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Case report

Paradoxical exacerbation of tuberculosis after TNFα antagonist discontinuation: Beware of immune reconstitution inflammatory syndrome

Claire Rivoisy[a], Lucile Amrouche[a], Guislaine Carcelain[b], Daniel Séréni[a], Anne Bourgarit[a,*,b]

[a] *Service de médecine interne, université Paris 7, hôpital Saint-Louis, AP–HP, 1, avenue Claude-Vellefaux, 75010 Paris, France*
[b] *Laboratoire d'immunologie cellulaire et tissulaire, UPMC, hôpital Pitié-Salpêtrière, AP–HP, Paris, France*

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ABSTRACT

Paradoxical worsening of tuberculosis associated with immune reconstitution during antiretroviral therapy in patients with HIV infection is known as the immune reconstitution inflammatory syndrome (IRIS). Here, we report a case of paradoxical worsening of IFN-alpha induced tuberculosis in a patient experiencing reconstitution of pathogen-specific immune responses after discontinuing TNFα antagonist therapy. This case serves to alert clinicians that complications such as tuberculosis may worsen after TNFα antagonist discontinuation. This situation may paradoxically require readministration of the immunosuppressive drug in some patients.

1. Introduction

Paradoxical worsening of tuberculosis during treatment was described as soon as effective antituberculous drugs were introduced [1]. More recently, worsening of tuberculosis in patients co-infected with the human immunodeficiency virus-1 (HIV-1) became a well-recognized complication of effective antiretroviral therapy, known as the immune reconstitution inflammation syndrome (IRIS) [2].

Biological agents used to treat inflammatory diseases, such as TNFα antagonists, can precipitate the reactivation of latent tuberculosis [3]. Discontinuation of these agents is followed by reconstitution of the immune system. Here, we report a case of paradoxical worsening of tuberculosis upon TNFα antagonist discontinuation and we review the relevant literature.

2. Case report

A 68-year-old woman was referred to our department for the management of a fever with a decline in general health one month after the initiation of treatment for disseminated tuberculosis during TNFα antagonist therapy. She had inflammatory bowel disease, which had been diagnosed in 1999 and treated from 2002 to 2005 with mercaptopurine. In January 2005, she started long-term glucocorticoid therapy for suspected giant cell arteritis. She experienced recurrent headaches with exacerbation of the laboratory signs of systemic inflammation. As she also had many adverse effects related to glucocorticoid exposure, adalimumab was started in January 2007 with the goal of decreasing the glucocorticoid requirements. A chest radiograph was normal and a tuberculin skin test negative before the initiation of adalimumab therapy. In March 2007, she was evaluated for a fever, dyspnea, joint pain, abdominal pain, and systemic inflammation (serum C-reactive protein [CRP], 157 mg/L). Multiple micronodules consistent with microabscesses were found in the liver and spleen. A liver biopsy showed tuberculoid granulomas without caseating necrosis. Cultures of bronchoalveolar lavage fluid grew a *Mycobacterium tuberculosis* strain susceptible to numerous antimicrobial agents. A repeat tuberculin skin test was negative. She reported untreated primary tuberculosis during childhood, which she had not mentioned during the evaluation for latent tuberculosis done before adalimumab initiation. Adalimumab was stopped and four antituberculous agents were given, starting on March 28, 2007, with 20 mg per day of oral glucocorticoid therapy to control the inflammatory processes. Five days later, she had no fever or hepatic pain and her markers for systemic inflammation had improved.

One month later, she was readmitted for fever, diffuse joint pain, nausea, and anorexia. Large tender inguinal lymphadenopathies were found bilaterally and the right upper quadrant was tender to palpation. Laboratory tests showed hepatic cytolysis (aspartate transaminase, 15N; and alanine transaminase, 4N) and inflammation (CRP, 90 mg/L). Computed tomography of the chest, abdomen, and pelvis visualized necrotic lymphadenopathies and a new cavity in the right lung base (Fig. 1, A and B). Bacteriological specimens were negative by microscopic examination and culturing. An IFN-γ ELISPOT assay done to assess the in vitro memory response to

* Corresponding author. Tel.: +33 142 499 764; fax: +33 142 499 769.
E-mail address: Anne.bourgarit@sls.aphp.fr (A. Bourgarit).

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Table 1
Reported cases of paradoxical worsening of tuberculosis in patients taking TNFα antagonist therapy.

Reference	Age (years)	Underlying disease	Time on TNFα antagonist therapy (months)	TNFα antagonist	Type of TB	Time to IRIS	Manifestations of Iris	Outcome	Specific treatment for IRIS
Arend et al. [8]	24	Crohn's disease	12	Infliximab	Pulmonary	4 months	Development of miliary lung disease and mediastinal lymphadenopathies	Recovered	None
Garcia Vidal et al. [9]	49	RA	2	Infliximab	Disseminated	5 weeks	Lymph node swelling	Recovered	Surgical excision of the lymphadenopathies
Garcia Vidal et al. [9]	48	RA	24	Infliximab	Disseminated	2 months	Lymph node swelling	Recovered	None
Garcia Vidal et al. [9]	56	AS	2	Infliximab	Pulmonary	9 weeks	Development of a lung cavity	Recovered	Glucocorticoids (1 mg/kg per day)
Garcia Vidal et al. [9]	21	Crohn's disease	1	Infliximab	Extra pulmonary	4 months	Persistent perianal ulcer and increased size of the inguinal lymphadenopathies	Recovered	NSAID
Belknap et al. [11]	73	RA	12	Infliximab	Pulmonary	3 months	Worsening lung infiltrate	Recovered	None
Youn et al. [10]	38	Crohn's disease	2	Infliximab	Disseminated	3 months	Drainage of a lymphadenopathy to the skin and development of lymphadenopathies at several sites	Recovered	Surgical excision of the lymphadenopathies
Szerszen et al. [12]	70	RA	5	Infliximab	Disseminated	4 days	Recurrent pleural effusion, prostration, confusion	Not reported	Glucocorticoids (60 mg per day)
Wallis et al. [13]	29	RA	8	Adalimumab	Pulmonary	13 days	Respiratory distress related to extension of the TB lesions to the contralateral lung	Recovered	Glucocorticoids, Adalimumab
Our patient	68	Crohn's disease and giant cell arteritis	3	Adalimumab	Disseminated	1 month	Development of a lung cavity and necrotic inguinal lymphadenopathies	Recovered	None

RA: rheumatoid arthritis; AS: ankylosing spondylitis; TB: tuberculosis; pulmonary TB: tuberculosis confined to the lungs and pleural membranes; disseminated TB: TB involving the lungs/pleural membranes and other sites; NSAIDs: nonsteroidal anti-inflammatory drugs; IRIS: immune reconstitution inflammatory syndrome; time to IRIS: time from TNFα antagonist discontinuation to the onset of the paradoxical response