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Granulomatosis With Polyangiitis Associated With Hemophagocytic Lymphohistiocytosis

A Rarely Reported Complication

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CASE PRESENTATION

A 71-year-old woman presented with a 6-month history of lethargy, low-grade fever, night sweats, and weight loss, as well as persistent nasal stuffiness and watery discharge. On physical examination, she was ill-appearing with a saddle-nose deformity. Laboratory tests revealed anemia (hemoglobin, 8.3 g/dL), an elevated erythrocyte sedimentation rate (94 mm/h), and an elevated C-reactive protein level (26 mg/dL). The clinical and laboratory findings were suggestive of chronic infection, malignancy, or an autoimmune disorder. Computed tomography (CT) scan of the head revealed extensive paranasal sinus mucosal thickening and amorphous soft tissue density in the sinuses (Fig. 1A). CT scan of the chest revealed bilateral pulmonary nodules (Fig. 1B). A comprehensive infectious disease evaluation was negative. Serologic studies revealed a c-ANCA titer of 1:80 (reference, <1:20) and proteinase-3 antibody titer of 13.2 Al (reference, <1.0 AI). A nasal biopsy revealed diffusely ulcerated sinonasal mucosa and chronic inflammation with foci of foamy histiocytes and multinucleated giant cells (Figs. 2A–B) without evidence of angiitis. A lung biopsy (Fig. 2C) revealed scant parenchyma with mixed acute and chronic inflammation, microabscess formation, and focal necrosis.

The constellation of clinical findings (lethargy, fever, weight loss, and saddle-nose deformity), laboratory findings (elevated erythrocyte sedimentation rate and C-reactive protein level, elevated c-ANCA and anti-proteinase-3 antibody titers), radiologic findings, and biopsy results were consistent with a diagnosis of granulomatosis with polyangiitis (GPA) with systemic involvement.[1,2] The patient was started on an induction regimen of intravenous methylprednisolone (1000 mg daily for 3 days) and rituximab (375 mg/m^2 weekly for 4 weeks). This was followed by 50 mg oral prednisone twice daily with atovaquone prophylaxis.

Following the first dose of rituximab, the patient began spiking fevers and became pancytopenic. The rituximab was discontinued and the patient was started on broad-spectrum antibiotics for a possible hospital-acquired infection; however, an infectious disease evaluation was negative. A secondary hemophagocytic lymphohistiocytic syndrome (sHLH), also referred to as macrophage activation syndrome (MAS) in the setting of rheumatologic disease, was considered. In addition to fever and pancytopenia, the serum ferritin was significantly elevated (7865 µg/L), and triglycerides were mildly elevated (163 mg/dL). Repeat imaging revealed splenomegaly. A bone marrow aspirate revealed frequent hemophagocytic histiocytes (Fig. 3A–C). Based on the HLH-2004 diagnostic guidelines,[3] a diagnosis sHLH-MAS was established.

The occurrence of sHLH-MAS in patients with GPA has been rarely reported.[4] The patient was treated with intravenous methylprednisolone (1000 mg daily for 5 days) while continuing oral prednisone and rituximab induction therapy for her underlying GPA, and showed gradual improvement.

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ISSN: 1076-1608
DOI: 10.1097/RHU.0000000000001432

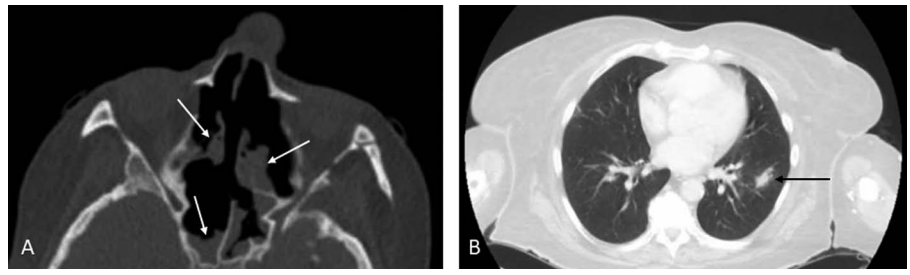

FIGURE 1. A, Computed tomography scan of head demonstrating extensive paranasal sinus mucosal thickening and amorphous soft tissue density (arrows). B, Computed tomography scan of chest showing a prominent nodule in the left lung (arrow).

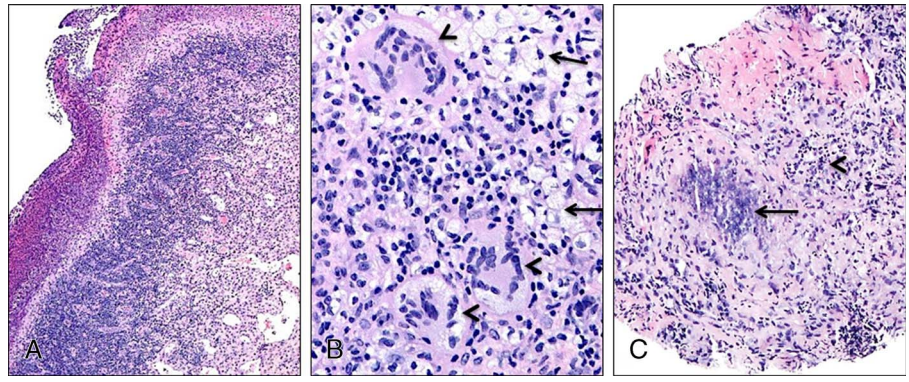

FIGURE 2. A, Nasal biopsy showing diffusely ulcerated sinonasal mucosa with underlying chronic inflammation (hematoxylin and eosin, ×200). B, Foci of foamy histiocytes (arrows) and loose foci of multinucleated giant cells (arrowheads) (hematoxylin and eosin, ×400). C, Lung tissue with focal necrosis (arrow) and lymphohistiocytic inflammation (arrowhead) (hematoxylin and eosin, ×100).

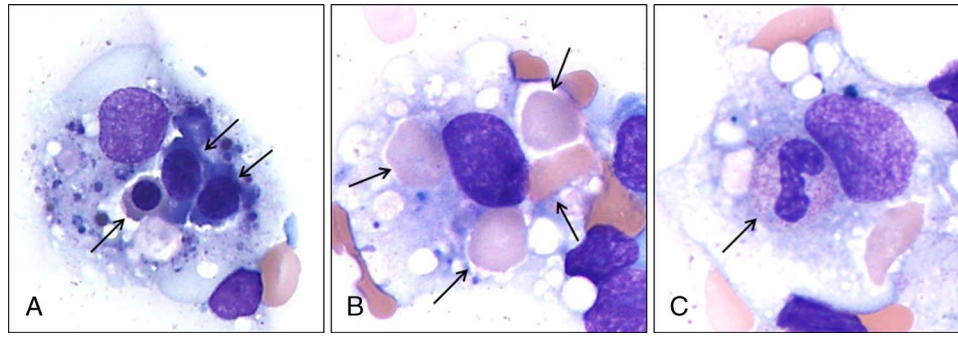

FIGURE 3. A–C, Hemophagocytic histiocytes with intracytoplasmic erythroid precursors (A, arrows), red blood cells (B, arrows), and neutrophil (C, arrow) (Wright stain, ×1000).