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ASTUTE CLINICIAN REPORT

Gastric Adenocarcinoma in the Context of X-linked Agammaglobulinemia

Case Report and Review of the Literature

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Abstract The hallmarks of X-linked Agammaglobulinemia (XLA) are panhypogammaglobulinemia, absent B-cells, and recurrent sinopulmonary and gastrointestinal infections starting at an early age, as well as other infections like cellulitis, meningitis, arthritis and sepsis. A number of non-infectious complications have been reported in these patients, including autoimmune diseases and malignancy, especially lymphomas. Here, we report the case of a 30-year old man who developed gastric adenocarcinoma in the context of XLA. Previous reports of, and hypotheses addressing the development of cancer in patients with XLA, are also summarized. Solid cancer in XLA affects mainly the gastrointestinal tract and seems to be related to chronic infection. A natural evolution can be traced back from gastric adenocarcinoma to megaloblastic anemia due to achlorhydria in the context of chronic infection; periodic endoscopy thus seems justified to detect and treat carcinoma in early stages.

Keywords Cancer · solid tumor · gastric adenocarcinoma · primary immunodeficiency · X-linked agammaglobulinemia · antibody defect · Bruton

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Abbreviations

XLA	X-linked agammaglobulinemia
BTK	Bruton's tyrosine kinase
GC	Gastric adenocarcinoma
HP	Helicobacter Pylori

X-linked Agammaglobulinemia (XLA) is a rare human genetic disorder with increased susceptibility to infections, particularly those by encapsulated bacteria, which results from a failure of B lymphoid development. XLA is caused by mutations in the X chromosome gene *BTK* that encodes an enzyme from the TEC family of protein kinases: Bruton's tyrosine kinase (BTK), involved in intracellular signaling and B-cell development [1]. The incidence is estimated in about 1:200,000 live male births; and more than 1,200 mutations have been identified. The hallmarks of XLA are: panhypogammaglobulinemia, absent B-cells (less than 2 % of CD19+ cells), and recurrent sinopulmonary and gastrointestinal infections starting at around 6–12 months of life, as well as other less common infections like cellulitis, meningitis, arthritis and sepsis [2]. Non-infectious complications include autoimmunity and malignancy, especially lymphomas [3]. Here, we report the case of a 30-year old man who developed gastric adenocarcinoma (GC), having been diagnosed with XLA at age 12. Previous reports, and hypotheses addressing the development of cancer in XLA patients, are also summarized.

Case Report

A male patient from Mexico started at 7 months with recurrent rhinosinusitis, pneumonia, otitis media, and pyogenic arthritis.

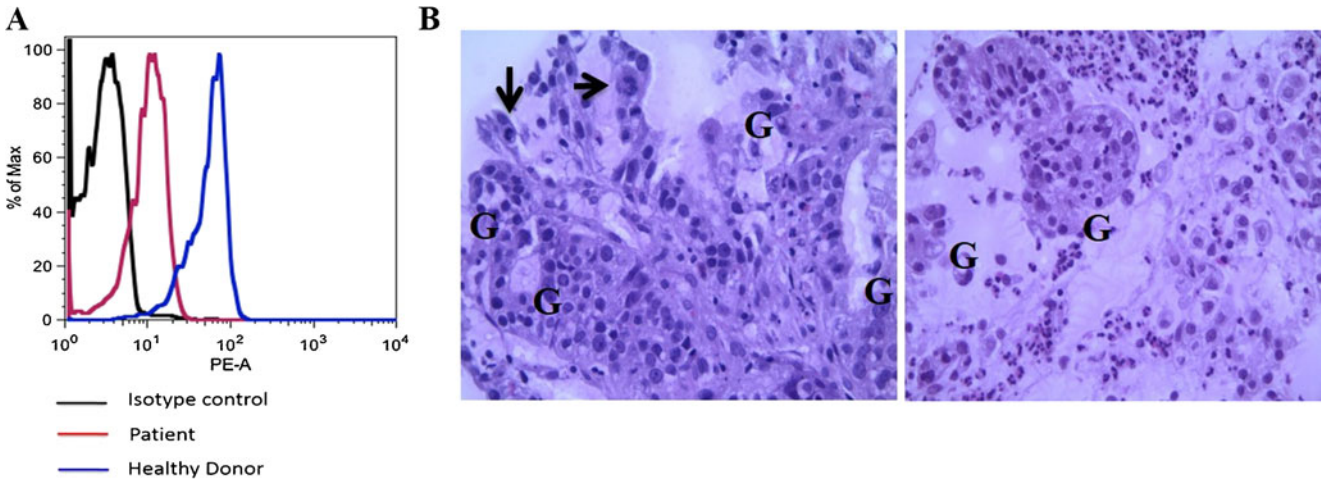

Fig. 1 **a** BTK intracellular expression in peripheral blood mononuclear cells (PBMC) from the patient (*red line*) as compared to a healthy control (*in blue*). **b** Hematoxilin/Eosin stained slides under light microscopy (40×) showing mitosis (*arrows*) and neoplastic glands (*G*) in biopsies from gastric mucosa

There was no family history of consanguinity, but a maternal cousin had died at age 3 years with sepsis; a nephew also had hypogammaglobulinemia. The patient was diagnosed with XLA at age 12 years, based on: panhypogammaglobulinemia, less than 2 % CD19+ cells, and absent BTK expression in monocytes (Fig. 1); and started on monthly endovenous gammaglobulin (IVIG), in spite of which he developed destructive bronchiectasis during the following years.

At age 28 he presented with phlebitis of the right leg, which resolved after 5 days of intramuscular cephalosporin. He complained of weight loss of 4.5 kg in 3 months. After a Hemoglobin (Hb) of 6.2 g/dL, bone marrow aspirate confirmed megaloblastic anemia with 55 % normoblasts and megaloblastic cell maturation. He developed postprandial vomiting and diarrhea with further weight loss (10 kg in 3 months). On physical examination he had splenomegaly and mild supraclavicular lymphadenopathy.

A chest and abdomen CT showed an over-expanded left lung, bilateral extensive atelectasis and fibrotic pleural disease. The stomach was enlarged with retained gastric contents and a thick pyloric wall, with compression and displacement of the inferior vena cava by lymph node masses, and marked ascites in Douglas pouch (not shown). A complete blood count (CBC) revealed Hb 6.68 g/dL, Mean cell volume (MCV) of 114 fL (normal 80–90 fL), Mean corpuscular Hb concentration (MCHC) 41.5 g/dL (normal 32–36 g/dL); negative Direct Coombs; serum IgA <6.34 mg/dL (normal range in adults: 64–297 mg/dL), IgG 625 mg/dL while on monthly IVIG (normal: 580–1,540 mg/dL), IgM <4.38 mg/dL (40–200 mg/dL), IgE <18 IU/ml; LDH 1,499 IU/L (normal 140–

Table I Gastric adenocarcinoma and other solid tumors reported in patients with X-linked agammaglobulinemia

Reference	Country	Solid tumor	Number	Stage	Age (years)	Outcome
Lavilla et al. [9]	Spain	Gastric adenoca.	1	Mets	23	Alive
Bachmeyer et al. [7]	France	Gastric adenoca.	1	NA	26	NA
Kinlen et al. [3]	United Kingdom	Gastric adenoca.	1	End	25	Dead
Lackmann et al. [8, 17]	Germany	Gastric adenoca.	1	Early	15	Alive and well
Vajdic et al. [5]	Australia	Gastric adenoca.	1	NA	45	NA
This report	Mexico	Gastric adenoca.	1	End	30	Dead
Van der Meer [12]	Netherlands	Colorectal cancer	2	NA	30, 36	Dead
Van der Hilst [2]. Chisuwa et al. [11]	Japan	Colorectal cancer	1	NA	NA	NA
Adachi et al. [13]	Japan	Colorectal cancer	1	Local	22	Alive
Brosens et al. [10]	Netherlands	Colorectal cancer	2	Local	45,37	Alive
Echave-Sustaeta et al. [14]	Spain	Lung squamous	1	TNM IV	32	Dead
Wang et al. [16]	China	Liver cancer	1	NA	7	Dead
Al Sasi et al. [15]	Saudi Arabia	Colon NEC	1	Mets	10	Dead

All patients were male

NA not available, *NEC* neuroendocrine carcinoma, *Mets* metastasized. *TNM* tumor-nodes-metastasis cancer staging system

280 IU/L); carcinoembryonic antigen (CEA) 122.4 ng/ml (normal <2.5 ng/ml), and normal alpha fetoprotein (AFP, 1.58 ng/mL). *Giardia lamblia* cysts and trophozoites were repeatedly reported as abundant in stool smears.

Gastric endoscopy showed a gastric ulcer and sub-total pyloric stenosis. Biopsy reported a poorly differentiated adenocarcinoma with lymph node invasion. He underwent exploratory laparotomy with jejunostomy at another hospital, where a large gastric tumor occupying the gastric body and antrum was found, with metastases to several regional lymph nodes (groups I, III and IV), as well as to peritoneum with malignant ascites. The tumor was considered incurable and the patient was offered palliative care. He died 3 months later. Permission to perform an autopsy was denied by his family.

Discussion

Patients with primary immunodeficiencies (PIDs) are known to have increased susceptibility to cancer, with a frequency up to 5 times greater than the general population; an incidence for non-Hodgkin lymphoma up to 23 times higher, and that of gastric adenocarcinoma 50 times higher [4]. Antibody defects are among those PIDs with greater excess cancer risk, particularly to hematologic malignancies and stomach cancer [5]. The prevalence of any malignancy in XLA has been estimated to be between 1.5 % and 6 % [6]. A literature search identified: 5 previous reports of gastric cancer in XLA patients [3, 5, 7–9], all of them males between 15 and 45 years old; and 6 patients with colorectal cancer [2, 10–13]; as well as 3 other cases of solid cancers [14–16] (See Table I).

Gastric adenocarcinoma has an estimated frequency of 1:116 in the general population, with a mean age at diagnosis of 65–70 years [18]. A number of mechanisms to explain the higher, earlier occurrence of cancer in XLA have been postulated, including NK depletion [19] and spontaneous malignant transformation of cells attributed to a defective Btk [20]. However, naturally occurring mutant mice (Btk-or *xid* mice) have a rather mild disease [1]; and there have been no reports of tumors in this animal model of XLA. Furthermore, inhibition of Btk induces apoptosis and limits proliferation [21]: Ibrutinib is a Btk inhibitor already in trials to treat autoimmune disorders and B-cell malignancies [22]. Hermaszewski and Webster reviewed the cases of 44 patients with XLA in the United Kingdom, and did not find associated cancer in 20 years [23], and yet Maarschalk-Ellerbroek et al. found colorectal adenomatous polyps in 2 of 4 patients with XLA who underwent screening endoscopy in the Netherlands [24]. Thus, cancer in BTK deficient patients is most probably a late complication attributable to chronic infection.

There is a unique susceptibility to enteroviruses in XLA, and a well-known susceptibility to gastrointestinal parasites and bacteria, including *Giardia lamblia*, *Campylobacter jejuni* and *Helicobacter pylori* (HP) in antibody defects [25]. Chronic infection with HP has been linked to the sequential development of chronic atrophic gastritis, hypochloryhdria, cobalamin deficiency, pernicious anemia, intestinal metaplasia and cancer [8, 26]. Evidence of chronic HP infection could not be found in our patient, but *Giardia lamblia* trophozoites and cysts were abundant in stool. Giardia is almost always found in co-infection with HP, and contributes to the pathogenesis by causing a deficit of Vitamin B12 that results in megaloblastic anemia and gastric atrophy.

The authors are aware of one report of GC in a 15 year-old patient with Autosomal-recessive Agammaglobulinemia, who also presented with chronic atrophic gastritis and weight loss [27]; and of several reports of GC in patients with Selective IgA Deficiency and Common-Variable Immunodeficiency [3, 4]. Other factors evoked to explain the increased incidence of GC in primary antibody defects include: decreased gastric IgA and hydrochloric acid [5], chronic antibiotic use and a high concentration of nitrites in gastric secretions [4].

The finding of megaloblastic anemia should alert the clinician for the final diagnosis of GC, since a natural evolution can be traced, and thus predicted: from chronic gastric infection to parietal cell dystrophia and to malignant transformation. Screening and surveillance methods for the prevention of GC include: upper gastrointestinal endoscopy, and serum pepsinogen testing; none of which has proven superior to the other [28]. Endoscopy and colonoscopy are justified in patients with hereditary agammaglobulinemia who present with digestive symptoms, to detect and treat carcinomas as early as possible. As the infectious management and prognosis for XLA patients improve, more of them will reach adolescence and adulthood with a great risk for malignancy.

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Conflict of Interest None of the authors has any potential financial conflict of interest related to this manuscript.

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