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Early-Onset Immune Reconstitution Inflammatory Syndrome After the Initiation of Antiretroviral Therapy in an AIDS-Stage Patient: A Case Report

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Abstract

Introduction: Immune reconstitution inflammatory syndrome (IRIS) can occur in patients with advanced HIV infection shortly after initiating antiretroviral therapy (ART). Although it usually manifests between 2 and 8 weeks of treatment, earlier presentations have been described, particularly in patients with very low CD4 counts and high viral loads. **Case Presentation**: A 43-year-old male, with a CD4 count of 10 cells/µL and a viral load of 432,000 copies/mL, was admitted due to respiratory failure secondary to Pneumocystis jirovecii infection and Candida findings in tracheal secretions. ART and trimethoprim-sulfamethoxazole (TMP-SMX) were initiated on day 1, together with high-dose corticosteroids (MEDURI protocol) for severe pneumocystosis. By day 5 of ART, he developed persistent fever (up to 40 °C), leukocytosis, and elevated inflammatory markers, without new microbiological findings despite broad-spectrum antibiotic therapy. A diagnosis of possible IRIS was considered, as the fever did not subside with antimicrobial coverage and other infections were ruled out. Clinical stabilization was achieved around day 20, highlighting the importance of early recognition of IRIS in critically ill AIDS patients. **Conclusions**: The presence of fever and clinical deterioration in the early stages of ART necessitates ruling out active or persistent infections; however, an inflammatory dysfunction such as IRIS can also occur before 2 weeks of treatment. This case report underscores the need for close surveillance and a multidisciplinary approach to optimize the management of complications in patients with advanced AIDS.

Key word: HIV, AIDS, immune reconstitution inflammatory syndrome, ART, pneumocystosis, candidiasis.

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Introduction

Immune reconstitution inflammatory syndrome (IRIS) is characterized by an exaggerated inflammatory response that may occur after initiating antiretroviral therapy (ART) in patients with advanced HIV infection.(1,2) Its prevalence is estimated at 10–25% in individuals with very low CD4 counts (especially <50 cells/µL) and high viral loads.(1,3) IRIS generally appears between the second and eighth week after ART initiation; however, there have been reports of an earlier onset, including within the first week, in patients with profound immunosuppression.(4,5)

IRIS is not limited to opportunistic infections; it can also be triggered in other contexts, such as autoimmune or neoplastic diseases, when partial immune recovery leads to disproportionate inflammation.(6) In pneumocystosis, cryptococcosis, or tuberculosis, the clinical presentation can easily be confused with the persistence or progression of infection. Therefore, distinguishing IRIS from an active infectious process is a diagnostic challenge that requires repeated microbiological studies and a careful assessment of clinical evolution.(7,8)

This article describes a patient with AIDS-stage HIV infection and severe pneumocystosis who developed a possible IRIS on the fifth day of ART. The objective is to emphasize the importance of considering IRIS as a differential diagnosis in very early stages of therapy, highlighting the need for a multidisciplinary approach that includes a thorough search for infections, adjustments in antimicrobial therapy, and control of inflammation.

Case report

Initial Data and Diagnosis

A 43-year-old male with no relevant medical history experienced a weight loss of approximately 23 kg in the previous

6 months. One month before admission, he reported persistent cough and progressive dyspnea, self-medicating with azithromycin and ivermectin without improvement. Due to worsening respiratory function, he was admitted to a private hospital where, owing to respiratory distress, desaturation, and tomography findings, acute respiratory distress syndrome (ARDS) was diagnosed and pneumocystosis was suspected. Considering the severity of the presentation, antibiotic therapy with meropenem and vancomycin was initiated. Laboratory tests revealed HIV infection with a CD4 count of 10 cells/µL and a viral load of 432,000 copies/mL. Microbiological tests confirmed Pneumocystis jirovecii by PCR in bronchoalveolar lavage. In addition, Candida species were isolated from tracheal secretions through quantitative culture and DNA sequencing on two occasions, indicating tracheal candidiasis (though the possibility of colonization remains controversial). The patient's initial leukocyte count was 3,200 cells/µL (with relative neutrophilia), and significant elevation of acute-phase proteins was observed. Due to the severity of respiratory failure and limited financial resources of his family, the patient was transferred to the ICU at our center, remaining on mechanical ventilation.

Initial Management

Given the diagnosis of severe pneumocystosis (PaO_2 64 mmHg on FiO_2 100%, pH 7.12, $PaCO_2$ 45 mmHg), immediate interventions were initiated. Antiretroviral therapy (ART) with dolutegravir/lamivudine/tenofovir was started on day one to address the underlying HIV infection. Trimethoprim-sulfamethoxazole (TMP-SMX), which the patient had already been receiving at the previous facility, was continued as the primary treatment for Pneumocystis pneumonia. Corticosteroids were administered according to the MEDURI protocol to manage severe hypoxemia and help modulate the inflammatory response. Due to clinical suspicion of histoplasmosis—prompted by the patient's lack of improvement and prior history from the referring facility—amphotericin B was added on the second day. Broad-spectrum antibiotics (meropenem and vancomycin) were maintained, as the patient had been on these agents previously, and there was concern for possible multidrug-resistant infections, particularly given his transfer from a hospital with a likely high prevalence of resistant pathogens.

Course and Persistent Fever

By day 5 of ART, the patient developed persistent fever of up to 40 °C, together with leukocytosis (>18,000 cells/µL) and elevated inflammatory markers (CRP, IL-6) (Table 1). No new radiological findings were detected (Figure 1). In view of the lack of improvement and the fact that test results would take at least 72 hours, ceftazidime-avibactam was initiated on day 9 to cover potential multidrug-resistant pathogens unresponsive to meropenem and vancomycin. Despite this, fever and high inflammatory markers continued. Once negative culture results were confirmed on day 12, ceftazidime-avibactam was discontinued on the third day of its use.

IRIS Suspicion and Clinical Course

Because no evidence of new infections was

Table 1

Daily evolution of clinical and laboratory parameters of the patient during 20 days of ICU stay

DAY	LEUKOCYTES (10³/µL)	NEUTROPHILS (10³/µL)	LYMPHOCYTES (10³/µL)	MONOCYTES (10³/µL)	EOSINOPHILS (10³/µL)	PLATELETS (10³/µL)	MPV (fL)	LDH (U/L)	IL-6 (pg/mL)	PCR (mg/L)	VIRAL LOAD (Copies/mL)	CD4 (Cells/µL)	BLOOD CULTURE	URINE CULTURE	TRACHEAL SECRETION	TEMPERATURE (°C)
1	12,07	10,89	0,53	0,16	0,49	205	11,3	385,6			432000	10	---	---	---	36,3 – 37,4
2	5,14	4,76	0,28	0,09	0,01	180	11,0	401,5	6,96		---	---	---	---	---	36,2 – 37,1
3	9,38	8,62	0,50	0,26	0,00	221	11,6	---	---		---	---	---	---	---	36,1 – 37,6
4	12,39	11,26	0,50	0,63	0,00	261	11,2	---	---		---	---	---	---	---	35,8 – 37,8
5	13,47	12,30	0,59	0,58	0,00	289	11,2	---	---		---	---	Neg.	Neg.	Neg.	36,7 – 37,8
6	21,42	19,17	1,35	0,90	0,00	326	11,4	662,4	---		---	---	---	---	---	37,6 – 38,1
7	20,39	18,31	1,33	0,75	0,00	293	11,3	---	17,6	212	---	---	---	---	---	37,8 – 39,4
8	18,24	16,92	0,88	0,44	0,00	286	11,6	---	---		---	---	---	---	---	38,2 – 39,6
9	17,64	15,96	1,08	0,55	0,05	271	11,9	---	---		---	---	---	---	---	38,1 – 39,8
10	22,88	20,47	1,65	0,71	0,05	272	11,9	---	---		---	---	---	---	---	37,9 – 39,3
11	25,86	22,73	1,99	1,14	0,00	277	11,9	---	---		---	---	Neg.	Neg.	Neg.	38,1 – 40,1
12	26,48	23,38	2,01	1,01	0,08	267	12,0	---	---		---	---	---	---	---	38,4 – 39,2
13	23,66	21,13	1,56	0,97	0,00	265	12,4	---	---		1280	17	---	---	---	38,1 – 39,4
14	22,21	19,96	1,47	0,78	0,00	227	12,1	---	---	47	---	---	---	---	---	38,3 – 38,9
15	22,76	21,01	1,07	0,68	0,00	229	12,3	---	---		---	---	---	---	---	37,7 – 39,4
16	15,86	14,75	0,62	0,49	0,00	194	11,8	---	---	31	---	---	---	---	---	37,4 – 38,3
17	11,47	10,76	0,48	0,23	0,00	147	12,0	---	---		---	---	---	---	---	36,9 – 38,8
18	9,50	9,00	0,36	0,13	0,01	150	12,2	---	---	49	---	---	---	---	---	36,8 – 38,1
19	8,31	7,85	0,29	0,17	0,00	120	12,2	---	---		---	---	---	---	---	36,1 – 37,8
20	8,41	7,83	0,39	0,19	0,00	107	12,1	---	---		---	---	Neg.	Neg.	Neg.	36,7 – 37,5

Initiation of antiretroviral therapy

Onset of acute inflammatory response

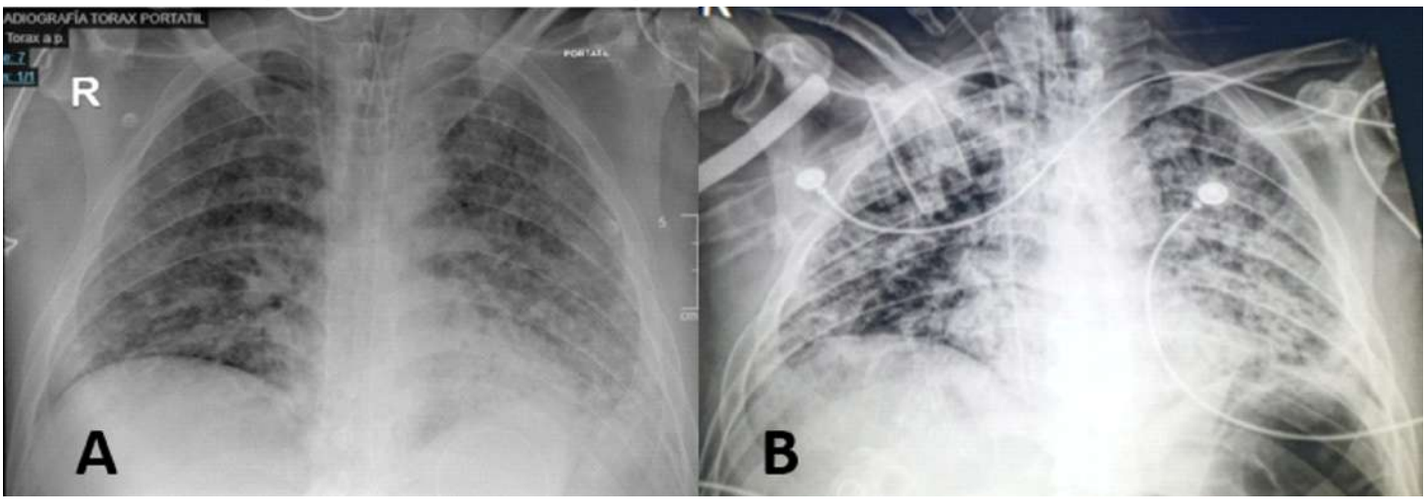
Days on Ceftazidime/Avibactam therapy

A progressive increase in the inflammatory response is observed starting on day 5 after the initiation of antiretroviral therapy, with no positive microbiological isolates, supporting the suspicion of early-onset Immune Reconstitution Inflammatory Syndrome (IRIS). Moreover, despite broad-spectrum antibiotic therapy, no changes in the trend of inflammatory markers are evident.

Source: *Clinical Laboratory, Pablo Arturo Suárez Hospital.*

Figura 1

Comparative chest radiographs: initial evaluation and during the inflammatory response



identified, the possibility of early-onset IRIS was considered. Viral agents such as cytomegalovirus (CMV) had been ruled out, and repeated tests for infectious processes yielded negative results. The inflammatory response continued until about day 20 of hospitalization, at which point the fever subsided and inflammatory parameters declined. The patient achieved stabilization of respiratory function, underwent a tracheostomy to optimize ventilator weaning, and gradually showed clinical improvement.

Written informed consent was provided by the patient's family for the academic use of clinical data.

Discussion

This case illustrates the complexity of managing a patient with advanced HIV infection (CD4 count of 10 cells/µL) and severe pneumocystosis, who developed persistent fever and inflammatory activation within the first 5 days of initiating ART. Although IRIS is typically described between 2 and 8 weeks after the start of antiretroviral therapy,(2,4) there are reports of earlier onset, particularly in settings of extreme immunosuppression and high viral load. (5,9)

Distinguishing IRIS from an active or persistent infection is clinically challenging, as both can present with fever and elevated inflammatory biomarkers.(10,11) In our case, the lack of response to broad-spectrum antibiotics (including meropenem, vancomycin, and ceftazidime-avibactam) and the absence of positive microbiological findings strengthened the IRIS hypothesis. Likewise, the adjunctive use of corticosteroids for severe pneumocystosis may have partially helped control the inflammatory response,(12,13) although it was not specifically aimed at treating IRIS.

It is worth noting that IRIS does not occur solely in response to opportunistic pathogens; exaggerated inflammatory reactions can also develop against autoimmune or even neoplastic processes.(6) In this patient, the rapid and marked decrease in viral load, combined with dysfunctional immune reconstitution, may have caused the "imbalance" leading to excessive inflammatory response.(11,14)

In this case, the patient presented with an opportunistic infection confirmed by RT-PCR (Pneumocystis jirovecii) at the time of HIV diagnosis, without microbiological evidence of active tuberculosis. When applying the diagnostic criteria proposed by French(1,2) for immune reconstitution inflammatory syndrome (paradoxical IRIS), the case was found to partially meet some key elements (prior infection, recent initiation of ART, favorable immunological response), but not others considered essential, such as clinical improvement before starting ART or clinical worsening of the opportunistic infection after its initiation.(2) Similarly, when applying the criteria proposed by Meintjes(1,2) for tuberculosis-associated IRIS, these were ruled out, since there was no prior diagnosis or treatment for tuberculosis, and no clinical or radiological findings compatible with tuberculosis were observed, in addition to two negative DNA-PCR tests for Mycobacterium tuberculosis.

Therefore, although the case does not fully meet the traditional criteria for paradoxical IRIS, the clinical context, the immunological response, and the reasonable exclusion of other causes support the diagnosis of early-onset IRIS after ART initiation in a patient with AIDS and a prior opportunistic infection due to Pneumocystis jirovecii.

Recent reports have described similar cases in which IRIS presents within the first week of ART initiation, particularly in the context of severe immunosuppression (CD4 <50 cells/µL) and high viremia.(9,14,15)

The management of IRIS remains challenging. In cases involving organ dysfunction, some authors recommend the use of corticosteroids,(2,5,10) although there is controversy regarding their routine indication due to the risk of masking or worsening concurrent infections. In the present case, the patient received corticosteroids for severe pneumocystosis from day one, which may have coincidentally helped to attenuate the inflammatory response associated with IRIS. Optimization of antimicrobial therapy, close monitoring, and multidisciplinary collaboration were essential

for achieving recovery.

Conclusion

When managing advanced HIV/AIDS patients initiating ART, several clinical nuances warrant consideration. Persistent fever and elevated inflammatory markers emerging within the first week of treatment may potentially indicate early immune reconstitution inflammatory syndrome, though this should remain a diagnosis of exclusion after thorough evaluation. A comprehensive infectious workup is particularly advisable in critically ill patients, given their susceptibility to multidrug-resistant organisms and occult opportunistic infections. In situations where inflammatory markers remain elevated despite appropriate antimicrobial coverage and negative microbiological studies, clinicians might reasonably consider IRIS in their differential.

The corticosteroids administered for severe pneumocystosis in this case may offer the additional benefit of tempering IRIS-related inflammation, though their use requires careful patient-specific consideration. These complex clinical scenarios highlight the value of multidisciplinary collaboration and ongoing reassessment when navigating the intricate interplay between ART initiation, opportunistic infections, and inflammatory complications in immunocompromised hosts.

Author contributions

Jorge Luis Vélez Páez, Hugo Tirapé Castro: Conceptualization, Methodology, Formal analysis, Data curation, Writing- Original draft preparation, Writing-Reviewing and Editing. **Christian Casro Bustamante, Manuel Gallegos Paredes**: Conceptualization, Methodology, Formal analysis, Data curation, Writing- Original draft preparation. **Erick Tutin Miniguano**: Writing- Original draft preparation, Visualization, Visualization, Validation, Writing-Reviewing and Editing.

Ethics statement

The authors declare that the present study was conducted under the strictest ethical conditions. Written informed consent was obtained from the patient's family for the publication of clinical data and images, ensuring confidentiality of the information.

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None.

Conflicts of interest

The authors declare no conflicts of interest.

Availability of data

The datasets generated and /or analyzed during current study available from the corresponding author on reasonable request.

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