Interstitial pneumonitis after treatment for hepatitis C virus infection

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Abstract

Pulmonary toxicity is a rare side effect of interferon treatment with a wide spectrum of lung tissue conditions, including interstitial pneumonitis, pulmonary sarcoidosis, bronchiolitis obliterans organizing pneumonia, pleural effusion, exacerbation of bronchial asthma, reversible pulmonary hypertension and acute respiratory distress syndrome. We report a case of interstitial pneumonitis in a patient treated with pegylated interferon α2-a and ribavirin for chronic hepatitis C virus infection, genotype 1. The case was marked by progression of the respiratory symptoms even after the withdrawn of the pegylated interferon. One-year treatment with systemic corticosteroid ensured a considerable resorption of CT lesions but only a moderate improvement of symptoms and diffusion capacity without a complete recovery.

Keywords: *interstitial pneumonitis, interferon treatment, side-effect, hepatitis C*

Rezumat

Pneumopatie interstițială difuză după tratament pentru infecția cu virus hepatitic C

Toxicitatea pulmonară este o reacție adversă rară la tratamentul cu interferon, cu o mare varietate de afectări pulmonare, printre care pneumopatia interstițială difuză, sarcoidoza pulmonară, bronșiolita obliterantă cu pneumonită de organizare, colecția lichidiană pleurală, exacerbarea astmului, hipertensiunea pulmonară reversibilă și sindromul de detresă respiratorie acută. Raportăm un caz de pneumopatie interstițială difuză la o pacientă tratată cu interferon α2-a pegilat și ribavirină pentru infecția cu virus hepatititc C, genotip 1. Cazul a fost marcat de progresia simptomelor respiratorii chiar după întreruperea tratamentului cu interferon. Un an de tratament corticosteroid sistemic a permis resorbția considerabilă a leziunilor vizibile computer tomografic, însoțită doar de ameliorare moderată a simptomelor și a capacității de difuziune, fără recuperare completă.

Cuvinte-cheie: *pneumopatie interstițială difuză, tratament cu interferon, reacție adversă, hepatită C*

Hepatitis C is one of the leading causes of chronic liver disease, cirrhosis, and liver cancer in the Republic of Moldova. Interferon α has been approved for hepatitis C treatment since 1991. The most important advance in hepatitis C treatment was the development of a long-acting interferon, pegylated interferon (PEG-INF), produced by the covalent attachment of polyethylene glycol to the interferon molecule. Higher treatment response rates were reported in patients with hepatits C virus infection (HCV) genotype 2 or 3 than among those with genotype 1[1]. Pulmonary complications associated with the use of interferon, although uncommon, have been reported.

Case report

A 49-year-old caucasian non-smoking woman with no drug or alcohol abuse, history of cured pulmonary tuberculosis (30 years ago, with calcifications in the left apical zone), type 2 diabetes mellitus (on metformin 500 mg daily) and autoimmune thyroiditis was evaluated by a hepatologist for chronic hepatitis C.

Laboratory tests at initial evaluation showed alanine aminotransferase (ALAT) 72 IU/l (normal <40 IU/l), aspartate aminotransferase (ASAT) 46 IU/l (normal <40 IU/l), γGTP 121 IU/l (N 5-45 IU/l), 50 x 10^6 copies/ml of HCV RNA by PCR and 1b HCV genotype. Alkaline phosphatase, bilirubin, urea, creatinine, C-reactive protein were in normal range. HBsAg, antiHBs, antiHBcor IgM, HBeAg, antiHBe antiHDV, antinuclear antibodies, antimicrosomal antibodies, anti-smooth muscle antibodies, anti-dsDNA antibodies, anti-cyclic citrullinated peptides, anti-liver-kidney microsome antibodies and anticardiolipin antibodies were negative. Hepatomegaly (right lobe 15.1 cm, left lobe 7.3 cm) and splenomegaly (13.9 x 5.8 cm) were identified by ultrasound examination. Assessment of Metavir score revealed stage F3 fibrosis, and a liver stiffness of 14,8 kPa on FibroScan. Liver biopsy prior to antiviral therapy was denied by the patient.

The patient was started on combined treatment PEG-INF α2-a 180 μg s/c once weekly and ribavirin 1,200 mg daily.

Two months after the initiation of treatment our patient experienced exertional dyspnea (disconsidered at that point) and ten weeks later she developed a rash with Quincke's edema. The antiviral therapy was withdrawn and dexamethasone (8 mg/day i/m) for three days and loratadine for three weeks were prescribed.

A chest radiography showed bibasilar and paracardiac interstitial as well as alveolar infiltrates, silhouette sign on the left and calcifications in the left apical zone (fig. 1).

Three weeks later the antiviral treatment was restarted but at the second dose of PEG-IFN α-2a the patient was admitted to the hospital for fever (38°C), increased dyspnea, cough, malaise and skin rash. Consequently, PEG-IFN α-2a was discontinued. Chest x-ray revealed bilateral diffuse patchy shadows (fig. 2).

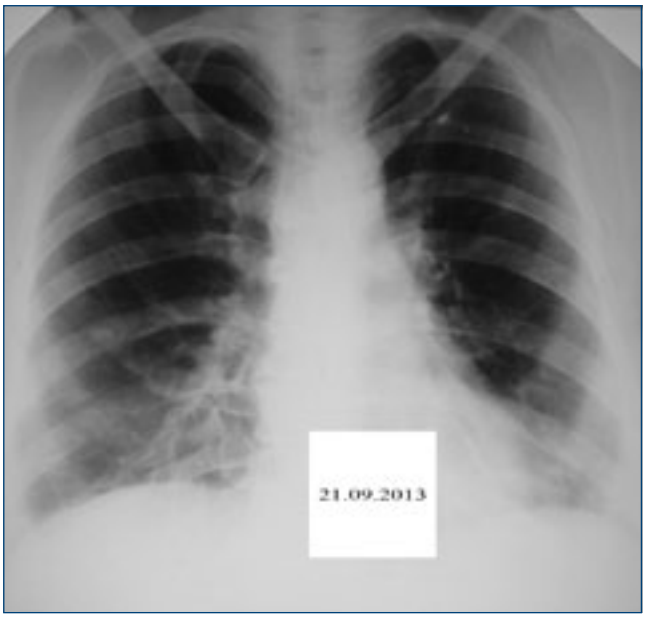

Figure 1. *Chest X-ray at the tenth week of antiviral treatment showed interstitial and alveolar infiltrates in the lower lung fields*

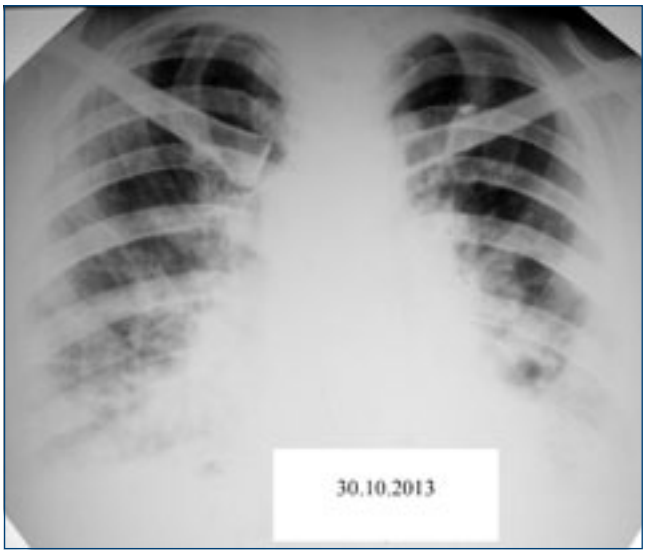

Figure 2. *Chest X-ray at the second week of restarted antiviral treatment (the eleventh weekly dose) showed a mixture of a coarse, diffuse reticular pattern and bibasilar and paracardiac heterogeneous opacities with air bronchograms and silhouette sign*

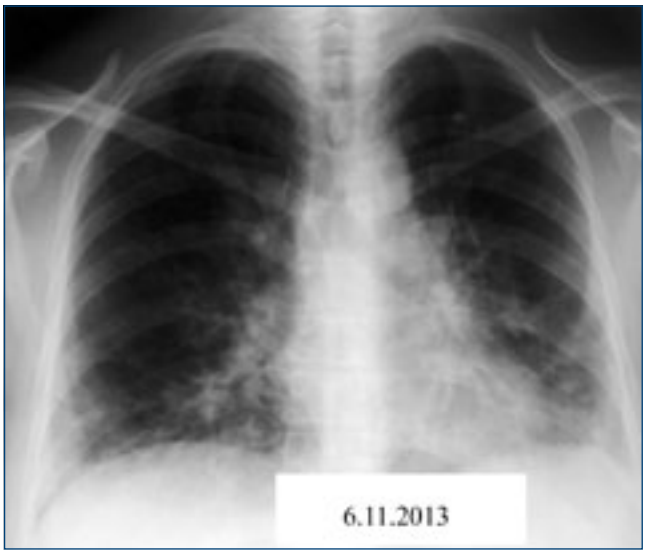

Figure 3. *After a week of discontinuation of antiviral treatment and institution of antibiotic treatment, frontal radiograph showed a resolution of some infiltrates, but the maintenance of linear and ground glass opacities in the lower lung fields*

HCV RNA by PCR was 12 x 10^6 copies/ml after 3 months of antiviral treatment.

Therapy with ceftazidime (4 g/day) was initiated to cover for possible community-acquired pneumonia. On day 3 of hospital admission the patient became afebrile but with progressive shortness of breath. Oxygen saturation saturation at that time was 88% while breathing room air. A possible pulmonary allergic reaction to pegylated interferon-α2a was suspected as the cause of symptoms and she was transferred to our hospital at the 7^{th} day for further management of persistent hypoxemia. Physical examination revealed bilateral lower lung field coarse crackles, respiratory rate 30/min, blood pressure 110/80, heart rate 100/min. There was no evidence of congestive heart failure.

Chest radiography at admission to our clinic revealed bilateral interstitial opacities in the lower fields (fig. 3).

Arterial blood gas levels were as follows: pO_2 89.5 mm Hg; pCO_2 26.9 mm Hg; and pH 7.54. The findings of the cardiac examination were normal, and the echocardiogram showed a normal left ventricular ejection fraction and no other evidence of congestive heart failure.

Pulmonary function tests indicated restriction and decreased diffusing capacity (FVC 50% predicted, TLC 64% predicted, and DLCO 31% predicted). Laboratory data on admission showed: elevated C-reactive protein (four fold upper limit) WBC 15,000 cells/μl and ESR 28 mm/h.

Results from bronchoalveolar lavage supported the diagnosis of drug-induced interstitial pneumonitis (cell count 0,3 x 106/ml, 44% lymphocytes) and were negative for bacteria, fungi, acid-fast bacteria and malignant cells.

Chest high resolution computed tomography (HRCT) scan showed bilateral reticular interstitial abnormality with areas of ground glass opacity predominantly involving the middle and lower lung fields (fig. 4).

Face mask oxygen therapy and 40 mg prednisolone orally lead to considerable improvement of the symptoms (less dyspnea and cough).

HRCT scan after 47 days showed less reticular interstitial abnormality with ground glass reduction bilaterally. After 2 months of systemic steroid treatment HCV RNA by PCR increased to 115 x 10^6 copies/ml. The dose of prednisolone was then decreased gradually to 10 mg per day.

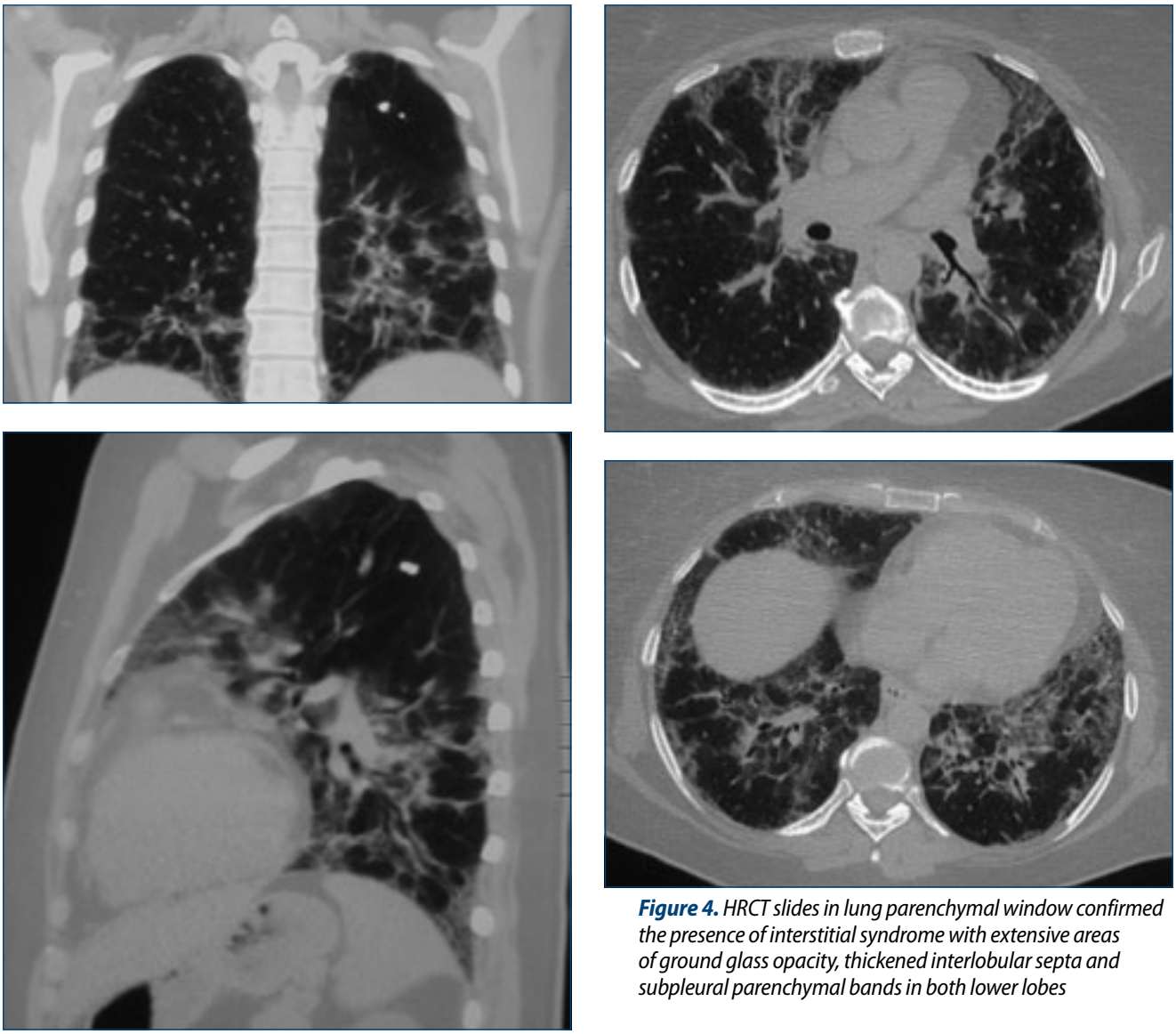

Figure 4. *HRCT slides in lung parenchymal window confirmed the presence of interstitial syndrome with extensive areas of ground glass opacity, thickened interlobular septa and subpleural parenchymal bands in both lower lobes*

No changes were observed on HRCT (fig. 6) after 7 months of steroid therapy (the last 2 months 10 mg per day of prednisolone), but DLCO improved to 56%. After 1 year of low dose prednisolone treatment (10 mg/day) the patient is clinicaly stable with moderate exertional dyspnea. Pulmonary function tests (PFTs) revealed a mild restrictive defect (FVC 86% predicted, TLC 72% predicted, RV 72% predicted) and a diminished diffusing capacity (DLCO 54% predicted).

Discussion

Though potentially successful, PEG-INF and ribavirin are known to cause various side effects in HCV hepatitis patients. The most common side effects include fatigue, influenza-like symptoms, gastrointestinal disturbances, neuropsychiatric symptoms, and hematologic abnormalities[1,4,6,7,12].

Cutaneous side effects (itching, skin dryness, eczema, lichenoid eruptions, rashes and malar erythema) have been reported either with IFN alone or in association with ribavirin (the incidence increase in the combination)[10,11].

Pulmonary toxicity is a rare (incidence <1%) but unanticipated side-effect of INF with a wide spectrum of lung tissue damage, including interstitial pneumonitis (IP), pulmonary sarcoidosis, bronchiolitis obliterans organizing pneumonia, pleural effusion, exacerbation of bronchial asthma, reversible pulmonary hypertension and acute respiratory distress syndrome[2,6,7,8].

Interferon toxicity is generally dose and duration dependent[3], which allows the speculation that pulmonary toxicity may occur more severely with long-acting PEG-INF; however, there was no reported effect of dosage on the occurrence of pneumonitis. Patients died due to different causes (e.g., hypoxia-induced cerebral edema, acute cholestatic hepatitis, and multi-organ failure), all induced by complications after the initial interstitial pneumonitis.

The precise incidence rate of IFN-induced IP is still unclear and is estimated to be 0.01-0.3%[13]. Pneumonitis can arise at any stage of the treatment, ranging from 2 to 48 weeks, usually in the first 12 weeks. Its most common symptoms are dyspnea, dry cough, fever, fatigue,

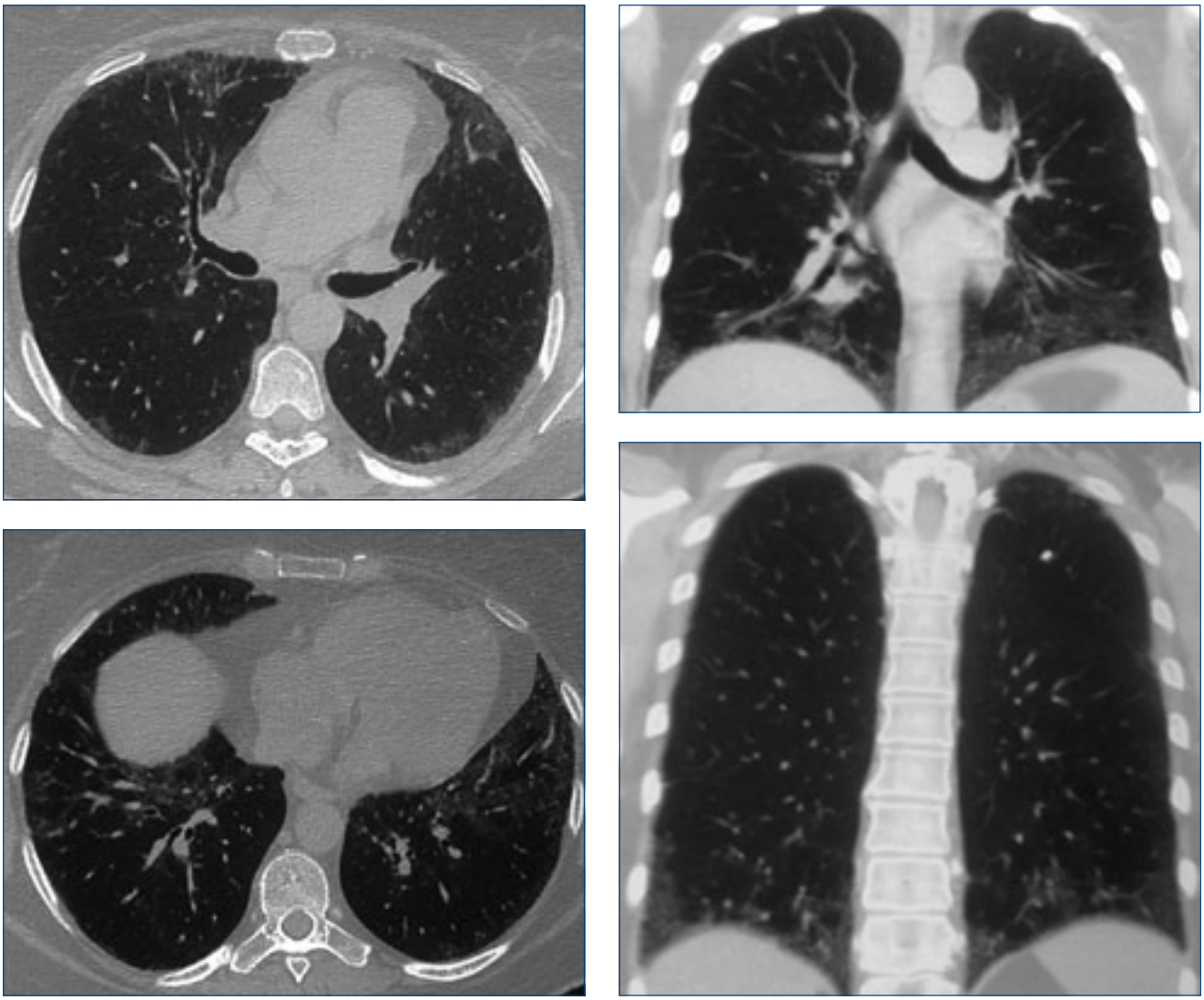

Figure 5. *HRCT after eight weeks of discontinuing PEG-IFN and ribavirin and six weeks of systemic steroid therapy showed improvement of the ground glass opacities*

arthralgia or myalgia, and anorexia, which are reversible in most cases after cessation of IFN therapy with a mean subsequent recovery time of 7.5 weeks[6,7].

The mechanism underlying IFN-induced IP has not yet been clarified. It has been suggested that IFN can induce lung tissue fibrosis by inhibiting suppressor T cells, increasing cytotoxic T cells, inducing proinflammatory cytokines, and exaggerating release of fibrinogenic cytokines. It is plausible that interferon triggers a lung-specific immune-mediated response resulting in interstitial pneumonitis, similar to other autoimmune diseases[7,14].

The diagnosis of IFN-induced IP is not easy, since no international diagnostic criteria for IFN-induced IP are available. One study revealed the frequent occurrence of DLCO declines of clinically relevant magnitude (>15% from baseline) during the treatment of chronic HCV with modified IFN α. These pulmonary changes persisted in some patients for 6 months after the end of treatment, but do not appear to be associated with an increased frequency of respiratory adverse events[9].

Patients with HCV who develop severe dyspnea during IFN therapy should have their respiratory function checked, in particular those who have a preexisting chronic pulmonary disease or CXR abnormalities, and should be referred to a pneumologist in case of clinically relevant reductions in PFTs. It remains controversial whether corticosteroids should be included in the treatment modality for IP associated with IFN therapy (corticosteroids increase HCV replication)[2,5,6,7,8]. Once evidence of pulmonary injury is demonstrated, INF therapy should be withdrawn immediately, and steroids may be administered if symptoms deteriorate progressively[2].

Despite a corticosteroid treatment being given to our patient, we observed a considerable resorption of CT lesions but only a moderate improvement of symptoms and DLCO without a complete recovery.

INF-associated interstitial pneumonitis is a severe complication in patients on treatment for HCV hepatitis, that require discontinuation of INF therapy despite the impairing of antiviral therapy success. INF discontinuation allow to prevent further pulmonary injury and/or death. ■

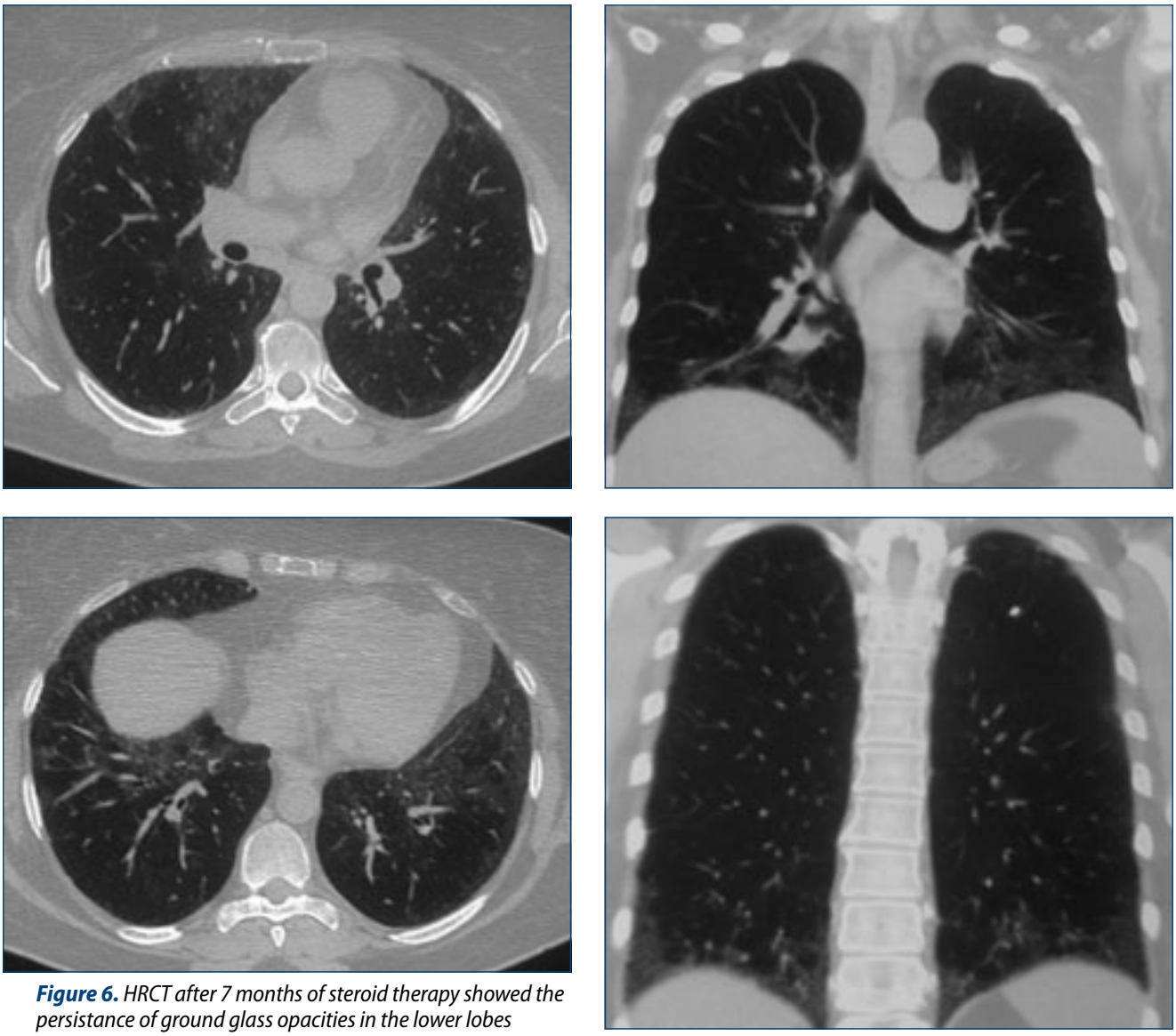

Figure 6. *HRCT after 7 months of steroid therapy showed the persistance of ground glass opacities in the lower lobes*

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