Case Report

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Pathology Section

Pure Red Cell Aplasia with Triple Pulmonary Co-infection and Shock-induced Organ Injury: An Autopsy-based Case Report

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ABSTRACT

Pure Red Cell Aplasia (PRCA) is a rare haematological disorder characterised by profound anaemia, reticulocytopaenia, and selective erythroid precursor depletion. While immunosuppressive treatment is a cornerstone of management, it significantly increases patient susceptibility to life-threatening opportunistic pathogens. The authors present the case of a 26-year-old male with PRCA and hypogammaglobulinaemia who presented with rapidly progressive respiratory failure. Despite intensive care, the patient succumbed within five days of admission. Bone marrow examination revealed marked erythroblastopenia and moderate hypocellularity. Post-mortem examination identified Diffuse Alveolar Damage (DAD) resulting from a concurrent pulmonary triple co-infection: *Pneumocystis jirovecii* (*P. jirovecii*), *Mycobacterium tuberculosis* (*M. tuberculosis*), and *Cytomegalovirus* (CMV). These findings were confirmed via specialised stains and Immunohistochemistry (IHC). Systemic findings included centrilobular hepatic necrosis and acute tubular injury, consistent with terminal cardiovascular collapse. The present case underscores the extreme vulnerability of immunocompromised individuals and highlights the necessity of aggressive surveillance, the consideration of polymicrobial involvement in deteriorating patients, and the potential role of expanded prophylaxis to reduce mortality in this high-risk population.

Keywords: Diffuse alveolar damage, Erythroblastopaenia, Hypogammaglobulinaemia, Immunocompromised host, Multiorgan failure, Opportunistic pathogens, Polymicrobial infection

CASE REPORT

A 26-year-old male, a known case of PRCA, was admitted on August 14, 2023, following a ten-day history of intermittent high-grade fever (102°F-103°F), mucoid cough, and rapidly progressive breathlessness. His haematological history began in April 2023 with severe anaemia {Hb: 4.5 g/dL (Normal: 13.5-17.5 g/dL), Reticulocyte count: 0.3% (Normal: 0.5%-2.5%)}. Peripheral blood smear at presentation demonstrated normocytic, normochromic red cells with reduced red cell density and adequate platelet numbers, without significant morphological abnormality of white cells. These findings led to a bone marrow biopsy confirming marked erythroblastopenia (Myeloid-to-Erythroid (M:E) ratio 84:1). Associated profound hypogammaglobulinaemia {Immunoglobulin G (IgG): 33 mg/dL (Normal: 700-1600 mg/dL)} was noted, and after a negative Parvovirus B19 Polymerase Chain Reaction (PCR), he was maintained on a regimen of steroids and ciclosporin (trough level: 106 ng/mL) with regular red cell transfusions. Upon his final admission on August 14, he was tachypnoeic {Respiratory Rate (RR): 28/min} and hypoxic (SpO_2: 80% on room air), with High-Resolution Computed Tomography (HRCT) of the chest showing diffuse bilateral ground-glass opacities and bronchiectatic changes. Initial management for a provisional diagnosis of community-acquired pneumonia included Inj. Meropenem, Inj. Cotrimoxazole, and Tab. Oseltamivir, alongside a single dose of Intravenous Immunoglobulin (IVIg) (0.4 g/kg) given on August 15. On August 17, refractory hypoxaemia (PaO_2: 36 mmHg)… and type 2 respiratory failure ($PaCO_2$: 88 mmHg), and he succumbed to the illness on August 19, 2023.

Autopsy Findings

The bone marrow was moderately hypocellular (40%-50% cellularity) with preserved myeloid and megakaryocytic maturation [Table/Fig-1]. However, there was a near-complete absence of erythroid islands, with an M:E ratio exceeding 80:1, consistent with the clinical diagnosis of PRCA.

Post-mortem examination of the lungs revealed heavy, boggy parenchyma with patchy consolidation. Histopathology confirmed DAD in the exudative phase, characterised by prominent hyaline membranes lining the alveolar spaces, interstitial oedema, and intra-alveolar fibrinous exudates [Table/Fig-2]. A remarkable finding was the presence of a triple pulmonary co-infection:

- *Pneumocystis jirovecii*: identified by crushed-cup-shaped cysts within intra-alveolar eosinophilic foamy exudates on Grocott's Methenamine Silver (GMS) stain and confirmed via IHC.
- *Mycobacterium tuberculosis*: characterised by small clusters of acid-fast bacilli on Ziehl-Neelsen (ZN) stain within areas of necrotising granulomatous inflammation with Langhans-type multinucleated giant cells [Table/Fig-3].
- *Cytomegalovirus* (CMV): evidenced by enlarged cells containing classic 'owl's eye' eosinophilic intranuclear inclusions, further highlighted by CMV-specific IHC [Table/Fig-4].

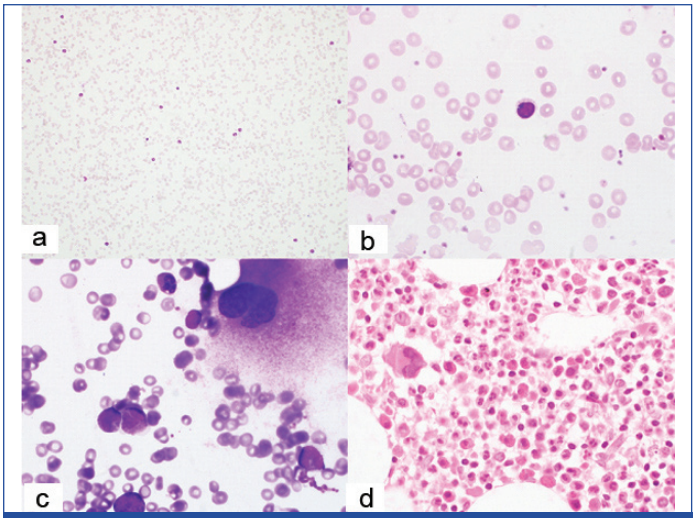
Systemic findings were indicative of terminal multi-organ dysfunction secondary to septic and hypoxic shock. The liver showed macro vesicular steatosis together with centrilobular (Zone 3) ischaemic necrosis [Table/Fig-5a,b], while the kidneys demonstrated preserved glomerular architecture with no significant glomerular pathology, alongside Acute Tubular Injury (ATI) with extensive epithelial sloughing and loss of the proximal convoluted tubule brush borders [Table/Fig-5c,d].

Final Anatomic Diagnosis

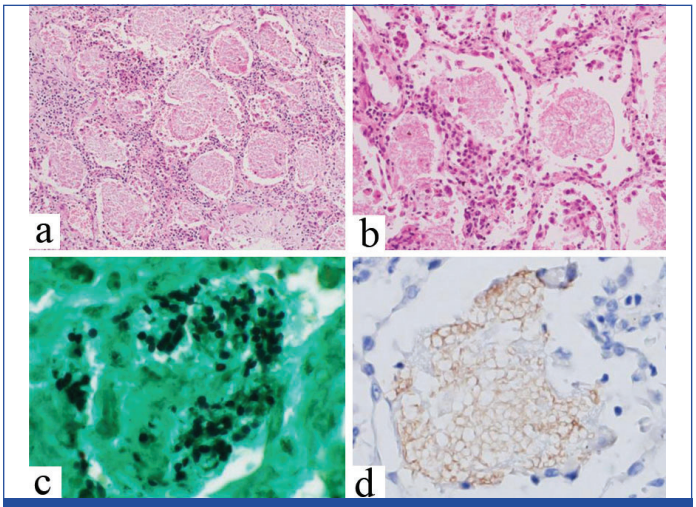
Primary haematological disease: PRCA with associated profound hypogammaglobulinaemia.

Immediate cause of death: Rapidly progressive respiratory failure due to DAD secondary to polymicrobial opportunistic pneumonia (*P. jirovecii, M. tuberculosis*, and CMV).

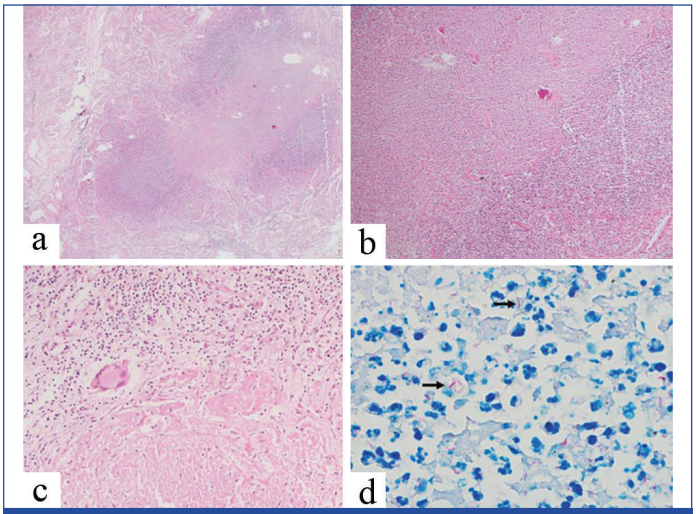
Secondary findings: Hepatic macrovesicular steatosis with centrilobular necrosis, and acute tubular injury consistent with terminal shock and systemic hypoxia; morphologically normal glomeruli.



[Table/Fig-1]: Peripheral smear and bone marrow findings: a) Peripheral smear showing reduced Red Blood Cell (RBC) density (Wright-Giemsa, ×100); b) Normocytic, normochromic red cells with adequate platelets (Wright-Giemsa, ×1000); c) Bone marrow aspirate with mature megakaryocyte and preserved myeloid lineage (Wright-Giemsa, ×400); d) Bone marrow biopsy showing hypocellularity with preserved myeloid and megakaryocytic lineages, absence of erythroid precursors (H&E, ×200).
H&E: Haematoxylin and Eosin



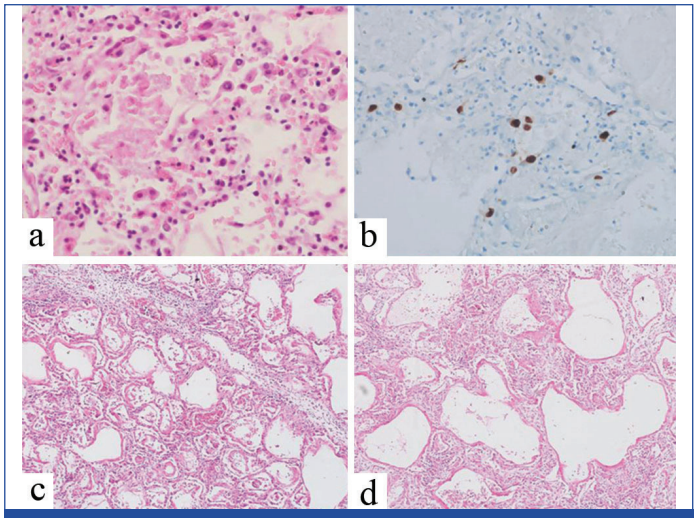
[Table/Fig-2]: Lung histology demonstrating *P. jirovecii*: a) Intra-alveolar eosinophilic foamy exudate (H&E, ×200); b) Mixed inflammatory infiltrate in alveolar septa (H&E, ×400); c) Crushed-cup-shaped cysts of *P. jirovecii* (GMS, ×1000); d) Positive 'chicken-wire' staining pattern for *P. jirovecii* (IHC, ×1000).



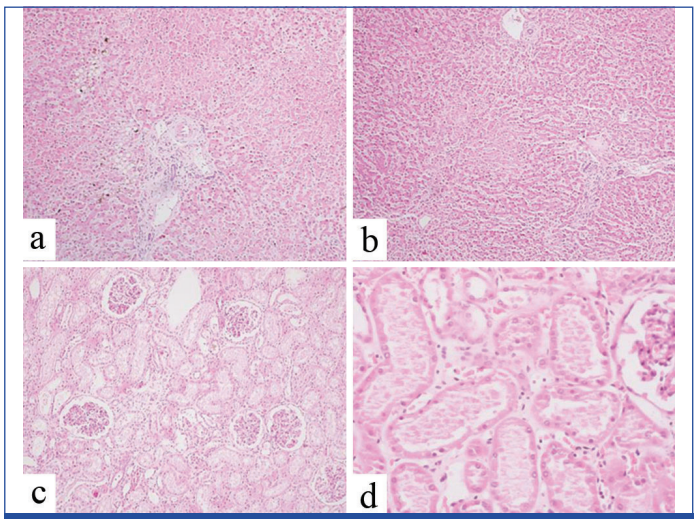
[Table/Fig-3]: Pulmonary tuberculosis: a-c) Necrotising granulomas with Langhans-type giant cells (H&E, ×100, ×200, ×400); d) Acid-fast bacilli (arrows) highlighted by Ziehl-Neelsen stain (×1000).

DISCUSSION

The PRCA is a rare erythroid disorder characterised by a near-complete absence of erythroid precursors in an otherwise normocellular marrow, with an estimated annual incidence of approximately 1.06 per million



[Table/Fig-4]: CMV pneumonia and DAD: a) Pneumocytes with CMV intranuclear inclusions (H&E, ×400); b) CMV nuclear positivity (IHC, ×400); c,d) DAD with hyaline membranes and interstitial oedema (H&E, ×100, ×400).



[Table/Fig-5]: Extra-pulmonary findings: a) Liver showing macrovesicular steatosis (H&E, ×200); b) Centrilobular ischaemic necrosis (H&E, ×200); c) Normal glomeruli (H&E, ×100); d) Acute tubular injury with epithelial sloughing and brush border loss (H&E, ×400).

[1,2]. The mainstay of management for acquired PRCA remains immunosuppression, with ciclosporin A (CsA) and corticosteroids representing the most established first-line agents, yielding overall response rates of approximately 63-77% and 40-47%, respectively [1,2]. However, the dual burden of a primary immunodeficiency-in the form of hypogammaglobulinaemia compounded by the secondary immunosuppressive effects of corticosteroids and CsA creates a profound and layered vulnerability to opportunistic infection. Prolonged corticosteroid use is well-documented to induce significant Cluster of Differentiation 4 (CD4) + T-cell lymphopenia and reduce serum IgG, thereby impairing both cellular and humoral defence mechanisms [3]. Concurrently, ciclosporin selectively impairs T-cell-mediated immunity, further expanding susceptibility to viral, fungal, and mycobacterial pathogens [4]. In patients with pre-existing hypogammaglobulinaemia, this iatrogenic immune suppression removes the last functional barriers to opportunistic infection, a scenario that proved catastrophic in our patient.

The pulmonary co-infection documented in the present case involving *Pneumocystis jirovecii* pneumonia (PJP), CMV pneumonitis, and *Mycobacterium tuberculosis* represents a highly unusual and severe clinical constellation. While dual co-infections involving PJP and CMV have been documented in the immunocompromised host, with in over half of patients without Human Immunodeficiency Virus (HIV) infection who had PJP in some cohorts [5-7], the simultaneous presence of three distinct pathogens from three entirely different microbiological classes-

fungal, viral, and mycobacterial in a non-HIV host has not been systematically catalogued. This 'triple-threat' pulmonary infection is exceptional and fundamentally distinguishes the present case from the existing literature, where most PRCA-associated infectious morbidity involves either Parvovirus B19 or single-class opportunistic pathogens [2]. In contrast to HIV-associated contexts where are frequently encountered [8], the patient's pathology was concentrated in the lung, with a far more explosive and rapidly fatal course. The hyperacute progression to Acute Respiratory Distress Syndrome (ARDS) within five days of presentation is strikingly different from most reported cases of PJP in non-HIV immunocompromised patients, who typically follow a subacute clinical trajectory over one to three weeks [9,10].

The pathophysiology underlying the rapid pulmonary deterioration in this case can be attributed to the synergistic alveolar injury inflicted by three distinct mechanisms. PJP characteristically produces diffuse ground-glass opacities and alveolar exudates through its attachment to type I alveolar epithelial cells, with a notably more fulminant course in non-HIV immunocompromised hosts than in HIV-positive patients [5,11]. CMV pneumonitis contributes through direct pneumocyte injury, classically manifested by cytomegalic cells bearing the hallmark 'owl's eye' intranuclear inclusions and associated interstitial inflammation [6]. Active pulmonary tuberculosis, meanwhile, indicates a fundamental failure of T-cell-mediated containment of mycobacterial bacilli, demonstrable by Ziehl-Neelsen positivity in tissue sections and associated with characteristic Langhans-type multinucleated giant cell formation [12]. The cumulative effect of these three insults is DAD, recognised as the histological hallmark of ARDS, characterised by hyaline membrane formation, interstitial oedema, and type II pneumocyte hyperplasia in the organising phase [13,14]. DAD resulting from infectious triggers is well-described, but the convergence of three simultaneous and distinct alveolar pathogens appears to have driven an unusually rapid and irreversible DAD progression in our patient [13].

The Intensive Care Unit (ICU) mortality of PJP in non-HIV patients is consistently reported as substantially higher than in HIV-positive individuals. A recent multinational post-hoc analysis documented an overall 30-day mortality of 52.7% in ICU-admitted PJP patients [10], and a bicentric retrospective cohort of 82 non-HIV ICU patients with PJP recorded an overall hospital mortality of 75.6%, considerably exceeding mortality figures reported in HIV-associated disease [15]. In such series, however, co-infection with both CMV and active tuberculosis is not reported, and the median time-to-death is not as abbreviated as in our case. A large multicentre review of HIV-negative versus HIV-positive PJP confirmed that non-HIV patients require mechanical ventilation more frequently and experience longer ICU stays, with overall in-hospital mortality for non-HIV patients ranging from 48% to 67% [16]. The five-day fatal course in our patient is exceptional even by these standards and most likely reflects the additive alveolar insult of concurrent CMV pneumonitis and tuberculous alveolitis, in a host whose dual immunodeficiency precluded any meaningful inflammatory containment.

Beyond the pulmonary compartment, the autopsy furnished compelling evidence of terminal multi-organ failure. The finding of centrilobular (Zone 3) hepatic necrosis is pathologically consistent with hypoxic hepatitis or 'shock liver', a well-recognised consequence of sustained circulatory and respiratory failure in the ICU setting [17]. Zone 3 hepatocytes are anatomically the most vulnerable to ischaemic injury, residing at the furthest point from the oxygenated portal blood supply; Centrilobular necrosis was observed in 80% (12/15) of patients with sepsis who died in the ICU on liver histopathology [18]. Renal injury in the form of ATI with epithelial sloughing and 'tubular detachment' represents a classic morphological marker of severe systemic insult, and its presence at autopsy underscores the multi-organ nature of the terminal physiological collapse [19]. Both findings are well-catalogued in critically ill patients dying of sepsis or hypoxaemia, yet their co-occurrence with an unusual triple pulmonary co-infection in a PRCA patient on immunosuppression has not, to our knowledge, been previously described in the literature.

A particularly salient feature of this case is the post-mortem discovery of active pulmonary Tuberculosis (TB), a pathogen that had not been identified ante-mortem despite the patient being in respiratory failure. This highlights the diagnostic challenge of 'silent' or radiographically atypical tuberculosis in profoundly immunocompromised patients, in whom the classic granulomatous response and cavitary infiltrates may be absent [20]. Recent literature on TB-ARDS emphasises that even in highly endemic regions the diagnosis is frequently delayed, and that molecular diagnostic tools such as GeneXpert MTB/RIF PCR (Mycobacterium tuberculosis / Rifampicin Polymerase Chain Reaction) offer a sensitivity approaching 89% and a specificity of 99%, with early initiation of anti-TB therapy within 72 hours demonstrably improving survival [20]. Had tuberculosis been actively suspected and bronchoscopically pursued via multiplex PCR, the diagnostic and therapeutic trajectory of this case might have been fundamentally altered.

The present case carries important implications for the clinical management of PRCA patients receiving immunosuppressive therapy, particularly those with pre-existing hypogammaglobulinaemia. Current evidence strongly supports routine co-trimoxazole {Trimethoprim/Sulfamethoxazole (TMP-SMX)} prophylaxis against PJP in patients receiving corticosteroids exceeding 15-20 mg prednisone-equivalent per day for more than four weeks, or in those receiving combination CsA and corticosteroid therapy [4]. Tuberculosis screening with Interferon-Gamma Release Assays (IGRAs) or tuberculin skin testing prior to commencing immunosuppression is indicated in all patients from endemic areas or with known exposure history. Bronchoalveolar Lavage (BAL) with multiplex PCR-based pathogen panels is the diagnostic cornerstone in immunocompromised patients with unexplained pulmonary infiltrates, enabling simultaneous detection of PJP, CMV, mycobacteria, and other opportunistic organisms [5,11]. The absence of pre-treatment tuberculosis screening and of PJP prophylaxis prior to this admission likely contributed directly to the catastrophic outcome. Furthermore, regular immunoglobulin replacement therapy should be considered in PRCA patients with documented hypogammaglobulinaemia to partially restore humoral defence during periods of therapeutic immunosuppression [3].

CONCLUSION(S)

The present case represents to our knowledge, the first documented report of a fatal triple pulmonary co-infection—PJP, CMV pneumonitis, and active tuberculosis—in a PRCA patient with combined primary hypogammaglobulinemia and iatrogenic immunosuppression. The hyperacute five-day progression to ARDS and multi-organ failure, confirmed at autopsy, underscores the exponential infectious risk conferred by layered immune deficiencies. It calls for a paradigm shift in the management of PRCA patients on immunosuppression: aggressive pre-treatment screening for latent tuberculosis, mandatory prophylaxis against PJP, early and broad-spectrum molecular diagnostics in the event of respiratory decompensation, and vigilant surveillance for 'silent' co-infections in the severely immunocompromised host.

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