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Immune reconstitution inflammatory syndrome in HIV-negative patients with hematological malignancies and hematopoietic stem cell transplantation: A case series and a literature review

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ABSTRACT

Immune reconstitution inflammatory syndrome (IRIS) is a potentially severe complication following the withdrawal of immunosuppressive agents, commonly studied in human immunodeficiency virus (HIV)-positive patients. However, its impact on individuals with hematological malignancies and those undergoing hematopoietic stem cell transplants is less understood. This study aimed to establish diagnostic criteria for IRIS in these populations and assess its incidence and clinical progression. A cross-sectional, prospective observational study was conducted with 159 chemotherapy patients and 96 hematopoietic stem cell transplant recipients. IRIS diagnosis criteria were derived from a literature review of 70 studies, and patients were monitored for 11 months. The review identified key IRIS diagnostic criteria, including paradoxical clinical worsening, antimicrobial refractoriness, and inflammatory signs following immunosuppressive therapy. Most IRIS cases were linked to pathogens like *Mycobacterium*, *Candida spp*., and *Aspergillus spp*. Among our patients, three cases of IRIS were identified: one related to the Bacillus Calmette-Guérin (BCG) vaccine, another with neutrophil recovery, and the third with chronic disseminated candidiasis. Treatment with corticosteroids and antimicrobial therapy allowed continued chemotherapy without impacting the underlying disease's outcomes. IRIS is an important complication in hematological and stem cell transplant patients. Early recognition and appropriate treatment, including corticosteroids and antimicrobial therapy, are critical for successful management and uninterrupted cancer treatment.

Keywords: Immune Reconstitution Inflammatory Syndrome. Immunosuppression Therapy. Opportunistic Infections. Hematologic Neoplasms.

INTRODUCTION

The immune reconstitution inflammatory syndrome (IRIS) is a group of inflammatory disorders initially described in patients living with the human immunodeficiency virus (HIV), given its high prevalence in this population. It is characterized by the recovery of CD4+ T lymphocytes and the normalization of immune responses to pathogens following the initiation of antiretroviral therapy.[1] Over the years, IRIS has been reported in various other contexts, such as in patients discontinuing anti-tumor necrosis factor (TNF)-α medications, neutrophil recovery after cytotoxic chemotherapy, hematopoietic stem cell engraftment, postpartum, and in solid organ transplant recipients.[2]

IRIS can manifest in two forms: unmasking IRIS, in which previously hidden infections are revealed due to

a lack of an earlier inflammatory response caused by transient immunosuppression, and paradoxical IRIS, characterized by the worsening of an initial clinical condition following improved immune function and inflammatory responses, even with adequate treatment of the initial infectious agent.[3]

The pathogenesis of IRIS has not yet been fully elucidated. Studies suggest that, after neutropenia, the innate immune system's recovery may drive the syndrome, whereas in post-transplant immunosuppression cessation, the adaptive immune response could play a role.[4,5] Understanding these mechanisms is critical since, in cases involving innate immunity, treatments like granulocyte colony-stimulating factors (*e.g.*, filgrastim or G-CSF) may exacerbate symptoms due to the rapid proliferation of immune cells.[5]

Given its potential to cause severe complications—such as distributive shock, liver failure, acute respiratory distress syndrome, and even death—, it is crucial to diagnose IRIS early.[3] Common signs and symptoms include fever, diarrhea, nausea, vomiting, jaundice, and right hypochondrial pain. These are nonspecific and can be mistaken for new active infections or antimicrobial resistance, making IRIS primarily a diagnosis of exclusion.[6]

We report the outcomes of IRIS in patients with hematological malignancies and bone marrow transplant recipients at a tertiary care hospital in Brazil, along with a literature review on the topic.

METHODS

Building the criteria to identify immune reconstitution inflammatory syndrome

Based on the guiding question "What are the criteria for the suspicion and diagnosis of IRIS in people not living with HIV?, a literature review was conducted using the following databases: Medical Literature Analysis and Retrieval System Online (Medline), Scopus, and ScienceDirect. The following descriptors and their combinations in Portuguese and English were used for the article search: *immune reconstitution inflammatory syndrome*, *immune reconstitution syndrome*, and *non-HIV immune reconstitution inflammatory syndrome*. The only exclusion criteria for the articles are as follows: the study involves research with people living with HIV; there is no text available for reading.

Participants

The study is a cross-sectional, prospective, and observational type. One hundred fifty-nine patients with hematological malignancies undergoing chemotherapy and 96 patients undergoing hematopoietic stem cell transplant were screened to assess their eligibility for participation in the study based on predefined inclusion and exclusion criteria. The inclusion criteria included hospitalized individuals undergoing chemotherapy or hematopoietic stem cell transplant who presented with suspected or confirmed immune reconstitution inflammatory syndrome. The exclusion criteria included individuals with HIV infection, those without a diagnosis of oncological and/or hematological disease, cases with insufficient documentation in medical records for study purposes, and those lacking laboratory tests necessary for clinical monitoring. Detailed information on how IRIS was suspected can be found in Table 1. The patients were monitored over a period of 11 months using information obtained from electronic medical records.

Institutional ethical committee approval was obtained for this trial, which was registered in the Hospital das Clínicas (Complexo do Hospital de Clínicas da Universidade Federal do Paraná, Curitiba, Paraná, Brazil) registry, and conducted in compliance with the Declaration of Helsinki.

Sample size calculation

In the absence of robust studies and extensive literature, the case series in this study relies on the authors cited throughout this work. By extrapolating data from Wong et al.[1] on individuals living with HIV to the population

Table 1. Criteria for defining immune reconstitution inflammatory syndrome based on the revised literature.

Parameter	Criteria	Requirement
Neutrophil count at the onset of symptoms	≥ 0.5 × 10^9/L	Mandatory
New symptoms of infection or inflammation	Onset of unexplained fever > 38°C, malaise, nausea, body aches, sweating, chills, leukocytosis, and increased C-reactive protein levels during or after neutrophil recovery	Mandatory
Refractoriness to antimicrobial therapy	Symptoms persist even after at least 72 hours of antimicrobial therapy	Mandatory
Rapid increase in neutrophil count	≥ 100% within one to three days	Optional
Filamentous fungal infection	Fungi from the Aspergillus, Fusarium genera, or fungi from the Mucorales order	Optional (at least one as an initial diagnostic hypothesis)
Yeast fungal infection	Fungi from the Candida or Cryptococcus genera	
Mycobacterium genus microorganism infection	Positive culture and/or positive smear microscopy and/or positive Xpert MTB/RIF	
Radiological worsening	Presence of new radiological signs such as infiltrates, lymphadenopathy, cavitations, ground-glass opacity, hemoptysis, pneumothorax	Optional

Source: Elaborated by the authors.

under study, it is estimated that 10–20% of patients undergoing chemotherapy treatment or hematopoietic stem cell transplant in our service may develop IRIS. Other authors[7,8] have also cited an overall incidence of 10 to 25% of IRIS in HIV-positive patients. The initial target sample size was 14 patients, based on the overall low incidence of IRIS. However, after 11 months of analysis, only three patients developed IRIS, for whom we prepared a brief case report.

Outcome parameters

The primary end point of this study was to describe the monitoring and incidence of IRIS in our population of patients with malignant hematological diseases or hematopoietic stem cell transplant. Secondary objectives were to identify the most common signs and symptoms presented by the studied population and to determine if these findings align with the literature based on the bibliographic review conducted by the authors.

RESULTS

Criteria to identify immune reconstitution inflammatory syndrome

The search using the mentioned descriptors generated 12,195 results. After reviewing the titles of the studies, 95 were selected for further reading. However, four of them did not have the full text available, and one was the same abstract published under two different doi codes. Among the 90 studies reviewed, 74.4% were full articles, and 25.6% were abstracts only. Despite the use of descriptors, 14 studies were excluded after full reading because they addressed cases involving individuals living with HIV, and five were excluded due to unclear information regarding whether the case was IRIS. This left 71 studies for the review.

Among them, 85.9% articles linked IRIS to the presence of specific pathogens, such as Cytomegalovirus, *Aspergillus* spp., *Candida* spp., *Pneumocystis jirovecii*, *Blastomyces dermatitidis*, the Bacillus Calmette-Guérin (BCG) vaccine, *Cryptococcus* spp., *Epstein-Barr virus*, *Histoplasma capsulatum*, *Mycobacterium* spp., *Nocardia* spp., and *Toxoplasma gondii*. All 71 studies reported the paradoxical worsening of the patient's clinical condition and antimicrobial therapy refractoriness as the primary guiding factors for suspecting IRIS. This diagnosis was confirmed through imaging that showed clinical deterioration (21.4%), biopsy or immunohistochemistry with inflammatory patterns but no evident microorganisms (15.7%), and signs of acute inflammation with elevated inflammatory markers (8.5%).

Additionally, all studies emphasized the need for recovery from a transient immunosuppressive state due to the use of immunosuppressants or chemotherapeutics, highlighting lymphocyte recovery as the cause of IRIS in patients with solid organ transplants or multiple sclerosis, or neutrophil recovery in hematological patients. The identification of a causative microorganism was not mandatory, as evidenced in 14.1% of the evaluated studies.

Detailed information on all studies can be found in Santiago (2025).[9]

Case report: patient 1

Our first patient is a 10-month-old male transferred to our service for a haploidentical bone marrow transplant (father as donor) for X-linked severe combined immunodeficiency (SCID) (T-B+NK-). Until 6 months old, he showed good weight gain and development without complications. At 6 months old, he developed a persistent cough, sought medical care, was hospitalized, and treated for bronchiolitis and pneumonia. Due to the lack of improvement, a gastric lavage was performed, identifying fragments of mycobacteria, prompting treatment with rifampin, isoniazid, and ethambutol. He was discharged home for one month before being transferred to our hospital. Persistent coughing was reported during this period. His brother had died at 10 months old from disseminated infection, likely mycobacteriosis, and was also diagnosed with SCID.

The patient only experienced mild respiratory discomfort due to his prior mycobacteriosis history, managed with inhaled salbutamol, without other significant clinical symptoms. Conditioning therapy included busulfan 10.4 mg/kg from D-5 to D-2, fludarabine 150 mg/m^2 from D-5 to D-2, and thymoglobulin 5 mg/kg from D-7 to D-5, with graft-*versus*-host prophylaxis using cyclophosphamide 100 mg/kg from D+3 to D+4, cyclosporine, and mycophenolate.

On D+3 post-transplant, he presented with fever but no signs of instability. A chest computed tomography (CT) scan showed no mediastinal or hilar lymphadenopathy, no gross consolidations, or reticular opacities suggestive of tuberculosis sequelae. There was evidence of bronchial wall thickening and air trapping.

On D+4, he developed a diffuse maculopapular rash on his trunk, upper and lower extremities (less prominent on the face and more intense on the back), along with a fever of 38.3°C. The fever decreased the following day without additional interventions. Blood cultures revealed multi-sensitive *Enterococcus faecium*, leading to the discontinuation of cefepime and initiation of ampicillin 200 mg/kg/day. The patient became afebrile after the antibiotic change, although the diffuse maculopapular rash persisted, consistent with heat rash.

Ampicillin was discontinued on D+13 after completing a 10-day course. However, later, on the same day, he experienced wheezing, respiratory distress, abdominal distension, hepatomegaly, and edema following a platelet transfusion. Methylprednisolone (1 mg/kg), inhaled salbutamol, and furosemide (0.5 mg/kg/dose) were administered with slight improvement. Abdominal ultrasound showed signs of aerobilia (in the main portal vein and hepatic parenchyma), a small amount of free fluid in the abdominal cavity, gallbladder wall edema, and mild intestinal distension. A reaction to the platelets or engraftment syndrome was questioned, and meropenem, methylprednisolone 8 mg every six hours, salbutamol every two hours, and furosemide 0.5 mg/kg every 12 hours were initiated. Neutrophil engraftment was confirmed on the same day.

The respiratory condition continued to worsen, and on D+17 the patient was admitted to the intensive care unit (ICU) due to respiratory deterioration and bronchospasm. He had audible wheezing without a stethoscope, moderate subcostal retractions, and head bobbing, but maintained adequate oxygen saturation with nasal cannula O_2. A diffuse maculopapular rash on his trunk was also present.

On D+19, the diffuse maculopapular rash, mainly on the scalp, malar region, and trunk, worsened compared to the previous day. A chest CT revealed atelectatic bands, and abdominal and pelvic CT showed increased colonic gas content, absence of signs suggestive of intestinal tuberculosis, mild pelvic ascites, and periportal edema. Despite these findings, the patient responded to ICU measures (methylprednisolone, salbutamol, furosemide, and a single dose of human immunoglobulin 400 mg/kg/day) and showed progressive improvement. By D+25, he was discharged from the ICU but continued receiving methylprednisolone on a tapering schedule.

On D+27 post-transplant, with methylprednisolone tapering at 0.3 mg/kg/day, the patient developed a fever of 37.9°C, and cefepime was initiated. He also had complaints of a cough, but no wheezing. On D+32, when methylprednisolone was further reduced to 0.2 mg/kg/day, palpable nodules appeared in the cervical region, and his temperature was 37.5°C. The following day, after reducing methylprednisolone to 0.1 mg/kg/day, he experienced fever episodes (37.9°C), subcutaneous nodules on the back and lower limbs, and inflammatory signs with nodulation at the BCG vaccine scar. Cervical and axillary lymph nodes were also palpable. A biopsy of one of the skin nodules was performed, antibiotics were escalated to meropenem, and the methylprednisolone dose was increased back to 1 mg/kg/day due to suspicion of IRIS.

On D+34, the biopsy results identified *Mycobacterium bovis*. The patient was afebrile, stable, and showed improvement in skin lesions within 24 hours of increasing the methylprednisolone dose. Meropenem was discontinued. By D+35, the skin lesions had completely resolved, and the patient was discharged from the hospital.

Case report: patient 2

Our second patient is a 68-year-old woman who began experiencing temporal and spatial disorientation in late January 2024. Initially, she sought care from a psychiatrist due to her previous follow-up for bipolar disorder, which led to an investigation for organic causes. A cranial CT scan revealed a lesion in the central nervous system, and she was admitted to a hospital for further evaluation. During this hospitalization, a biopsy was performed, but no records or descriptions of the procedure could be found. According to the patient's husband, after the biopsy, she became unable to speak or walk. She was discharged on dexamethasone and phenytoin, and following immunohistochemistry results, she was referred to our service with a diagnosis of primary diffuse large B-cell lymphoma of the central nervous system.

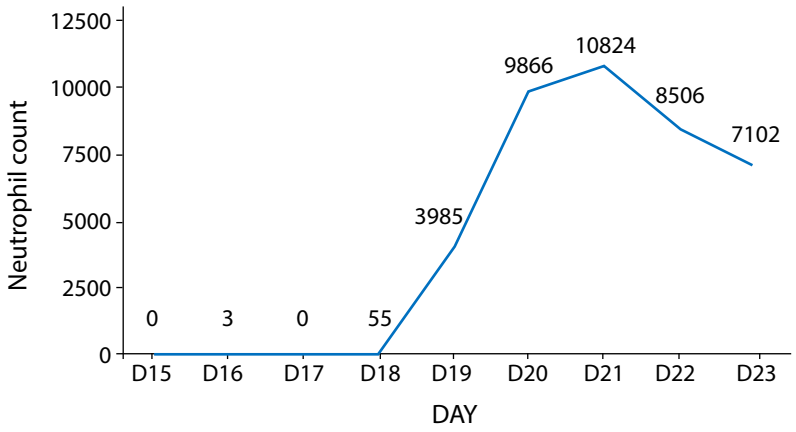
For treatment, the patient was started on the MATRIX protocol (rituximab at 375 mg/m^2 on days 1–2, high-dose methotrexate at 3.5 g/m^2 on day 3, and cytarabine at 2 g/m^2 every 12 hours on days 4–5).

In addition to the protocol, prophylaxis with acyclovir, voriconazole, and sulfamethoxazole-trimethoprim was prescribed, with the latter initiated after methotrexate levels became undetectable. On day 7, the patient developed oral candidiasis, which was treated with fluconazole for five days. On day 12 of the protocol, daily filgrastim was initiated. On day 14, she developed a fever of 38.5°C, prompting the prescription of cefepime. The nursing team also observed swelling and erythema in the left labia majora, along with a plaque-like lesion on the medial right arm. A differential diagnosis of bartolinitis or a fungal infection was considered, although it wasn't possible to determine a causative microorganism associated with her skin symptoms.

By Day 15 (day 2 of cefepime), her fever persisted at 37.7°C. Swelling in the left vulvar region continued to increase, but there was no evidence of fluctuation or drainage. The plaque-like lesion on her right arm also persisted. Blood cultures revealed growth of multi-sensitive *Pseudomonas aeruginosa*, leading to a de-escalation from cefepime to ceftazidime (2 g every eight hours) and the addition of linezolid (600 mg every 12 hours) to target the genital/vulvar lesion.

Despite the adjusted antibiotic regimen, the patient continued to experience fever (38.5°C) over the next three days. On Day 20, she developed fever episodes, and additional blood cultures were collected, but turned out negative. The erythema and edema in the pelvic and perineal regions worsened. However, a pelvic CT scan showed no evidence of subcutaneous gas, abscess formation, or deeper tissue involvement.

By Day 22, the erythema in the vulvar region had extended to the hip, with more pronounced borders. In consultation with the infectious disease team, the worsening condition was interpreted as a paradoxical IRIS, likely triggered by the rapid neutrophil count increase caused by the G-CSF use according to the protocol (Fig. 1). As a result, linezolid was discontinued.



Source: Elaborated by the authors.

Figure 1. Graph showing the fast neutrophil recovery presented by patient 2.

The patient experienced progressive improvement in her skin lesions without requiring corticosteroids for IRIS management. She subsequently completed additional cycles of the MATRIX protocol without further recurrence of IRIS.

Unfortunately, six months later, the patient succumbed to disease progression in the central nervous system.

Case report: patient 3

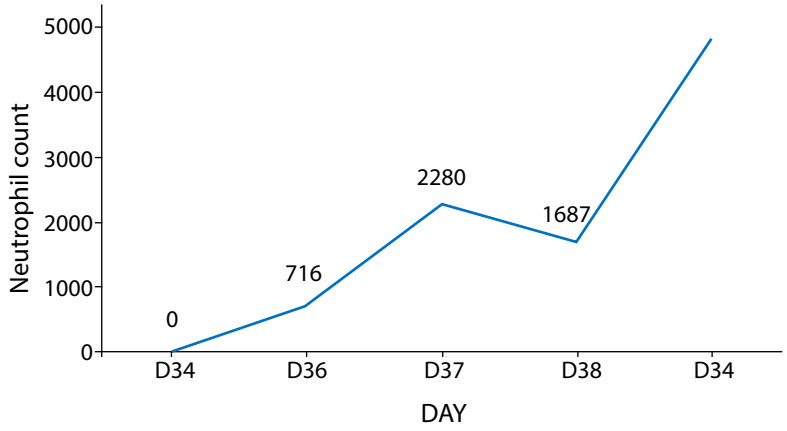
The last patient is a 5-year-old girl referred to our service due to pancytopenia. Upon admission, she presented with significant epistaxis that required intranasal adrenaline after local compression failed to stop the bleeding. She also complained of pain in her right lower limb, which caused difficulty ambulating. During this period, she experienced episodes of vomiting associated with epistaxis and was started on empirical antibiotic therapy with cefepime. Diagnostic tests confirmed acute lymphoblastic leukemia, and partial blood culture results identified gram-positive cocci, prompting initiation of vancomycin. On the same day, she began treatment according to the 2021 protocol of the Brazilian Group for the Treatment of Childhood Leukemias, starting with prednisolone at 40 mg/m^2. Subsequent blood cultures confirmed *Staphylococcus gallinarum*, leading to the discontinuation of cefepime, while vancomycin was maintained based on susceptibility testing. Vancomycin was later discontinued four days after initiation due to clinical improvement.

Ten days after starting the leukemia treatment protocol, a totally implantable catheter was placed. The following day, the patient presented with pain, fever, and erythema at the catheter site, suggesting a possible surgical site infection. Vancomycin and cefepime were started. After four days of persistent fever, her antibiotics were escalated to meropenem, and the patient achieved full clinical improvement after eight days of therapy.

On Day 22 of treatment, the patient experienced three febrile peaks and reported periumbilical abdominal pain, odynophagia leading to decreased oral intake, and liquid stools. She also presented with bilateral leg edema graded as +4 up to the knees. Due to febrile neutropenia, with a complete blood count showing white blood cells at 270/µL, neutrophils at 3/µL, and platelets at 7,000/µL, empirical antibiotic therapy with meropenem was initiated, along with fluconazole at 6 mg/kg/day. Vancomycin was added the following day due to persistent fevers.

By Day 29, the patient continued to experience multiple daily febrile peaks, persistent abdominal pain, and oxygen desaturation (79% SpO_2) in room air, with diminished breath sounds in the right lung base. She required supplemental oxygen. A chest CT revealed findings consistent with pneumonia and bilateral pleural effusion. On the same day, tapering of corticosteroid therapy (prednisolone) began, and fluconazole was escalated to micafungin.

In the following days, she continued to have daily febrile episodes, with temperatures reaching 40°C. On Day 36, she developed bradycardia following morphine administration, another episode of oxygen desaturation requiring nasal oxygen at 0.5 L/min, and complaints of periumbilical and chest pain. Echocardiography revealed a small pericardial effusion, for which furosemide was prescribed. Laboratory results indicated hypoalbuminemia, with a serum albumin level of 2.7 g/dL, necessitating albumin replacement. She also presented a fast neutrophil recovery on this exact day, as presented in Fig. 2.



Source: Elaborated by the authors.

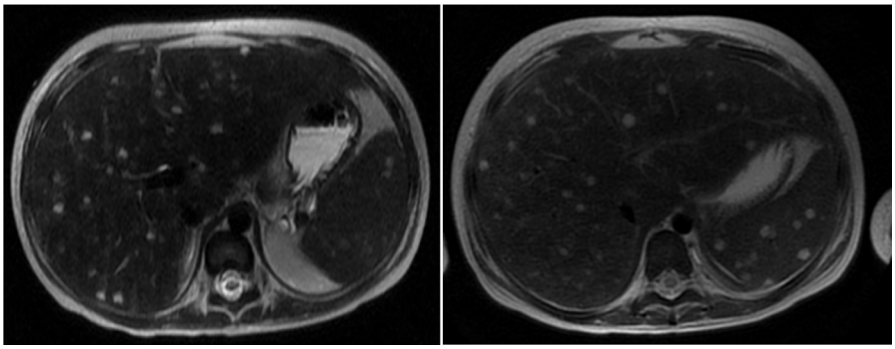
Figure 2. Graph showing the fast neutrophil recovery presented by patient 3.

On Day 37, the patient persisted with daily febrile episodes and experienced two pain crises alongside oxygen desaturation to 84% in room air, requiring nasal oxygen at 1 L/min. She continued to complain of periumbilical and chest pain. By Day 40, although daily fevers persisted, her abdominal pain and pain crises resolved, and her oral intake improved. Micafungin, administered for 10 days, was switched to voriconazole, and vancomycin, administered for 15 days, was switched to linezolid. Meropenem was continued, reaching 18 days of treatment due to persistent fevers. Corticosteroid therapy with prednisolone was discontinued after 40 days.

On Day 43, the patient continued to experience daily fevers and developed symptoms, including oxygen desaturation (90% SpO^2), tachycardia, and right upper quadrant abdominal pain. Her mother reported that the patient described seeing insects on the walls and exhibited involuntary hand movements. The patient appeared slightly jaundiced, with total bilirubin at 2.13 mg/dL, aspartate transaminase (AST) at 17 IU/L, and alanine transaminase (ALT) at 44 IU/L. Laboratory tests, abdominal ultrasound, electroencephalogram (EEG), cerebrospinal fluid analysis, and cranial CT were performed. The EEG showed no epileptic activity,

cerebrospinal fluid contained 0.3 leukocytes and 33 mg/dL of protein, and the cranial CT showed no masses or bleeding. Linezolid was discontinued due to suspected psychiatric side effects, and meropenem was also stopped. Abdominal ultrasound findings included hepatosplenomegaly, focal parenchymal lesions, and colonic distension, particularly in the right colon.

The patient's condition remained unchanged, with persistent daily fevers and frequent oxygen desaturation, until day 53, when an abdominal magnetic resonance imaging (MRI) revealed hepatosplenomegaly with multiple nodular lesions smaller than 10 mm, characterized by high signal intensity on T2, restricted diffusion, and peripheral contrast enhancement. These findings were suggestive of disseminated fungal infection with hepatic and splenic microabscesses, likely hepatosplenic candidiasis (Fig. 3). Following consultation with infectious disease specialists, treatment with anidulafungin and systemic corticosteroids was initiated. Liver biopsy revealed marked sinusoidal dilation but no evidence of fungal elements. Despite multiple blood cultures collected during periods of high fever and desaturation, no microorganisms or yeasts indicative of an invasive fungal infection were identified. It remains unclear whether this was due to her continuous 38-day antifungal treatment prior to the MRI scan on day 53 or if there was no invasive fungal infection to begin with.



Source: Elaborated by the authors.

Figure 3. Magnetic resonance imaging scan of abdomen of patient 3. Liver and spleen with increased dimensions, presenting multiple nodular lesions with high signal intensity on T2, poorly defined, measuring less than 10 mm, associated with diffusion restriction, and peripheral enhancement with contrast medium. Suggestive of hepatosplenic candidiasis.

The patient continued treatment for her underlying leukemia, with hematologic recovery deemed essential for fungal clearance. Despite the daily fever that resolved two months later, the patient did not have any worsening or new clinical symptoms after the start of corticosteroids. Currently, the patient remained in treatment for acute lymphoblastic leukemia, was clinically stable, asymptomatic, and on daily oral fluconazole at 150 mg.

DISCUSSION

Immune reconstitution inflammatory syndrome is a phenomenon first reported in the literature in the 1950s, when physicians observed a worsening of the clinical condition of patients with tuberculosis (TB) after initiating anti-TB treatment with isoniazid and streptomycin.[10] Similarly, the introduction of antiretroviral therapy transformed HIV infection from an almost invariably progressive and fatal condition into a chronic one. However, in 10 to 20% of patients starting treatment, immune reconstitution becomes dysregulated, leading to high morbidity since its description in 1992.[1] Over the years, researchers have recognized that HIV- or TB-related IRIS is merely a manifestation of a broader phenomenon—an immune-mediated pathology associated with the rapid reversal of immunosuppression, no longer necessarily tied to either pathogen.[11]

IRIS in immunocompromised patients involves a shift in the normal response of anti-inflammatory T-helper lymphocytes (Treg and Th2) and pro-inflammatory lymphocytes (Th1 and Th17).[12] Initially, the use of immunosuppressants in transplant patients, the immunosuppressive state during pregnancy for

embryo implantation, and neutropenia in chemotherapy patients cause the anti-inflammatory response of Th2 and Treg lymphocytes to predominate over Th17 and Th1.[13] Upon removal of the immunosuppressive agent, there is an abrupt shift from an anti-inflammatory state to pathological pro-inflammatory responses mediated by interleukin-17, interleukin-2, interferon-γ, and TNF-α. This state is perpetuated as these cytokines inhibit the differentiation of Treg and Th2 lymphocytes.[13,14]

The pro-inflammatory response and manifestations of IRIS can be divided into two distinct categories: paradoxical response, and unmasking response. Paradoxical IRIS results in an inflammatory process against known or unknown self-antigens (autoimmune process), exogenous antigens such as pharmacological agents, or even fragments of dead microorganisms from previously treated infections.[14,15]

According to our research, unmasking IRIS is the most reported form in the literature (85.7%) due to its association with opportunistic infections (OIs).[13] In this case, the syndrome occurs after the improvement of immunosuppression, leading to the restoration of innate and/or adaptive immune functionality and, consequently, the recognition of the OI by the individual's immune cells. This triggers the release of specific pro-inflammatory cytokines against the microorganism involved or a nonspecific cytokine storm.[12,15] The pathogens involved in IRIS are diverse, as shown in full detail in Santiago (2025).[9] However, infections caused by fungi of the *Candida* and *Aspergillus* genera and microorganisms of the *Mycobacterium* genus are prominent in the literature.[4,13,16]

On the other hand, beyond OIs, studies suggest that the pathophysiology of IRIS may vary depending on the type of immunosuppression preceding the syndrome, as suggested by the review conducted by Sun and Singh (2009).[13] The authors discuss calcineurin inhibitors such as tacrolimus and cyclosporine in solid organ transplant recipients, as these drugs inhibit Th1 in favor of Th2 and Treg responses. The type of pharmacotherapy-induced immunosuppression is crucial since post-transplant IRIS occurs due to the withdrawal or reduction of immunosuppressive drugs, and the resulting pro-inflammatory storm is associated with organ rejection. Singh et al. (2005)[17] reported that two of three kidney transplant patients with IRIS lost their grafts.

Despite the wide spectrum of symptoms and causative agents, IRIS is distinguished from other health conditions by the emergence of multiple signs after the withdrawal of the immunosuppressive agent, such as: worsening of the patient's general clinical condition unexplained by other factors like the underlying disease; persistence of inflammatory signs refractory to antimicrobial therapy; cutaneous manifestations unrelated to allergies or other causes; and worsening ventilatory patterns and respiratory function, with or without radiological changes.[4,12,18]

Generally, the prognosis of IRIS is favorable and often self-limiting. However, in some patients, it can lead to severe and potentially fatal symptoms, including respiratory failure, hepatosplenic granulomatous lesions, abscess formation, graft failure, pulmonary infiltrates, bone and joint involvement, distributive shock, and death.[3,5,6,19,20]

Unfortunately, few robust clinical studies exist to consolidate IRIS therapy, such as the study[21] on prednisone use in TB-related IRIS in people living with HIV, and the publication by the Infectious Diseases Society of America[19] on cryptococcosis-associated IRIS, managed with corticosteroids (0.5–1.0 mg/kg per day prednisone equivalent).

The consensus from various case reports suggests that IRIS treatment has two approaches: corticosteroid therapy alone or combined with targeted treatment for the causative pathogen, with a duration ranging from two to six weeks.[3,19,22] A case report[23] shows that in addition to their case of IRIS associated with chronic disseminated candidiasis in an acute lymphoblastic leukemia patient, at least 35 other oncohematological patients in similar conditions benefited from corticosteroid therapy.

Based on the information obtained through our literature review, we have created a table (Table 1) to objectively present the key information for suspecting IRIS in our patients. We marked as "mandatory" those

requirements that were most frequently mentioned in the review, and which are the most classic/defining symptoms of IRIS. These include the need for confirmation of prior immunosuppressive status (indicated by the absolute neutrophil count in our table), the appearance of new symptoms associated with clinical worsening that cannot be explained by a new infectious process, and resistance to antimicrobial therapy. Additionally, the suspicion of a fungal infection or infection by microorganisms of the *Mycobacterium* genus helps further confirm the patient's immunosuppressive state and seems to be the most common in patients as mentioned in 40 of the works reviewed. However, confirmation of a microorganism is not required for the diagnosis of IRIS, as evidenced in 14.2% of the studies we reviewed (See Santiago, 2025).[9]

Although the overall incidence is low (three cases identified among 255 patients treated), our three patients presented a clinical course consistent with what has already been reported in the literature. For patient 1, IRIS associated with antigens from the BCG vaccine was identified, as described by other studies in a similar setting.[24–26] The patient developed IRIS upon discontinuation of the immunosuppressive agent, in this case methylprednisolone, which is one of the classic factors in unmasking IRIS. This occurs when the gradual recovery of the immune system after a period of immunosuppression causes it to overreact to antigens of microorganisms that were not previously causing infection.

For patient 2, it remained unclear whether the *Pseudomonas* isolate in the blood cultures was associated with her skin symptoms. However, it was deemed unlikely to be the cause, as the erythema extended to the hip and continued to worsen eight days after the initiation of appropriate antibacterial treatment. As previously mentioned, the use of G-CSF may have exacerbated symptoms due to the rapid proliferation of immune cells.[5] In hematological patients, IRIS appears to be associated with a rapid increase in neutrophil count.[2] For our patient, this is what occurred, as shown in Fig. 1, therefore it was deemed paradoxical IRIS.

In the case of patient 3, we highlight the occurrence of hepatosplenic candidiasis-related IRIS in a child with acute lymphoblastic leukemia. This condition is rare in patients with acute leukemia, affecting less than 5% of cases.[23] Unlike previous case reports,[23,27–29] our patient did not have blood cultures indicative of fungal infection, although that is not mandatory for the diagnosis of hepatosplenic candidiasis.[6] However, MRI imaging was highly suggestive of candidiasis (Fig. 3). There was a clear temporal association between neutrophil recovery (Fig. 2), the progressive tapering of the immunosuppressive agent (corticosteroids), and the worsening of her symptoms. Notably, her condition improved after corticosteroids were reintroduced. The combination of appropriate antifungal therapy and corticosteroids allowed the patient to continue chemotherapy without compromising the hematologic outcomes of her leukemia.

IRIS can be a potentially life-threatening complication, making its recognition essential, despite being challenging. Through this study, we aimed to raise awareness about this syndrome, which remains underreported in the Brazilian population. We also hope to inspire further research so that, together, we can improve the methods for identifying and appropriately treating IRIS in our hematologic patients and those undergoing hematopoietic stem cell transplantation.

STUDY LIMITATIONS

One important limitation of this study was the inability to fully achieve the secondary objective of identifying the most common signs and symptoms presented by the studied population and determining their alignment with the existing literature. Several factors contributed to this limitation. Firstly, incomplete or inconsistent documentation in medical records made it difficult to comprehensively extract and categorize clinical presentations. Additionally, the sample size may have limited the representativeness of certain symptom patterns, especially for less frequently reported manifestations. As a result, it was not possible to systematically compare the clinical findings of our population with those described in the bibliographic review conducted by the authors. These limitations highlight the need for more studies to better characterize the clinical presentation of IRIS and validate findings against established literature.

CONFLICT OF INTEREST

Nothing to declare.

DATA AVAILABILITY STATEMENT

Supplementary material are available at https://doi.org/10.6084/m9.figshare.29936858.v1

AUTHORS' CONTRIBUTIONS

Substantive scientific and intellectual contributions to the study: Paula LS, Breda GL and Fontana RM; **Conception and design:** Paula LS, Breda GL and Fontana RM; **Acquisition of data:** Paula LS; **Analysis and interpretation of data:** Paula LS, Breda GL and Fontana RM; **Technical procedures:** Breda GL and Fontana RM; **Histopathological examinations:** Breda GL and Fontana RM; **Statistics analysis:** Paula LS and Breda GL; **Manuscript preparation:** Paula LS and Breda GL; **Manuscript writing:** Paula LS; **Critical revision:** Breda GL and Fontana RM. **Final approval:** Paula LS, Breda GL and Fontana RM.

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REFERENCES

1. Wong C-S, Richards E, Pei L, Sereti I. Immune reconstitution inflammatory syndrome in HIV infection: taking the bad with the good. Oral Diseases. 2016;23(7):822–7. https://doi.org/10.1111/odi.12606
2. Thapa S, Shrestha U. Immune reconstitution inflammatory syndrome. PubMed. Treasure Island (FL): StatPearls Publishing; 2022 [cited Aug 18, 2025]. Available from: https://www.ncbi.nlm.nih.gov/books/NBK567803/
3. Barretto J, Wirk B. Early recognition of immune reconstitution inflammatory syndrome leads to avoidance of endotracheal intubation. World J Oncol. 2012;3(4):194–8. https://doi.org/10.4021/wjon527w
4. van Lier DP, Janssen NA, Snoeren MM, Verweij PE, Blijlevens NM, van der Velden WJ. Ernstige inflammatie tijdens herstel van neutropenia: het immuunreconstitutie-inflammatoir-syndroom na chemotherapie [Severe inflammation during recovery from neutropenia: the immune reconstitution inflammatory syndrome following chemotherapy]. Ned Tijdschr Geneeskd. 2015;159:A8968. Available at: https://pubmed.ncbi.nlm.nih.gov/26246060/
5. Alawin IA, Karnath BM. Paradoxical immune reconstitution syndrome presenting as acute respiratory distress syndrome in a leukemia patient during neutrophil recovery. Case Rep Hematol. 2012;2012:670347. https://doi.org/10.1155/2012/670347
6. Bicakci Z, Koca D and Bozbeyoğlu G. Immune reconstitution inflammatory syndrome associated with hepatosplenic candidiasis in a patient with acute myeloblastic leukemia: possible pathogenesis and treatment in the light of current knowledge. Austin Hematol. 2021;6(2):1039. Available at: https://austinpublishinggroup.com/austin-hematology/fulltext/hematol-v6-id1039.php

7. Novak RM, Richardson JT, Buchacz K, Chmiel JS, Durham MD, Palella FJ, et al. Immune reconstitution inflammatory syndrome. AIDS. https://doi.org/10.1097/QAD.0b013e3283511e91

8. Ratnam I, Chiu C, Kandala N-B, Easterbrook PJ. Incidence and risk factors for immune reconstitution inflammatory syndrome in an ethnically diverse HIV type 1-infected cohort. Clin Infect Dis. 2006;42(3): 418–27. https://doi.org/10.1086/499356

9. Santiago L. Immune reconstitution inflammatory syndrome in HIV-negative patients with hematological malignancies and hematopoietic stem cell transplantation: a case series and a literature review. figshare. Dataset. 2025. https://doi.org/10.6084/m9.figshare.29936858.v1

10. Church LWP, Chopra A, Judson MA. Paradoxical reactions and the immune reconstitution inflammatory syndrome. Microbiol Spectr. 2017;5(2):10.1128/microbiolspec.tnmi7-0033-2016. https://doi.org/10.1128/microbiolspec.tnmi7-0033-2016

11. Barber DL, Andrade BB, Sereti I, Sher A. Immune reconstitution inflammatory syndrome: the trouble with immunity when you had none. Nat Rev Microbiol. 2012;10(2):150–6. https://doi.org/10.1038/nrmicro2712

12. Shahani L, Hamill RJ. Therapeutics targeting inflammation in the immune reconstitution inflammatory syndrome. Transl Res. 2016;167(1):88–103. https://doi.org/10.1016/j.trsl.2015.07.010

13. Sun HY, Singh N. Immune reconstitution inflammatory syndrome in non-HIV immunocompromised patients. Curr Opin Infect Dis. 2009;22(4):394–402. https://doi.org/10.1097/QCO.0b013e32832d7aff

14. Sueki H, Mizukawa Y, Aoyama Y. Immune reconstitution inflammatory syndrome in non-HIV immunosuppressed patients. J Dermatol. 2018;45(1):3–9. https://doi.org/10.1111/1346-8138.14074

15. Breton G. Syndrome inflammatoire de reconstitution immune. Médecine/Sciences. 2010;26(3):281–90. https://doi.org/10.1051/medsci/2010263281

16. Jung J, Hong HL, Lee SO, Choi SH, Kim YS, Woo JH, Kim SH. Immune reconstitution inflammatory syndrome in neutropenic patients with invasive pulmonary aspergillosis. J Infect. 2015;70(6):659–67. https://doi.org/10.1016/j.jinf.2014.12.020

17. Singh N, Lortholary O, Alexander BD, Gupta KL, John GT, Pursell K, Munoz P, Klintmalm GB, Stosor V, delBusto R, Limaye AP, Somani J, Lyon M, Houston S, House AA, Pruett TL, Orloff S, Humar A, Dowdy L, Garcia-Diaz J, Fisher RA, Husain S; Cryptococcal Collaborative Transplant Study Group. Allograft loss in renal transplant recipients with cryptococcus neoformans associated immune reconstitution syndrome. Transplantation. 2005;80(8):1131–3. https://doi.org/10.1097/01.tp.0000180530.17683.02

18. Dhamija E, Meena P, Ramalingam V, Sahoo R, Rastogi S, Thulkar S. Chemotherapy-induced pulmonary complications in cancer: Significance of clinicoradiological correlation. Indian J Radiol Imaging. 2020;30(1):20–6. https://doi.org/10.4103/ijri.IJRI_178_19

19. Perfect JR, Dismukes WE, Dromer F, Goldman DL, Graybill JR, Hamill RJ, Harrison TS, Larsen RA, Lortholary O, Nguyen MH, Pappas PG, Powderly WG, Singh N, Sobel JD, Sorrell TC. Clinical practice guidelines for the management of cryptococcal disease: 2010 update by the infectious diseases society of america. Clin Infect Dis. 2010;50(3):291–322. https://doi.org/10.1086/649858

20. Miceli MH, Maertens J, Buvé K, Grazziutti M, Woods G, Rahman M, Barlogie B, Anaissie EJ. Immune reconstitution inflammatory syndrome in cancer patients with pulmonary aspergillosis recovering from neutropenia: Proof of principle, description, and clinical and research implications. Cancer. 2007;110(1):112–20. https://doi.org/10.1002/cncr.22738

21. Meintjes G, Wilkinson RJ, Morroni C, Pepper DJ, Rebe K, Rangaka MX, Oni T, Maartens G. Randomized placebo-controlled trial of prednisone for paradoxical tuberculosis-associated immune reconstitution inflammatory syndrome. AIDS. 2010;24(15):2381–90. https://doi.org/10.1097/QAD.0b013e32833dfc68

22. Mahomed N, Reubenson G. Immune reconstitution inflammatory syndrome in children. SA J Radiol. 2017;21(2):1257. https://doi.org/10.4102/sajr.v21i2.1257

23. Mosleh S, Rabaia D, Zidan T. Successful treatment of chronic disseminated candidiasis complicated by immune reconstitution inflammatory syndrome in a child with acute lymphocytic leukemia. Cureus. 2023;15(8):e44103. https://doi.org/10.7759/cureus.44103

24. Liu S, Huo F, Dai G, Wu J, Qin M, Mao H, Wang Q. Case Report: Immune reconstitution inflammatory syndrome after hematopoietic stem cell transplantation for severe combined immunodeficiency. Front Immunol. 2022;13:960749. https://doi.org/10.3389/fimmu.2022.960749

25. Arora S, Rastogi N, Upasana K, Yadav A, Thakkar D, Satya Prakash Y. Cytokine release syndrome with immune reconstitution inflammatory syndrome post haploidentical hematopoietic stem cell transplantation in a child with severe combined immunodeficiency and disseminated BCG infection. J Pediatr Hematol Oncol. 2022;7(4):S26. https://doi.org/10.1016/j.phoj.2022.10.072

26. Corbali O, Gemici Karaaslan HB, Aydemir S, Onal P, Kendir Demirkol Y, Nepesov S, Kiykim A, Cokugras H. Immune reconstitution inflammatory syndrome after hematopoietic stem cell transplantation in a FOXN1 -deficient patient. J Pediatr Hematol Oncol. 2023;45(5):275–7. https://doi.org/10.1097/MPH.0000000000002677

27. Candon S, Rammaert B, Foray AP, Moreira B, Gallego Hernanz MP, Chatenoud L, Lortholary O. Chronic disseminated candidiasis during hematological malignancies: an immune reconstitution inflammatory syndrome with expansion of pathogen-specific T helper type 1 cells. J Infect Dis. 2020;221(11):1907–16. https://doi.org/10.1093/infdis/jiz688

28. Reddy NA, Addala S, MBS, Lashkari HP. Subcutaneous microabscesses and myositis as part of immune reconstitution inflammatory syndrome due to chronic disseminated candidiasis in a child with acute lymphoblastic leukemia. J Pediatr Hematol Oncol. 2023;45(4):e555–9. https://doi.org/10.1097/MPH.0000000000002640

29. Al Yazidi LS, Elsidig N, Wali Y, Nazir H. Chronic disseminated candidiasis in children and the role of corticosteroids therapy. Pediatr Infect Dis J. 2023;42(5):e146–e151. https://doi.org/10.1097/INF.0000000000003859