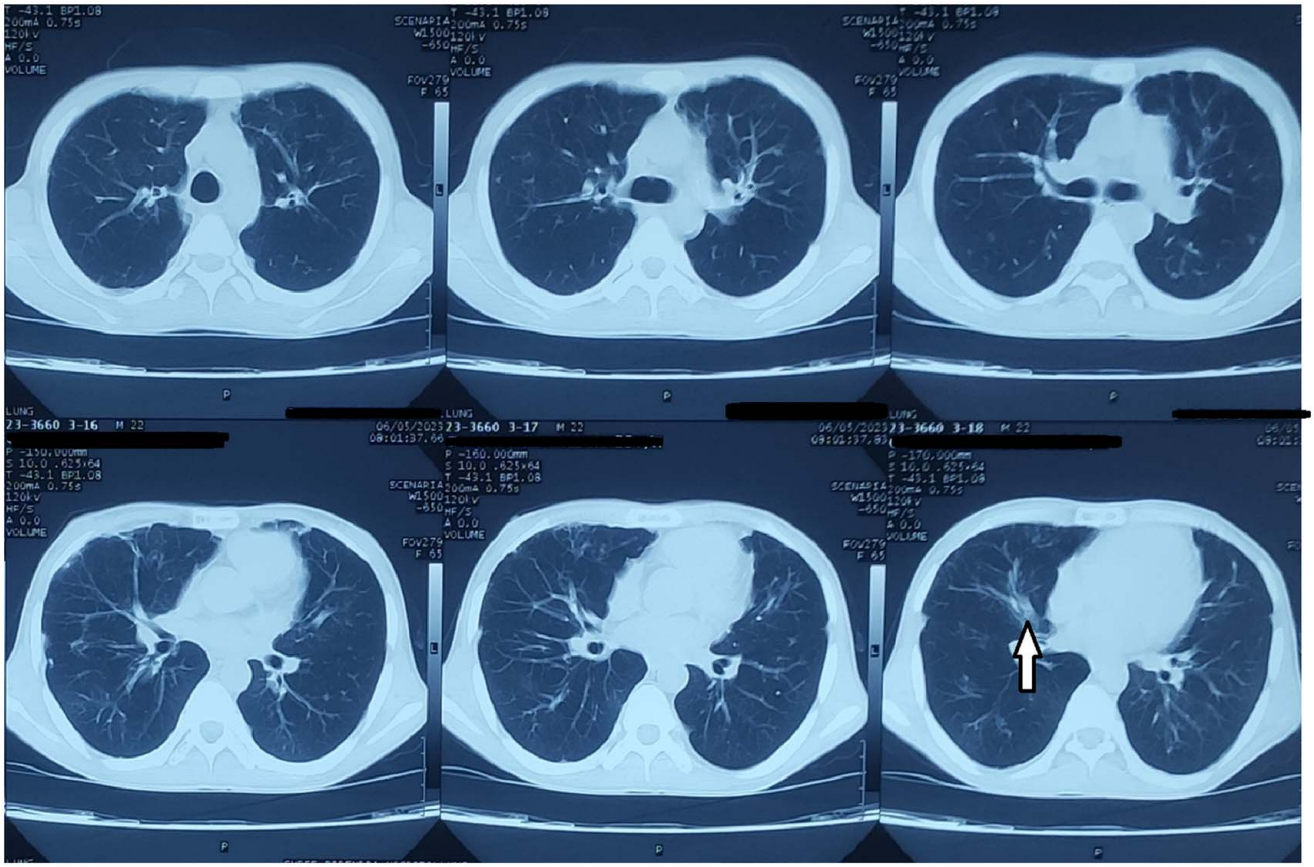

Figure 2. HRCT (high-resolution computed tomography) of chest showing multiple centrilobular nodules in tree-in-bud appearances in both lungs. White arrow shows consolidative opacity in the right lung.

LFT (liver function test) showed total bilirubin 0.68 mg/dl (Ref: 0.3–1.2), direct bilirubin 0.46 mg/dl (Ref: 0–0.2), SGPT (serum glutamic pyruvic transaminase) 249.4 U/l (Ref: 13–40), SGOT (serum glutamic oxaloacetic transaminase) 125.1 U/l (Ref: 13–40), ALP (alkaline phosphatase) 297 U/l (Ref: 42–128), GGT (gamma-glutamyl transferase) 627 U/l (Ref: 0–40), total serum cholesterol 65.7 mg/dl (Ref: 0–200), HDL (high-density lipoprotein) cholesterol 65.7 mg/dl (Ref: 40–60), LDL (low-density lipoprotein) cholesterol 93 mg/dl (Ref: 0–130) and triglyceride 97.5 mg/dl (Ref: 0–150). CRP (C-reactive protein) was positive.

Sputum culture showed positive for *C. krusei* and negative for other organisms after 5 days from the collection of the specimen. GeneXpert test for tuberculosis was negative.

High-resolution computed tomography (HRCT) of the chest showed subtle patchy ground-glass changes and few consolidative opacities; centrilobular nodules with some tree-in-bud appearances were seen at places in both lungs. Mild bronchiectasis associated with bronchial wall thickening was present in bilateral lungs involving all the lobes along with bilateral apical pleural thickening (left > right). Based on the clinical history, HRCT and sputum culture, an active pneumonia is established (Fig. 2).

Intervention

During his hospital stay, initially he received prophylactic treatment with intravenous amikacin and oral azithromycin. After confirmation of *C. krusei* infection, intravenous voriconazole and intravenous liposomal amphotericin B were used to control the infection. Additionally, intravenous hydrocortisone and intravenous prednisolone were given to control immune reactions. He was closely monitored by consultant doctors from the Department of Medicine, Haematology and Nephrology for drug toxicity and progression of treatment.

Follow-up and outcomes

The patient was kept under observation to prevent any further exacerbation of symptoms. Over the course of a few weeks, his condition improved and was discharged with a strict follow-up schedule. He has been strictly following his medications with no any noticeable adverse reaction to any of the medications.

Discussion

PNH is a rare clonal haematologic disorder caused by a somatic mutation in the PIGA gene located on the Xp22.2 chromosome[17], leading to a deficiency of GPI anchor proteins in the blood cells rendering the cells susceptible to complement-mediated lysis[4]. The clinical manifestations of PNH are characterised by a triad of features: haemolytic anaemia, thrombosis, and impaired bone marrow function[18]. Our patient had initially presented with symptoms such as haematuria, dark-coloured

urine and abdominal pain, which raised suspicion of PNH[19]. Diagnosis of PNH was confirmed in 2015 using the relevant blood investigations, bone marrow biopsy, Ham's test and Flow Cytometry[3].

Treatment options for PNH include supportive interventions such as blood transfusion, antithrombosis prophylaxis and thrombolytic therapy[20]. The introduction of the C5 inhibitor eculizumab has provided a newer modality of treatment[21]. However, allogeneic bone marrow transplant remains the only curative therapy for PNH despite the associated risks including GVHD[22,23]. Our patient developed chronic GVHD, 2 years following HSCT, with symptoms such as rashes, dryness of the skin and mucosal membranes. Chronic GVHD was confirmed based on clinical symptoms and a liver biopsy[24].

Patients undergoing long-term immunosuppression for GVHD are at high risk of developing various infections[25]. Moreover, high ferritin levels and previous infection with cytomegalovirus are independent risk factors for invasive fungal infections (IFIs)[26–28], both of which were present in our patient. In 2023, he developed pneumonia, which was confirmed on HRCT of the chest. The pathogen responsible was subsequently identified as *C. krusei* through sputum culture. Fever and tachypnea are common manifestations; however, cough, hemoptysis, chest pain and expectoration of purulent secretion may also be present[29,30].

Candida pneumonia is reported to be one of the most difficult candidal infections to diagnose[30], attributed to its rare occurrence and non-specific symptoms[30]. Non-albicans *Candida* (*C. glabrata* and *C. krusei*) rarely cause pneumonia and primarily affect immunosuppressed patients with unfavourable outcomes[31]. Recent studies show a changing trend in *Candida* infections, with fewer *C. albicans* cases and more infections caused by non-albicans *Candida*[15]. This shift can be associated with the increased prophylactic use of fluconazole in immunocompromised patients[32]. In this case report, we highlighted the changing trend of *Candida* infection, challenges in the diagnosis of it, and prompt treatment.

Treatment generally includes azoles and amphotericin B[33]. However, lifelong follow-up of HSCT recipients is crucial to monitor and check for further complications, thus improving outcomes. Prompt administration of prophylactic and empirical therapy for IFI is essential. The challenges of GVHD and IFI in HSCT need more study and development of diagnostic and therapeutic strategies to improve patient outcomes.

Conclusion

PNH has shown excellent outcomes for cure without relapse of disease through allo-HSCT. Although substantial progress has been made in the management of the complications of HSCT, infection still remains an important cause of post-transplant morbidity and mortality. Therapies used to prevent and treat GVHD are potential risk factors for IFI. Hence, this delicate balance of immunosuppression and infection necessitates personalised care with careful monitoring and prompt management of the patient's condition.

Patient perceptive

The patient is well aware of his condition and satisfied with the medical treatment he has been receiving. He hopes that sharing his experiences can help healthcare professionals better manage similar cases and prevent others from experiencing the same condition.

Ethical approval

Not applicable.

Consent

Written informed consent was obtained from the patient for the publication of this case report and accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal on request.

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Author contribution

All the authors equally contributed to the study concept or design, writing and reviewing the paper.

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The authors declare no conflicts of interest.

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