Author's response to reviews

Title: Interferon-beta Induced Pulmonary Sarcoidosis in a 30-year-old Woman Treated for Multiple Sclerosis: a Case Report

Authors:

Nayia Petousi (nayiapetousi@doctors.org.uk)
Enson C Thomas (enson.thomas@bedfordhospital.nhs.uk)

Version: 2 Date: 24 April 2012

Author's response to reviews: see over
Dear Journal of Medical Case Reports Editorial Team,

Thank you for your email in which you invite us to submit a revised version of our manuscript "Interferon-beta Induced Pulmonary Sarcoidosis in a 30-year-old Woman Treated for Multiple Sclerosis: a Case Report", Manuscript number: 2114273003655415.

We hereby submit a revised version of the manuscript taking into account the Reviewers' comments, which have helped to significantly improve the paper.

Please find at the end of this letter our replies to the reviewers' comments.

We are looking forward to hearing from you soon.

Yours sincerely,

Nayia Petousi and Enson C. Thomas
Authors’ reply to Reviewer 1:

The authors would like to thank the reviewer Spyros Papiris for his comments and for finding our report “an interesting case report with clinical implication for patients receiving interferon treatment”. The following is our response to the comments raised by the reviewer.

Comment 1: In the Introduction Section, paragraph 2, the references about sarcoidosis related to interferon alpha treatment should be stated.
Reply: Three references are stated here. Please refer to the revised manuscript.

Comments 2 and 3: In the Introduction Section, paragraph No 3 should be shortened because it is very well developed in the case presentation paragraph. In the Introduction Section, the last paragraph should be omitted as it is a part of the discussion section.
Reply: Many thanks for the suggestions, which have been implemented. Please refer to the revised manuscript.

Comment 4: In the Case presentation Section, data about the BAL of the bronchoscopy should be provided as well as a picture of the histopathology of the transbronchial biopsy.
Reply: Please refer to the revised manuscript, which now states “At bronchoscopy, the mucosa was fragile and hyperaemic. Bronchoalveolar lavage (BAL) was negative for malignancy and infection. Acid fast bacilli were not detected on microscopy or culture of the BAL specimen. A transbronchial lung biopsy showed the presence of histiocytes, giant cells and non-caseating granulomas (Fig 3), consisted with the diagnosis of pulmonary sarcoidosis”. The CD4/CD8 lymphocyte ratio is not an investigation offered in our district general hospital.

Data should also be provided about the tuberculin skin test of the patient, the cultures for acid fast bacilli.
Reply: The patient did not have a tuberculin skin test; the cultures of acid fast bacilli in the BAL are mentioned above.

An explanation should be given why the patient diagnosed with sarcoidosis without dyspnea or systemic symptoms was treated with corticosteroids.
Reply: In the revised manuscript an explanation is given, reproduced here for convenience “Although the patient felt better after the interferon-β was discontinued, she continued to report fatigue and a persistent dry cough; she had persistent and extensive bilateral parenchymal changes in her lungs and some degree of impairment in her lung function test (e.g. reduced TLCO). For these reasons, she was treated with oral corticosteroids ...”

Further data should be provided about the differential diagnosis of multiple sclerosis and neurosarcoidosis.
Reply: Indeed, neurosarcoidosis and multiple sclerosis can present with similar clinical features. For example, like multiple sclerosis, neurosarcoidosis can present with similar clinical features such as cranial neuropathy (optic neuritis and ophthalmoplegia), hemisphere involvement (psychiatric problems or seizures), spinal cord involvement (paralysis and sensory loss) and unlike multiple sclerosis it can also affect the peripheral nervous system. MRI in neurosarcoidosis can also show demyelinating lesions as in multiple sclerosis. CSF analysis is crucial in differentiating between multiple sclerosis and neurosarcoidosis in that oligoclonal bands are found only in multiple sclerosis. A raised CSF ACE would support a diagnosis of neurosarcoidosis. Our patient had a secure diagnosis of multiple sclerosis with no features suggesting sarcoidosis at the time of this diagnosis. Pulmonary sarcoidosis became apparent after interferon-beta was commenced, with no additional neurological symptoms or signs. She was stable as far as the multiple sclerosis was concerned but a differential
A search at the www.pneumotox.com shows that both amitryptilline and omeprazole could be responsible for lung disease with pulmonary infiltrates. A comment on the potential drug toxicities in the lung should be made.

**Reply:** We would like to thank the reviewer for highlighting these potential drug toxicities. Indeed, amitryptilline has been reported to associated with pulmonary infiltrates and Eosinophilia (eosinophilic pneumonia). This was reported by Noh et al in 2001 (Yonsei Medical Journal) as acute eosinophilic pneumonia when amitryptiline was newly introduced in a haemodialysis patient. Our patient was stable on amitryptilline for years – i.e. it was not a newly introduced drug – and did not have features of eosinophilia. On the other hand, omeprazole has only been implicated in Omeprazole-induced intractable cough (lone cough).

**Comment 5:**
In the Discussion Section references should be provided in paragraph 3 and 4 about interferons and about the autoimmune processes related to interferon treatment

**Reply:** Please see revised manuscript

An additional paragraph should be written about the differential diagnosis of pulmonary infiltrates and lymphadenopathy in patients treated with interferon (e.g BOOP-AFOP, interstitial lung disease with granulomatous component, infections)

**Reply:** We would like to thank the reviewer this comment. An additional paragraph is now added to the manuscript as suggested.

**Comment 6:** A last comment concerns the use of the term “sarcoidosis” for the granulomatous reaction of the lung to interferon. In www.pneumotox.com the reaction is called interstitial lung disease with granulomatous component with or without mediastinal lymphadenopathy.

**Reply:** Indeed, on www.pneumotox.com the reaction is called “interstitial lung disease with granulomatous component with or without mediastinal lymphadenopathy”. To our understanding, this refers to interferon-induced pulmonary sarcoidosis as the reference given in www.pneumotox.com, as evidence for this, is Reference 10 in our manuscript “Bobbio-Pallavicini E, Valsecchi C, Tacconi F, et al. Sarcoidosis following beta-interferon therapy for multiple myeloma. Sarcoidosis 1995; 12:140-142”.
Authors’ reply to Reviewer 2:

The authors would like to thank the reviewer Katerina Antoniou for her comments and for finding our report “an interesting case describing the development of sarcoidosis after IFN-β treatment for MS, as it is a rare treatment-related complication”. Below, find replies to the points the reviewer raised.

Comment 1: Did the patient have abnormal blood gases?
Reply: The patient did not have blood gases as she had a normal (>95% Oxygen saturation and acceptable lung function tests.

Comment 2: Bronchoscopy findings are not described such as CD4/CD8 lymphocyte ratio.
Reply: The CD4/CD8 lymphocyte ratio is not an investigation offered in our district general hospital. In the text (under case presentation) several bronchoscopy findings are described. In our revised manuscript we state: “At bronchoscopy, the mucosa was fragile and hyperaemic. Bronchoalveolar lavage (BAL) was negative for malignancy and infection. Acid fast bacilli were not detected on microscopy or culture of the BAL specimen. A transbronchial lung biopsy showed the presence of histiocytes, giant cells and non-caseating granulomas (Fig 3), consisted with the diagnosis of pulmonary sarcoidosis”

Comment 3: SACE is not present.
Reply: Yes, SACE was not performed. According to the 2008 BTS guidelines on ILD (which include sarcoidosis) in 2008, the serum ACE level has only limited role in diagnosis (low sensitivity of 60% and poor specificity) and does not contribute to the management in patients with pulmonary sarcoidosis when added to serial lung function and imaging.

Comment 4: What dose of cs did the patient receive?
Reply: The patient initially received oral prednisolone at a dose of 40mg daily for 4 weeks, and then continued on a reducing regime over the next six months. This is now mentioned in the manuscript.

Comment 5: HRCT after 6mo is maybe useful.
Reply: We would like to thank the reviewer for this suggestion. A HRCT was not performed at 6 months as the patient remained well, with no deterioration and had complete resolution of the interstitial changes on CXR. HRCT is a valuable and useful test and will be considered in the future should there be a change in the patient’s condition.

Comment 6: What dose of IFN-# did the patient receive?
Reply: The patient received 44mcg of interferon-β subcutaneously three times weekly at the time of presentation. This is now mentioned in the manuscript.

Comment 7: Did the authors check the patient for other systems’ involvement of sarcoid?
Reply: Yes. The patient had an ECG as a screening test for cardiovascular involvement and this was normal. She did not complain of symptoms suggestive of cardiac disease (e.g. palpitations or exertional breathlessness); the authors agree that further cardiac investigations such as a 24-hr holter monitor and echocardiography are indicated only if there are cardiac symptoms or signs.

There were no signs of extrathoracic lymphadenopathy or hepatosplenomegaly clinically. The patient had a normal full blood count.

She had blood tests (on a serial basis) such as electrolytes (including calcium), renal and liver function and these were all normal thereby the possibility of liver or renal involvement.
She had urine investigations – normal urine dipstick (serially in clinic, with no protein) and normal 24-hr urinary calcium.

Sarcoidosis can also affect the neurological system. The patient has a secure diagnosis of Multiple Sclerosis and was under a neurologist. Her disease was stable, with no new features suggesting sarcoid involvement and so no further investigations were arranged by us.