Peritoneal tuberculosis in the setting of ustekinumab treatment for psoriasis

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INTRODUCTION

Biologics have revolutionized the treatment of moderate-to-severe psoriasis, but serious infection is a risk with these immunosuppressive agents.[1] An increased risk of tuberculosis (TB) reactivation in patients with latent TB infection is well recognized with anti–tumor necrosis factor (TNF)-α agents, as TNF has a central role in TB immunity, and anti–TNF-α agents interfere with innate and cell-mediated immune responses.[2] Testing for and treating latent TB before starting therapy reduces the risk of reactivation of TB on biologic agents.[3]

Ustekinumab is a fully human monoclonal antibody that targets the p40 subunit of the cytokines interleukin (IL)-12 and IL-23 and is licensed in the treatment of psoriasis and psoriatic arthritis (PsA).[4,5] Studies found that IL-12 and IL-23 are important in the defense against bacterial, parasitic, and intracellular pathogens.[6,7] Patients with inborn errors of the IL-12/23 interferon-c circuit are at risk, particularly for mycobacterial infections, especially atypical mycobacterial infections and *Mycobacterium tuberculosis*.[8]

Abbreviations used:

IL:	interleukin
MDR:	multidrug resistant
PsA:	psoriatic arthritis
TB:	tuberculosis
TNF:	tumor necrosis factor

CASE REPORT

A 36-year-old Filipino female presented in July 2015 with a 2-month history of abdominal pain, abdominal swelling, fevers, and weight loss of 10 kg. She had been living in Ireland for 16 years, having moved there from the Philippines, and had last visited the Philippines 1 year previously. She had a background of severe psoriasis and PsA from 2008. She was receiving treatment with ustekinumab, which was started in November 2013, and the frequency was increased from every 12 weeks to every 8 weeks which resulted in good control of her psoriasis. Other treatments she received for psoriasis before ustekinumab therapy included narrow-band ultraviolet B phototherapy, cyclosporine, methotrexate, etanercept, and adalimumab.

In 2008, while on treatment with methotrexate and before starting treatment with etanercept, she was investigated for TB as part of her prebiologic screening. A chest radiograph was normal. She had a tuberculin purified protein derivative skin test result of greater than 5 mm, which is a positive result according to the National Institute for Health and Care Excellence UK guidelines.[9] She was treated for 9 months with isoniazid, 300 mg daily, and pyridoxine, 20 mg daily.

In 2013 an ulcerated hyperkeratotic plaque developed on her abdomen (Fig 1). Multiple biopsies were taken from the abdominal plaque, and histopathologic examination found noncaseating granulomas. A skin biopsy section taken from the plaque for culture of mycobacterium and atypical mycobacterium was normal. Polymerase chain reaction was negative for *M tuberculosis* complex. She had a

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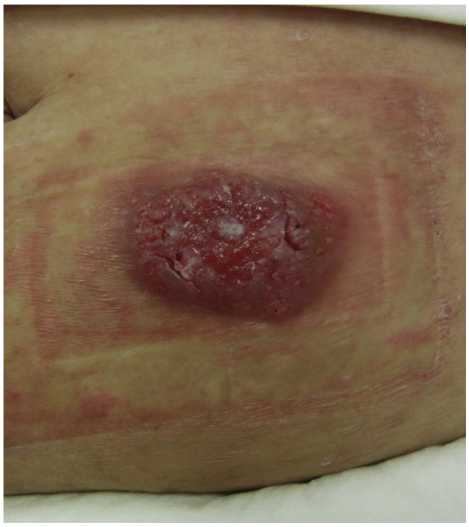

Fig 1. Ulcerated plaque of the abdomen.

concurrent deterioration in renal function, and a renal biopsy found an interstitial nephritis with prominent eosinophilia considered to be induced by adalimumab. She was treated with oral corticosteroids for 6 months, and adalimumab treatment was discontinued. The plaque resolved off adalimumab treatment.

Later in 2013 her psoriasis flared, and ustekinumab treatment was considered. Results of a serum QuantiFERON-TB Gold (Qiagen, Venlo, The Netherlands) test and chest radiograph were normal, and ustekinumab treatment was initiated.

On presentation with abdominal pain, an initial urine β human chorionic gonadotrophin test result was positive. An ultrasound scan of the abdomen showed fluid, and an ectopic pregnancy was considered. Laparotomy found chronic inflammatory bowel deposits, omental caking, and abdominal and pelvic adhesions typical of peritoneal tuberculosis. A serum β human chorionic gonadotrophin test was negative subsequently. Acid-fast bacilli were present on the ascitic fluid aspirate and the omental biopsy. A chest radiograph showed no evidence of TB. Human immunodeficiency virus result was negative. Ustekinumab treatment was discontinued. She started empiric treatment for *M tuberculosis* with Rifater (Sanofi Aventis Ireland Ltd, Dublin, Ireland) (rifampacin 720 mg daily, isoniazid 300 mg daily, pyrazinamide 1800 mg daily), ethambutol 1600 mg daily, and pyridoxine 20 mg daily. Polymerase chain reaction found *M tuberculosis* complex that was rifampacin sensitive, and ethambutol treatment was discontinued. Mycobacterial culture confirmed *M tuberculosis*. The abdominal pain settled, and she received treatment for peritoneal TB for 12 months.

The psoriasis began to flare 6 months after ustekinumab treatment was discontinued, and narrow-band ultraviolet B phototherapy failed to control her psoriasis. She developed a flare of PsA on her right ankle, which responded to an intralesional corticosteroid injection and a course of prednisolone, 15 mg daily titrating to zero over 2 weeks, from the rheumatology team.

The psoriasis became unstable, and she was admitted to the hospital. Liraglutide, a glucagon-like peptide-1 analogue licensed for the treatment of diabetes, was started along with intensive topical therapy (white soft paraffin/liquid paraffin and coal tar paste) in an attempt to avoid immunosuppressive agents in the setting of treatment for active TB. There are case reports and case series of the benefit of liraglutide treatment in psoriasis.[10] She became erythrodermic and hypotensive and required admission to the high-dependency unit. After consultation with the nephrology and infectious disease teams, cyclosporine treatment was initiated up to a dose of 5 mg/kg with improvement, but the psoriasis remained extensive. Secukinumab, a novel anti−IL-17A monoclonal antibody, was commenced. The psoriasis cleared and joint pain settled on secukinumab treatment, and cyclosporine treatment was withdrawn. She was discharged home after a 6-week inpatient hospital admission. Her psoriasis and PsA have remained under excellent control on secukinumab treatment without adverse effects for the last 9 months.

DISCUSSION

There is an increased risk of reactivation of TB, particularly in extrapulmonary sites, in patients treated with TNF-α inhibitors.[11] To our knowledge, this is the first case of peritoneal TB reported in a patient receiving ustekinumab treatment. There is one other case of TB reported in a patient with psoriasis receiving ustekinumab therapy.[12] This patient, who had not received anti-TB treatment based on a negative purified protein derivative skin test and a negative QuantiFERON-TB Gold serum test and who had an abnormal chest radiograph at screening, had asymptomatic reactivation of pulmonary TB 2 months after receiving the first dose of ustekinumab. Our patient previously received treatment for latent TB of an adequate duration. Peritoneal TB in our patient may represent reactivation of TB, or the patient may have been re-infected with TB after a trip to the Philippines. It is possible also that the granulomatous plaque of the abdomen, which developed on adalimumab treatment, may have been cutaneous TB despite both polymerase chain reaction and culture being negative for

M tuberculosis. Thus, a causality of TB from ustekinumab use is difficult to confirm.

In patients who are at risk for multidrug-resistant TB (MDR TB) and present with clinically suspected TB, a rapid diagnostic nucleic acid amplification test for rifampacin resistance on primary specimens is useful.[9] The Philippines is not reported by the World Health Organization as a country with a high proportion ($\geq 5\%$) of new TB cases that are MDR.[13] Our patient was, however, at risk for MDR TB given that she had previously received treatment for latent TB and had re-presented with active TB. On diagnostic nucleic acid amplification testing, the *M tuberculosis* isolate was found to be rifampacin sensitive, and she had a complete response to TB therapy.

We report a patient who developed peritoneal TB on ustekinumab treatment for psoriasis and PsA, with a background of having received multiple immunosuppressive therapies, and after having been treated for latent TB.

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