Postinfectious Interstitial Pneumonia After COVID-19 Infection

To the Editor

A 62-year old man with diabetes mellitus was hospitalized with 10 days of chest pain, malaise, myalgia, cough, and dyspnea. A nasopharyngeal polymerase chain reaction confirmed COVID-19 and a chest CT scan showed bilateral ground-glass opacities. The patient required 10 L of oxygen by nonrebreather oxygen mask and was treated with ceftriaxone, enoxaparin, ivermectin, and tocilizumab. Forty-eight hours after admission, his respiratory condition deteriorated, requiring prone positioning, methylprednisolone 500 mg IV once and high flow oxygen (FiO₂ = 100%).

Seventy-two hours after admission, his respiratory condition was unchanged, but his radiological appearance deteriorated. His lymphocyte count was decreased and lactate dehydrogenase, ferritin, and d-dimer worsened. A new dose of tocilizumab and IV methylprednisolone 500 mg for 3 days were administered. Because no evidence of over imposed infection was found, antibiotics were discontinued, and the patient was left on oxygen supplementation and enoxaparin, but the FiO₂ could not be decreased below 50% thereafter.

Fourteen days after admission, the patient had increased oxygen requirements. His markers of inflammation had normalized. Repeated chest imaging showed progressive radiographic deterioration with extensive interstitial infiltrates (Fig. 1). Nineteen days after admission, the radiological infiltrates deteriorated further. Repeated polymerase chain reaction for COVID-19 and for viral respiratory pathogens was negative. Sputum culture, AFB in sputum ×3, and serum galactomannan were all negative. Rheumatoid factor, antinuclear antibodies, antineutrophil cytoplasmic antibodies, antithrombocytopenic lupus anticoagulant, anti-Smith, anti-Ro/SSA, anti-La/SSB, and anti-Scl-70 were nonreactive. Postinfective interstitial pneumonitis was diagnosed by physicians' consensus based on clinical and radiological manifestations and elimination of other causes. The patient received IV methylprednisolone 1 g daily for 3 days followed by 80 mg daily for 7 days. No additional antibiotics were given.

Twenty-five days after admission, the patient's condition improved markedly. A chest CT scan revealed resolution of the inflammatory component and the patient was discharged home with 1 L/min of oxygen.

COVID-19 infection evolves from a febrile illness with minimal constitutional symptoms into adult respiratory distress syndrome with a hyperinflammatory host response (stage III). Our patient evolved thru those stages, including a moderate phase III, but 24 days after disease onset, he experienced deterioration in the absence of a prominent inflammatory response. We ruled out persistent coronavirus infection, viral coinfection, bacterial or fungal superinfection and collagenopathies. Self-induced lung injury, caused by high transpulmonary pressures due to vigorous inspiratory effort was also rejected because deterioration occurred very late and the patient improved without need for mechanical ventilation.

We believe our patient developed a nonspecific interstitial pneumonia (NSIP) associated with organizing pneumonia (OP). Although we lack proof of histological evidence, current

FIGURE 1. A, Peripheral and central bilateral ground-glass opacities without consolidation on day 1 of hospitalization (day 10 of illness). B, Bilateral ground-glass opacities with extensive areas of consolidation suggestive of air space inflammation (black arrow), smooth thickening of interlobular septum forming “arches” or “rings” and traction bronchiectasis. Additionally there is craving paving pattern (white arrow). High dose steroids are started on day 16 of hospitalization (day 26 of illness). C, Marked improvement of alveolar inflammatory compromise, with persistent septal thickening and some areas of ground-glass opacification on day 24 of hospitalization (day 34 of illness and day of home discharge). D, Control tomography 30 days after discharge.
guidelines accept radiological parameters and multidisciplinary consensus as sufficient for a diagnosis of interstitial lung disease.\(^3\) Our case had evidence of diffuse homogenous ground glass opacities with occasional subpleural compromise (as seen in NSIP) along with subpleural and peribronchial consolidation (typical of OP). In both entities, severe fibrosing presentations have been described, however most cases have excellent response to steroids. This allows to differentiate it from acute interstitial pneumonia, which courses with diffuse alveolar compromise and has high mortality despite steroidal treatment.

The overlap syndrome NSIP/organized pneumonia (OP) has been described previously. Huo et al\(^4\) found up to 79% of OP findings in his NSIP series. The prognosis depends on the degree of associated fibrosis. We postulate the favorable response of our patient was because of the lack of a fibrotic component.

Postinfectious organizing pneumonia has been described following viral infections, particularly influenza.\(^5\) It remains an elusive diagnosis because of the lack of specific clinical manifestations. A report from China has described 106 cases of organizing pneumonia among COVID-19 patients, but the timing of the radiological findings in relation with the onset of disease argues against OP as a different entity from the primary infection.\(^6\)

Patients affected by SARS in earlier 2000s developed diffuse alveolar damage (DAD) manifested clinically as adult respiratory distress syndrome.\(^7\) Secretion of transforming growth factor-\(\beta\) (regulated by renin–angiotensin II system) was the key factor in the development of subsequent interstitial lung disease in those patients.\(^8\) Another group of patients however developed eventual evidence of interstitial lung disease, despite initial clinical recovery and hospital discharge,\(^9\) suggesting other mechanism of lung injury such as upregulation of the monocyte chemoattractant protein-1 (MCP-1), a chemokine downregulated by the use of steroids.

Similarly, during the COVID-19 pandemic, cases of interstitial lung disease occur in relation with DAD associated with microthrombosis, however other proinflammatory pathways may be potentially involved into the development of subsequent interstitial lung disease.\(^10\)

Clinical suspicion for NSIP/OP overlap syndrome should arise in patients with COVID-19 who deteriorate several weeks after presentation, with newly developing opacities and in whom no other etiology is recognized. High dose steroid therapy will be highly beneficial in those cases.

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