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It Took a Village: Good's Syndrome

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PRESENTATION

A complex medical history became even more tangled when a 52-year-old man presented with a 4-week history of dry cough, dyspnea, weight loss, chills, subcutaneous nodules on his extremities, and fatigue. He had no fever. Initially, his primary care physician examined him and prescribed a course of clindamycin. Although the patient completed therapy, the nodules continued to progress, and they began to drain purulent material.

He had been diagnosed with myasthenia gravis 7 years prior to this episode, and he was maintained on prednisone 20 mg daily and pyridostigmine. An associated thymoma had metastasized to his lung, and he had been treated with chemotherapy and radiation 2 years before this presentation. The course of his illness was further complicated by thymoma-associated pure red cell aplasia, which was successfully managed with cyclosporine.

ASSESSMENT

On admission, the patient had a temperature of 98.4°F (36.9°C), blood pressure of 115/71 mm Hg, a heart rate of 82 beats per minute, a respiratory rate of 12 breaths per minute, and oxygen saturation of 97% on 2 liters of oxygen. He appeared chronically ill, but he was able to speak in full sentences. Breath sounds were decreased at the left lung base, and his extremities bore golf-ball-sized nodules (**Figure 1**). There were several irregular ulcerations with purulent material in the left inguinal crease, along with sinus tract formation (**Figure 2**). The patient did not have fatigue on superior gaze, and cranial nerves II-XII were intact. While he was able to spontaneously move all 4 extremities, he declined a gait examination due to fatigue.

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Laboratory analysis was significant for leukocytosis (15.7×10^3 cells/μL with 89% neutrophils) and normocytic anemia (hemoglobin, 10.6 g/dL). Results from chemistry and hepatic function panels were significant for a low albumin of 2.2 g/dL. A chest radiograph revealed a new left-sided pleural effusion with adjacent consolidation (**Figure 3**). Computed tomography (CT) angiography of the thorax disclosed an increase in the size of the anterior mediastinal mass, along with new bilateral pulmonary nodules and a loculated pleural effusion. Empiric broad-spectrum antibiotic therapy was initiated with vancomycin, piperacillin and tazobactam, and azithromycin. Cyclosporine was held.

DIAGNOSIS

Diagnostic and therapeutic thoracentesis demonstrated gram-positive cocci in chains. Broad-spectrum antibiotics were continued, pending further identification and a sensitivity profile of the organism. A dermatology consult

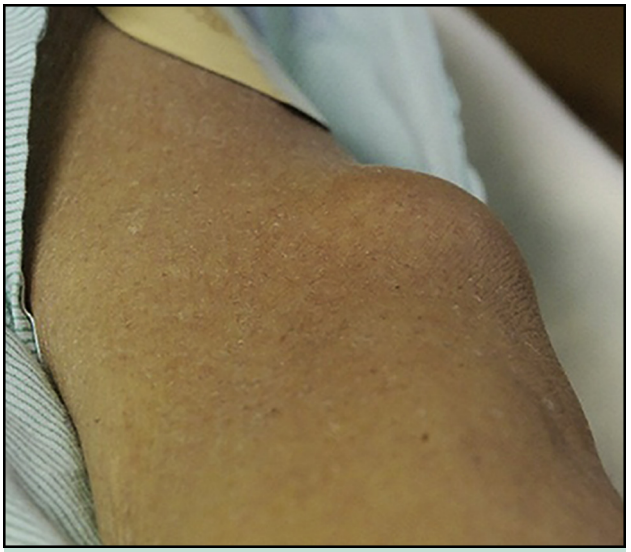

Figure 1 The patient presented with golf-ball-sized nodules on his extremities.

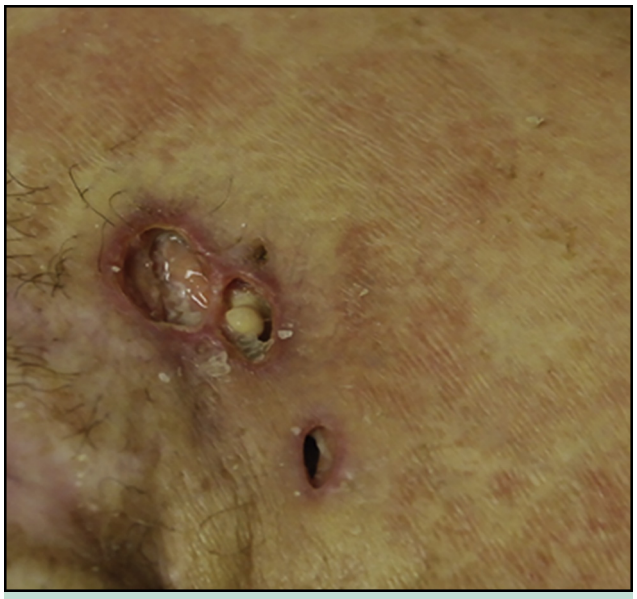

Figure 2 Several irregular ulcerations with purulent material and sinus tract formation were noted in the left inguinal crease.

included a biopsy of a subcutaneous nodule on the right lower extremity. Tissue cultures of the nodule remained nondiagnostic. Infectious disease specialists recommended an additional workup, including fungal serologies and a QuantiFERON-TB Gold test; both were negative. General surgery was then consulted to obtain deep tissue cultures of a left upper extremity nodule.

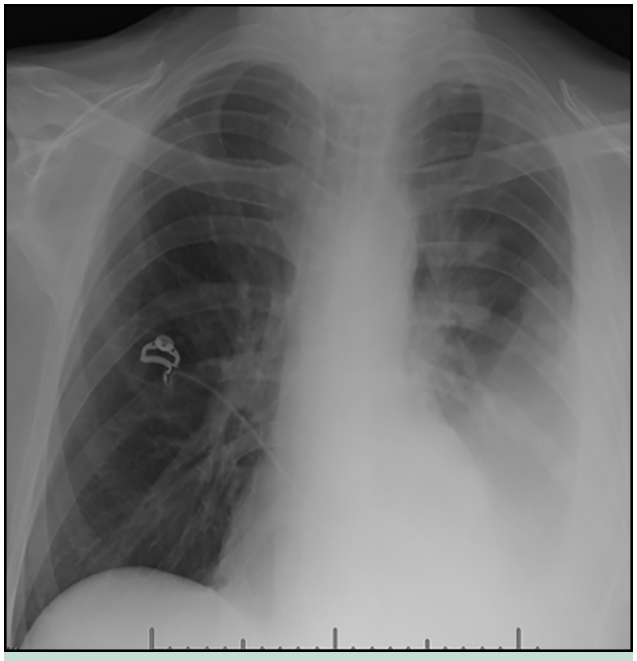

Figure 3 A chest radiograph revealed a new left-sided pleural effusion with adjacent consolidation.

The gram stain and culture from the deep specimens revealed gram-positive branching rods. This prompted a reevaluation of the initial pleural fluid analysis and previous dermatologic biopsy. Subsequently, a unifying diagnosis of disseminated *Nocardia farcinica* infection was made. CT of the brain and a lumbar puncture were pursued after the patient developed headache and delirium, yet the results of these procedures were unrevealing. Magnetic resonance imaging (MRI) of the brain showed 2 enhancing hyperintense lesions, measuring 0.3 cm and 1 cm, in the cerebellum (**Figure 4**). A neurosurgery consult resulted in a recommendation for medical management for disseminated nocardiosis.

Because thymoma can be associated with Good's Syndrome, the patient's immunoglobulin levels were checked. IgG was 297 mg/dL (normal limits, 620-1520 mg/dL) and IgM was 15 mg/dL (normal limits, 50-370 mg/dL). In the setting of a thymoma and opportunistic infection with hypogammaglobulinemia, the diagnosis of Good's syndrome, an immunodeficiency that occurs in some 6-11% of patients with a thymoma, was confirmed.[1,2] It is characterized by a variety of immune defects, including decreased immunoglobulin levels, decreased B cells, reversed T4:T8 ratio, and a reduced CD4+ T cell level. Recurrent sinopulmonary infections, cytomegalovirus infections, and chronic mucocutaneous candidiasis are typical infectious complications. Patients frequently have an autoimmune disease; pure red blood cell aplasia is most common, followed by myasthenia gravis.

Treatment of Good's Syndrome consists of immunoglobulin replacement, however, the mortality from infectious complications remains high. Good's syndrome portends a poorer prognosis when compared to X-linked agammaglobulinemia and common variable immune

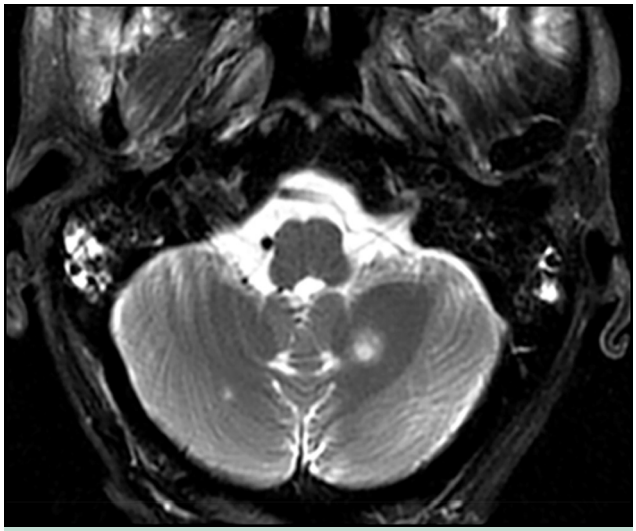

Figure 4 Magnetic resonance imaging of the brain demonstrated 2 enhancing hyperintense lesions, measuring 0.3 cm and 1 cm, in the cerebellum.

deficiency. It has a 10-year survival rate of 33% vs 95% in the other 2 diseases; likely due to an increased risk of opportunistic infections, underlying autoimmune disease, or hematologic complications.[1]

Nocardiosis is an uncommon infection that can be challenging to diagnose.[2,3] Immunocompromised patients, who account for roughly two-thirds of all cases, are at particular risk.[4] Primary pulmonary involvement occurs in 39%, and systemic infection, which typically originates in the lung, occurs in 32%. Less often, the primary central nervous system (9%), primary cutaneous locations (8%), or other single extra-pulmonary sites are involved. Any immunocompromised patient presenting with subcutaneous nodules merits dermatologic consultation for skin biopsies, histopathology, and deep tissue culture for bacterial, fungal, and mycobacterial organisms. As illustrated in our patient's case, a diagnosis of *Nocardia* infection may require surgical biopsy for confirmation.

MANAGEMENT

Trimethoprim-sulfamethoxazole is the classic drug of choice, but resistance has been reported. Imipenem was found to be 4-fold more active than meropenem and 16-fold more active than ertapenem in an in vitro activity study against 51 isolates of *Nocardia* species.[5] Typically, severe systemic infections are treated with 2-3 intravenous agents while awaiting susceptibility results (for example, trimethoprim-sulfamethoxazole and imipenem might be supplemented by amikacin or ceftriaxone). Linezolid has been reported as an effective alternative to trimethoprim-sulfamethoxazole in nocardiosis involving the central nervous system or disseminated disease.[6,7] However, serious adverse effects associated with long-term linezolid therapy, specifically, myelosuppression and peripheral neuropathy, combined with its high cost, limit the drug's usefulness. The optimal duration of therapy, which can range from 3-12 months or more, depends on the extent of infection and the immune status of the patient.

To target nocardiosis, we prescribed directed therapy with meropenem and high-dose intravenous trimethoprim/sulfamethoxazole. Our patient also received intravenous immunoglobulin. After 2 weeks of treatment, he underwent a repeat chest CT, which showed improvement in the pulmonary nodular opacities. However, brain MRI showed interval worsening of the bilateral cerebellar lesions and a new enhancing lesion. Meropenem was replaced with imipenem to improve penetration of the blood brain barrier. Linezolid was added while awaiting susceptibility reports. Ultimately, the *N.farcinica* isolate was found to be susceptible to fluoroquinolones, imipenem, trimethoprim-sulfamethoxazole, and linezolid.

Fluoroquinolones were not thought to be an optimal treatment for our patient, since they can trigger myasthenia gravis flares. Literature reviews indicated that *N.farcinica* infection with brain involvement could be successfully treated with linezolid, so imipenem was discontinued.[8] Instead, the patient received parenteral trimethoprim/sulfamethoxazole and linezolid for a total of 8 weeks. He was then transitioned to oral trimethoprim/sulfamethoxazole. Repeat brain MRI at 4 weeks and 8 weeks showed improvement. At 6 months of follow up, imaging showed complete resolution of cerebellar lesions and improvement in pulmonary nodules, and he was continued on oral trimethoprim/sulfamethoxazole. Treatment was to last for an additional 6 months, at which point, infectious disease specialists would reassess him.

Good's syndrome should be part of the differential diagnosis for patients who present with thymoma and opportunistic or recurrent infections. Immunoglobulin levels are easily measured, and deficiencies can be augmented with immunoglobulin therapy, improving the outlook for an otherwise potentially devastating diagnosis. Nocardiosis, though uncommon, is an important invasive pathogen to consider in immunocompromised patients. As illustrated here, a high degree of suspicion and clinical persistence may be required to accurately make the diagnosis. Tailoring antibiotics to culture data and monitoring the efficacy of treatment are mainstays in achieving a cure for the infection.

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