ACG CASE REPORTS JOURNAL

CASE REPORT | SMALL BOWEL

Beware of the Patient with Thymectomy: Good's Syndrome in a Patient Presenting with Diarrhea

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Abstract

Good's syndrome is a rare cause of immunodeficiency in adults associated with thymoma. We describe an 80-year-old female with chronic diarrhea, multiple opportunistic infections, and cytopenias. She underwent a thymectomy 5 years ago for a thymoma. Laboratory tests revealed neutropenia, hypogammaglobulinaemia, complete B-cell lymphopenia, and low CD4 T cells with inverted CD4:CD8 ratio, which is consistent with Good's syndrome. We recommend checking immunoglobulin levels in all patients with a history of thymoma. Good's syndrome should be considered as a differential diagnosis if patients present with chronic diarrhea, cytopenias, or recurrent infections. Cytomegalovirus (CMV) infection should be considered in patients with immune deficiency as a cause of chronic diarrhea.

Introduction

Good's syndrome (GS) is a rare cause of immunodeficiency associated with thymoma. It was first described by Dr. Robert Good in 1954,[1] yet there still exists no formal set of diagnostic criteria. GS is most consistently characterized by low circulating B-lymphocytes and hypogammaglobulinaemia, among other immunological and hematological abnormalities. Gastrointestinal abnormalities, particularly unexplained diarrhea, are common. The incidence of hypogammaglobulinaemia in patients with thymoma is 6–11%.[2]

Case Report

An 80-year-old woman was admitted to hospital with watery, non-bloody diarrhea up to 6 times per day and fever (39.4°C). There was no history pointing to a focus of infection. Her examination was unremarkable. Five years earlier, the patient underwent a thoracotomy to remove a 12 x 9 x 10.8-cm type AB minimally invasive thymoma (WHO classification).[3] Prior to this admission, the patient had a 4-year history of watery diarrhea and 10 kg of weight loss. Colonoscopy 4 years ago showed indeterminate colitis, after which she was started on oral mesalazine. With the exception of one positive culture for *Campylobacter jejuni*, stool cultures were persistently negative for pathogens. She previously underwent 3 hospital admissions for worsening diarrhea, which responded well to short courses of intermediate dose prednisone (10–20 mg) and loperamide.

One month prior to admission, the patient underwent a flexible sigmoidoscopy to investigate worsening diarrhea. This showed left-sided colitis suggestive of ulcerative colitis. She was commenced on 50 mg daily of prednisone, which led to a significant improvement. Surprisingly, colonic biopsies revealed diffuse active chronic inflammation and atypical cells with inclusion bodies that stained positive for cytomegalovirus (CMV). A CMV DNA PCR from blood was positive with 48,900 copies/mL. Given her improvement on steroids, it was thought the CMV

ACG Case Rep J 2013;1(1):33–35. doi:10.14309/crj.2013.13. Published online: October 8, 2013.

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represented a coincidental bystander rather than the cause of the patient's colitis, and a decision was made not to start antiviral therapy.

On admission, her prednisone had been weaned to 25 mg daily and her diarrhea had worsened again. Admission blood tests showed leukopenia (1.0 x 10^9/L), neutropenia (0.2 x 10^9/L), anaemia (107 g/L) and an elevated C-reactive protein (137 mg/L). Initial blood cultures grew *Enterobacter aerogenes*, while urine and stool cultures were negative. A repeat CMV viral load was 10,179 copies/mL. She was commenced on intravenous piperacillin and tazobactam 4.5 g three times daily, and subcutaneous granulocyte colony stimulating factor (G-CSF) 300 µg daily. Her steroids were weaned.

Over the next 2 weeks, the patient's diarrhea, leukopenia, neutropenia, and C-reactive protein were improving, but her fevers persisted despite multiple courses of antibiotics and negative cultures. During this time the patient was diagnosed with CMV retinitis and a herpes simplex virus 1 (HSV) dendritic corneal ulcer after developing a painful right eye. She was commenced on intravenous ganciclovir 5 mg/kg every 12 hours for 2 weeks for disseminated CMV infection as well as intravitreal ganciclovir and topical acyclovir ointment. Late in her admission, our patient also had *Candida glabrata* isolated from her urine. Given her ongoing fevers, this was treated with oral fluconazole 400 mg daily for 7 days.

A bone marrow aspirate and trephine showed a hypercellular marrow, disorganised erythropoiesis, and a left shift in myelopoiesis. Blood lymphocyte subsets revealed an absence of CD19 B cells (0.00 x 10^9/L; normal 0.05–0.41 x 10^9/L), decreased CD4 count (0.31 x 10^9/L; normal 0.4–1.32 x 10^9/L), with an inverted CD4:CD8 ratio (0.37; normal 0.6–2.5). There was marked hypogammaglobulinaemia: IgA 0.21 g/L (normal 0.7–3.12 g/L), IgG 1.78 g/L (normal 6.39–15.6 g/L), and IgM <0.18 g/L (normal 0.5–3.0 g/L). Her HIV serology was negative. With her history of thymoma and characteristic pattern of immunodeficiency, a diagnosis of Good's syndrome with disseminated CMV infection was made. She received an infusion of intravenous immunoglobulin (IVIG) followed by monthly maintenance infusions. She was also started on lifelong CMV and *Pneumocystis jiroveci* pneumonia prophylaxis with oral valganciclovir and trimethoprim-sulfamethoxazole. She became afebrile and her diarrhea settled 2 days after receiving IVIG, 10 days after commencing ganciclovir. CT and PET scans showed no evidence of residual thymoma.

Discussion

Good's syndrome is a rare acquired primary immunodeficiency associated with thymoma. Up to 1–2% of patients with primary antibody deficiency requiring immunoglobulin replacement have a diagnosis of GS.[4] The mean age of presentation is 59 years (range 25–90 years).[5] Males and females are equally affected.

The pathogenesis of GS is still unknown. Two possible mechanisms for the association of hypogammaglobulinaemia and thymoma have been suggested.[2] The first is the possible presence of a cytokine secreted by marrow stromal cells, which may influence both thymic and B-cell precursor differentiation. The second possible mechanism is that T cells from patients with thymoma have been shown to inhibit pre-B cell growth and immunoglobulin production.

The diagnosis of thymoma may precede (42.4%), follow (19.7%), or occur simultaneously (37.9%) with the clinical syndrome of hypogammaglobulinaemia, infections, and diarrhea.[5] The interval between thymoma diagnosis and clinical manifestations of GS can be up to 18 years. Since removal of the thymoma does not reverse the immunological abnormalities, GS has been reported after thymectomy,[6,7] as in this patient. The full manifestations of GS are usually established within 6 years of initial presentation.[8]

The principal immunological findings in GS are hypogammaglobulinaemia (100%), absent B cells (87%), and low CD4 T helper cells (73.2%), with a low CD4:CD8 ratio (76.1%). Leukopenia and neutropenia occur less commonly, in 46.5% and 15.1% of patients, respectively.[5] The reduced number of peripheral B cells differentiates GS from common variable immunodeficiency (CVID).

Patients with GS are at increased susceptibility to infections. The most common infections reported are recurrent sinopulmonary infections, especially from encapsulated organisms.[8] As featured in our patient, the most common opportunistic pathogens include viral infections (CMV and HSV) and candidiasis. *Mycobacterium tuberculosis*, *Toxoplasma gondii*, and systemic fungal infections are uncommon in GS, in contrast to acquired human immunodeficiency syndrome (AIDS).[2]

Chronic diarrhea affects almost half of GS patients.[8] Occasionally, pathogens such as *Salmonella* spp, *Campylobacter jejuni*, *Giardia lamblia*, and CMV are isolated. In this patient, it was initially uncertain whether the CMV found on her colonic biopsies represented a nonpathogenic bystander or a causative factor in her colitis. The pathogenicity of CMV in the context of inflammatory bowel disease (IBD) has been a longstanding topic of debate.[9] Although the later discovery of CMV retinitis made CMV colitis a likely cause of her worsening diarrhea, it is unclear why she initially responded to high-dose steroids. Inflammatory lesions similar to those

seen in IBD that respond to treatment with systemic steroids have also been described in GS, suggesting an autoimmune cause.[10] This may explain our patient's chronic diarrhea prior to presentation.

Although thymectomy does not reverse the immunological abnormalities in GS, it is recommended to prevent local invasion and distant metastasis of thymomas and to achieve favourable outcomes for associated autoimmune conditions including myasthenia gravis, pure red cell aplasia, pernicious anaemia, and thyroid disease.[11] Completeness of thymoma resection is the most important indicator of long-term prognosis in GS.[5] Immunoglobulin replacement is the mainstay of therapy for immunodeficiency and results in reduced infection rates.[5,8]

A diagnosis of GS carries a worse prognosis compared to other hypogammaglobublinaemia diseases such as CVID or X-lined agammaglobulinaemia. The 5- and 10-year survival rates for GS are 70% and 33%, respectively.[12] The principal cause of death is infection.

Conclusion

We report a case of GS with chronic diarrhea and multiple opportunistic infections 5 years post-thymectomy. We recommend checking immunoglobulin levels in all patients with current or previous thymoma. A diagnosis of GS should be considered if these patients present with unexplained diarrhea, cytopenias, or recurrent infections, as early recognition and treatment may prevent mortality. It is important to keep a high index of suspicion for opportunistic infections, particularly CMV, as a possible cause of chronic diarrhea. Thymectomy, IVIG, and aggressive antimicrobial treatment are the mainstay of treatment.

Disclosures

Author contributions: K. Liu drafted the article, completed the literature review and research of case, corrected revisions, and is the article guarantor; J.L. Cowlishaw critically revised the article and approved the final draft.

Financial disclosure: The authors deny any financial support of the manuscript, and any potential financial or other conflicts of interest.

Received: May 11, 2013; Accepted: September 10, 2013

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