Case Study: Tuberculosis complicating hepatitis C therapy with pegylated interferon and ribavirin

Tuberculosis complicating hepatitis C therapy with pegylated interferon and ribavirin: new infection in a high tuberculosis incidence area

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Introduction

Interferon and ribavirin therapy for hepatitis C is associated with a variety of side-effects. These include haematological, autoimmune, dermatological, metabolic and infectious complications. The propensity of this combination of treatment to readily cause neutropaenia, and in some instances, lymphopaenia, renders patients susceptible to a wide range of severe bacterial infections. Evidence from studies that have included reports on adverse outcomes indicates that tuberculosis is included in these infections. Unlike other immunomodulatory therapies, such as anti-tumour necrosis factor, there is no requirement to exclude latent tuberculosis infection prior to the initiation of pegylated interferon or ribavarin. Sub-Saharan Africa has a high incidence of tuberculosis, with an incidence of 255 per 100 000 population per year, according to the 2012 World Health Organization statistics. Tuberculosis, as a complication of antiviral therapy for hepatitis C with pegylated interferon and ribavirin, potentially poses more of a threat to patients receiving this therapy in high-incidence areas of tuberculosis. This case study highlights the complexity of the diagnosis and management of tuberculosis in the context of antiviral therapy with pegylated interferon and ribavirin for hepatitis C.

Case study

The patient was a 56-year-old woman with known seropositive rheumatoid arthritis. She had been treated with a combination of immunosuppressant drugs over the years, including methotrexate. She also had hypertension and dyslipidaemia. She had never been treated for tuberculosis, nor was she infected with the human immunodeficiency virus (HIV). She was diagnosed with hepatitis C infection during the workup for abnormal liver function tests, and was subsequently referred to our liver clinic.

She was found to be infected with genotype 5a hepatitis C virus, and had a viral load of 1.8 million copies/ml at initial presentation. Her liver biopsy indicated that she was a Metavir stage activity score A1, and fibrosis score, F2.

Her immunosuppressant therapy was stopped prior to the initiation of anti-hepatitis C virus therapy. A decision was made to manage her rheumatoid arthritis by intra-articular corticosteroid injection of the actively inflamed joints, when deemed necessary.

The patient did not have any tuberculosis symptoms. A chest X-ray performed prior to the initiation of therapy for hepatitis C was normal. However, a sputum smear for tuberculosis, the Mantoux test and an interferon-gamma release assay were not performed prior to the initiation of this therapy.

Upon initiation, her therapy with pegylated interferon and ribavirin was immediately complicated by neutropaenia, lymphopaenia, anaemia and marked weight loss (Figure 1). There were no other symptoms or signs of ill health. A search for underlying infection with chest radiography and ultrasonography of the abdomen did not yield the potential source of a chronic infection. Although a decision was taken to reduce her dose of ribavirin to minimise the side-effects, her response to therapy was maintained as she still managed to achieve a rapid virological response with an undetectable viral load at four weeks (Table I).

The patient was admitted to hospital with fatigue, severe weight loss and a suspected underlying infection in week 18 of the therapy. Samples

Figure 1: Neutrophil, lymphocyte and erythrocyte sedimentation rate changes during therapy for hepatitis C virus infection

Keywords: hepatitis C, tuberculosis, pegylated interferon, ribavarin therapy
of her blood and urine were obtained for culture and a repeat HIV test performed. All of these tests were negative. Further admission at week 25 yielded *Escherichia coli* on culture of her urine that was an extended-spectrum beta-lactamase producer. Her response to therapy with broad-spectrum antibiotics and later, sensitivity-directed antibiotic treatment of the *E. coli*, was poor, with ongoing features of sepsis. This prompted termination of the anti-hepatitis C therapy. Blood sampled to test the hepatitis C viral load upon termination of the therapy for hepatitis C yielded an undetectable viral load.

Blood cultures for *Mycobacterium tuberculosis* and bone marrow aspirate and trephine biopsy (BMAT), performed at 18 and 25 weeks specifically to investigate for tuberculosis, were negative. These tests for tuberculosis were repeated at week 26 of therapy for hepatitis C. The patient was then initiated on empiric therapy for tuberculosis, but unfortunately she demised a week later.

The blood culture for the tuberculosis result was positive for *M. tuberculosis* sensitive to first-line antituberculosis treatment. However, this culture was only positive 36 days after incubation, in keeping with the slow-growing nature of the *Mycobacterium* spp. The patient’s BMAT histology results, obtained 15 days after the biopsy, showed a large necrotic granuloma.

**Discussion**

Hepatitis C virus infection and tuberculosis are linked on many fronts. There is limited evidence to suggest that patients with chronic hepatitis C infection are at a higher risk of developing tuberculosis than matched controls. This risk is evident, even after correcting for confounding factors, such as immunosuppression.

There is reasonably strong evidence to show that patients with chronic hepatitis C virus infection have an increased risk of developing drug-induced hepatitis when exposed to antituberculosis therapy.

The risk of developing tuberculosis has not been quantified in the context of pegylated interferon and ribavirin therapy. This research has only been undertaken in the hepatitis C and HIV co-infected population. This research information is difficult to interpret, given that HIV-infected patients are inherently at a high risk of tuberculosis.

Tuberculosis has repeatedly been recorded, albeit at very low incidence, in clinical trials involving this combination of therapy in which adverse events and outcomes were reported. It has also been demonstrated in case reports that therapy with ribavirin and pegylated interferon led to the reactivation of latent tuberculosis. It is this latter fact that warrants vigilance with regard to awareness for tuberculosis potentially complicating treatment is warranted once a patient has been initiated on treatment for hepatitis C. The complexity lies in the fact that many of the complications of hepatitis C therapy are similar to the symptoms of tuberculosis, and this can potentially lead to a delay in the diagnosis of tuberculosis. This was demonstrated in a study that examined the incidence of tuberculosis in the hepatitis C and HIV co-infected population.

Marked similarities in the features of tuberculosis and sarcoidosis, a condition to which patients on pegylated interferon are also predisposed, is a further complexity with regard to the investigations of ill patients on anti-hepatitis C therapy. The scenario of a histological finding of granulomas in the absence of bacteriological confirmation, which may be delayed by days to weeks while the culture is in progress, is further compounded by the fact that treatment for sarcoidosis involves immunosuppression, while that for tuberculosis involves antibacterial and other antituberculosis agents. This delay was evident in the case of our patient.

**Conflict of interest**

The authors of this article do not have any commercial or other interests to declare that might have posed a conflict of interest.

**Declarations**

Financial support was not received by any members of the team towards the production of this manuscript.

**References**