A 49-Year-Old Woman With Hepatitis, Confusion, and Abnormal Chest Radiograph Findings*

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A 49-year-old woman with a 10-year history of hepatitis C was admitted to Indiana University Hospitals after several weeks of fatigue, nausea, vomiting, and confusion. Dehydration was noted on two visits to the emergency department (ED) in the 2 weeks prior to hospital admission, and her symptoms responded satisfactorily, but transiently, to IV fluids. During the second ED visit, as part of a metabolic evaluation for confusion, a normal ammonia level was found, serum sodium was 128 mmol/L, and total serum calcium was 11.9 mg/dL.

The patient had a 10-year history of hepatitis C but was otherwise healthy. One year prior to hospital admission, she had fatigue, nausea, and liver function abnormalities. A subsequent liver biopsy showed bridging fibrosis, and she was treated with interferon-α (IFNα) and ribavirin. She remained asymptomatic on this regimen for >10 months. For the last 3 weeks, however, she has been ill with vomiting, fatigue, and confusion. She states that the only days she can function are the 2 to 3 days after she is treated with IV fluids in the ED.

**Physical Examination**

On admission, she was tachycardic and confused, but in no acute distress and with no focal neurologic deficit. Dry mucous membranes were noted. There was no cervical, supraclavicular, axillary, or inguinal lymphadenopathy. Lungs were clear to auscultation, and cardiac examination revealed no abnormalities. The abdomen was soft and nontender with no organomegaly. No clubbing, edema, or skin lesions were noted.

**Laboratory data**

WBC count was 4.6 × 10^9/μL; with 77% neutrophils; hemoglobin, 12.0 g/dL; platelet count, 92/μL; international normalized ratio, 0.93. Serum electrolytes were as follows: sodium, 129 mmol/L; potassium, 3.8 mmol/L; chloride 98, mmol/L; bicarbonate, 23 mmol/L; BUN, 36 mg/dL; creatinine, 1.9 mg/dL; total calcium, 12.4 mg/dL; glucose, 78 mg/dL; total protein, 5.7 g/dL; albumin, 2.4 g/dL; total bilirubin, 0.2 mg/dL; alkaline phosphatase, 100 U/L; aspartate aminotransferase, 23 U/L; and alanine aminotransferase, 16 U/L. Ammonia was normal.

**Hospital Course**

The admission chest radiograph showed a normal cardiac silhouette, no mediastinal lymphadenopathy, and bilateral interstitial markings (Fig 1). A previous radiograph obtained 9 months earlier was clear. The patient was treated initially with hydration followed by the addition of low-dose furosemide. Her confusion and abdominal symptoms rapidly improved as her calcium levels declined. Pulmonary function tests showed normal spirometry (FEV₁, 2.40 L, and 85% of predicted; and FVC, 3.13 L, and 90% of predicted; FEV₁/FVC, 0.77, and 95% of predicted); lung volumes were at the lower limit of normal (total lung capacity, 4.18; 80% of predicted); and diffusing capacity was moderately decreased (15.70 mL/min/mm Hg; 48% of predicted).

**What is the likely diagnosis?**

**How can the diagnosis be confirmed?**

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Figure 1. Chest radiograph at hospital admission.
**Diagnosis: Toxicity of IFA therapy: sarcoid reaction presenting as hypercalcemia**

The first report of sarcoidosis associated with IFA treatment, for renal cell carcinoma, was published in 1987. The first case of sarcoidosis in a patient with hepatitis C treated with IFA was reported in 1994. To date, >30 cases of patients with sarcoidosis during IFA for active chronic hepatitis C have been reported.

IFA is used for its antiviral and antiproliferative effects in patients with hepatitis C. It is an immunomodulator that regulates the differentiation of helper T cells by inhibiting T-helper type 2 activation, inducing the production of interferon-γ (IFG), up-regulating interleukin-12 receptor expression and production, and inhibiting interleukin-4 signaling. Although the pathogenic mechanism of sarcoidosis remains unknown, it is generally characterized by exaggerated T-helper type 1 (Th1) immune responses, with accumulation of CD4+ Th1 lymphocytes and mononuclear phagocytes in affected organs. This inflammatory process culminates with formation of the hallmark noncaseating granuloma. Thus, the administration of exogenous IFA most likely skews CD4 T cells toward a Th1 immune response, resulting in clinical disease in susceptible individuals.

Other factors may play a role in the development of sarcoid reactions in this patient population. The part played by ribavirin in the induction of sarcoidosis is unknown, and no case of sarcoidosis associated with ribavirin monotherapy has been reported. Ribavirin, however, selectively inhibits T-helper type 2 cytokine production while preserving Th1 responses, and therefore might facilitate the induction of sarcoidosis in these patients. Additionally, the hepatitis C virus itself may be a cofactor in the pathogenesis of sarcoidosis in patients receiving IFA therapy. Hepatitis C virus activates a Th1 immune response, and two cases of sarcoidosis diagnosed in untreated patients with hepatitis C have been reported. It is intriguing as well that HIV infection is associated with sarcoidosis during CD4 immune reconstitution in patients receiving highly active antiretroviral therapy. The common theme is that restoring the Th1 IFG response in the context of a chronic viral infection and ongoing antigenic stimulation predisposes to sarcoidal reactions.

Another interesting feature of this case is that sarcoidosis initially presented as symptomatic hypercalcemia. It is generally considered that hypercalcemia occurs in approximately 10% of patients with sarcoidosis. Hypercalcuria is more frequent and has been found in up to 40% of patients with sarcoidosis. Hypercalcemia associated with sarcoidosis, as well as with mycobacterial infections and other granulomatous disorders, is caused by overproduction of 1,25-dihydroxyvitamin D₃ (1,25(OH₂)D₃) by activated macrophages.

1,25(OH₂)D₃ is the most potent vitamin D metabolite. It results from the conversion of 25-hydroxyvitamin D₃ (25(OH)D₃) to 1,25(OH₂)D₃ by an enzyme belonging to the P₄₅₀ complex: 25-hydroxyvitamin D₃ 1α-hydroxylase (1α-hydroxylase). Under physiologic conditions, 1,25(OH₂)D₃ is secreted almost exclusively by the proximal tubule in the kidney, and its production is tightly regulated by parathyroid hormone (PTH), calcitonin, phosphorus, calcium, and 1,25(OH₂)D₃ itself. Endogenous vitamin D production can increase after sunlight exposure due to vitamin D generation in the skin.

In sarcoidosis, abnormal calcium metabolism results from activated 1α-hydroxylase activity in activated macrophages. The enzymes present in the kidney proximal tubule and in macrophages have similar substrate specificities and kinetic profiles, they share the same structure, and both result from the expression of the same gene. The difference is in the metabolic control of 1α-hydroxylase activity in the macrophage, which increases in a dose-dependent manner under stimulation by IFG. In contrast, macrophage 1α-hydroxylase is relatively insensitive to stimulation by calcium or PTH. As a result, the production of 1,25(OH₂)D₃ depends mainly on IFG stimulation and substrate availability. Thus, the ability of IFA to promote a high IFG environment, which in turn drives 1,25(OH₂)D₃ production in macrophages, is likely responsible for the sarcoid-related hypercalcemia in this patient.

In the present patient, symptomatic hypercalcemia and interstitial pulmonary infiltrates were the presenting signs. After the hypercalcemia was corrected with fluid replacement, pulmonary measures were obtained that showed a reduced diffusing capacity, and bronchoscopy was subsequently performed. BAL revealed a lymphocytic alveolitis with 73% alveolar macrophages, 26% lymphocytes, and 1% granulocytes. The CD4:CD8 T-cell ratio was normal at 2.1:1. The tracheobronchial tree had a submucosal nodular appearance consistent with sarcoid “cobblestoning.” Transbronchial (and endobronchial) biopsies demonstrated scattered necrotizing granulomas with multinucleated giant cells (Fig 2). Culture findings were negative for mycobacteria and histoplasma. These findings confirm the diagnosis of sarcoidosis. Other supportive laboratory tests included an angiotensin-converting enzyme level that was elevated at 104 U/L (upper limit of normal, 56 U/L), as was 1,25-di-hydroxy-vitamin D level, at 91 pg/mL. PTH was low at 3 pg/mL.

IFA and ribavirin were discontinued, and the
The patient was started on oral corticosteroids (prednisone 40 mg/d), which were rapidly tapered. Hydroxychloroquine (200 mg/d po) was also added to the regimen as adjunctive therapy for sarcoid-related hypercalcemia. The patient did very well and was asymptomatic within a week of therapy. She had complete clearing of the interstitial infiltrates on her chest radiograph. IFA therapy was not restarted, and both the prednisone and hydroxychloroquine were stopped after 5 months with no signs of relapse at 1 year.

**Clinical Pearls**

1. *IFA immunotherapy skews the immune system toward a Th1 response and can cause Th1-mediated toxicities.*
2. *Sarcoidosis is a common Th1-mediated complication of IFA treatment, particularly in the context of chronic hepatitis C infection.*
3. *IFA immunotherapy stimulates IFG, which drives excess production of 1,25(OH2)D3 by macrophages, and can precipitate clinically important hypercalcemia.*

**Suggested Readings**