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A 47-Year-Old Female with Shortness of Breath

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This patient is a 47-year-old female with a history of end-stage liver disease secondary to hepatitis C virus (HCV) complicated by hepatic encephalopathy, obstructive sleep apnea, asthma, and severe peripheral neuropathy who presents to the hospital with complaints of shortness of breath and cough. The patient was recently discharged from an outside hospital 2 days prior to this admission where she was treated for pneumonia and an asthma exacerbation but her symptoms have not improved. She complains of shortness of breath at rest and severely decreased exercise tolerance with dyspnea while walking across the room. Her cough is persistent and non-productive. Review of systems is also positive for fevers at the outside hospital and worsening peripheral neuropathy which has not responded to treatment with gabapentin. Social history is positive for 20 pack-year smoking history (quit 10 years ago), and heavy alcohol use in the past.

On presentation to the hospital the patient was dyspneic and in moderate respiratory distress. She was afebrile and hypoxic to 91% on 2 liters of oxygen via nasal cannula. She had coarse breath sounds and wheezing throughout her lung fields, significant abdominal distension, and 2 + lower extremity pitting edema bilaterally. Initial chest x-ray revealed bilateral patchy airspace opacities and low lung volumes. Admission labs were within normal limits.

Hospital Course

The initial differential diagnosis included influenza, pneumonia, congestive heart failure exacerbation, interstitial lung disease,

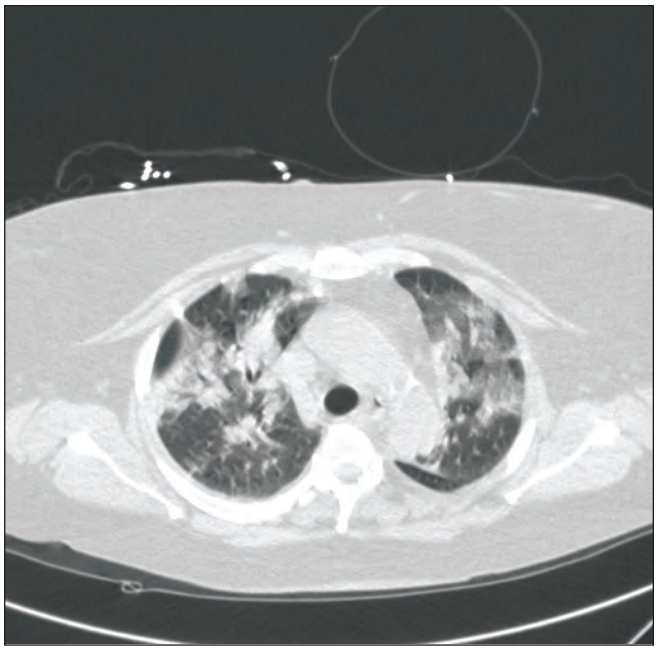

Figure 1. *CT scan showing bilateral infiltrative disease*

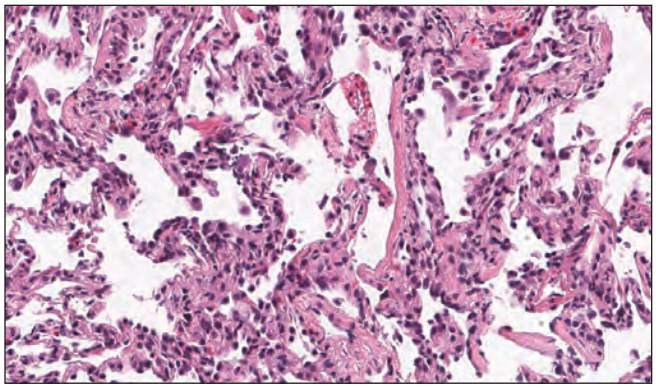

Figure 2. *Lung tissue from transbronchial biopsy showing interstitial pneumonitits*

COPD or asthma exacerbation, and hepatopulmonary syndrome. On admission, the patient was empirically treated for health care acquired pneumonia with broad spectrum antibiotics as well as steroids and nebulizer treatments for asthma/COPD exacerbation. Echocardiogram showed normal left and right ventricular function without significant valve abnormalities or intrapulmonary shunting. Shortly after admission the patient's oxygen needs increased and she became lethargic requiring transfer to the intensive care unit and initiation of high flow nasal cannula to maintain her oxygen saturation. On hospital day # 3 the patient's respiratory PCR came back positive for H1N1; however, a chest CT obtained on hospital day #4 revealed airspace disease worse than expected from influenza alone (**Figure 1**), and she underwent bronchoscopy with transbronchial biopsies on hospital day #5; pathology reports revealed interstitial pneumonitis (**Figure 2**). Subsequent lab work, including 9% cryocit and decreased complement levels, supported the diagnosis of cryoglobulinemia with pulmonary involvement. Patient underwent treatment with plasmapheresis and high dose steroids with temporary improvement. However, she subsequently required intubation for worsening respiratory distress. Since the patient's underlying HCV had been refractory to treatment in the past, the decision was made to withdraw care at this point.

Discussion

Cryoglobulins are single or mixed immunoglobulins that undergo reversible precipitation at low temperatures (<37°).[5] Cryoglobulinemia is the presence of these immunoglobulins in the serum which results in a clinical syndrome characterized by systemic inflammation. Cryoglobulins are divided into 3 types via the Broucet classification system. Type 1 consists of single monoclonal gammaglobulins and is most commonly found in patients with lymphoproliferative disorders such as

multiple myeloma and Waldenstrom's macroglobulinemia. Types 2 and 3 (the mixed cryoglobulinemias) consist of polyclonal IgG in complexes with either monoclonal IgM RF or polyclonal IgM RF, respectively.[1] Mixed cryoglobulinemia presents as systemic leukocytic vasculitis of small and medium sized vessels with multi-organ involvement.[6] Mixed cryoglobulinemias are often associated with underlying infectious diseases, autoimmune and inflammatory disorders, and malignancy. The most commonly associated disease is HCV with almost 90% of patients with mixed cryoglobulinemia being infected.[2] Other associated diseases include hepatitis B virus (HBV), lupus, rheumatoid arthritis, and Sjogren's syndrome.[1]

Cryoglobulinemia is diagnosed by a combination of laboratory, pathologic, and clinical findings. Major laboratory criteria include a cryocit (percent of precipitating cryoglobulins in the serum) >2% and low C4. Minor criteria include the presence of rheumatoid factor, HCV and HBV. The major pathologic criterion is a finding of leukocytoclastic vasculitis and the minor criterion is the presence of clonal b-cell infiltrates under light microscopy. Clinical findings include purpura, chronic hepatitis, and signs of systemic vasculitis.[5]

HCV results in cryoglobulinemic vasculitis through the polyclonal activation of B cells resulting in the production of autoantibodies including rheumatoid factor and cryoprecipitable immune complexes. These complexes are then deposited on endothelial surfaces of the affected vessels leading to systemic vasculitis.[2] Low levels of circulating cryoglobulins are found in approximately 50% of patients with HCV but only a small number of patients actually develop symptoms. Risks for the development of cryoglobulinemia in the setting of HCV infection include age, cirrhosis, and the absence of immunosuppression.[7]

The syndrome of mixed cryoglobulinemia is characterized clinically by purpura, weakness, and arthralgias; and by a series of pathological conditions representing end organ damage by the precipitating cryoglobulins. These include membranoproliferative glomerulonephritis, alveolitis, peripheral neuropathy, skin ulcers, Raynaud's phenomenon, and less frequently, lymphatic and hepatic malignancies.[6]

Respiratory symptoms of cough, dyspnea, and pleuritic pain are reported in 40-50% of patients with cryoglobulinemia. The findings of pulmonary vasculitis and interstitial infiltrates, as seen in our patient, have only been demonstrated in case reports. Three cases of patients with chronic HCV published in CHEST in October, 2001 are summarized here. The first is a 45-year-old female who presented with shortness of breath leading to respiratory failure and mechanical ventilation. Her bronchoscopy demonstrated alveolar hemorrhage and pathology showed diffuse interstitial infiltrates composed of lymphocytes. She improved with plasmapheresis. The second patient is a 42 -year-old female who presented with progressive weakness and sensory loss of her upper and lower extremities consistent with peripheral neuropathy. She subsequently developed respiratory failure requiring mechanical ventilation. Pathology from her bronchoscopy also demonstrated lymphocytic alveolitis with diffuse alveolar damage. She improved with plasmapheresis. The third patient is a 54-year-old male who presented with cough and dyspnea. Pathology demonstrated diffuse pneumonitis with prominent interstitial lymphocytes. He improved with supportive care. All three patients had bilateral patchy ground glass opacities on chest CT and an elevated cryocit as were seen in our patient.[2]

The mainstay of treatment for the cryoglobulinemic syndrome in most patients is to address the underlying HCV, usually with interferon and an antiviral such as ribavirin. Other treatments include immunosuppression with steroids or oral cyclophosphamide, as well as plasma exchange to remove the circulating cryoglobulins.[5] Evidence shows that cryoglobulinemia should be treated with antivirals even if no other indication for treating HCV exists.[6] One study looking at the effectiveness of treating mixed cryoglobulinemia with interferon reported a response rate of approximately 70% which correlates with normalization of ALT and decreased RNA HCV titers. However, sustained response, defined as maintaining undetectable cryoglobulin levels at 6 months, only occurred in 14% of patients. Good response to interferon is associated with male sex, lower viral load, and favorable genotype. Lack of sustained response, especially with severe end organ manifestations of cryoglobulinemia, may ultimately be secondary to a higher HCV viral load.[4] It is important to note that even if a patient is having improvement in their laboratory values there may not be any appreciable symptomatic improvement. One hypothesis for this is that the virus forms complexes with the cryoglobulins. So even when treatment seems to be leading to decreased ALT and circulating HCV RNA there is still a large amount of virus contained in the cryoglobulin complexes.[6]

Conclusion

Pulmonary involvement secondary to cryoglobulinemia is rarely on the differential of a patient presenting with cough and respiratory distress. However, the increasing prevalence of HCV makes the recognition of mixed cryoglobulinemia and its sequelae more important. A better understanding of the pulmonary manifestations of cryoglobulinemia, such as were seen in our patient, may lead to earlier identification and treatment of patients with this disease.

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