CLINICAL VIGNETTE

A Case of Good's Syndrome

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A 78-year-old male with a history of hypertension, hyperlipidemia, IBS, GERD, and oropharyngeal dysphagia presented to the Allergy Immunology for evaluation of hypogammaglobulinemia. Five years prior, he developed a physical bulge in his chest. Following a core needle biopsy, he was diagnosed with a benign type B2 thymoma which was surgically removed. In the year following the thymoma resection, he developed recurrent sinus infections with prolonged episodes occurring three times per year and one bout of pneumonia, all of which required oral antibiotics. At the follow-up visit with his Hematology Oncology physician, he reported the recurrent infections, prompting a laboratory evaluation for immunodeficiency. He was advised that he had low serum immunoglobulin levels, started on intravenous immunoglobulin replacement (IVIG), and was referred to Allergy Immunology for further evaluation. At the time of his visit with Allergy Immunology, he was unsure if he needed to continue IVIG. He sought a second opinion to clarify whether the treatment was required and, if so, the recommended duration.

His past medical history was notable for a recent diagnosis of oral lichen planus and IBS with chronic diarrhea. He was a non-smoker and reported occasional alcohol use. The physical exam was significant for multiple oral lichen planus lesions of the buccal mucosa. A review of the patient's documents included labs consistent with pan hypogammaglobulinemia with low IgG 400mg/dL, low IgA <7mg/dL and low IgM <5 mg/dL. Buccal mucosal biopsy revealed *"Dense subepithelial lymphoid infiltrate with epithelial erosion, consistent with erosive oral lichen planus."* Chest X-ray imaging showed *"a large mass in the mediastinum projecting over the left hilum, with no evidence of a pleural effusion."* CT chest non-contrast imaging showed *"A 7.3 x 6.4 cm smoothly marginated anterior mediastinal mass present."* Core needle biopsy of the anterior mediastinal mass showed it was consistent with a retrosternal lesion, benign thymoma type B2. Surgical trans-sternal resection was recommended due to the size of the mass.

In summary, this patient has a benign Type B2 thymoma associated with adult-onset symptomatic hypogammaglobulinemia with recurrent sinus infections, pneumonia and autoimmune disease (oral lichen planus), which is concerning for Good's Syndrome (GS). We discussed the risk of serious bacterial sinopulmonary infections is generally higher when IgG is less than 400 mg/dL. However, additional laboratory evaluation would be necessary to evaluate for a combined immunodeficiency.

Good's syndrome is a rare adult-onset immunodeficiency disease characterized by thymoma, hypogammaglobulinemia, low or absent mature B lymphocytes (B cell lymphopenia), decreased T lymphocytes, inverted CD4+/CD8+ T cell ratio and reduced T-cell mitogen proliferation response associated with autoimmunity and myelodysplastic features. According to the WHO, thymomas are classified based on histology or rarely based on immunohistology, such as immature T cell counts. The thymoma subtypes include type A (including an atypical variant), type AB, type B (separated into B1, B2, and B3), micronodular thymoma with lymphoid stroma and metastatic thymoma. The thymoma is localized and benign in 90% of GS patients. GS develops in 3-6% of thymoma patients.[1,2]

While there are primary immunodeficiencies with defects in B cell differentiation and antibody production (hypogammaglobulinemia), such as Common Variable Immunodeficiency (CVID) and X-linked Agammaglobulinemia (XLA), GS is unique due to its identity as an adult-onset combined immunodeficiency with low or absent B cells.[3] The distinction of hypogammaglobulinemia in GS from hypogammaglobulinemia due to XLA and CVID is summarized in Table 1.

GS differs from CVID due to the age demographic of patients affected and the immune phenotype. While 90% of CVID patients have normal to moderately reduced peripheral B cell numbers with the added finding of low memory B cells, less than 5% of GS patients have normal peripheral B cell numbers. GS is found almost exclusively in adults over 40, while CVID also occurs in children.[2] Lastly, compared to CVID patients, those with GS have a higher frequency and severity of invasive encapsulated bacterial infections, opportunistic infections (viral, fungal infections), and autoimmune complications.[3]

GS is distinct from XLA due to the clinical phenotype of a combined immunodeficiency with defective T cells and B cells, a defect in B cell differentiation, and resultant B cell development arrest. Moreover, GS patients suffer from recurrent opportunistic infections (mucocutaneous candidiasis, *Pneumocystis Jirovecii* and reactivation of latent viruses such as CMV, HSV, and VZV), which is diagnostic of a T cell deficiency. In contrast, XLA patients have only a B cell deficiency and do not have opportunistic infections as part of their phenotype.[2,4] Additionally, while 100% of patients with XLA have absent peripheral B cells and 99% of GS patients have significantly reduced or absent peripheral B cells, the two immunodeficiencies differ in the stage at which B cell development is

arrested. In GS, B cell progenitors are arrested at the Pro-B cell stage, while XLA patients have B cell development arrest at the Pre- B cell stage due to a defect in B cell receptor signaling.[2]

Labs for our patient showed normal CD3 Tcell, CD4 Tcell, and CD8 Tcell counts with low naive CD4 Tcells, normal effector and memory CD4 Tcell lymphocyte counts. They further indicated profound CD19 Bcell absenteeism at zero, low NK cells, a low ALC, reduced mitogen lymphocyte proliferation, protective tetanus antibody levels, normal CH50 levels, low normal CD4: CD8 ratio, and low Strep pneumonia IgG titers (1 of 23 serotypes > 1.3 μg/mL). The panhypogammaglobulinemia, thoroughly compromised Tcell function, thymoma, recurrent infection history, and erosive oral lichen planus are all consistent with combined immunodeficiency and a diagnosis of GS.

Thymectomy is the first step in treating GS, as 90-95% of tumors are localized. Unfortunately, thymectomy does not reverse hypogammaglobulinemia. The patient was advised that a diagnosis of GS is associated with a high risk for severe invasive bacterial infections, opportunistic (viral, fungal) infections, and reactivation of latent viral infections. We recommended he continue immunoglobulin replacement indefinitely to reduce the risk of infections and hospitalization. In patients with severe lymphopenia, prophylaxis for candida and pneumocystis is advised. We discussed that the erosive oral lichen planus is likely a manifestation of GS as autoimmune diseases such as oral lichen planus can be seen in 48% of GS patients.[5] Given his recent diagnosis of IBS, he was referred to a Gastroenterologist as GS is also linked to chronic diarrhea in 50% of patients. In GS, diarrhea can be due to a pathogenic infection such as bacterial overgrowth, *C. difficile*, *Giardia lamblia*, or CMV. It can manifest as an autoimmune disease (autoimmune enteropathy, graft versus host-like colitis).[3] The patient was advised to follow up regularly as the infectious manifestations of GS determine the prognosis and are inextricably linked to the extent of Bcell and Tcell dysfunction. Additionally, in cases where the associated autoimmune diseases require treatment with immunosuppressive medications, this often exacerbates infectious complications.

This case demonstrates the varied presentation of immunodeficiencies. Clinicians should be aware of the signs and symptoms of immunodeficiency, which include recurrent infections (severe, unusual pathogen, opportunistic infections), autoimmunity (multi-system, onset before age 5, strong family history of autoimmunity), and immune dysregulation (lymphoproliferation, gastrointestinal diseases).[6] Clinicians should have a low threshold to consider GS and measure serum immunoglobulins in every patient with a history of thymoma and recurrent infections.

Table 1. Comparison of XLA, GS and CVID

	XLA	GS	CVID
Characterization	Absent/significant reduction in B- cells and ALL serum immunoglobulins	Acquired combined T and B cell immunodeficiency with thymoma, hypogammaglobulinemia, low/absent B cells, reduced T-cells, inverted CD4+/CD8+ Tcell- ratio, poor T cell mitogen proliferation, autoimmune features, and myelodysplastic manifestations	Recurrent sino-pulmonary infections, low/normal B cells, low IgG and IgA or IgM, inverted CD4+/CD8+ Tcell- ratio, decreased switched memory B cells (CD27+IgD−IgM−), poor response to polysaccharide vaccines
Prevalence	1 per 1,400,000	1 per 700,000	1 per 25,000 -1 per 50,000
Diagnostic Criteria			
Thymoma	-	**+** **40-60 years**	-
Hypogammaglobulinemia	+	**+** **Low IgG 100%** Low IgA 86% Low IgM 93%	+
Peripheral B Cells	**Absent 100%**	Absent 44% Significant reduction 50%	Normal/moderate 90%
Age			
Diagnosed in childhood Age at presentation	**100%** 6-9months old 0-2 years	<1% **40-60 years**	20% 20-40 years
Autoimmune complications	-	**>50%**	20-30%
Associated Conditions	-	**Anemia 50-85%** (Pure red cell aplasia, hemolytic, pernicious, aplastic, myelodysplastic syndrome) **Myasthenia gravis 30-45%** **Lichen planus** **Chronic diarrhea 50%**	**ITP** Autoimmune hemolytic anemia **Lymphadenopathy** **Splenomegaly** **Gastrointestinal involvement 9-20%** (Colitis, enteritis, gastritis, bacterial overgrowth, IBD)
Infections			
Invasive bacterial	+++	+++	+++
Opportunistic	-	++	+
Genes identified	BTK	-	**10% (TACI, CD40, CTLA, BAFF-R)**

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