# Epistaxis, *Pneumocystis jirovecii* pneumonia and aplastic anaemia: chicken or egg?

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## Introduction

Aplastic anaemia is a rare disease in young children that arises from damage to the bone marrow and resident haematopoietic stem cells. Affected patients are susceptible to bacterial and invasive fungal infections due to profound persistent neutropenia.[1] *Pneumocystis jirovecii* pneumonia (PJP) is rarely reported in patients with aplastic anaemia. We review a case of early presentation of PJP associated with very severe aplastic anaemia and the associated literature.

## Case report

A 31-month previously healthy boy with normal growth and development presented with a 2-month history of profound epistaxis, easy bruising and petechial rash. Apart from a 1-day history of fever prior to admission, he displayed no constitutional symptoms. There was no history suggestive of consumption of herbal or over-the-counter medicine and no family history of haematological disease or malignancy. He was an only child. Complete blood picture revealed pancytopenia (haemoglobin level of 7 g/dL, white blood cell count of $0.3\times10^9$/L, platelet count of $3\times10^9$/L, reticulocyte count of <0.2%) and after further workup he was diagnosed with very severe aplastic anaemia. Liver function tests were deranged with raised alanine aminotransferase level of 1687 IU/L, alkaline phosphatase level of 347 IU/L, gamma-glutamyl transferase level of 128 IU/L, and total bilirubin level of 11 μmol/L, but the levels of ammonia and lactate were normal. Ultrasound of the liver was suggestive of mild hepatic parenchymal disease such as hepatitis.

Bone marrow trephine showed severe deficiency of all cell lines, markedly hypocellular marrow (overall cellularity <10%) and no abnormal infiltrations. Immunophenotyping of the lymphoid population revealed marked lymphopenia with a reversed CD4:CD8 ratio at 0.3:1. His CD4 count was very low. Within one week of presentation, he developed antibiotic-resistant pneumonia. He was commenced initially on piperacillin/tazobactam but switched to meropenem and micafungin due to fever and progressive chest X-ray changes of bilateral infiltrates (Fig 1). He had increased respiratory distress and required support with high-flow oxygen therapy in the paediatric intensive care unit. Computed tomography scan of the chest revealed bilateral extensive patchy changes, most severe at both anterior segments of the upper lobe and posterior segments of the lower lobes (Fig 2). Prompt bronchoalveolar lavage was performed and Grocott methenamine silver staining revealed the pathogen to be *P jirovecii* (Fig 3). Bronchoalveolar lavage culture also showed scanty growth of alpha-haemolytic *streptococcus* (<1000 CFU/mL) with no white cells seen on microscopy. He was treated with a 21-day course of co-trimoxazole (120 mg/kg/day) and oral prednisolone (2 mg/kg/day for 5 days, 1 mg/kg/day for 5 days, then 0.5 mg/kg/day for 11 days). The pneumonia gradually resolved and his liver function tests normalised. Nonetheless he remained pancytopenic.

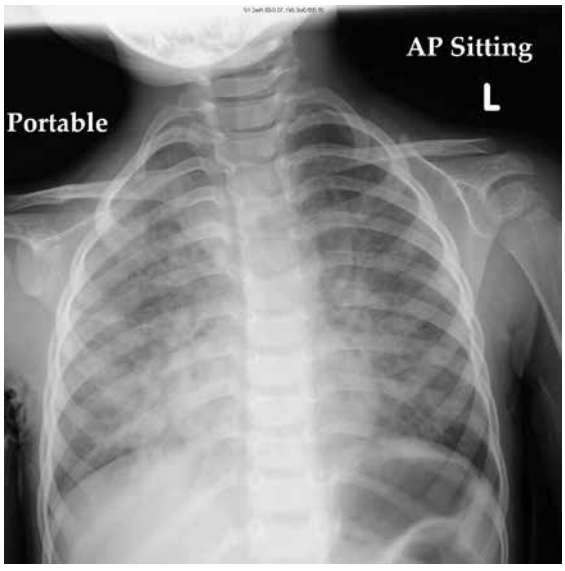


FIG 1. Chest X-ray–bilateral patchy and confluent airspace opacities in both lungs of the patient, which were more pronounced over the middle and lower zones with consolidation over the right middle and lower zones

 

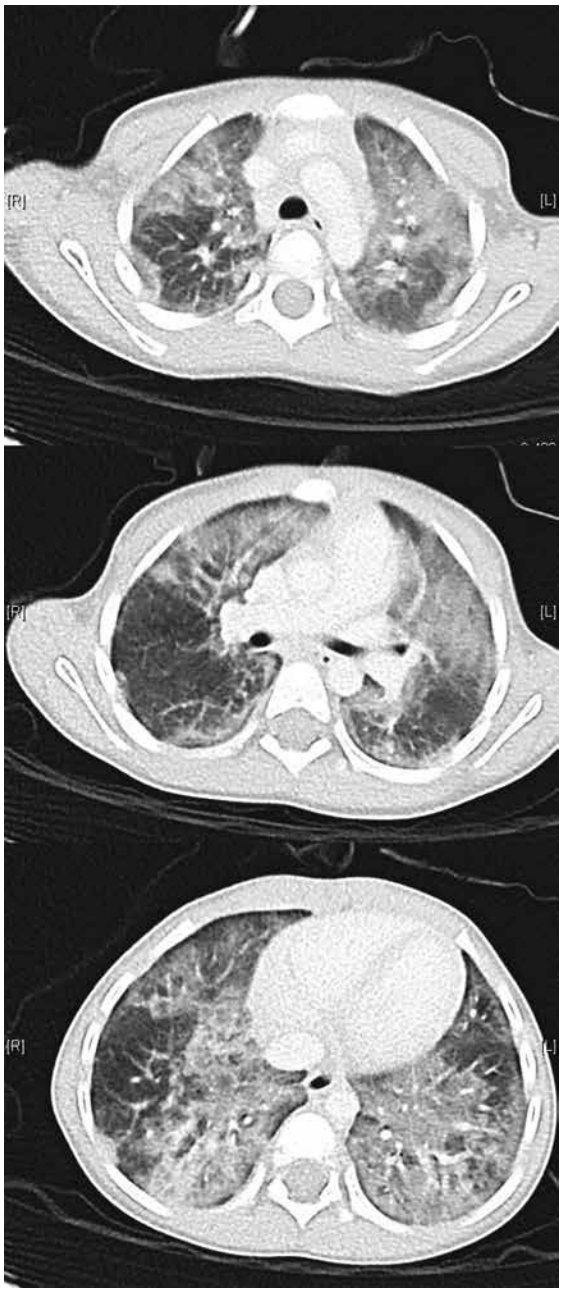


FIG 2. Computed tomography scan of the thorax–bilateral extensive opacities with consolidations and ground glass opacities, which were most severe at both anterior segments of the upper lobe and posterior segments of the lower lobes

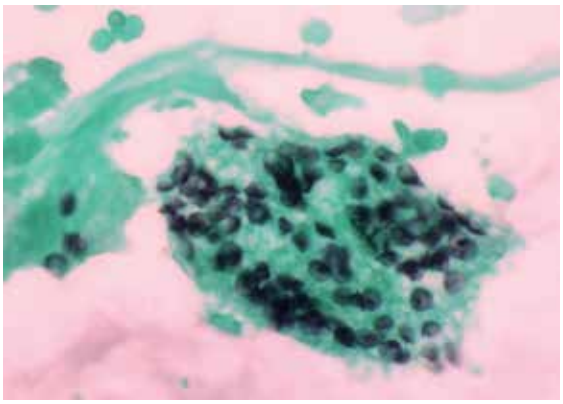

FIG 3. Grocott methenamine silver stain of bronchoalveolar lavage specimen of the patient showing *Pneumocystis jirovecii*

No test was suggestive of an inherited marrow failure syndrome or recent infection. Bronchoalveolar lavage for viral polymerase chain reaction and culture, *Legionella* culture, and acid-fast bacillus culture were also negative. No drug history was identified that could account for his aplastic anaemia. Autoimmune screening (immunoglobulin A [IgA], IgG, IgM, complement component 3, complement component 4, antinuclear antibody, and anti-extractable nuclear antigen) was likewise insignificant.

The child was commenced on immunosuppressive therapy with methylprednisolone, cyclosporin A, and lymphocyte immune globulin, antithymocyte globulin after treatment of the PJP. He has been on immunosuppressive therapy for >1 year and is demonstrating a good response to treatment.

## Discussion

Aplastic anaemia is a potentially life-threatening clinical syndrome characterised by pancytopenia with a hypocellular bone marrow in the absence of abnormal infiltration or increased reticulin.[2] It is a rare disorder with an incidence of about two cases per million population per year. Nonetheless the incidence is two- to three-fold higher in Asia than in Europe.[3,4]

Persistent neutropenia is the major risk factor for the development of all types of infection in patients with aplastic anaemia, while bacterial and invasive fungal infections are the major causes of mortality.[1,2] Respiratory tract infection is one of the common manifestations of infection in children with aplastic anaemia, and pneumonia in particular can be life-threatening.[2] Detection of an infectious agent may be possible in only approximately 12% to 20% of cases, and diagnosis is mainly based on clinical symptoms and radiological investigations.[5,6] Previous reviews of respiratory infection in patients with severe aplastic anaemia and very severe aplastic anaemia revealed common causes such as invasive fungal infection (*Aspergillus* and *Zygomycetes*) and respiratory viral infections (influenza A and B, respiratory syncytial virus, parainfluenza virus,

adenovirus, and cytomegalovirus).[2,5,7] *Pneumocystis jirovecii* pneumonia is rarely reported in patients who have commenced immunosuppressive therapy, and no case of PJP has been reported in three large studies of patients prescribed antithymocyte globulin and cyclosporin A.[1,8]

The risk of PJP in patients with aplastic anaemia has not been defined in the literature, but the risk should be low since the T cells are not defective.[1] T cells ($CD4^+$) are crucial for PJP clearance as they coordinate inflammatory responses in the host by recruiting and activating effector cells.[9] Only three cases of PJP in patients with Diamond–Blackfan anaemia and one case in a patient with Fanconi's anaemia have been reported and all were receiving high-dose corticosteroids.[10,11] Our patient is possibly the first reported case of PJP in a patient with aplastic anaemia not yet started on any immunosuppressive therapy. The development of PJP was probably due to the immune deficiency of aplastic anaemia rather than the aetiology, as evidenced by the reversed CD4:CD8 ratio. Patients with aplastic anaemia are usually not considered to be at risk of PJP, hence prophylaxis is not routinely prescribed.[12] Nonetheless PJP in aplastic anaemia should not be overlooked as the mortality of PJP in human immunodeficiency virus–seronegative patients is significant (32%-50%).[13,14] Our patient developed PJP within a week of diagnosis, before he was started on any immunosuppressive therapy. This raises a broader question of whether PJP prophylaxis (eg, co-trimoxazole, dapsone and pentamidine) should be considered in patients with aplastic anaemia, especially those who fulfil the criteria of very severe aplastic anaemia.

The Red Book 2018 suggests that standard precautions should be taken,[15] while the Centers for Disease Control and Prevention in the United States[16] and Health Protection Scotland[17] both recommend that patients with PJP should not share a hospital room with other immunocompromised patients. Although there have been clusters of PJP cases reported in wards of immunocompromised patients, and a study has also shown that airborne person-to-person transmission of *P jirovecii* is possible, we believe there is insufficient evidence to warrant mandatory isolation.[18] It is more important to identify patients at risk of PJP and commence prophylaxis.[19]

## Conclusion

*Pneumocystis jirovecii* infection is probably due to immune deficiency in aplastic anaemia, not the aetiology of aplastic anaemia. Clinical and radiological pictures of PJP in a patient with aplastic anaemia are not specific for *P jirovecii*. All such patients with symptoms of lung infection resistant to antibacterial and antifungal therapy should be examined for PJP. Our patient is possibly the first reported case of PJP in a patient with aplastic anaemia prior to commencement of immunosuppressive therapy. Although standard guidelines do not recommend PJP prophylaxis in patients with aplastic anaemia, further studies should assess whether the benefits of chemoprophylactic agents outweigh the risks in those considered to have very severe aplastic anaemia.

### Author contributions

Concept or design: KKY Leung, KL Hon.
Acquisition of data: KKY Leung, KL Hon.
Analysis or interpretation of data: All authors.
Drafting of the manuscript: KKY Leung, KL Hon.
Critical revision of the manuscript for important intellectual content: All authors.

All authors had full access to the data, contributed to the study, approved the final version for publication, and take responsibility for its accuracy and integrity.

### Conflicts of interest

As an editor of the journal, KL Hon was not involved in the peer review process. Other authors have disclosed no conflicts of interest.

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### Ethics approval

The patient was treated in accordance with the Declaration of Helsinki, with informed consent provided for treatment, procedures, and publication.

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