CASE REPORT

UPDATED Case Report: Tuberculosis IRIS: a mediastinal problem [v2; ref status: indexed, http://f1000r.es/1e5]

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Latest published: 07 Aug 2013, **2**:54 (doi: 10.12688/f1000research.2-54.v2)

Abstract

We present a case of a 39-year-old male patient with Acquired Immune Deficiency Syndrome (AIDS) who developed *Mycobacterium tuberculosis* related Immune Reconstitution Inflammatory Syndrome (IRIS) after initiation of Highly Active Antiretroviral Therapy (HAART) treatment. The inflammatory response resulted in mediastinal necrotic lymphadenopathy and subsequent perforation of the esophageal wall.

Open Peer Review

Referee Status: ✓ ✓ ✓

	Invited Referees 1	2	3
UPDATED version 2 published 07 Aug 2013	✓	✓ report	✓
version 1 published 18 Feb 2013	✓ report	✓ report	✓ report

1 **Eric Daar**, University of California, Los Angeles USA

2 **Susana Asin**, Dartmouth Medical School USA

3 **Paul Klenerman**, University of Oxford UK

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Comments (0)

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UPDATED **Changes from Version 1**

We have made several minor changes to the new version. We added more details regarding the treatment regimen and incorporated suggestions made by the referees.

See referee reports

Presentation

A 39-year-old man with a history of Acquired Immune Deficiency Syndrome (AIDS) presented to the emergency room with fever, productive cough, fatigue, diarrhea, and weight loss. Three weeks prior, he had been initiated on antiretroviral therapy (ART) with darunavir, ritonavir and combination tenofovir and emtricitabine. At that time, he had a CD4 count of 85 cells/μL (9%) and HIV-1 viral load of 336,950 RNA copies/mL. He was now febrile (41.0°C), with a heart rate of 100 beats/min and respiratory rate of 24/min. Physical examination revealed oral thrush and palpable cervical, supraclavicular and axillary lymphadenopathy. His laboratory evaluation was significant for a CD4 count of 28 cells/uL (10%), HIV-1 viral load of 3,410 RNA copies/mL, and hemoglobin of 6.6 g/dL. Chest radiograph on admission (not shown) demonstrated a 2.9 × 4.4 cm soft tissue mass in the anterior mediastinum.

The initial computed tomography (CT) scan of the chest showed multiple low-attenuation mediastinal lesions, indicative of abscesses or necrotic lymphadenopathy (Figure 1), as well as esophageal discontinuity in the subcarinal region, a sign of esophageal fistula or perforation (Figure 2). Multiple cavitary lung nodules were also present (Figure 3).

Diagnosis

Mediastinoscopy revealed purulent fluid drainage from necrotic lymph nodes on day 3 of hospitalization. An esophagogastroduodenoscopy (EGD) demonstrated a 2 cm linear tear in the esophagus with proximal perforation at the 29–31 cm level.

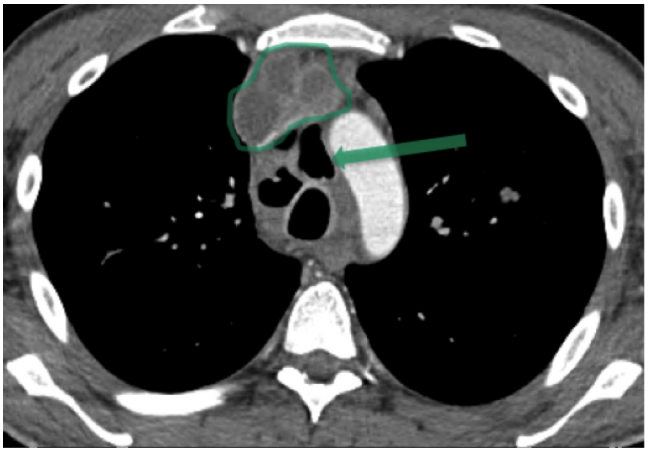

Figure 1. Contrast-enhanced CT scan of the chest on admission revealed multiple low-attenuation necrotic lymph nodes (free-hand-circle) and gas-containing mediastinal collection, representing a mediastinal abscess (arrow).

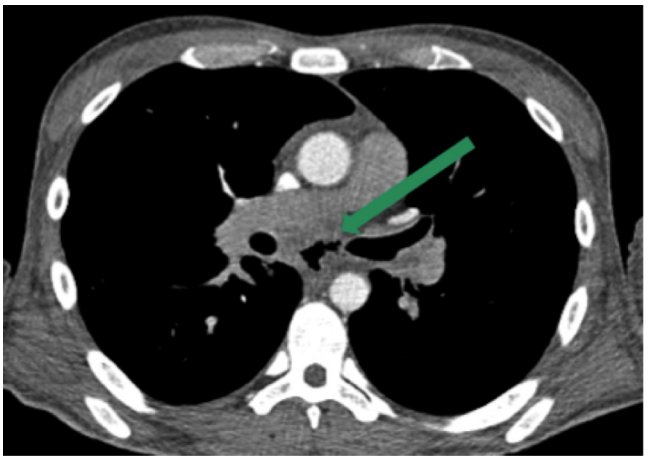

Figure 2. Chest CT on admission revealed esophageal discontinuity in the subcarinal region representing esophageal perforation (arrow).

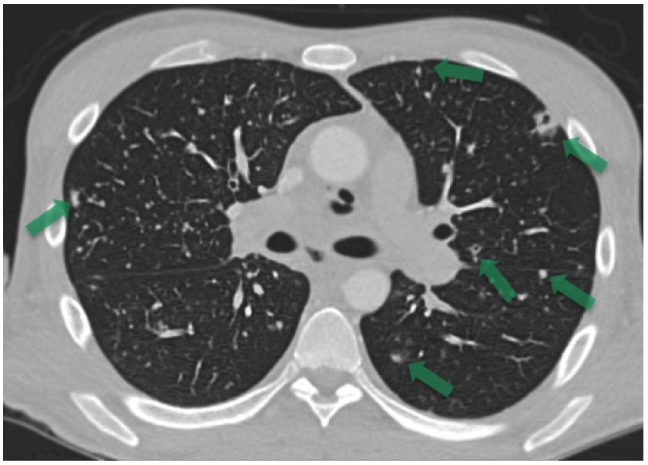

Figure 3. Chest CT on admission revealed multiple cavitary and non-cavitary lung nodules (arrows), suspicious for mycobacterial infection.

The mediastinal fluid was found to be 4+ acid-fast bacilli (AFB) smear positive. PCR of the mediastinal fluid was also positive for *Mycobacterium tuberculosis* (MTB) complex on day 5 of hospitalization and the patient was started on IV linezolid, amikacin, rifampin and levofloxacin and transitioned to standard 4 drug anti-tuberculosis therapy (isoniazid, rifabutin, ethambutol and pyrazinamide) on day 8 when gastrointestinal access was obtained. Antiretroviral therapy had been held on day 2 and was subsequently resumed on day 9. The clinical presentation, recent initiation of ART, current 2-log decrease in viral load, and thoracic CT findings suggested a diagnosis of unmasking MTB immune reconstitution inflammatory syndrome (IRIS).

Discussion

IRIS, previously known as immune restoration disease (IRD) and immune reconstitution syndrome (IRS) is a paradoxical deterioration in the clinical status of a patient after initiation of antiretroviral

therapy[1,2]. The pathophysiology is related to the inflammation that occurs when the recovered immune system targets either live microorganisms or antigens from dead microorganisms[3–7]. Although recently proposed criteria for IRIS differ slightly, most criteria include the evidence of a recovered immune system along with a decrease in HIV viral load and/or increase in CD4 cell count. IRIS may occur as a paradoxical worsening of a known disease that has been under control with treatment, or an unmasking of a previously unsuspected disease[4]. Common pathogens associated with IRIS include tuberculous and non-tuberculous mycobacteria, cytomegalovirus, *Pneumocystis jirovecii*, JC virus, *Cryptococcus neoformans*, herpes simplex virus, hepatitis B virus, hepatitis C virus and Kaposi sarcoma[4,5]. Non-infectious diseases such as sarcoidosis, Grave's disease and thrombotic thrombocytopenic purpura have also been described, suggesting that IRIS is not only an exuberant reaction to live or non-viable organisms, but also a manifestation of an unbalanced immune system[8]. While IRIS can occur acutely for up to 18 months after initiation of ART, most cases occur within the first two weeks to two months after initiation. IRIS is more likely to occur in the setting of high viral loads and low CD4 counts at the time of initiation of ART[9–11].

In pre- and early Highly Active Antiretroviral Therapy (HAART) studies, the most common cause of lymphadenopathy (as seen on imaging) for an HIV patient with a CD4 count less than 50 cells/μL is mycobacterial infection[12]. Determining the presence of IRIS is not always straightforward; however, several key features help support correct diagnosis. The most common imaging feature in MTB-IRIS includes lymph node enlargement with central necrosis, most commonly located in the abdominal, axillary and mediastinal distributions[13]. The marked mediastinal lymphadenopathy in our patient is of particular interest, as this is common in patients with MTB-related IRIS[14].

This patient initiated ART with a low CD4 count of 85 cells/uL (9%) and a high HIV viral load of 336,950 RNA copies/mL. After initiation of ART, his viral load decreased by 2 logs to 3,410 RNA copies/mL. While the absolute CD4 count decreased, the percentage increased. The absolute CD4 decrease was likely related to mycobacterial bone marrow invasion and subsequent inflammation causing pancytopenia and total leukocytosis. Because of this common phenomenon, some authors question the efficacy of CD4 rise as part of a proposed standardized IRIS diagnostic criteria[3].

The exaggerated immune response to our patient's mediastinal mycobacterial burden resulted in extension of inflammation from necrotic lymphadenopathy to the esophageal wall, which underwent necrosis and perforation. This resulted in a gas collection replacing the necrotic lymph nodes (Figure 1). Esophageal perforation can occur from extensive coughing and retching in an MTB patient, with or without an underlying infectious esophagitis.

Management

Although definitive management of IRIS has not been established by carefully controlled studies, current management may include the addition of corticosteroids and in severe cases, temporarily withholding ART. Case reports suggest non-steroidal anti-inflammatory drugs (NSAIDS) may offer symptomatic relief, however randomized evidence of this effect is lacking[15]. Future management may include evaluation for a combination of cytokines and inflammatory markers such as interleukin 7, interleukin 6 and/or C-reactive protein to predict who is at higher risk of developing IRIS, which can be assessed prior

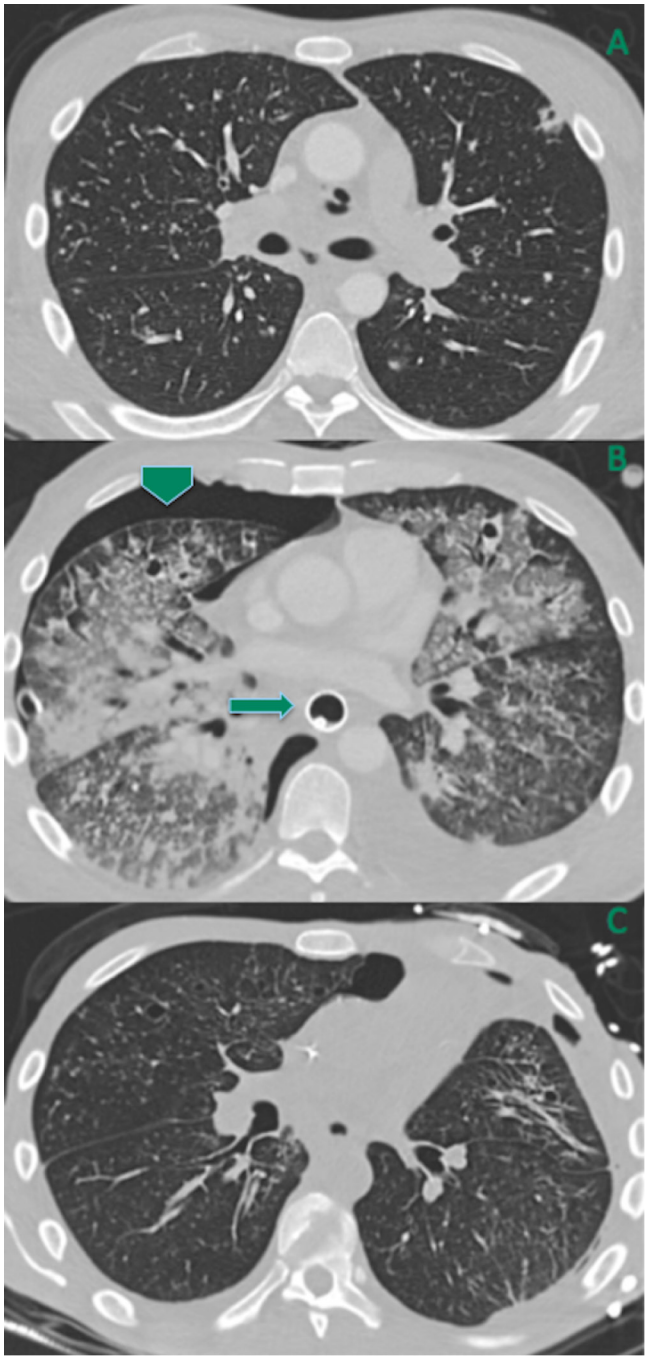

Figure 4. Sequential chest CT studies. (**A**) Multiple cavitary and non-cavitary lung nodules (same as Figure 3). (**B**) Hospital day 6: increased pulmonary tree-in-bud nodules and consolidations, new small right-sided pneumothorax (arrowhead), and new esophageal stent (arrow). (**C**) One month follow-up: nearly-resolved pulmonary opacities decreased tiny right pneumothorax, and removal of esophageal stent.

to initiation of ART[16,17]. Future therapies may include immunomodulatory medications (C-C chemokine receptor 5 inhibitors, TNF antagonists or interleukin 6 receptor inhibitors) to temper the vigorous immune reconstitution.

Our patient had a complicated hospitalization including recurrent pneumothoraces (Figure 4), empyema, and unmasking of cutaneous Kaposi sarcoma. Antiretroviral therapy was continued, except for a brief interruption between hospital days 2 and 9, throughout the hospitalization. As previously mentioned, antituberculous treatment was started after active *M. tuberculosis* infection was confirmed and the treatment regimen included isoniazid, rifabutin, ethambutol, and pyrazinamide.

The esophagus in a patient with a low CD4 count is vulnerable to infection[18]. Our case illustrates a mediastinal infectious process in which TB-IRIS was the etiology and causative factor for an esophageal perforation that further complicated the treatment of this patient with AIDS.

Consent

Written informed consent for publication of clinical details and clinical images was obtained from the patient.

Author contributions

Leonardo Valentin and Andrew DiNardo wrote the manuscript. Elizabeth Chiao, Laila Woc-Colburn, and Arun Nachiappan revised the manuscript. Arun Nachiappan selected the images. All authors approved the final manuscript for publication.

Competing interests

No competing interests were disclosed.

Grant information

The author(s) declared that no grants were involved in supporting this work.

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PubMed Abstract

Open Peer Review

Current Referee Status: ✓ ✓ ✓

Version 2

Referee Report 23 January 2014

doi:10.5256/f1000research.1805.r3282

Eric Daar
David Geffen School of Medicine, University of California, Los Angeles, Los Angeles, CA, USA

I have read this submission. I believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Competing Interests: No competing interests were disclosed.

Referee Report 19 August 2013

doi:10.5256/f1000research.1805.r1526

Susana Asin
Department of Microbiology and Immunology, Dartmouth Medical School, Hanover, NH, USA

This revision has been significantly improved. The authors have addressed my comments and comments from additional reviewers

I have read this submission. I believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Competing Interests: No competing interests were disclosed.

Referee Report 09 August 2013

doi:10.5256/f1000research.1805.r1398

Paul Klenerman
Nuffield Department of Clinical Medicine, University of Oxford, Headington, Oxford, UK

I have read this submission. I believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Competing Interests: No competing interests were disclosed.

Version 1

Referee Report 12 June 2013

doi:10.5256/f1000research.305.r998

Paul Klenerman
Nuffield Department of Clinical Medicine, University of Oxford, Headington, Oxford, UK

This is an interesting short case report and the images are striking.

A couple of points:

- The actual therapy for this patient was not described in any detail.
- The timing of therapy for TB/HIV disease could be discussed.
- The evidence for use of anti-inflammatory agents could be discussed and referenced.
- It would help to expand on the apparent drop in CD4+ T cell count and anemia. What were the other blood indices and how did these recover over time?
- As a small point the 1st line of abstract should be “39 year-old”.

I have read this submission. I believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Competing Interests: No competing interests were disclosed.

Referee Report 15 May 2013

doi:10.5256/f1000research.305.r953

Susana Asin
Department of Microbiology and Immunology, Dartmouth Medical School, Hanover, NH, USA

This is an interesting case report, about a mediastinal manifestation of unmasking Tuberculosis Immune Reconstitution Inflammatory Syndrome (IRIS). Specific remarks are:

1- Since the optimal time to start ARV in the course of anti-tuberculosis treatment is unclear detailed comments about case management i.e. TB-treatment are encouraged.

2- The discussion should consider the fact that even though ARV decrease HIV-1 viral load, CD4 levels after three weeks of treatment were even lower (85 cells/ul compared to 28 cells/ul). Was this a clear indication of a recovering immune system? Should an increase in CD4 cells count have been expected?.

3-This report underscores the relevance of an inflammatory response targeting either live microorganisms or antigens from dead microorganisms as the pathophysiology of IRIS. Is there any evidence to support ARVs as a contributing factor to the on-going inflammatory response?

I have read this submission. I believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Competing Interests: No competing interests were disclosed.

Author Response 16 Jun 2013

Leonardo Valentin, Baylor College of Medicine, USA

Thank you for your review Dr. Asin. See below for our response:

- The patient had been inconsistently receiving anti-retroviral treatment since his diagnosis of HIV 10 years ago. Three weeks after having restarted antiretroviral therapy (ART) the patient presented to the emergency department with fever, productive cough, diarrhea, fatigue and weight loss. During his admission ART was continued, albeit with a brief interruption between hospital days 2 and 9, during his admission. Mediastinoscopy was performed on hospital day 3. The following day, PCR for TB was positive and the patient was started on four-drug anti-tuberculous therapy (ATT) consisting of Isoniazid, Rifabutin, Ethambutol, and Pyrazinamide.

- While the absolute CD4 count decreased, the percentage increased. We believe the absolute CD4 decrease was likely related to mycobacterial bone marrow invasion and subsequent inflammation causing pancytopenia & total leukocytosis. In addition CD4 increases are known to lag behind viral load decrease and are relatively delayed to the IRIS event. Some authors question the efficacy of CD4 rise as part of a proposed standardized IRIS diagnostic criteria.

  Reference:
  Achenbach, C. J. *et al.* 2012). Paradoxical immune reconstitution inflammatory syndrome in HIV-infected patients treated with combination antiretroviral therapy after AIDS-defining opportunistic infection. Clin Infect Dis. 54(3), 424–33. doi:10.1093/cid/cir8023.

  While the pathophysiology is unclear, the varied and multiple presentations of IRIS can provide some insight. There are probably some cases in which IRIS occurs due to neither dead nor live organisms, but an unbalanced immune system. Manifestations like thrombotic thrombocytopenic purpura, Grave's thyroiditis, and other autoimmune conditions provide some examples of the non-infectious presentations.

  Reference:
  Mounzer K, DiNardo A, Goldstein K: Thrombotic thrombocytopenic purpura during immune reconstitution.AIDS. (2007); 21: 2559–60.

Competing Interests: None

Referee Report 14 March 2013

doi:10.5256/f1000research.305.r836

Eric Daar
David Geffen School of Medicine, University of California, Los Angeles, Los Angeles, CA, USA

This is an interesting case report of a somewhat novel manifestation of TB IRIS. The comments related to IRIS are relevant and of some value. Minor comments include:

- The discussion under management probably should at least raise the importance of continuing pathogen specific therapy and the potential role of nonsteroidal anti-inflammatory agents.
- Page 3, bottom of column 1, top of column 2 states “The esophagus in a HIV patient is particularly vulnerable to pathology.” The use of the term “HIV Patient” is awkward and the overall statement is not supported by any data or citation.

I have read this submission. I believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Competing Interests: No competing interests were disclosed.

Author Response 13 Jun 2013

Leonardo Valentin, Baylor College of Medicine, USA

Thank you for your report Dr. Daar. Please find below the response to some of the comments:

- Case reports suggest NSAIDS may offer symptomatic relief, however randomized evidence for this is lacking. There is a BIII recommendation to use NSAIDS for TB- associated IRIS according to the updated IDSA/CDC guidelines.

  References:
  Murdoch DM. Incidence and risk factors for the immune reconstitution inflammatory syndrome in HIV patients in South Africa: a prospective study. AIDS. 2008;22(5):601

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- Patients with very low CD4 counts commonly have esophageal pathology, most commonly due to *Candida*, CMV or HSV and more rarely due to HPV, mycobacteria, idiopathic ulceration, syphilis or *H. ducreyi.*

  Reference:
  Wilcox CM. Esophageal disease in acquired immunodeficiency syndrome: etiology, diagnosis, and management. Am J Med 1992 Apr 92 412-421.

Competing Interests: None