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【 CASE REPORT 】

Young Patient with X-linked Agammaglobulinemia Presents with Advanced Gastric Cancer and Extensive Atrophic Gastritis

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Abstract:
X-linked agammaglobulinemia (XLA) is associated with an increased risk of gastrointestinal cancers including gastric cancer (GC). We herein report the case of a 30-year-old male patient with XLA who developed GC and extensive atrophic gastritis. He tested positive in the urea breath test, thus indicating the presence of *Helicobacter pylori*. Distal gastrectomy and chemotherapy were performed without any complications; however, the died two years after this diagnosis. Immunoglobulin deficiency makes these patients susceptible to progressive atrophic gastritis and the associated risk of GC. Therefore, patients with XLA are advised to undergo an evaluation for *Helicobacter pylori* infection as well as monitoring for GC.

Key words: X-linked agammaglobulinemia, gastric cancer, *H. pylori* infection, atrophic gastritis

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Introduction

Patients with primary immunodeficiency (PID) have a higher incidence of cancer, particularly hematologic malignancies, such as non-Hodgkin lymphoma and leukemia (1). X-linked agammaglobulinemia (XLA), one of the most common PIDs, is characterized by severe hypogammaglobulinemia and the absence of circulating B cells in the peripheral blood (2). Patients with immunoglobulin deficiencies such as XLA may have an increased risk of hematologic malignancies and gastrointestinal cancers, including gastric cancer (GC) (3). However, GC cases in patients with XLA are rare and their clinical features are still not well understood. This report details the case of a young patient with XLA who developed advanced GC and underwent distal gastrectomy and chemotherapy. We also reviewed previously reported cases of GC in patients with XLA.

Case Report

At the age of two, the patient experienced recurrent infections, such as cellulitis, and was diagnosed with agammaglobulinemia. Based on the deletion of five base pairs in *Bruton's tyrosine kinase (BtK)* gene (c.241_245del, p.Arg81_Arg82del), he was diagnosed with XLA. At the time of diagnosis, the patient had no family history of XLA. He thereafter underwent regular intravenous immunoglobulin replacement therapy every three weeks since his diagnosis to maintain trough levels between 450 mg/dL and 550 mg/dL. Throughout the treatment period, the patient remained infection-free.

At 30 years of age, he experienced postprandial nausea and abdominal pain and underwent esophagogastroduodenoscopy (EGD). EGD revealed a gastric tumor, and he was referred to our hospital for treatment. He neither smoked nor drank alcohol. A physical examination revealed no abnor-

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Table 1. **Patient's Laboratory Findings.**

	This patient	Reference values
White blood cell count	6,240	3,300-8,600 /μL
Red blood cell count	511×10^4	$435\text{-}555\times10^4$ /μL
Hemoglobin	12.7	13.7-16.8 g/dL
Mean cell volume	79.3	83.6-98.2 fL
Mean cell hemoglobin	24.9	27.5-33.2 pg
Mean cell hemoglobin concentration	31.4	31.7-35.3 g/dL
Platelet count	38.1×10^5	$15.8\text{-}34.8\times10^5$ /μL
Immunoglobulin G	367	861-1,747 mg/dL
Immunoglobulin A	<3	93-393 mg/dL
Immunoglobulin M	6	33-183 mg/dL
CEA	3.28	0.00-3.40 ng/mL
CA19-9	16.8	0.0-37.0 ng/mL
Vitamin B12	332	233-914 pg/mL
Folic acid	11.7	3.6-12.9 ng/mL

CEA: carcinoembryonic antigen, CA19-9: carbohydrate antigen 19-9

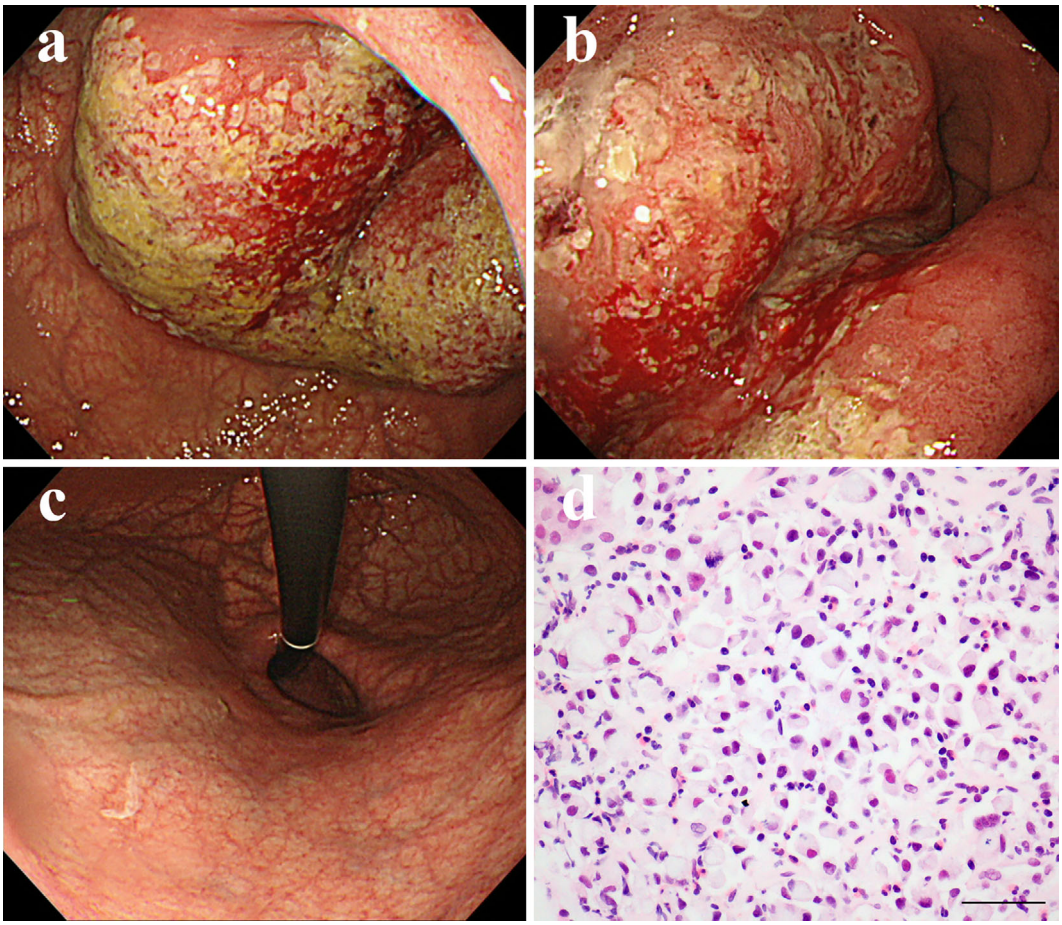

Figure 1. **Esophagogastroduodenoscopy revealed a semi-circumferential, thick and tense, protruding lesion in the greater curvature of the gastric antrum (a). The center of the lesion was depressed, and yellowish-white plaques were visible on the surface (b). The gastric mucosa was extensively atrophic [c, Kimura-Takemoto classification (22) of O-3]. The biopsy specimen from this lesion was diagnosed to be signet ring cell carcinoma (d, Hematoxylin and Eosin staining). The bar line corresponds to 50 μm.**

malities. Laboratory tests (Table 1) revealed mild microcytic anemia and decreased serum immunoglobulin levels. The levels of tumor markers, such as carcinoembryonic antigen and carbohydrate antigen 19-9, as well as gastrin, vitamin

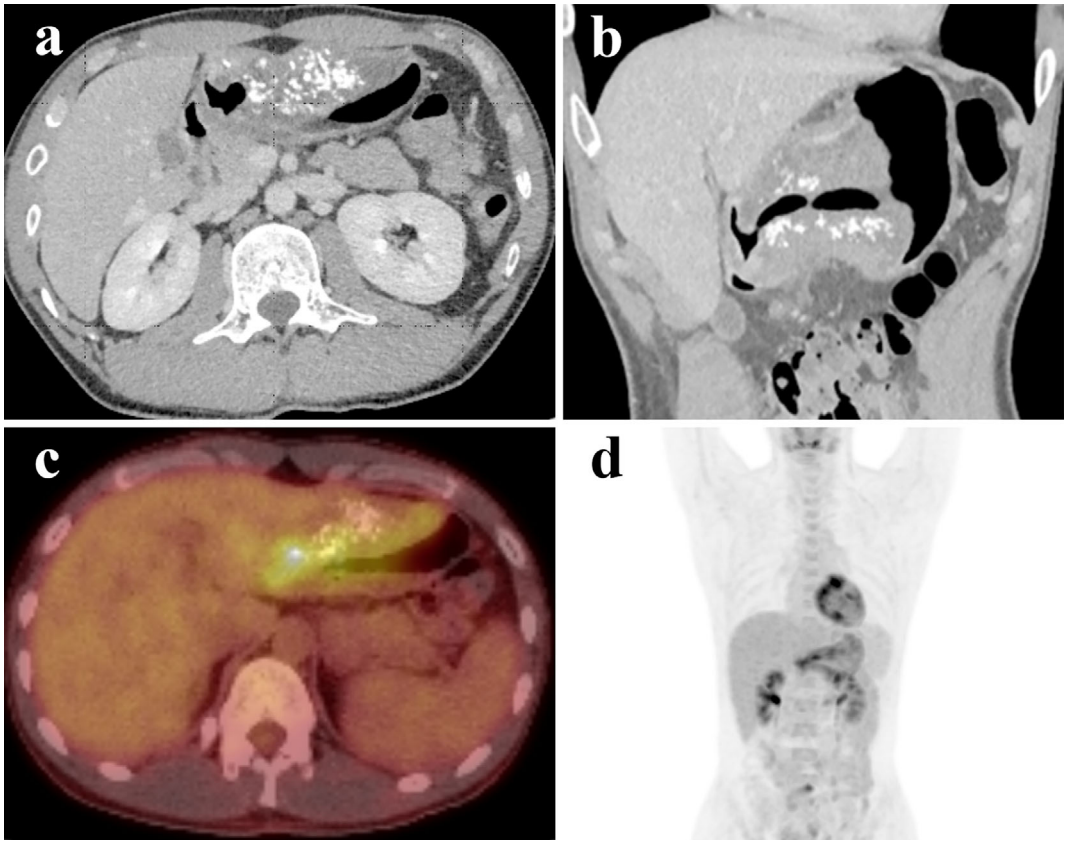

Figure 2. **The axial (a) and coronal (b) sections of computed tomography revealed significant wall thickening in the gastric antrum with white dots indicating calcification. The positron emission tomography/computed tomography with ^{18}F-fluorodeoxyglucose scan revealed fluorodeoxyglucose accumulation (maximum standardized uptake value of 6.55) in the thickened gastric wall (c), without any detectable accumulation in either the lymph nodes or distant organs (d).**

B12, and folic acid, were all within the normal ranges. No elevated hepatobiliary enzyme levels or renal dysfunction was observed. The urea breath test showed high levels (9.4 ‰), thus suggesting a potential *Helicobacter pylori* (HP) infection. EGD showed a semicircular tumor with a thick ridge in the gastric antrum (Fig. 1a, b) and extensive gastric mucosal atrophy (Fig. 1c). A biopsy of the tumor showed signet ring cell carcinoma (Fig. 1d), and the expression of human epidermal growth factor receptor 2 was negative. Computed tomography (CT) revealed a thickened wall with calcification in the gastric antrum (Fig. 2a, b), no enlarged lymph nodes, and no obvious signs of metastasis. Positron emission tomography/CT with ^{18}F-fluorodeoxyglucose (FDG-PET/CT) revealed an FDG uptake with thickening of the gastric wall (Fig. 2c) and no lymph node metastasis or distant metastasis (Fig. 2d). The clinical stage, according to the TNM classification (4), was cT4aN0M0, Stage IIB. We treated the patients with S-1 (120 mg/day, from day 1 to 21 every 35 days) and cisplatin (60 mg/m^2/day, on day 8) as neoadjuvant chemotherapy. However, after a chemotherapy cycle, CT revealed a slight growth of the GC and swollen lymph nodes at the lesser curvature. Distal gastrectomy was performed. A histopathological examination of the surgically resected specimen revealed punctate calcification on the surface and inside the gastric tumor (Fig. 3a, b), and signet ring cells with abundant extracellular mucin in the submucosal layer (Fig. 3c-e). The histopathological results were LM, Gre-Ant-Less, type 2, 110×100 mm, muc > sig, pT4a (SE), INFc, Ly1a, V0, pPM0 (30 mm), pDM0 (10 mm), grade 2b, pN3a (9/23), and stage IIIB according to TNM classification (4). He underwent postoperative adjuvant chemotherapy with S-1 (120 mg/day, from days 1 to 28 every 42 days). During the third cycle of postoperative adjuvant chemotherapy, grade 3 leukopenia and neutropenia were observed, thus leading to a reduction in the S-1 dosage (from 120 mg/day to 100 mg/day). Throughout surgery and chemotherapy, his trough IgG levels remained above 500-700 mg/dL with regular intravenous immunoglobulin replacement therapy. The patient remained recurrence-free for a year. However, a build-up of fluid in the abdomen (ascites) was evident on the follow-up CT scan. As a result, we switched the treatment to ramucirumab (8 mg/kg on days 1 and 15 every 28 days) and paclitaxel (100 mg/m^2 per day on days 1, 8, and 15 every 28 days). After four cycles, CT showed increased ascites, enlarged mediastinal lymph nodes, and peritoneal dissemination (Fig. 4a-c). The patient died two years after the initial diagnosis of GC.

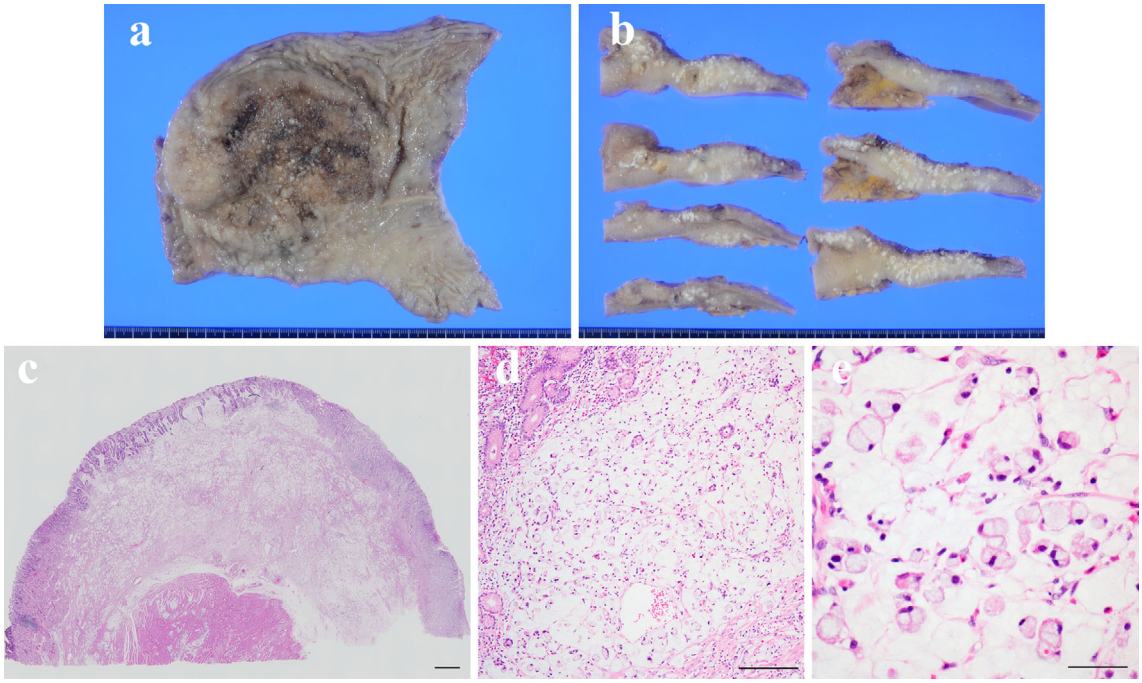

Figure 3. **The images depict a surgically resected gastric cancer at the macroscopic (a) and sectional (b) levels. White spots are visible on the surface (a) and within the wall (b). Necrotic tissue resulting from chemotherapy and signet ring cell carcinoma invading the serosa was observed [c, Hematoxylin and Eosin (H&E) staining, the bar line corresponds to 1,000 μm]. The signet ring cell carcinoma was present in abundant amounts of mucus (d, H&E staining, the bar line corresponds to 200 μm). High magnification image (e, H&E staining, the bar line corresponds to 50 μm).**

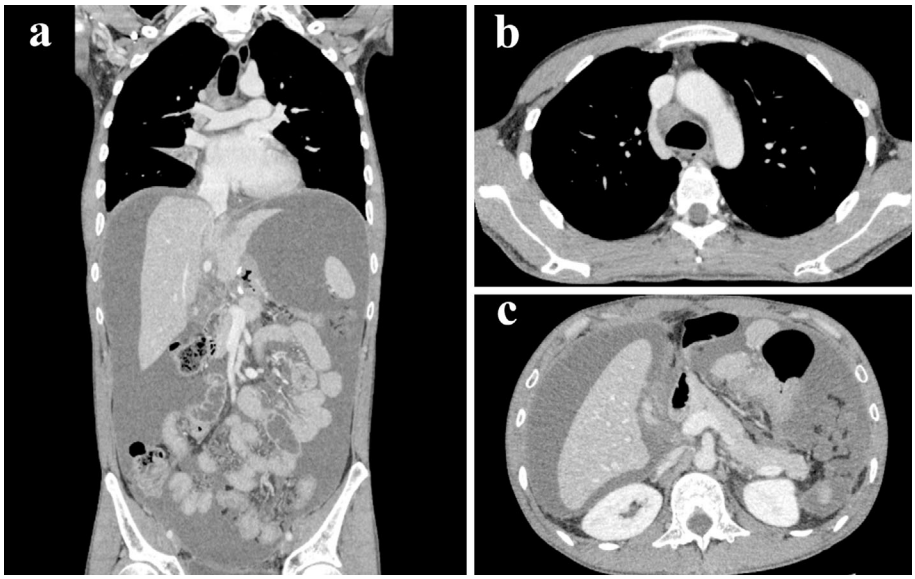

Figure 4. **One year after postoperative adjuvant chemotherapy with S-1, the presence of ascites was evident on a follow-up CT scan. We switched the regimen to ramucirumab. After three cycles, a CT scan showed increased ascites (a), enlarged mediastinal lymph nodes (b), and peritoneal dissemination (c).**

Discussion

We herein report a rare case of a young patient with XLA who had advanced GC and extensive atrophic gastritis associated with HP. Additionally, to our knowledge, this is the first report to review the characteristics of GC associated with XLA, including seven previously reported cases, and we also discuss the mechanisms contributing to the development of the disease.

Table 2. Clinical Features of Current and Previously Reported Patients with X-linked Agammaglobulinemia and Gastric Cancer.

Age/Sex	Symptoms	Anemia	HP	Infection	Gastritis	Stage of GC at diagnosis	Treatment of GC	Outcome
25/M (3)	ND	ND	ND	ND	ND	IV	ND	Dead
23/M (10)	Body weight loss, diarrhea, loss of appetite	Macrocytic	ND	*Giardia lamblia*	Chronic atrophic gastritis and intestinal metaplasia	ND	Subtotal gastrectomy	Died 2 years after diagnosis
26/M (11)	Body weight loss, loss of appetite	ND	-	ND	Chronic atrophic gastritis	ND	ND	ND
15/M (12)	Anemia	Macrocytic	-	ND	Chronic atrophic gastritis and intestinal metaplasia	I	Total gastrectomy	Survived for more than 10 years
30/M (13)	Weight loss, loss of appetite	Macrocytic	ND	*Giardia lamblia*	ND	IV	Palliative treatment	Died 3 months after diagnosis
25/M (14)	Anemia	Microcytic	+	*Campylobacter jejuni*	Gastric atrophy and inflammation	I	Subtotal gastrectomy	Alive 1 year after surgery
30/M (Our case)	Nausea, abdominal pain	Microcytic	+	-	Extensive gastric atrophy (O-3*)	III	Distal gastrectomy and chemotherapy	Died 2 years after diagnosis

XLA: X-linked agammaglobulinemia, GC: gastric cancer, HP: *Helicobacter pylori*, M: male, ND: not described

*The Kimura-Takemoto classification (22).

XLA is a primary immunodeficiency disorder characterized by severe hypogammaglobulinemia, antibody deficiency, and increased susceptibility to infections. Initially reported by a pediatrician named Bruton in 1952 (5), XLA is caused by mutations in the *Btk* gene on the long arm of the X chromosome (Xq21.3-Xq22), almost exclusively affecting males. While most cases of agammaglobulinemia result from an X-linked inheritance of mutations in the *Btk* gene, approximately 10% of such cases result from autosomal genetic mutations. The *Btk* mutation-induced B cell development defect in patients leads to reduced B cell counts in tissues and blood, and less plasma cell differentiation, ultimately causing lower immunoglobulin levels (5). Infants with XLA do not experience recurrent infections until 6-8 months of age, when maternal antibodies wane, but thereafter they suffer from recurrent issues, such as conjunctivitis, upper respiratory tract infections, deep skin infections, and purulent otitis media (2). While there is no cure, regular immunoglobulin replacement therapy and therapeutic and prophylactic antibiotic use can prevent infections and help these patients reach adulthood (6). As long-term survival has become possible, reports of cancer complications have increased (7).

Patients with PID are known to have a higher incidence of cancer (8). The overall risk of cancer in PID patients is estimated at 4.7-5.7%. A relative cancer risk increase of 1.4-1.6 times has been reported for PID (8). Patients with PID are reported to have an increased relative risk of hematological malignancies, such as non-Hodgkin lymphoma and leukemia (9). In patients with antibody deficiencies, such as XLA, there is an increased risk of hematological malignancies and gastrointestinal cancers, such as GC (3).

Seven cases of GC complications in patients with XLA have been previously reported (Table 2) (3, 10-14). The average age of the patients was 25 years (range, 15-30 years). Four patients were diagnosed with symptoms, such as weight loss, loss of appetite, diarrhea, nausea, and abdominal pain, all in advanced stages. Most cases are short-term, with a prognosis of up to two years following diagnosis. At the time of diagnosis, three patients had macrocytic anemia and two had microcytic anemia. Chronic gastritis can lead to achlorhydria, which, in turn, may cause megaloblastic anemia associated with vitamin B12 deficiency. Two cases, including ours, tested positive for HP infection. Two cases showed no evidence of HP infection but were found to be infected with *Giardia lamblia*, which is almost always co-infected with HP. Chronic atrophic gastritis was observed in all the confirmed cases. Therefore, we hypothesized that chronic gastritis with HP at a young age may lead to the early onset of GC in patients with XLA.

Patients with antibody deficiencies, such as XLA, are susceptible to gastrointestinal parasites and bacteria, including *Giardia lamblia*, *Campylobacter jejuni*, and HP. This susceptibility is due to reduced IgA levels in the gastrointestinal tract and hydrochloric acid in the stomach (15). Mucosal IgA and IgG are involved in the immune defense against HP in infected patients. In contrast to IgG, IgA is transported to the gastric lumen and serves as the first line of defense (16). It has been reported that there is no difference in the rate of HP-positive subjects between IgA-deficient patients and healthy individuals (17). However, the incidence of extensive atrophic gastritis is significantly higher in IgA-deficient patients (17). IgA is hypothesized to play a crucial role in preventing the progression of atrophic gastritis following HP infection. Consequently, patients diagnosed with XLA undergo screening for HP infections. It is crucial to note that assessing HP infection via antibody titers is not feasible in patients lacking immunoglobulins. If the patient tested positive for HP, subsequent eradication therapy was recommended. Meticulous monitoring is therefore required before

and after eradication therapy.

GC with calcification is rare, occurring in less than 3% of cases (18). One report indicated that calcifications in GC are CT features of mucinous GC (19). Mucinous adenocarcinoma is an uncommon histological type of GC, classified by the World Health Organization as poorly differentiated and often marked by significant mucinous pools within the tumor (20). Accordingly, the histopathological subtype in our case was signet ring cells with mucinous adenocarcinoma. However, no cases of GC with calcification have previously been reported in patients with XLA.

There are no guidelines for immunoglobulin replacement therapy during the perioperative period or chemotherapy in patients with XLA. Previous studies have reported that surgery can be safely performed by maintaining IgG levels above 500-700 mg/dL (21). Conversely, there are no reports of chemotherapy for GC in patients with XLA receiving immunoglobulin supplementation. In this case, we could safely perform surgery as well as chemotherapy, while keeping the IgG level above 500-700 mg/dL.

In this report, a patient with XLA who presented with advanced GC and extensive atrophic gastritis was safely treated with surgery and chemotherapy via immunoglobulin replacement therapy, but he unfortunately could not be completely cured. Moreover, patients with XLA are at a risk of developing GC at a young age. The early onset of GC might be the underlying cause of extensive atrophic gastritis associated with IgA deficiency. Therefore, it is advisable that patients with XLA be screened for HP infection and undergo regular surveillance through EGD from an early age.

The authors state that they have no Conflict of Interest (COI).

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