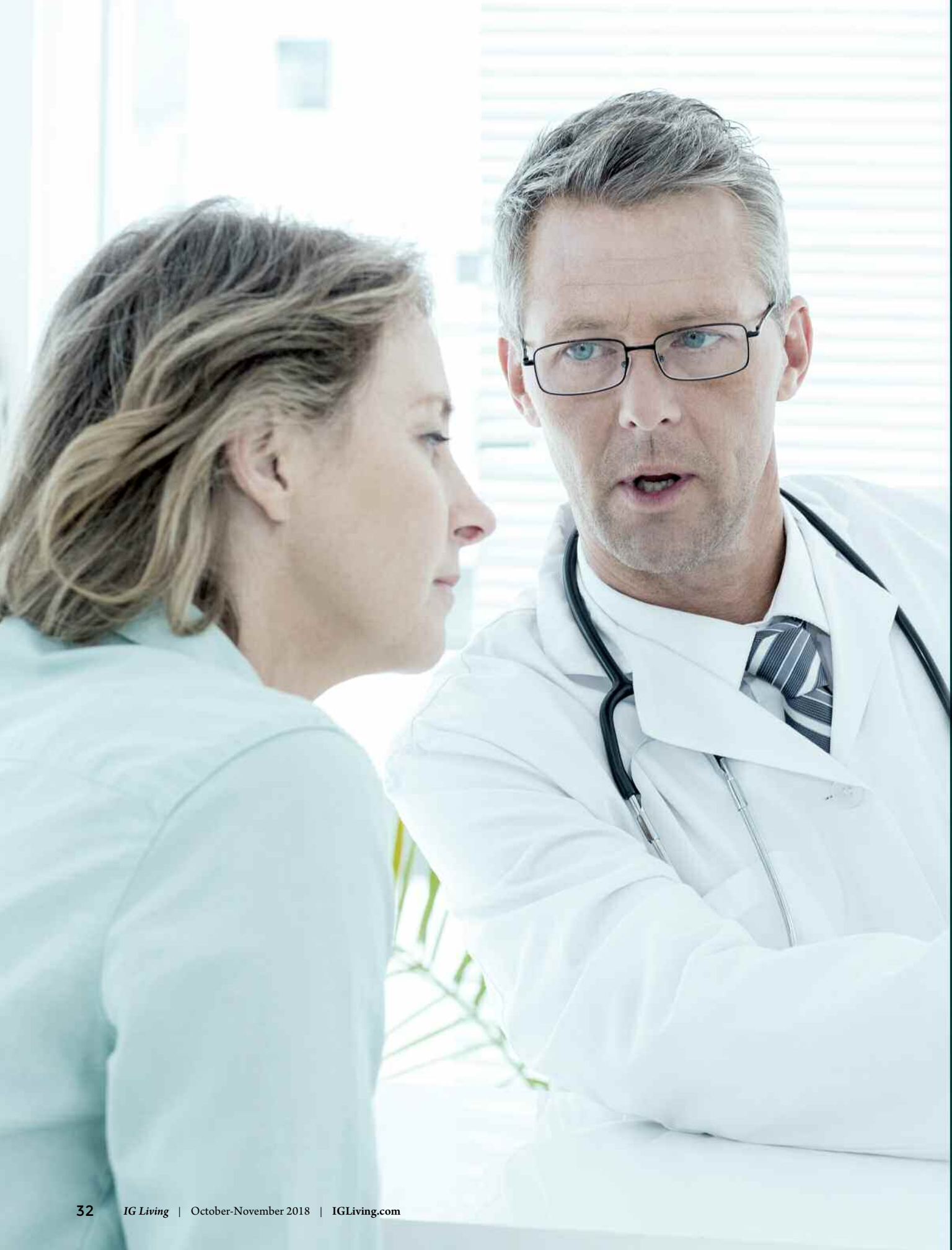

GOOD'S SYNDROME:

A RARE DISORDER ASSOCIATED WITH PI

Six decades after its discovery, this rare disease is still little understood, making diagnosis difficult and treatments less effective.

By Ronale Tucker Rhodes, MS

ALSO KNOWN AS immunodeficiency with thymoma, Good's syndrome (GS) is a rare, adult-onset primary immunodeficiency (PI) characterized by low immunoglobulins (hypogammaglobulinemia) and a benign thymic tumor (thymoma). Eosinophils (white blood cells) may also be very low or undetectable in these patients.[1]

The association between immunodeficiency and thymoma was first recognized by Robert Good, MD, in 1954. It is classified as a distinct entity by the expert committee of the World Health Organization/International Union of Immunological Societies on PIs.

Patients with GS may experience immunodeficiency prior to or after the diagnosis of a thymoma. And, while GS was noted in 7 percent of adults with PI attending a chest clinic, it is believed this figure is influenced by referral bias, with the actual incidence in PI patients more likely to be between 1 percent and 2 percent. Conversely, the incidence of hypogammaglobulinemia in patients with thymoma is between 6 percent and 11 percent. GS affects men and women equally, and while it can occur in children, it is extremely rare. Typically, GS is diagnosed in the fourth or fifth decade of life — much later than when most PIs are diagnosed.[2]

Symptoms of GS

While symptoms vary from person to person, the initial clinical features are varied (Table 1). The primary feature of GS is infection. Patients are susceptible to recurrent infections caused by bacterial, viral and fungal pathogens due to extensive hypogammaglobulinemia and lymphopenia (low levels of white blood cells). Most infections occur in the sinuses and respiratory tract, but infections can also occur on the skin and in the urinary tract. Diarrhea is also common. Sinopulmonary infections manifest with a cough, nasal discharge, fever and headaches, while diarrhea, abdominal pain, cramping and weight loss are typical signs of gastrointestinal infection. Other symptoms can include cytomegalovirus (CMV) retinitis (a sight-threatening disease), mucocutaneous candidiasis (yeast or candida infections), herpes simplex virus and human herpesvirus 8. In rare cases, central nervous system infection can occur.[3]

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The second main feature of GS is tumor of the thymus gland (thymoma), with up to 42 percent of patients having a confirmed diagnosis prior to the onset of infections. In addition, thymomas are associated with a number of autoimmune disorders. Up to 50 percent of patients present with signs and symptoms of myasthenia gravis. But, other patients present with pemphigus, Sjögren's syndrome, pure red cell aplasia and systemic lupus erythematosus. In up to 10 percent of patients, hypogammaglobulinemia may be severe even after successful removal of thymomas and is the main cause of mortality.[3]

Causes of GS

Since its discovery in 1954, little more has been found out about its pathogenesis. However, there are two possible pathogenic mechanisms for the association between antibody deficiency and thymoma. The first explanation is that "cytokines, possibly secreted by bone marrow stromal cells, may influence both thymic and B cell precursor growth and differentiation." A second explanation "comes from studies of paraneoplastic phenomena in thymoma, such as pure red cell aplasia, which show that T cells or autoantibodies can directly or indirectly inhibit erythropoiesis [production of red blood cells]. T cells isolated from patients with thymoma can inhibit immunoglobulin production by B cells and pre-B cell growth in healthy controls."[2]

Diagnosing GS

Diagnosing GS can be very difficult due to its various symptoms that can be present at different periods.

GS is usually first suspected when a thymic tumor is detected. Unfortunately, there are cases when a thymoma is not detected, resulting in misdiagnosis. Indeed, GS is often misdiagnosed as common variable immunodeficiency due to lack of awareness and recognition.[4] Because thymomas can be "a subtle feature on chest X-rays, and in one study, 25 percent of tumors were missed with a diagnostic delay of 41 months," it is recommended to perform a computed tomography (CT) scan of the chest if a thymoma is suspected. A CT scan can define the extent and stage of the thymoma, as well as whether bronchiectasis is present.[2]

In approximately half of the cases of patients with a thymoma, the history of recurrent infections precedes the detection of the thymoma.[1] As such, GS should be suspected in PI patients aged 40 years and older. Patients who present with thymoma should have serum immunoglobulin values and B and T cell subsets measured. Even if these are normal, the measurements should be repeated every second year since cases of progressive immunodeficiency have been found. If immunoglobulin values are found to be low, response to the tetanus, diphtheria, pneumococcus and haemophilus vaccines should be measured. Failure to mount an adequate antibody response to these vaccines indicates an immunodeficiency is present.[2]

Table 1. Symptoms of GS

Occurring in 80 percent to 90 percent of GS patients
- Decreased antibody level in blood
- Mediastinal lymphadenopathy
- Thymoma

Occurring in 30 percent to 79 percent of GS patients
- Bronchiectasis
- Cough
- Dysphagia (poor swallowing)
- Dysphonia (inability to produce voice sounds)
- Dyspnea
- Fatigable weakness
- Ptosis (drooping upper eyelid)
- Recurrent skin infections
- Recurrent urinary tract infections
- Sinusitis

Occurring in 5 percent to 29 percent of GS patients
- Anemia
- Aplasia/hypoplasia of the thymus (absent/small thymus)
- Diabetes mellitus
- Diarrhea
- Recurrent respiratory infections
- Thrombocytopenia (low platelet count)

Source: National Institutes of Health Genetic and Rare Diseases Information Center. Immunodeficiency with Thymoma. Accessed at rarediseases.info.nih.gov/diseases/8622/good-syndrome.

Treating GS

Treatment for GS includes resection of the thymoma and immune globulin (IG) therapy to prevent infections. Yet, while removal will not cure the immunodeficiency, it may help other symptoms.[1] If bronchiectasis is present, patients may need postural drainage, prophylactic antibiotics and, in some cases, more intensive IG treatment. Patients with stage 3 or 4 disease thymomas often require radiotherapy and combination chemotherapy.[2]

IG therapy is the only way to prevent infections caused by PI. In one review of the efficacy of IG treatment for GS, 23 of 30 patients had a reduction in the numbers of bacterial sinopulmonary infections.[2] Another study conducted just recently at a large tertiary referral hospital in Thailand investigated the clinical outcomes of GS patients after treatment with intravenous IG (IVIG) therapy from January 2005 through December 2015. Nine GS patients with a median age at diagnosis of 53 years presented with pneumonia and sepsis as the most common clinical manifestations. Six patients also presented with infectious organisms suggestive of cell-mediated immunity defects, including CMV, Mycobacterium tuberculosis, Mycobacterium

abscessus, herpes simplex virus, pneumocystis jirovecii and Aspergillus. Mean serum IgG level was 317 mg/dL, eight patients had very low to undetectable B cells, and all patients had either low CD4 number or impaired T-cell function, and one had both. All patients received monthly IVIG replacement therapy at a dose of 0.4 g/kg. The mean trough IgG level was 881 mg/dL. After treatment, seven patients had favorable clinical outcomes, but two died due to septicemia.[5]

Late-onset diagnosis of GS can be problematic. In a case report published this year, a 57-year-old man was admitted to the hospital with a history of thymectomy due to thymoma six years previously. He developed weight loss and recurrent persistent diarrhea caused by isospora belli (an intestinal infection). His chest CT scan revealed bilateral bronchiectasis, and his labs showed hypogammaglobulinemia. After a diagnosis of GS, he was treated with monthly IVIG, but he lost his vision on the left side due to CMV retinitis; he also developed nail candidiasis.[6]

Treating GS patients who also present with autoimmune disorders can be even more complicated. In one case report in 2017, a 65-year-old woman was admitted to the hospital with ptosis (drooping upper eyelids) and abdominal muscle weakness. Based on the presence of anti-acetylcholine receptor antibodies, she was diagnosed with myasthenia gravis (MG). At the same time, invasive thymoma of Masaoka stage IVa was detected. After being treated with chemotherapy followed by high-dose corticosteroids, the thymoma regressed and the MG went into remission. However, several months later, the woman developed repeated bacterial respiratory tract infections, CMV infections and esophageal and systemic candidiasis. Lab tests revealed a marked decrease in IgG levels and severe reduction in B cells, as well as a decrease in the CD4+CD5+T cell to CD4+CD5-T cell ratio indicative of deregulation of CD4-T cell activation, suggesting the patient had impaired humoral and cell-mediated immune responses. She was continued on antibiotics and given regular IVIG therapy.[7]

Clinical Outlook

GS is a rare association of thymoma and adult-onset immunodeficiency that is often difficult to diagnose and frequently presents with autoimmune disorders. Since it was first discovered, understanding of this syndrome has improved considerably. According to the most recent reports, the mean survival rate of patients with GS is 14 years, and overall mortality rates are between 45 percent and 57 percent.[3] Ultimately, for better awareness of this disease and its early diagnosis and treatment, more research is needed to uncover its cause. ■

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Organizations Supporting GS

Immune Deficiency Foundation
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www.primaryimmune.org

Jeffrey Modell Foundation (JMF)
www.info4pi.org

Canadian Immunodeficiencies Patient Organization (CIPO)
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International Patient Organization for Primary Immunodeficiencies (IPOPI)
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