SIDE EFFECTS OF ANTIVIRAL THERAPY IN HEPATITIS C VIRUS INFECTION–SARCOIDOSIS - CASE REPORT

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SIDE EFFECTS OF ANTIVIRAL THERAPY IN HEPATITIS C VIRUS INFECTION – SARCOIDOSIS (CASE REPORT) (Abstract): Standard therapy in chronic hepatitis C virus infection is still a combination of peginterferon alfa2a/2b and ribavirin for 48 weeks. As of side effects, there are organic side effects, such as hematologic disorders, and functional side effects, reflected in the quality of life of hepatitis C patients. Up to 30% of the patients develop specific side effects such as headache, fever, fatigue. Sarcoidosis, known as a granulomatous disease of uncertain cause, is an uncommon finding in this category of patients. This cause-effect relation is accounted for by the convergent action of peginterferon and ribavirin of stimulating type 1 T helper cells and reducing type 2 helper T cells activation. We present the case of male patient known with chronic hepatitis C who developed pulmonary sarcoidosis following antiviral therapy. The first manifestation of the disease was unexplained fever accompanied by pulmonary tract disease. The diagnosis was established by immunophenotyping in bronchial aspirate. **Keywords:** HEPATITIS C, INTERFERON ALPHA, SARCOIDOSIS.

COMBINATION THERAPY USING PEGINTERFERON ALPHA2 A/2B AND RIBAVIRIN FOR 48 WEEKS IS STILL THE GOLD STANDARD OF TREATMENT FOR CHRONIC HEPATITIS C. NEARLY 30% OF PATIENTS DEVELOP NONSPECIFIC SIDE EFFECTS (HEADACHE, FEVER, FATIGUE) DURING THIS TREATMENT. SARC OIDOSIS ASSOCIATED WITH THIS TREATMENT IS RARE, BEING DESCRIBED IN LESS THAN 1% OF HEPATITIS C PATIENTS. THE ASSOCIATION BETWEEN SARC OIDOSIS AND ANTIVIRAL THERAPY IS EXPLAINED BY THE IMMUNOMODULATORY ACTION OF BOTH SUBSTANCES EXPRESSED IN THE STIMULATION OF TYPE 1 T HELPER (TH1) CELLS ACTIVITY AND DECREASE IN TYPE 2 T HELPER LYMPHOCYTES (TH2) ACTIVITY. WE PRESENT A CASE OF SARCOIDOSIS DIAGNOSED IN A PATIENT WITH CHRONIC HEPATITIS C TREATED WITH PEGINTERFERON ALPHA-2A AND RIBAVIRIN.

CASE REPORT

MD, 43-year-old male, was diagnosed in 2009 with chronic HCV infection (HCV RNA - 907,000 IU/ml; pathology findings: chronic hepatitis of moderate activity Ishak ANI score = 7, fibrosis = 3, metavir A₂F₂). Based on liver function testing, antiviral therapy with peginterferon alpha-2a (180 mcg/week) and ribavirin (1000 mg/day) was initiated. As the 4-month assessment revealed that viral load became undetecta-
ble, the patient continued the initially recommended therapy. Also, during this period no notable side effects were reported. Starting with the fifth month of antiviral treatment the patient complained of fever, chills, sweating, fatigue, chest pain, and headache. Physical examination revealed fever 38°C, submandibular adenopathy, and sonorous and subcrepitant rales in the right lung area. Laboratory findings: severe thrombocytopenia without radiological pulmonary changes (tab. I).

<table>
<thead>
<tr>
<th>TABLE I</th>
<th>Laboratory findings during febrile syndrome</th>
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<tr>
<td></td>
<td>Z 1</td>
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<tr>
<td>Hb –</td>
<td>12.4 g%</td>
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<tr>
<td>GA –</td>
<td>5.080/mm³</td>
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<td>Tr –</td>
<td>48.000/mm³</td>
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Discontinuation of antiviral therapy for 7 days and administration of single-drug antibacterial therapy for 2 days (ampicillin), and then, because of febrile syndrome persistence, administration of dual antibacterial therapy (Ampicillin - Ciprofloxacin) were decided. Radiological reassessment after 7 days of antibacterial therapy detected a focus of right infrahilar condensation. Clinically, the respiratory manifestations gradually faded within 14 days, and biologically an improvement of thrombocytopenia was found. Radiological examination at 21 days revealed a decrease in size of the initial inflammatory focus. Clinical and biological monitoring during the remaining seven months of antiviral therapy showed fluctuations in platelet and leukocyte count, reason why no temporary reductions in antiviral drug dosage were necessary. Clinically, the patient continued to complain of fatigue, intermittent fever, and dry cough. As these manifestations have not outlined any ongoing clinical syndrome, they were classified as clinical adverse reactions of antiviral therapy and treated symptomatically.

After 48 weeks of antiviral medication, the patient complained again of respiratory manifestations: progressive dyspnea, and cough with purulent expectoration. Radiological examination revealed bilateral hilar lymphadenopathy (fig. 1). Additional tests detected significant pulmonary and cardiac changes (tab. II).

![Fig. 1. Bilateral hilar lymphadenopathy](image-url)
Side effects of antiviral therapy in hepatitis C virus infection – sarcoidosis (case report)

TABLE II

Additional examination 50 weeks after the initiation of antiviral therapy

- IDR 2u PPD – negative
- Fibrobronchoscopy: friable mucosa, abundant secretion
- Bronchial aspirate – BAAR negative
- Anatomopathological examination of bronchial aspirate - inflammatory smear with metaplasia and moderate dysplasia
- Bronchial aspirate immunophenotyping - 21% Ly, 20% - LT, TCD4/CD8 ratio = 3.3
- Pulmonary function tests: FEV1 - 77.7%, FVC - 77.4%, PEF - 90.1%, MEF50 - 64.1%. Conclusion: mild restrictive dysfunction
- ECG - sinus rhythm, supraventricular extrasystoles with aberrant conduction
- Chest CT (fig. 2):
  - mediastinal lymph nodes: enlarged, confluent, bilateral and relatively symmetric, noncalcified, without necrosis, uncompressed
  - parenchymal changes: round, small, perilymphatic nodules, nodular or irregular areas of increased „ground glass” attenuation, and peripheral, subpleural peribronchovascular condensations
  - retroperitoneal lymph nodes, interaorticocaval ~ 2cm, celiomesenteric < 1cm

As the patient did not present peripheral adenopathy and the risk of a mediastinal biopsy was higher that its benefit (immuno-suppressed background), this test (pathology) required for differential diagnosis (tuberculosis, lymphoma, sarcoidosis) was not performed. Phenotypic analysis of bronchoalveolar lavage sample (Tab. II) showed criteria suggestive of sarcoidosis. In the absence of other consistent evidence for a diagnosis of lymphoma or tuberculosis, we interpreted these findings as stage II sarcoidosis. Prednisone therapy was instituted; fever disappeared after a week, the patient being monitored by an infectious disease specialist. Viremia after 18 months of therapy remained undetectable.

DISCUSSION

The first case of sarcoidosis associated with interferon therapy was published in 1978. Since then, similar cases have been reported in the literature, but not being a widespread phenomenon it did not lead to
the cessation of the above mentioned therapy (3).

Chronic hepatitis C infection currently affects over 170 million people worldwide. Current standard therapy of this disease is the association of two antiviral drugs (peginterferon alpha2a/2b - ribavirin) with immunomodulatory role, amplifying the immune system response on infected cells. (2). In 40-50% of cases, subjective side effects (fatigue, myalgia, headache, depression) and others representing well-defined organ dysfunctions (e.g. autoimmune thyroiditis) are reported.

Sarcoidosis diagnosed in patients on antiviral treatment for hepatitis C is recognized as a side effect of interferon therapy. Interferon-induced sarcoidosis is known to be a chronic multisystem inflammatory disease of unknown cause manifest by the appearance of non-caseous granulomas in various organs/systems: lung (90%), lymphatic system (33%), liver (50/80%), eyeball (11-83%), and skin (25%).(1) As to its pathogenesis, it requires the intervention of one or more factors (infectious, tumor antigens/autoantigens) that prime immune mechanisms through which a prolonged stimulation of T lymphocytes with the appearance of an exaggerated T-helper cell response is produced: predominance of Th1 cells over Th2 cells. Interferon-alpha stimulates Th1 cell differentiation and decrease in Th2 lymphocytes activity leading to the formation of granulomas (6, 8). Compared to its predecessor, peginterferon-alpha has a higher influence on Th1 response, and therefore an increased risk for sarcoidosis. (4, 5, 9) Ribavirin, guanosine analogue, also stimulates Th1 lymphocytes and decreases Th2 lymphocyte activity. Thus, this association accounts for the increased predisposition to sarcoidosis of hepatitis C patients on antiviral therapy. In this category of patients, sarcoidosis can occur during treatment or after its discontinuation (7).

We presented a case of pulmonary sarcoidosis induced by peginterferon-alpha2a - ribavirin antiviral therapy in a 43-year-old patient. In this patient the onset of prolonged febrile syndrome associated with respiratory symptoms occurred after the first four months of therapy. In the absence of clear evidence (absence of superficial or deep lymph nodes), the clinical picture was initially interpreted as a right lower lobe pneumonia favored by drug induced leukopenia. Fever, fatigue, and cough are frequent adverse reactions in patients on long-term antiviral therapy. Our interpretation of patient’s symptoms was revised only when after antiviral treatment discontinuation at 48 weeks radiological examination showed a bilateral hilar lymphadenopathy. Pulmonary examinations completed this information puzzle leading to a correct interpretation of the picture. Bronchoalveolar fluid immunophenotyping is the key diagnostic test on which the disease was diagnosed in the absence of other criteria.

**CONCLUSIONS**

Antiviral therapy with peginterferon alpha2a/2b and ribavirine in patients with hepatitis C has many functional and organic side effects. Before therapy, these reactions, which can be temporary, have to be divulged while obtaining consent. During the long-term antiviral therapy the physician has to pay attention to all side effects that can appear and take measure for preventing or diminishing their actions. Sarcoidosis is an uncommon occurrence, and in our case we misinterpreted the first disease manifestations: fever of unknown origin and pneumonia. Following the detection of mediastinal adenopathy, the addi-
tional investigations made us realize that all manifestations could be interpreted as pulmonary sarcoidosis. Therapy with prednisone was initiated and fever disappeared within a week. So it is important to keep in mind that respiratory disorders occurring in hepatitis C patients on antiviral therapy can be early signs of sarcoidosis.

REFERENCES


EXPOSURE TO CIGARETTE SMOKE AND THE PATHOGENESIS OF RESPIRATORY INFECTION

Staphylococcus aureus, conditioning pathogenic bacteria, can colonize the upper respiratory tract and can cause severe infections under favorable conditions such as exposure to cigarette smoke (CS). CS has immunosuppressive and irritant effects on human cells. A recent study released by Kulkarni R and colleagues show that CS also affect the microorganisms by normal microbiota and potentiate their virulence. CS increased S. aureus ability to form biofilm and to adhere to the host cell. Oxygen free radicals present in CS inhibit Accessory Gene Regulator (agr) system responsible for dispersing bacterial biofilms. Also these compounds determine transcriptional induction of bacterial oxidoreductases. By inducing transcription of fnbA (encoding fibronectin binding protein A), increases the ability of S. aureus to bind fibronectin and thus CS can favor bacterial adherence to the host cell. This study concluded that the bioactive effects of CS may extend to the resident microbiota with implications for the pathogenesis of infection (Kulkarni R, Antala S, Wang A et al. Cigarette smoke increases Staphylococcus aureus biofilm formation via oxidative stress. Infect Immun, 2012; 80 (11): 3804-11).

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