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CASE REPORT

# Children's pure white cell aplasia: two cases report

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## Abstract

Pure white cell aplasia is a rare inhibition of granulopoiesis, with normal megakaryopoiesis and erythropoiesis, presenting as severe neutropenia. The pathological mechanism and causes are still poorly understood. Recurrent infection is the most frequent complication of this disease, with sepsis being the main cause of death. This is the ?rst case report of pure white cell aplasia in children, presenting two cases of pediatric patients with similar manifestations but different outcomes, aiming to contribute to an early diagnosis and adequate clinical management of affected patients, with the discussion of possible complications of the disease.

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## INTRODUCTION

Pure white cell aplasia (PWCA) is a rare inhibition of granulopoiesis, with normal megakaryopoiesis and erythropoiesis[1,2], presenting as severe neutropenia[3]. The pathological mechanism is poorly understood[4]. Some evidence suggests the presence of autoantibodies against myelocyte maturation receptors[5,6] and possible involvement of the complement system and T cells[1,6]. There is no defined cause, but it may be related to autoimmune or infectious diseases, medications or thymomas[7]. The most frequent complication of PWCA is recurrent infections[3], with sepsis being the main cause of death[1].

Reports of PWCA in the literature are in adults, and there are not enough publications in the pediatric population to support treatment in children. Extrapolation of the descriptions in adults is made, in which removal of the offending agent is reported[7,8], in addition to immunosuppression with corticosteroids, cyclosporine, immunobiologicals, granulocyte colony-stimulating factor (G-CSF), immunoglobulin (IVIG), plasmapheresis[4,5,6,7,9] and bone marrow transplantation[1,3]. It is important to emphasize that the use of G-CSF alone is ineffective[1,6].

Aiming to contribute to early diagnosis and adequate clinical management of affected patients, we describe the evolution of two pediatric patients with pure white cell aplasia.

## CASE 1

A previously-healthy 11-year-old male developed fever, otalgia, odynophagia and cervical lymph node enlargement in June 2020. Oral antibiotic therapy was initiated, but the patient kept his fever and developed prostration, cough, bullous lesions in the armpits, diarrhea, perianal pain, and severe neutropenia. He was hospitalized for intravenous antibiotic therapy. A myelogram and bone marrow biopsy (BMB) were performed, which ruled out neoplastic disease and showed an intense reduction in myeloid precursors, with the erythroid and megakaryocytic sectors being normal, characterizing agranulocytosis, compatible with PWCA. He received G-CSF without response, and methylprednisolone 2 mg/kg/day and cyclosporine 5 mg/kg/day were initiated. He developed a perirectal abscess fistulized to the rectum, justifying the expansion of antibiotic coverage. The sequencing of an expanded genetic panel for inborn errors of immunity did not show mutations, although serum dosage demonstrated IgA deficiency. After 22 days of cyclosporine and corticosteroid therapy, the patient presented a bone marrow response with normal myelogram and BMB and granulocyte recovery. However, the patient continued with a fever, abdominal pain and multiple splenic abscesses on ultrasound, we performed a laparoscopic aspiration, which direct analysis suggested fungus, and Amphotericin B was associated with




**Figure 1**. Images A and B with multifocal hypoechoic images in the spleen on abdominal ultrasound, suggestive of microabscesses. Post-splenectomy spleen in image C. Image D with a bone lesion on the left, suggestive of chronic osteomyelitis.

the immunosuppressive regimen. However, the patient maintained the fever and positive inflammatory tests; and splenectomy was indicated (Figure 1), but the fungal test was negative in the surgical specimen, and the hypothesis of Immune Reconstitution Inflammatory Syndrome (IRIS) was raised, with complete improvement of fever after surgery, and the antifungal was changed to Fluconazole. The patient was discharged from the hospital after 64 days of hospitalization and continued in outpatient follow-up, with gradual reduction of corticosteroid therapy until discontinuation 2 months after discharge, maintaining the use of antifungal for 6 months and cyclosporine for 1 year. During follow-up, the patient developed a lesion in the left femur (Figure 1), suspected of chronic osteomyelitis, but with negative bone culture, corroborating the hypothesis that the bone lesion was due to IRIS during the bone marrow recovery phase. Currently, the patient is 15 years old, not taking continuous medication, asymptomatic, under hematological follow-up, and has not had a repeat bone marrow analysis due to normal control blood counts.

## CASE 2

A 7-year-old male, previously healthy, developed fever, cough, runny nose, and vomiting in January 2022, with a positive rapid COVID-19 test. With no improvement in his condition, oral antibiotic therapy was started, but he developed large bilateral cervical lymph node enlargement and severe neutropenia, being hospitalized for intravenous antibiotic therapy. A myelogram and BMB were performed, which ruled out neoplastic disease and showed agranulocytosis, with a diagnosis of PWCA. Prednisone was started at 2 mg/kg/day and cyclosporine at 5 mg/kg/day. However, as he developed liver toxicity with encephalopathy and acute kidney injury, cyclosporine was suspended and IVIG was prescribed at 1 g/kg/dose for 2 days. After improvement in liver function, cyclosporine was reintroduced at a lower dose (2 mg/kg/day), showing a bone marrow response, with a normal myelogram 22 days after starting therapy and 5 days after restarting cyclosporine. He developed enterorrhagia, epistaxis, ecchymosis and petechiae, presenting severe thrombocytopenia without response to platelet transfusion, and was given IVIG 1g/kg/dose for 2 days and pulse therapy with methylprednisolone to treat concomitant Immune Thrombocytopenic Purpura (ITP). He was discharged after 60 days of hospitalization, taking cyclosporine and gradual reduction of corticosteroid therapy.

After 29 days at home, he presented fever, diarrhea, vomiting and abdominal pain, with recurrence of severe neutropenia and abdominal tomography suggestive of appendicitis. He underwent appendectomy and broad-spectrum antibiotic therapy. Myelogram and BMB were again compatible with PWCA. Corticosteroid therapy was restarted and an attempt was made to increase the dose of cyclosporine to 3mg/kg/day, but there was again liver involvement, and the tolerated dose of 2mg/kg/day was resumed and Rituximab was prescribed. Six days after starting the immunobiological treatment, with normal granulocytes, the fever and abdominal pain returned, with an abdominal tomography showing multiple lesions in the liver and spleen suggestive of microabscesses (Figure 2), a condition compatible with systemic candidiasis and probable IRIS. Micafungin was started, to which he had an allergic reaction, and was replaced by fluconazole. Myelogram and BMB control were normal. He completed the 4-dose regimen of Rituximab and began a gradual reduction of corticotherapy on an outpatient basis. He was discharged 42 days after this hospitalization, and cyclosporine was suspended after 7 months of use, considering that he maintained subtherapeutic levels of the medication. He completed 6 months of use of fluconazole and remained asymptomatic, with normal control blood counts and an

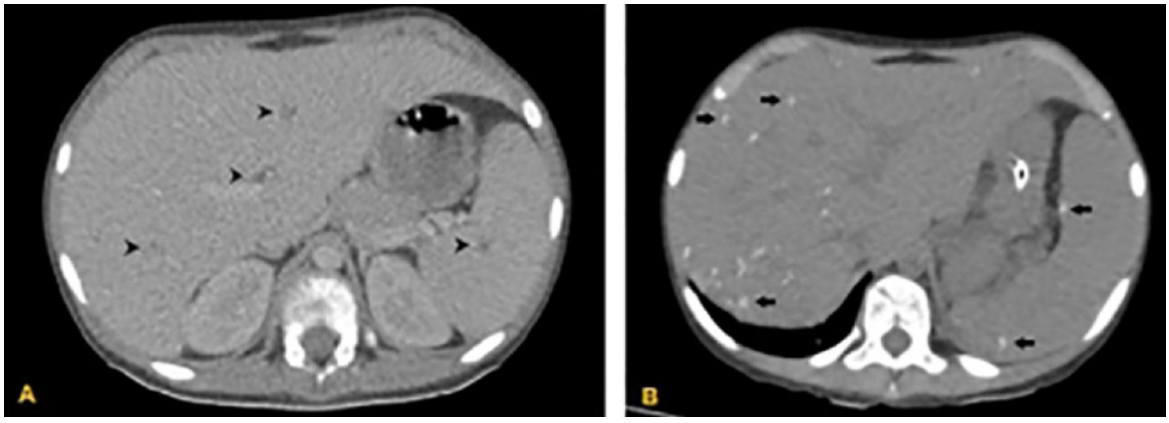



**Figure 2.** In image A, hypoattenuating lesions in the liver and spleen (arrowhead), suggestive of microabscesses. In image B, hyperattenuating regions such as residual calcified lesions (arrows), arising after resolution of microabscesses.

abdominal tomography showing calcified hepatosplenic lesions (Figure 2).

In July 2023, the patient presented with new fever with tonsillitis, cervical lymph node enlargement, cervical mass with extrinsic airway compression, and severe neutropenia. Myelogram and BMB were again compatible with PWCA. Broad-spectrum antibiotic therapy, corticosteroid therapy, cyclosporine, IVIG, and weekly rituximab were initiated. A biopsy of the cervical mass ruled out neoplasia but was positive for Candida parapissilosis, and amphotericin B was added to the antimicrobial regimen, in addition to acyclovir for herpes virus infection. However, the patient continued to have persistent fever, an increase in the cervical mass, and respiratory failure due to extrinsic compression. In control myelograms, the PWCA remained despite treatment, with no bone marrow response, evolving into refractory septic shock and death.

## DISCUSSION

PWCA is a rare disease, of little-known cause and pathophysiology, in which there is an absence of myeloid precursor cells in the bone marrow, maintaining preserved erythropoiesis and megakaryopoiesis[1], evolving with recurrent infections and severe neutropenia. All the literature search returned adult patients with a mean age of 56 years[3], describing PWCA related to malignancy[6,7], autoimmunity[5], use of medications[10] or infectious diseases[6], and this is probably the first report in the pediatric age group.

The main differential diagnoses are diseases that can occur with neutropenia, such as infections, hematologic neoplasms, rheumatologic diseases such as systemic lupus erythematosus (SLE), hemophagocytic syndrome (HPS) and immunodeficiencies.

The two cases in this study initially presented as an airway infection and cervical lymph node enlargement, evolving with febrile neutropenia. In both cases, the myelogram and BMB were compatible with PWCA, showing agranulocytosis, with normal erythroid and megakaryocytic sectors. Differential diagnoses were extensively investigated, and the following were ruled out: neoplastic diseases due to negative BMB and normal immunophenotyping; rheumatological diseases were ruled out, with negative autoantibody testing; genetic panel for inborn errors of immunity was negative; they did not meet the criteria for HFS, in addition to the absence of hemophagocytosis in the bone marrow; and they presented negative viral serologies, except for case 2, who tested positive for COVID-19 at the first presentation.

Corroborating the description in the literature, case 1 did not respond to monotherapy with G-CSF, with neutrophil recovery occurring only after immunosuppression with corticosteroid therapy and cyclosporine. Case 2 presented toxicity to cyclosporine, requiring a subdose of this medication, in addition to corticosteroid therapy and IVIG. This patient presented recurrence of the disease, responding more sustainably after rituximab. There are also other reports showing concomitant immune thrombocytopenia with PWCA[7], as occurred in case 2.

In both cases, after neutrophil recovery, the patients maintained fever, despite antimicrobial therapy, evolving with multifocal hepatosplenic lesions, of probable fungal etiology. This is disseminated candidiasis, which does not respond adequately to antifungals and, in patients in the immunological recovery phase, may represent a form of IRIS[11,12], where there is intense release of cytokines, after long periods of agranulocytosis with rapid and exacerbated resolution of neutropenia[13,14]. The recommended treatment is with antifungals (amphotericin B, echinocandin or fluconazole), and fluconazole should be continued for a prolonged period until clinical stabilization or calcification of multifocal lesions[12], sometimes requiring splenectomy when there is no clinical improvement, as occurred in case 1. In addition, studies demonstrate the benefit of concomitant corticosteroid therapy[14,15] in patients who have difficult-to-control fever in IRIS, for example with prednisone 0.5 to 1 mg/kg/day[11], a therapy also used in the patients described.

Case 1 did not have relapses of the disease; however, case 2 presented two new symptoms compatible with PWCA after the initial presentation, not responding to therapy in the last event, evolving to death due to sepsis.

The two cases reported demonstrate the particularities between the symptoms of the same disease and the severity of the pathology, with high morbidity and mortality and prolonged hospitalizations. As there are still no previous reports in the pediatric population, further studies are needed to describe appropriate therapy for this age group.

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