

A PATIENT WITH MULTIPLE IRIS

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The immune reconstitution inflammatory syndrome (IRIS) is a frequent early complication of antiretroviral therapy (ART), particularly in patients who commence ART with low CD4 counts and established opportunistic infections. IRIS results from a pathological inflammatory response to pre-existing infective, host or other antigens, alive or dead, causing clinical deterioration in HIV-infected patients after initiating ART.¹ A case definition for IRIS is shown in Table I. The most common forms of IRIS described occur in association with mycobacterial and herpesvirus infections.³ We describe here a patient who presented with IRIS in association with tuberculosis (TB), then cryptococcosis, and later varicella zoster virus (VZV).

TABLE I. CRITERIA FOR DIAGNOSIS OF IRIS PROPOSED BY SHELburnE AND COLLEAGUES²

- HIV-positive
- Receiving highly active antiretroviral therapy (HAART)
 - Decrease in HIV-1 RNA level from baseline
 - Increase in CD4+ cells from baseline (may lag behind HIV-1 RNA decrease)
- Clinical symptoms consistent with inflammatory process
- Clinical course not consistent with:
 - Expected course of previously diagnosed opportunistic infection
 - Expected course of newly diagnosed opportunistic infection
 - Drug toxicity

A 38-year-old man from the Democratic Republic of Congo was diagnosed with disseminated TB on the basis of a sputum culture which grew *Mycobacterium tuberculosis*. The isolate was sensitive to isoniazid and rifampicin. A fine-needle aspirate of a peripheral lymph node was also positive for acid-fast bacilli. His chest radiograph from this time is shown in Fig. 1. The patient was commenced on regimen 1 TB treatment. An HIV test was reactive and his CD4 count was 9 cells/ μ l. Good adherence to TB treatment was reported.

He was referred for ART, but the clinic delayed initiation because of social problems. Three months later he was re-admitted with cryptococcal meningitis. Cerebrospinal fluid (CSF) results are shown in Table II. He received 5 days of intravenous amphotericin B, followed by oral fluconazole 400 mg daily. His headache and vomiting resolved on this treatment.

Two weeks after the cryptococcal diagnosis he was started on ART (stavudine, lamivudine and efavirenz). Fluconazole, TB



Fig. 1. Chest radiograph at the time of TB diagnosis showing right mediastinal adenopathy with sparse bilateral fine linear and nodular opacities in the middle and lower zones of the lungs.

TABLE II. CSF RESULTS AT CM AND CM-IRIS DIAGNOSIS

Timing of LP	CM diagnosis	CM-IRIS diagnosis
Polymorphs (cells/ μ l)	1	5
Lymphocytes (cells/ μ l)	3	45
Erythrocytes (cells/ μ l)	215	187
Glucose (mmol/l)	2.6	2.8
Protein (g/l)	1.08	1.5
VDRL	Negative	Negative
Cryptococcal latex antigen test (CLAT)	>1:4 (not quantified)	1:256
Cryptococcus culture	Positive	Negative

treatment and co-trimoxazole were continued. Ten days later he presented with a 4-day history of severe right-sided pleuritic chest pain and fevers. No cough or headaches were reported. He had lost 6 kg in 2 weeks and had a temperature of 38°C. Chest auscultation revealed crepitations bibasally. No lymph node enlargement was detected. Blood oxygen saturation was normal. The chest radiograph from this time is shown in Fig. 2. A diagnosis of TB-IRIS was made, but he was also given antibiotics to cover the possibility of bacterial chest infection. One week later he reported symptomatic improvement, but still had mild chest pain, a tachycardia and a low-grade fever.



Fig. 2. Chest radiograph at the time of TB-IRIS diagnosis. The right mediastinal adenopathy is again noted. The pulmonary infiltrate has become more intense compared with the initial radiograph. Bilateral mid- and lower zone coarse linear opacifications with scattered sparse nodules are seen, as well as foci of confluent irregular opacities up to 1.8 mm in size. A 1.8 cm confluent opacity at the left hemidiaphragm is also noted.

Four weeks after starting ART he was re-admitted with a 5-day history of severe headaches and vomiting. He was afebrile and had lost 2 kg since his last visit. He had new axillary and submental adenopathy. Terminal neck stiffness was present but fundoscopy, visual fields and eye movements were normal. His CD4 count had risen to 30 cells/ μ l. A lumbar puncture had an opening pressure of 56 cm H₂O. CSF results are shown in Table II.

A diagnosis of cryptococcal meningitis IRIS (CM-IRIS) was made. He was treated with amphotericin B while awaiting a CSF fungal culture result to exclude treatment failure as a cause of his symptoms. Prednisone at 1.5 mg/kg for 2 weeks was added. He also had regular lumbar punctures to decrease his raised intracranial pressure. His CSF fungal culture was negative after 2 weeks' incubation. His symptoms resolved on this treatment.

Two months after starting ART he developed a VZV rash involving the left V₁ dermatome of his face. The cornea was not affected. Acyclovir 800 mg 5 times daily was prescribed and the rash resolved on this treatment.

This patient had several of the documented risk factors for IRIS: opportunistic infections prior to ART, disseminated TB, low baseline CD4 count and ART initiation soon after CM diagnosis.⁴⁻⁷

He presented with three episodes of IRIS in the first 2 months of ART, each related to different infections. Within 2 weeks of commencing ART the patient was diagnosed with TB-IRIS. This diagnosis was made on the basis of recurrent respiratory symptoms and fever, and particularly because the chest radiograph showed worsening features of TB. TB-IRIS typically presents 1 - 4 weeks after ART initiation.^{5,8}

The most common manifestations of TB-IRIS are fever and recurrence of TB symptoms, as in our patient. A wide range of other manifestations have been described and include worsening radiographic pulmonary infiltrates, lymph node enlargement, cold abscesses, serous effusions, hepatic and splenic involvement and meningitis.⁹

When this patient presented with TB-IRIS, his chest radiograph demonstrated bilateral lower zone linear opacifications and an increase in size of mediastinal lymph nodes. Radiographic imaging plays an important role in diagnosing and monitoring TB-IRIS. Radiographically, TB-IRIS manifests as new or increased pulmonary parenchymal disease, lymphadenopathy or pleural effusions alone or in combination. It is not uncommon for patients with advanced immunosuppression and TB undergoing a TB-IRIS episode with radiological worsening to have had a normal chest radiograph at initial TB diagnosis. Conversely, patients presenting with clinically significant signs and symptoms of TB-IRIS do not always manifest with radiographic worsening. In one study the mean time from beginning of radiographic worsening to beginning of improvement was 7 weeks for pulmonary disease, 13 weeks for adenopathy, and 4 weeks for pleural effusions.¹⁰

This patient's presentation with a lymphocytic meningitis 4 weeks after starting ART was diagnosed as CM-IRIS. This is often associated with raised intracranial pressure, as in this case, and in one study the median duration from ART to CM-IRIS was 28 days.⁷ The finding of a negative fungal culture excluded cryptococcal treatment failure and supported the diagnosis of CM-IRIS. The increase in white cell count in the CSF compared with initial diagnosis, as in this case, was found to occur in CM-IRIS in the study mentioned above.⁷ Treatment of CM-IRIS involves therapeutic lumbar punctures to relieve raised intracranial pressure and corticosteroids in severe or refractory cases, although there is no prospective evidence regarding the management of any form of IRIS.¹¹

His presentation with a VZV rash 2 months after starting ART was probably also an IRIS event, or could have been related to the corticosteroid therapy given earlier. Although this was a typical monodermatomal presentation of this infection, the finding that patients are at a 5-fold higher risk of presenting

with VZV in the first 4 months of ART¹² suggests that immune reconstitution is playing a role in such presentations. Management is with acyclovir.

Currently IRIS is a diagnosis of exclusion, as there is no confirmatory test. Important exclusions include treatment failure due to antimicrobial resistance or poor adherence, another infection or drug toxicity. A thorough patient history is important as initial improvement on specific treatment for an opportunistic infection followed by deterioration after ART initiation is characteristic of IRIS. IRIS has resource implications in terms of the increased need for investigations and treatment interventions, as demonstrated by our patient's repeated admissions. This case highlights the risks faced during immune reconstitution in patients who commence ART with advanced immunosuppression.

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