CLINICAL VIGNETTE

Bronchiectasis and Thymoma: Have You Got the Good's?

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Introduction

Bronchiectasis is a common lung disorder. It is characterized by dilated airways and excessive sputum production which come about through a vicious cycle of inflammation and remodeling. In patients with reversible causes of bronchiectasis, obtaining a diagnosis is pivotal as focused interventions may have a significant impact on outcome. While rare, the diagnosis of hypogammaglobulinemia is one such disorder. Prior disease of the thymus is a clue suggesting this diagnosis and an excellent reminder of the impact of developmental immunology on adult disease.

Report of Case

A 55-year-old man with a history of stage IVa malignant thymoma with metastases to the pleura diagnosed ten years ago was referred to pulmonology for management of bronchiectasis of unclear etiology. His thymoma had metastasized to the pleura and was diagnosed by percutaneous pleural biopsy. His disease was complicated by very severe restrictive (FVC 28% predicted) and obstructive lung disease (FEV1 22% predicted, FEV1/FVC 61%) requiring home oxygen therapy.

He was well most of his adult life until diagnosed with thymoma. Mycobacterium tuberculosis grew from a bronchoalveolar lavage performed to evaluation extensive reticulonodular infiltrates seen on staging computed tomography (CT) of his chest. He completed 9 months of anti-tuberculous therapy with improvement in the infiltrates and resolution of his cough. He then received 4 months of a platinum doublet chemotherapy regimen followed by approximately 8 years of palliative pemetrexed with stability of his left pleural tumor burden. During those 8 years, despite his malignancy's relatively indolent course, he began to suffer from recurrent pneumonias as well as chronic productive cough.

Bronchiectasis was first diagnosed by high-resolution CT approximately 9 years prior to current presentation. Upon review of prior CT images, it was noted that while pleural disease had improved over the previous two years, his bronchiectasis had progressed (Figure 1). He had no associated sinus or joint disease, asthma, infertility, or family history of lung or liver disease. He was born in the Philippines but had not traveled since his thymoma was diagnosed.

Discussion

Good's Syndrome (GS), the combination of hypogammaglolubinemia and thymoma, was suspected in this middle-aged patient with cylindrical bronchiectasis and a past thymoma diagnosis. His immunoglobulin (Ig) levels including a low IgG level (505 mg/dL; normal 650 to 1600 mg/dl) and low IgM level (26 mg/dL; normal 50 to 300 mg/dl) prompted further diagnostic testing. Despite receiving the pneumococcal 23-valent polysaccharide vaccine only 11 months prior, there were protective titers for only 7 of 11 antigens indicating a poor immunologic response. Finally, as is often seen in Good's Syndrome, he had marked B cell lymphopenia (9/cumm; normal 90 to 728/cumm).

Good's Syndrome (GS) was named after Robert A. Good. In the 1950s, as the advent of gel electrophoresis enabled gammaglobulin quantification and macrolide antibiotics allowed patients to survive recurrent sinopulmonary infections, Dr. Good published the case of a man with acquired hypogammaglobulinemia resulting in 17 lobar pneumonias over a period of 4 years despite the excision of his thymoma and an "addiction to Terramycin".[1,2]

Today, GS is thought to complicate 7-11% of thymomas.[3] Like Common Variable Immunodeficiency (CVID) patients, GS patients have both hypogammaglobulinemia and deficits in specific immunoglobulin types. Unlike CVID, which is commonly diagnosed in young adults, GS patients are typically in their 50s or 60s.[4] It is associated with autoimmune manifestations such as anemia or pure red cell aplasia, and less frequently, leukopenia, thrombocytopenia, thyroiditis, and myasthenia gravis.[3]

The pathogenesis of GS is not well understood. It is hypothesized that cytokines from the bone marrow or the diseased thymus affect production of B cell precursors or that autoantibodies inhibit production of B-cells.[3] Both CVID and GS patients exhibit reduced levels of IgA and IgG, and less pronounced reductions in IgM production, that impair humoral immune function. Respiratory tract infections due to encapsulated bacteria are therefore a principal cause of morbidity in untreated patients.

While CVID patients may have fewer mature B cells, GS patients exhibit markedly reduced CD19 counts on flow cytometry as well as reduced cell mediated immunity with reduced CD4:CD8 ratios and cutaneous anergy.[3] They are

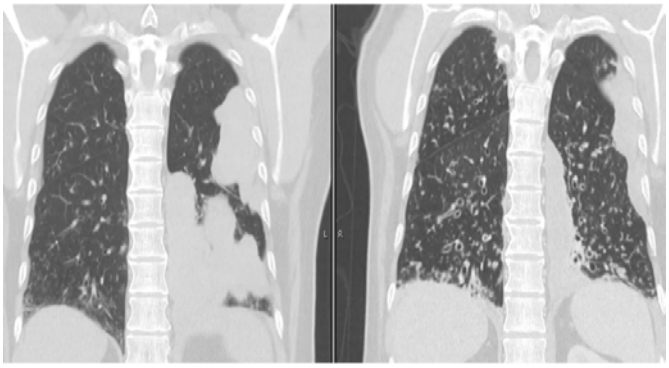
therefore uniquely susceptible to opportunistic infections including viruses such as cytomegalovirus (CMV) and Herpes simplex virus (HSV) as well as fungal infections such as mucocutaneous candidaisis and *Pneumocystis jiroveci*.[4] CMV in particular has been frequently reported. Although this patient was treated for Mycobacterium tuberculosis, it occurred and resolved prior to any signs of bronchiectasis and it is unclear whether hypogammaglobulinemia predisposed him to this infection.

It is recommended by some that serum immunoglobulin levels be measured in all patients with bronchiectasis of unclear etiology.[5] Bronchiectasis in the absence of immunodeficiency typically causes elevated levels of IgA and IgG due to increased immune activity in the bronchial mucosa, so confirmatory testing is needed for any reduction in Ig levels.[6] This confirmatory testing includes humoral responses to specific antibodies such as polysaccharide and protein based vaccination rather than routine IgG subclass measurement, as the clinical significance of isolated IgG subclass deficiency is unclear.[5]

The benefit of routine intravenous immunoglobulin (IVIG) replacement in GS patients has been reported in the form of case reports and case series.[4,7-9] In CVID populations where data includes the use of historical controls and prospective cohorts, IVIG replacement reduces the incidence of infections, including pneumonias, and prevent progression of pulmonary disease.[10] IVIG replacement is FDA approved for CVID.

The prognosis of GS may not be as dire as once believed. Mortality estimates in unmatched case series have been as high as 44-55%.[4,11] However, a unique recent prospective cohort study surveying the authors of 67 European case reports and a European immunology registry suggested a 5 year survival of 82% for GS patients compared with 95% survival for age matched 60 year olds.[11] Even considering this somewhat more sanguine data, the survival of our patient for over 10 years despite hypogammaglobulinemia, severe respiratory dysfunction and metastatic malignancy is notable.

Figure 1: CT of the chest showing diffuse, bilateral, cylindrical bronchiectasis in both upper and lower lobes. Pleural disease is noted to have improved since CT two years ago (left) while bronchiectasis has increased on most recent scan (right).



Conclusion

Good's syndrome is a rare cause of bronchiectasis. However, it represents a subcategory of bronchiectasis diagnoses in which focused interventions such as IVIG are available. For this reason, quantitative immunoglobulins should always be measured in patients with bronchiectasis, especially those with a past history of thymus disease.

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