Unexpected outcome (positive or negative) including adverse drug reactions

Interferon α –induced sarcoidosis to a patient with polycythemia vera

M Sionidou, D Spyratos, D Chloros, L Sichletidis

Pulmonary Department, Aristotle University of Thessaloniki, Thessaloniki, Greece

Correspondence to Lazaros Sichletidis, sichlet@med.auth.gr**Summary**

Treatment with interferon (IFN) can precipitate a variety of inflammatory conditions, including sarcoidosis. Although many other systems can be affected, the clinical picture in this case mostly includes cutaneous and pulmonary symptoms. The prognosis is better than the idiopathic form of the disease, and the most effective treatment is considered the discontinuation of antiviral therapy alone or in combination with corticosteroid administration. The authors present the case of a 36-year-old man who developed sarcoidosis stage I after 2 years of IFN α therapy for polycythemia vera.

BACKGROUND

As interferons (IFNs) are increasingly prescribed in a variety of conditions, clinicians should be aware of their potential to induce sarcoidosis. IFN α is used for the treatment of many infectious and malignant diseases, especially *hepatitis C virus* (HCV) and *hepatitis B virus* (HBV) infection, melanoma, multiple myeloma, multiple sclerosis and chronic myelogenous leukaemia.^{1 2} Sarcoid reactions are well-recognised adverse events during IFN α therapy, including multisystem or isolated cutaneous involvement. They are frequently underdiagnosed, because of being

misinterpreted as IFN α side effects even though the cutaneous localisation may offer a clue to an early diagnosis and therapy.¹ There is widespread documentation that IFN can induce, uncover or exacerbate pre-existing autoimmunity, including thyroid disease, autoimmune hepatitis, thrombocytopenia, haemolysis, diabetes mellitus and systemic lupus erythematosus.³

CASE PRESENTATION

A 36-year-old male, non-smoker, in very good physical condition, was admitted to our department for investigation

Figure 1 Chest x-rays showing enlarged hilar dimensions bilaterally.

Figure 2 CT of the chest revealed lymph node enlargement in the mediastinum, the right hilum and in both armpits.

Figure 3 Gallium-67 scanning test with the characteristic 'panda' sign.

of cough, fever during the afternoon and arthralgias mainly after awaking. These symptoms were presented for the last 6 months.

The patient suffered from polycythemia vera treated with hydroxyurea 3 years ago. Due to its toxic action on gametocytes, treatment was changed to second-line therapy with IFN α (15 million units subcutaneous three

times per week) in the last 2 years. During IFN therapy, the patient developed hypothyroidism and received levothyroxine (100 μ g once daily).

INVESTIGATIONS

Physical examination revealed enlarged, painless axillary lymph nodes (2–3 cm maximum diameter). Haematocrit

Figure 4 Biopsy of a right axillary lymph node: non-caseating granulomas and Langhans cells.

was 52%, haemoglobin 17.1 g/dl, white cell counts $5000/\text{mm}^3$ and platelets were $750 \times 10^3/\text{mm}^3$. Biochemistry analysis and thyroid hormones were within normal limits. C reactive protein was slightly elevated (2.9 mg/dl).

Chest x-ray showed an increase in both hilar dimensions (figure 1). Chest CT revealed lymph node enlargement of the mediastinum, right hilum and in both armpits (figure 2).

Patient had elevated angiotensin-converting enzyme (106 μl), spirometry within predicted values and normal urine calcium concentration. The bronchoalveolar lavage (BAL) appeared to have elevated numbers of neutrophils, lymphocytes and foamed macrophages, with a normal ratio of CD4/CD8 lymphocyte subpopulations. Sputum culture for common bacteria and serological test for Chlamydia pneumoniae, Legionella pneumophila and brucellosis were negative. Mantoux test was negative. Autoimmune antibodies for connective tissue diseases and tumour markers were within normal values. BAL cytological examination was negative for malignant cells as well.

The gallium-67 scanning test showed high-drug concentration to parotids and submandibular nodes ('panda' sign, figure 3). The biopsy of a right axillary lymph node showed pattern compatible with sarcoidosis (non-caseating granulomas and Langhans cells, figure 4).

DIFFERENTIAL DIAGNOSIS

The differential diagnosis for this case included lymphoma, tuberculosis, infection, connective tissue disease and sarcoidosis.

OUTCOME AND FOLLOW-UP

Based on clinical examination, radiological examinations and histology, we established the diagnosis of sarcoidosis (stage I) induced by IFN α treatment. After consulting with the haematologist regarding the treatment of polycythemia vera, the IFN α therapy was ceased and replaced by hydroxyurea. Before starting the new therapy, we suggested him to address a semen-keeping bank and return for follow-up in 2 months.

During the follow-up visit, we decided to prescribe a moderate dose of methylprednisolone (16 mg orally daily for 30 days, 8 mg/day for 30 days and 4 mg/day thereafter) as general symptoms (fever, arthralgias and fatigue) influenced his quality of life. Patient responded very well and 3 months later he was completely asymptomatic.

DISCUSSION

To our current knowledge, this is the first case report of IFN-induced sarcoidosis in a patient with underlying polycythemia vera. However, there are a few cases of sarcoidosis that preceded polycythemia vera.⁴

Meanwhile, IFN α by itself can cause sarcoidosis by activating Th1 cells and by the production of interleukin-2 and IFN γ .² This fact is evidenced by series of patients with sarcoidosis, treated with IFN α for a variety of diseases⁵ especially for HBV and HCV infection, and also for melanoma⁶ and neoplastic haematological diseases.

In the most recent review, 89 cases of sarcoidosis after IFN α treatment were presented. The main indications for IFN α were HBV and HCV infection. The mean time of revealing symptoms was from 1 to 6 months and skin lesions were observed in 56% of patients, mostly in the form of erythema nodosum, subcutaneous nodules, plaques and scars. Non-specific respiratory symptoms were noticed in 54% and mediastinal lymphadenopathy in 50% of the patients. The authors underline the importance of an accurate dermatological assessment during the IFN therapy. In this case, skin biopsy was offered as an easy way for early diagnosis.¹

According to current bibliography, there are some patients who develop chronic or progressive disease. In these cases, cease of IFN α therapy is not adequate and systemic corticosteroids are required for a short period.^{7 8}

In a retrospective study, three cases of biopsy-proven sarcoidosis were identified in a population of 667 HCV-positive patients who had received IFN α (an incidence of 0.44%). A review of the literature follows identifying 57 cases with a 10-month mean interval between the IFN α initiation and diagnosis of sarcoidosis. The most common manifestations were from skin and respiratory system. Management of the disease was discontinuation of IFN α either alone or in combination with corticosteroid administration. The majority of patients experienced resolution or at least improvement of symptoms, however, few of them (11%) had a persistent or relapsing course. In this case, additional immunosuppressive treatment was needed.⁷

A previous analysis of 68 cases of sarcoidosis after IFN α treatment for HCV infection suggests that spontaneous remission occurs in two of three of patients with discontinuation of IFN α alone, whereas 10% presented with chronic or progressive disease. Systemic corticosteroids were needed in 35% of them. The authors recommended

a chest x-ray examination before starting antiviral therapy and follow-up focused on possible cutaneous or respiratory symptoms. In case of manifestations suggestive of sarcoidosis, discontinuation of antiviral therapy is the first step and escalation of treatment should be individualised.⁸

Learning points

- ▶ IFN therapy may cause sarcoidosis.
- ▶ The most commonly affected organs are lungs and skin.
- ▶ Cease of therapy is usually the only needed intervention.
- ▶ A baseline x-ray before starting IFN therapy is needed.

Competing interests None.

Patient consent Obtained.

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