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Case Report

Non-type A autoimmune gastritis in a patient with IgA deficiency

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Abstract: Selective IgA deficiency is the most common primary immunodeficiency. Gastrointestinal infections, autoimmune diseases and even malignancies have been reported in patients with IgA deficiency. We present a case of a 60-year-old man with selective IgA deficiency, iron deficiency anemia and a normal B12 level that was found to have IgA related gastrointestinal manifestations. Biopsies from the antrum and body demonstrate diffuse antral-type mucosa with chronic inactive gastritis, which is compatible with autoimmune gastritis. There is focal intestinal metaplasia in the antrum but no neuroendocrine hyperplasia. Autoimmune gastritis has been rarely reported in association with selective IgA deficiency. Therefore, the morphologic features along with the clinical history of a male with a normal B12 level suggest the patient has independent autoimmune gastritis associated with IgA deficiency rather than type A autoimmune gastritis. It is important to take the entire clinical picture into account along with the morphologic features identified on biopsy material. If histologic changes are considered in isolation from the clinical picture, the histologic findings can lead to misdiagnosis. Together with the clinical picture, this patient's histologic features of independent autoimmune gastritis on biopsy can be attributed to manifestations of IgA deficiency, rather than other causes such as type A autoimmune gastritis.

Keywords: Autoimmune gastritis, IgA deficiency

Introduction

Immunoglobins are produced by plasma cells and are integral to the function of the immune system. Not only do immunoglobulins recognize and neutralize pathogens, but they also function in cancer surveillance, humoral immunity and immune homeostasis. There are five types of immunoglobulins: IgG, IgA, IgM, IgE and IgD. Of these, the most abundant immunoglobin in the human body is IgA. Although levels of IgA are low in serum, high quantities are found in saliva, tears, breast milk, respiratory tissues and gastrointestinal tract secretions [1]. The abundance and wide distribution of IgA highlights the fact that it plays an imperative role in mucosal immunity, defense against pathogens entering through mucosa, and immune tolerance [1, 2]. Having proper function and quantities of IgA is necessary for proper immune response.

Selective IgA deficiency is the most common primary immunodeficiency. The cause of such deficiency is defective terminal mutation of B cells into IgA-secreting plasma cells, therefore resulting in reduced IgA levels but normal IgG and IgM levels [3]. Although most patients with IgA deficiency are asymptomatic, patients can present with recurrent infections, autoimmune diseases or malignancies [4]. In general, patients with selective IgA deficiency have milder symptoms than those with common variable immunodeficiency (CVID), since CVID patients have reductions in two different immunoglobulins. IgA deficiency has been thought to be on the milder end of the same spectrum as CVID. In fact, one deficiency can even develop into the other one within the same patient [5].

Although a variety of gastrointestinal manifestations can be found in CVID, quite a few can occur in selective IgA deficiency as well. Specifically, gastrointestinal infections in selective IgA deficiency are commonly caused by *Giardia* species, *Campylobacter* species, *Salmonella* species, rotavirus, enterovirus, and bacterial overgrowth. Inflammatory gastrointes-

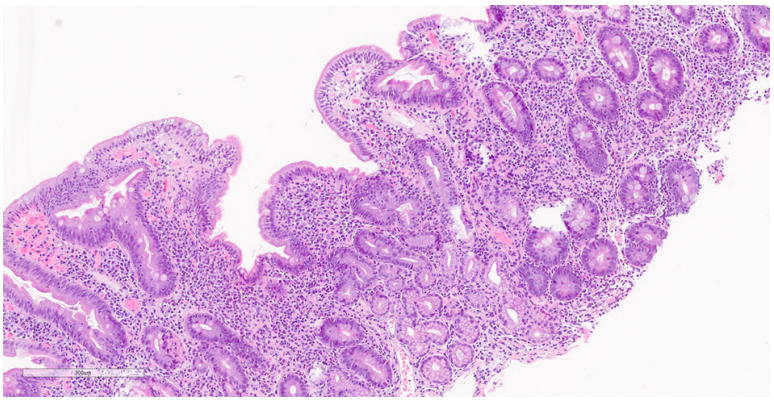

Figure 1. Duodenum shows inflamed mucosa with slight blunting of villi compatible with celiac disease (10X).

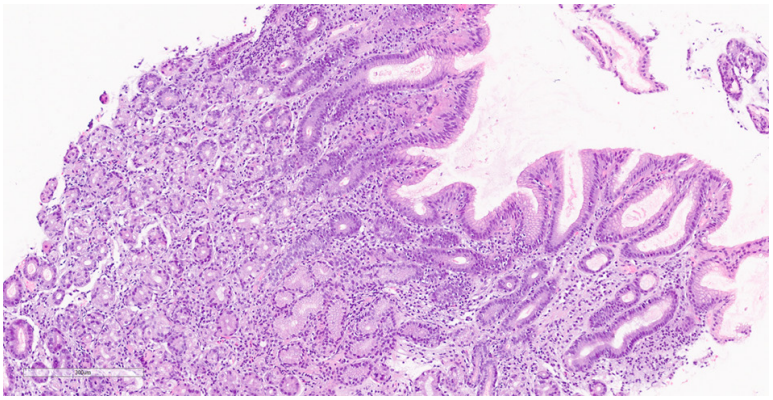

Figure 2. Antralized mucosa of the gastric body (10X).

tinal manifestations consist of nodular lymphoid hyperplasia (NLH), celiac disease, microscopic colitis, ulcerative colitis, Crohn disease, and villous atrophy. Autoimmune diseases include pernicious anemia, autoimmune hepatitis, primary biliary cirrhosis and achlorhydria [4]. Rarely, patients can present with autoimmune gastritis [6, 7]. Malignancies include stomach adenocarcinoma and lymphoma [4]. We present a patient with selective IgA deficiency that was found to have celiac-like histological changes and autoimmune gastritis on biopsy.

Clinical summary

A 60-year-old gentleman was well until he developed cryptococcal meningitis seven years prior. He was hospitalized and received antifungal therapy, which was complicated with renal failure. Upon recovery, he subsequently developed cryptococcal skin infections and lichenified dermatitis in the scrotum. He also has a history of chronic sinusitis status post rhinoplasty and sinus surgery. Colonoscopies nine and five years prior were reportedly normal. Currently, laboratory investigations reveal low CD4 levels despite multiple negative HIV tests, low IgA levels, normal IgM and IgG levels, lymphocytopenia, iron deficiency anemia, and hypoalbuminemia. Vitamin B12 is within the normal range. Rheumatoid Factor IgM antibody is strongly positive. The antinuclear antibody (ANA) titer is negative. Also, IgA and IgG antibodies to transglutaminase and gliadin as well as IgG autoantibodies to Sjögren's-syndrome antigen A (SS-A/RO) and Sjögren's-syndrome antigen B (SS-B/LA) are not detected. Anticardiolipins (IgG, IgM) are within the normal range, and IgA anticardiolipins are not detected. A gastrin level, serum H. pylori antibody test and further autoantibody tests (anti-intrinsic factor, anti-pareital, anti-smooth muscle antibody) are not done. A CT scan of the abdomen reveals diffuse fold thickening and wall thickening of the small bowel. Upper and lower endoscopy shows the gastric mucosa is congested, atrophic and poorly distensible. There is nodular mucosa in the gastric antrum. In the duodenal bulb as well as in the second and third parts of the duodenum, there is moderate mucosal abnormality characterized by vertical lines. Biopsies are taken for pathological analysis.

Pathologic findings

Biopsies of the duodenum show inflamed mucosa with slight blunting of villi compatible with celiac-like changes (**Figure 1**). No lymphoid hyperplasia, dysplasia or malignancy is present. Gastric biopsies from the antrum, distal body, mid gastric body, and proximal body show diffuse antral-type or antralized mucosa with chronic inactive gastritis, consistent with autoimmune gastritis (**Figure 2**). There is focal intes-

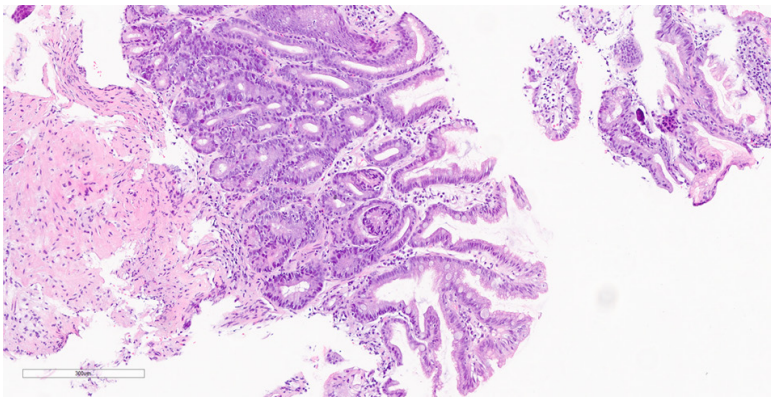

Figure 3. Stomach antrum with antral-type mucosa with chronic inactive gastritis and focal intestinal metaplasia (10X).

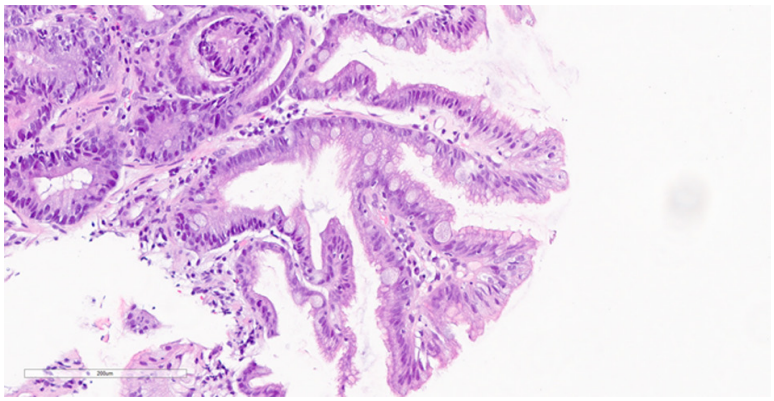

Figure 4. Stomach antrum with antral-type mucosa with chronic inactive gastritis and focal intestinal metaplasia (20X).

tinal metaplasia present in the antrum, but there is no evidence of pancreatic metaplasia or neuroendocrine hyperplasia (**Figures 3**, **4**). There are no *Helicobacter pylori* organisms (H&E stain), lymphoid hyperplasia, dysplasia or malignancy present. Biopsies of the esophagus, terminal ileum, colon and rectum show no specific pathologic features.

Disscussion

Clinically, the patient was found to have selective IgA deficiency with infectious complications of recurrent cryptococcal infections and chronic sinusitis. Stomach biopsies were compatible with autoimmune gastritis. In general, autoimmune gastritis is a chronic inflammatory disorder where metaplastic and atrophic mucosa replaces native gastric glands with parietal cells in either the antrum or the body of the stomach. There are two main types of atrophic gastritis: multifocal atrophic gastritis (type B gastritis) and autoimmune atrophic gastritis (type A gastritis). Type B gastritis is associated with long-standing *Helicobacter pylori* infection and affects the antrum as well as the oxyntic mucosa of the corpus and fundus. In contrast, type A gastritis primarily affects only the corpus and fundus and is associated with antiparietal and anti-intrinsic factor antibodies. This, in turn, leads to intrinsic factor deficiency, decreased B12 availability, and pernicious anemia [8, 9]. An independent autoimmune gastritis related to other factors, such as IgA deficiency, is extremely rare.

Histopathologically, there are three main phases in type A autoimmune gastritis. In the first phase, the oxyntic mucosa is involved by an inflammatory infiltrate composed of plasma cells, lymphocytes, mast cells and eosinophils that predominately involves the full thickness of the lamina propria. As a result, there is low acid secretion which eventually leads to achlorhydria. In the second phase, there is oxyntic gland atrophy, absence of parietal cells, pseudopyloric metaplasia and intestinal metaplasia. The lack of parietal cells as well as the presence of anti-intrinsic factor antibodies may lead to pernicious anemia. In response, the gastric antrum shows foveolar hyperplasia without significant inflammation or metaplasia. Because of this, there is increased gastrin secretion. In the third phase, usually only present in patients with pernicious anemia, the oxyntic glands are markedly reduced and inflammation may be minimal. However, there can be extensive pseudopyloric, pancreatic and intestinal metaplasia. In this phase, florid neuroendocrine hyperplasia may also be present which is due to increased gastrin secretion [8, 9].

In the present case, the patient's biopsies from the antrum and body are compatible with auto-

immune gastritis because there is diffuse antral-type mucosa with chronic inactive gastritis. Interestingly, there is focal intestinal metaplasia in the antrum but no neuroendocrine hyperplasia. Autoimmune gastritis has been rarely reported in association with selective IgA deficiency [6, 7]. Therefore, the morphologic features along with the clinical history of a male with a normal B12 level suggest the patient has independent autoimmune gastritis associated with IgA deficiency rather than type A autoimmune gastritis.

Additionally, biopsies of the duodenum show celiac-like histologic changes. In patients with selective IgA deficiency, there is a 10- to 20-fold increased risk for celiac disease [4]. This relationship could have a genetic basis due to sharing of specific HLA-extended haplotypes. However, since both celiac disease and IgA deficiency have a relatively high incidence of occurrence, the relationship between them could also be coincidental [4].

Celiac disease is diagnosed by confirming the presence of IgA antibodies to tissue transglutaminase, endomysial and gliadin. However, in a patient who is IgA deficient, these tests may not be accurate. In our patient, the IgA transglutaminase antibody was negative. However, IgG antibodies to transglutaminase and gliadin were negative also, which would be more accurate in the present case. The patient does have duodenal biopsies with celiac-like histologic changes, but in the absence of specific gastrointestinal symptoms and negative IgG transglutaminase and gliadin, it is also likely that the celiac disease-like histologic features may instead be related to infection [6].

Autoimmune diseases and immunodeficiency have a well-established relationship. For instance, patients with autoimmune diseases have an increased prevalence of IgA deficiency, and vice versa. Specific autoimmune diseases that have been found to be associated with IgA deficiency include autoimmune thyroiditis, sclerosing cholangitis, systemic lupus erythematosus, chronic arthropathy, autoimmune hemolytic anemia, juvenile idiopathic arthritis, celiac disease, vitiligo, ulcerative colitis, Sjogren's disease, polyarteritis nodosa, psoriasis, sarcoidosis, Kawaskai disease and Bechet's disease [1]. Therefore, it is not surprising that our patient has biopsies with celiac and autoimmune gastritis histologic changes.

A genetic link between autoimmune disease and immunodeficiency may exist since there seems to be a higher incidence of autoimmunity in first degree relatives with IgA deficiency [10]. Also, there is vertical transmission of IgA transmission in mothers, which is greater than that found in fathers [1].

One genetic factor that predisposes to IgA deficiency can be found in the major histocompatibility complex (MHC). This predisposing locus, IGAD1, seems to be associated with increased risk of developing IgA deficiency [1]. The most common haplotype in patients with IgA deficiency is Haplotype 8.1 (ancestral haplotype HLA-A1, B8, DR3, DQ2), which is found in 45% of IgA deficiency patients and 16% of the general population [1, 11]. Furthermore, Haplotype 8.1 is also associated with autoimmune diseases associated with IgA deficiency such as celiac disease, rheumatoid arthritis, type 1 diabetes and autoimmune thyroiditis [1, 11]. Other non-MHC genes that have been associated with IgA deficiency include the *IFIH1* gene and the *CLEC16A* gene [12].

Besides infectious and autoimmune manifestations, the patient also had evidence of atopy in the form of lichenified dermatitis. There may be a relationship between IgA deficiency and atopy, although there is conflicting data and this idea is controversial [1]. The patient had other complications that could be explained by the clincopathological picture, however. For instance, proximal small intestinal enterocytes are responsible for iron uptake. When the duodenum is involved by celiac disease, there is impaired iron absorption, which can explain this patient's iron deficiency anemia [13]. Likewise, the patient's presentation of hypoalbuminemia can also be explained by malabsorption, thus highlighting the relationship between the histologic picture and the clinical presentation.

In conclusion, it is important to take the entire clinical picture into account along with the morphologic features identified on biopsy material. If histologic changes are considered in isolation from the clinical picture, the histologic findings can lead to misdiagnosis. Together with the clinical picture, this patient's celiac-like histologic features and independent autoimmune gastritis on biopsy can be attributed to manifestations of IgA deficiency, rather than other causes such as type A autoimmune gastritis.

Disclosure of conflict of interest

None.

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