Case Report

Pegylated Interferon-Induced Sarcoidosis Presenting With Anterior Uveitis in a Patient with Chronic Hepatitis C - Case Report

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ABSTRACT: Sarcoidosis is a chronic inflammatory systemic disorder of unknown etiology. It is known to be triggered by an autoimmune process, and is currently recognized as a rare adverse event to interferon therapy for Hepatitis C Virus Infection. Clinical presentation of interferon-triggered sarcoidosis is varied, but ocular manifestation as a first symptom was only once, previously reported. We report the case of a 32 year old woman, infected with hepatitis C, for whom antiviral therapy was initiated. Prior to treatment, the patient had outstanding medical history. Three months from the initiation, patient accused pain and redness of the left eye and mild visual loss. The diagnosis of Interferon induced sarcoidosis was established. We are presenting this case because it illustrates the possibility of sudden and severe complications and we want to emphasize the importance of performing ophthalmological examination in patients treated with pegylated interferon α.

***KEYWORDS**: interferon, sarcoidosis, side effects, autoimmune, uveitis*

Introduction

Interferons are cytokines with antiviral activity, antiproliferative and immunomodulatory properties in response to hepatitis C virus infection.[1] The conjugation of PEG reagent (bi-monomethoxypolyethylene glycol) with interferon alpha-2a forms the pegylated interferon alfa-2a, thus increasing the molecular mass, shielding it from proteolytic enzymes and improving pharmacokinetics.[2] Pegylated interferon showed slowed clearance compared with non-pegylated interferon, thus rationalizing the once-weekly administration. In the majority of randomized controlled-trials, including the large randomized IDEAL trial, the combination of therapy yielded 66% sustained virological response.[3] Due to their immunomodulatory effects, interferons have been frequently associated with autoimmune disorders. Most frequent manifestations were thyroid disorders, hematological disorders, renal and dermatological manifestations, and rarely, de novo induction of antibodies. [7-17] The first case of Interferon-induced sarcoidosis was reported in 1987 in a woman treated with IFN beta for renal cell carcinoma. [18]

Case report

A 32 year old woman was referred for investigation for elevated liver enzymes.

This study has obtained approval from the Ethics Committee of the University of Medicine and Pharmacy of Craiova. The patient signed an informed consent, she was previously handed a form in which she was presented all the information related to the participation in the study and use of personal data. Clinical data and the collection of biological material were achieved after obtaining written informed consent from the patient.

She was diagnosed with chronic hepatitis C infection, genotype 1a, viral load 222.459 UI/ml- 5.35 log UI/ml.

The Fibrotest® examination showed A2 inflammatory activity and F3 fibrosis according to the METAVIR score. Past medical records were unremarkable and negative for arterial hypertension, diabetes, dyslipidemia, obesity, smoking, regular use of medication or illicit drug use. Pegylated Interferon α 2b 100 µg and Ribavirin 800 mg was initiated at 4 Jun 2013. Prior to the initiation of therapy, a routine ophthalmological examination was performed. The check-up was normal, with a visual acuity of 20/20 and normal intraocular tension in both eyes. Treatment was well tolerated except for flu-like symptoms and arthralgia.

Three months later, on the 14th of August 2013, she was admitted in the hospital for redness and visual loss in the left eye.

The body temperature was 36.7 degrees C. Blood pressure was 120/70 mmHg, heart rate= 67 bpm, oxygen saturation 98%, and respiratory rate of 16 breaths/min. Baseline investigation revealed ASAT (aspartate aminotransferase) of

153 U/l, ALAT (alanine aminotransferase) of 86 U/l, Hemoglobin – 11.1 g%, Leukocytes-5500/mmc, bilirubin 0.75 mg/dl, glucose- 71 g/dl, Creatinine 0.58 mg/dl, pancreatic elastase-500 μg/g, γ-glutamyltransferase 26 UI/l, and angiotensin-converting enzyme levels were 158 U/l (NR, 35-115 U/L).

The ophthalmological examination revealed a visual acuity of 6/9 OS. Intraocular tension was normal. The cornea showed mutton fat keratin precipitates on the lower third of the left cornea, and there were no synechiae. Slit lamp examination revealed hypopyon in the anterior chamber of the eye (Fig.1).

The diagnosis of anterior uveitis was established.

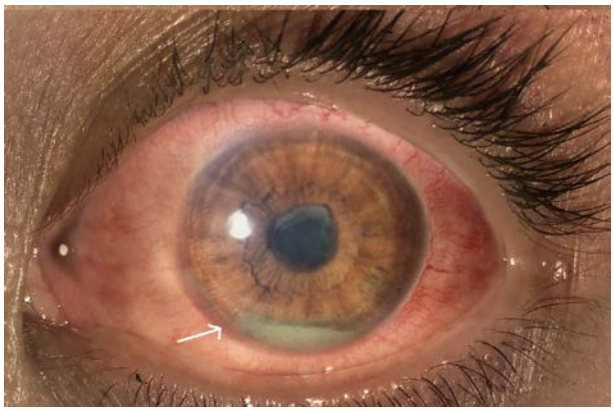

Fig.1.Slit lamp examination showing hypopyon in the anterior chamber of the left eye.

An autoimmune disorder was suspected. Further investigation showed a HLA B27 – negative. An MRI (Fig 2). was performed to investigate a possible ankylosing spondylitis, but showed no erosions at the corners of vertebral bodies with reactive sclerosis, calcifications or syndesmophyitic modifications. All blood cultures were negative for bacteria; she tested negative for fungi also. ESR test was elevated-42 after 1 hour and 78 at hour 2. The pharynx exudate was normal, and ASLO test was 170 UI/mL. Three morning sputum tests were performed; all tests were negative for acid-fast bacilli, and negative PPD test.

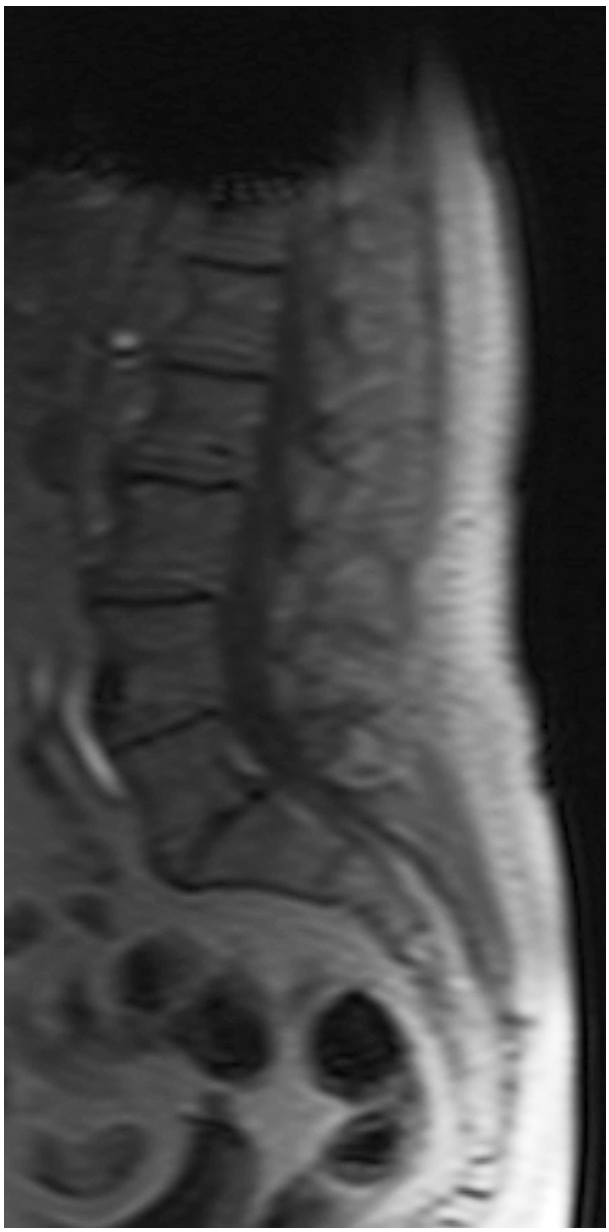

Fig.2. MRI showing normal bone structure and intervertebral spaces.

She had no complaints of cough or shortness of breath, but a chest X-ray was performed. Pulmonary tests were all in range with a full vital capacity of 3.68 L, and forced expiratory volume of 3.11 L. The X-ray showed mediastinal widening and reticulonodular infiltrations with bilateral hilar lymphadenopathy. A chest and abdominal CT was performed in order to further investigate.(Fig 3) The results were conclusive for sarcoidosis, showing small, defined nodules with symmetric distribution and a tendency to coalescence. Biopsies revealed noncaseating granulomas, consistent with sarcoidosis.

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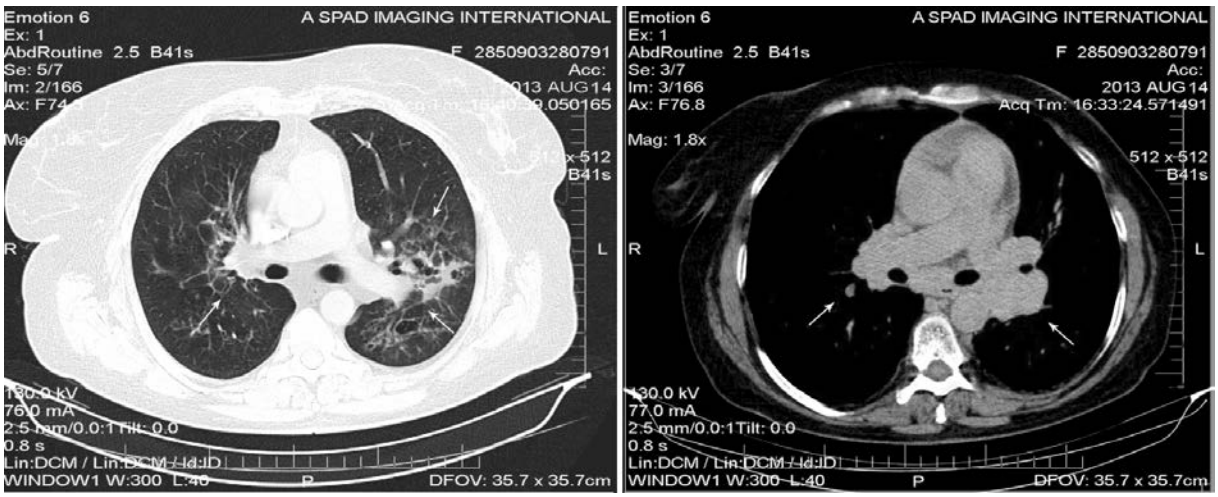

Fig.3. Chest CT showing hilar lymphadenopathy and diffuse fibrosis.

Antiviral treatment was immediately ceased. She was started with topical steroid eye-drops (tobramycin 0.3% and dexamethasone 0.1% 2 drops every 6 hours) and prednisolone acetate 1% with phenylephrine 0.12 %(two drops, four times a day) on the 27th August 2013.

No other treatment was required for the ocular complication. On the 20th January 2014, at the follow up, she had a complete resolution of her visual symptoms, visual acuity of 6/6 with a normal eye examination. CT scans performed, showed resolution of pulmonary nodules and significant decrease in lymph nodes. Treatment with Pegylated Interferon and Ribavirin was reinitiated one month later. The patient achieved sustained virological response on the 17th of November 2014, with undetectable viral load al week 56 of therapy. Four months after the completion of therapy, she continues to be asymptomatic, with normal visual acuity and normal Chest CT. (Fig 4.)

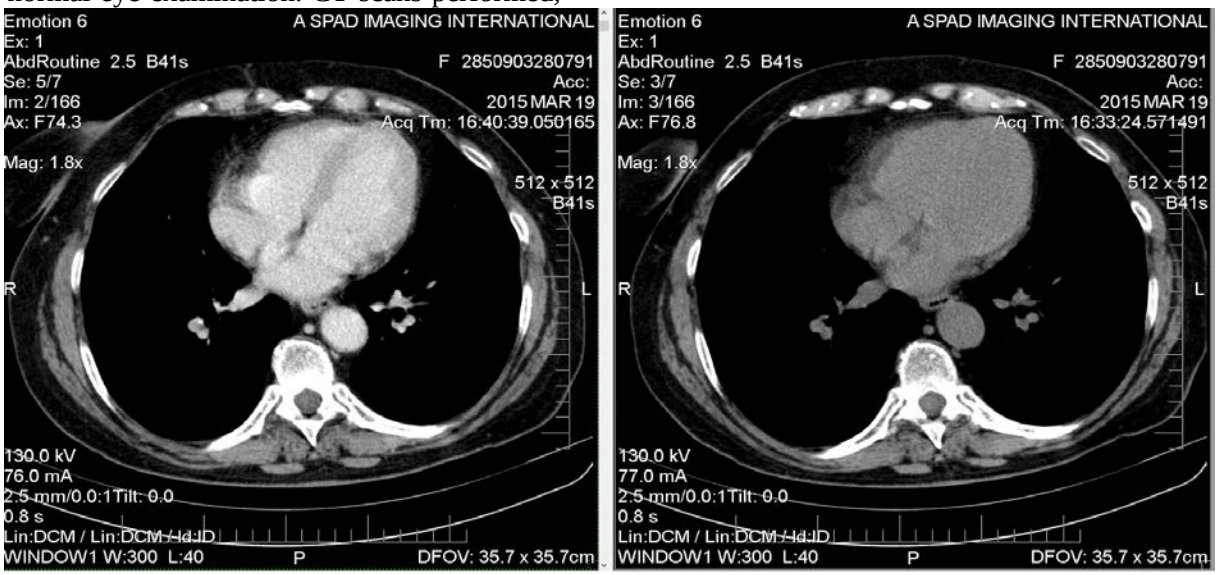

Fig.4. Normal CT scan 4 months after completion of therapy

Discussions

Ocular complications of antiviral therapy have been described in detail in many important works, and have been reported in less than 1% of the cases as potentially serious adverse events. [6] The incidence of retinal hemorrhages and cotton-wool spots has been reported as 6 to 13 %. [4] These changes usually occur in patients with diabetes, hypertension or atherosclerotic conditions. [5] In our case there were no such ophthalmological modifications, and the patient had unremarkable medical past except for Hepatitis C Virus infection.

Sarcoidosis is a systemic inflammatory disease, involving abnormal collections of granulomas that can form nodules in multiple organs. [19] Granulomas are formed in response

to persistent antigenic stimuli that induce a T-helper cell mediated immune response [20]. In response to T helper cell mediated response, macrophages are activated, releasing inflammation mediators, thus leading to Th 1 cell accumulation. This process induces a continuous inflammation contributing granuloma formation. It is known that IFN have been associated with pulmonary macrophage activation, a characteristic feature of sarcoidosis. [20-23]

The first Interferon-induced sarcoidosis was reported in 1987 by Abdi et al. [18] in a patient treated with Interferon beta for an advanced renal cell carcinoma. Since then, multiple similar cases have been reported. Over 70 cases of sarcoidosis were reported since the introduction of Interferon therapy, [18, 21, 23-60] with various clinical manifestations. To our knowledge only under 10 other cases of ocular sarcoidosis was reported in literature, [34, 59-62] and only two previous cases presenting with anterior uveitis as the only symptom for interferon-triggered sarcoidosis. [63, 64]

The incidence of sarcoidosis in hepatitis C virus infected patients undergoing antiviral therapy was reported as 0.09% varying up to 0.2%. [60, 61] Comparing the statistics of general population incidence, the occurrence of sarcoidosis in HCV patients is significantly higher. [65] In a study conducted on 68 patients, the relationship between chronic hepatitis C and sarcoidosis was investigated.[60] The findings related to patterns of association, clinical characteristics and the role of antiviral therapy. In most patients, sarcoidosis was triggered after 6 months of therapy with a higher incidence in patients undergoing combined antiviral therapy. These findings suggest an additional role of Ribavirin in the induction of autoimmune disorders, although no such connections were successfully made.

As etiology for sarcoidosis continues to remain uncertain, treatment courses have not yet been completely established. Corticosteroid therapies have been proven effective in reducing granulomatous processes.

Related to drug-induced sarcoidosis, as in our case, it has been proven that

remission or improvement is strongly connected to discontinuation of therapy. After cessation on antiviral therapy, our patient achieved complete remission, with normalization of visual parameters and resolution of pulmonary nodules.

Conclusions

Chronic hepatitis C infection in treatment with Pegylated Interferon can lead, amongst various complications, to unilateral anterior uveitis. It is of great importance, for the physician, to rigorously evaluate an anterior uveitis and consider, in the context of antiviral therapy, an onset of sarcoidosis with ocular involvement.

Our case reflects the possibility of severe, sudden and unexpected side effects to

Pegylated Interferon and Ribavirin therapy. In conclusion, we would like to emphasize the importance of conducting ophthalmological examinations prior to each antiviral therapy initiation, regardless of past medical history, age or Interferon dose.

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