

Autoimmune gastritis presenting as iron deficiency anemia in childhood

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Abstract

AIM: To characterize clinical, laboratorial, and histological profile of pediatric autoimmune gastritis in the setting of unexplained iron deficiency anemia investigation.

METHODS: A descriptive, observational study including pediatric patients with a diagnosis of autoimmune gastritis (positive parietal cell antibody and gastric *corpus* atrophy) established in a 6 year period (2006-2011) in the setting of refractory iron deficiency anemia (refractoriness to oral iron therapy for at least 6 mo and requirement for intravenous iron therapy) investigation, after exclusion of other potentially contributing causes of anemia. *Helicobacter pylori* (*H. pylori*) infection and anti-secretory therapy were also excluded. Data were retrospectively collected from clinical files, including:

demographic data (age, gender, and ethnic background), past medical history, gastrointestinal symptoms, familial history, laboratorial evaluation (Hb, serum ferritin, serum gastrin, pepsinogen I / pepsinogen II, B12 vitamin, intrinsic factor autoantibodies, thyroid autoantibodies, and anti-transglutaminase antibodies), and endoscopic and histological findings (HE, Periodic Acid-Schiff/Alcian blue, gastrin, chromogranin A and immunochemistry analysis for CD3, CD20 and CD68). Descriptive statistical analysis was performed (mean, median, and standard deviation).

RESULTS: We report a case-series concerning 3 girls and 2 boys with a mean age of 13.6 ± 2.8 years (3 Caucasian and 2 African). One girl had type I diabetes. Familial history was positive in 4/5 cases, respectively for autoimmune thyroiditis (2/5), sarcoidosis (1/5) and multiple myeloma (1/5). Laboratorial evaluation on admission included: Hb: 9.5 ± 0.7 g/dL; serum ferritin: 4.0 ± 0.9 ng/mL; serum gastrin: 393 ± 286 pg/mL; low pepsinogen I / pepsinogen II ratio in 1/5 patients; normal vitamin B12 levels (analyzed in 3 patients). Endoscopy findings included: duodenal nodularity (2/5) and gastric fold softening (2/5), and histological evaluation showed *corpus* atrophic gastritis with lymphocytic infiltration (5/5), patchy oxyntic gland mononuclear cell infiltration (5/5), intestinal and/or pseudo-pyloric metaplasia in *corpus* mucosa (4/5), and enterochromaffin cell hyperplasia (4/5). Immunochemistry for gastrin on *corpus* biopsies was negative in all cases. Duodenal histology was normal. All biopsies were negative for *H. pylori* (Giemsa staining and cultural examination).

CONCLUSION: We highlight autoimmune gastritis as a diagnosis to be considered when investigating refractory iron deficiency anemia in children, particularly in the setting of a personal/familial history of autoimmune disease, as well as the diagnostic contribution of a careful immunohistological evaluation.

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Key words: Autoimmune gastritis; Iron deficiency anemia; Children

Core tip: Autoimmune gastritis (AIG) is a rare entity at young age. Although classically associated with pernicious anemia in adulthood, its presentation as iron-deficiency anemia (IDA) has been recently reported, particularly in younger patients. Our study aimed to further contribute to a better characterization of clinical and histological expression of AIG at pediatric age, highlighting IDA as a precocious hematological manifestation and the diagnostic contribution of a careful immunohistological evaluation. Furthermore, in the setting of personal and/or familial history of autoimmune disease, the importance of taking AIG into account and including parietal cell antibodies in the autoimmune screening panel is emphasized.

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INTRODUCTION

Autoimmune gastritis (AIG) is an inflammatory condition of the stomach, typically restricted to the *corpus* and characterized by the presence of autoantibodies against the proton pump H⁺/K⁺ adenosine triphosphatase (present in gastric parietal cells), and to a lesser extent to intrinsic factor^[1-3]. The immunopathogenic basis for this process seems to involve the activation of parietal cell-specific T helper type 1 CD4-T cells^[4,5]. Macroscopically, gastric mucosa becomes thinner and the folds soften. Histologically it is characterized by the loss of gastric glandular structures in the oxyntic mucosa, which are inappropriately replaced by glands^[6]. Histological features result in achlorhydria, low serum pepsinogen I, and hypergastrinemia. Additionally, a proliferation of enterochromaffin-like cells (ECL) occurs due to trophic stimulus induced by hypergastrinemia^[4,7,8].

AIG is a well-known cause of pernicious anemia in middle-aged and elderly adults, and is usually expressed by cobalamin deficiency and megaloblastic anemia. Its role in iron deficiency anemia (IDA) (a recognized complication of achlorhydria) has recently been evaluated, and seems to be more prevalent in young patients with AIG compared to older patients in whom pernicious anemia is the most prevalent hematologic condition^[1,9,10]. Hershko *et al*^[10] reported a significant frequency of AIG in adults with IDA without gastrointestinal symptoms and a progressive increase in mean corpuscular volume with age^[9].

AIG accounts for up to 10% of cases of gastritis in adults^[11] and it has an estimated overall prevalence closer

to 20% in the general population, as assessed by the serological biomarker of parietal cell antibody^[12]. However, its true incidence worldwide remains unclear, because it is usually asymptomatic before clinical presentation as pernicious anemia in adulthood.

In children, AIG is considered a very rare condition^[13,14]. There are only a few reports of AIG in pediatric patients^[8,15-18] and, in such cases, it is rarely associated with IDA^[16]. In fact, in the two series that have been published to date, gastric autoimmunity has been incidentally disclosed in the setting of type 1 diabetes^[18] and thyroiditis^[19].

The present study describes 5 pediatric cases of AIG diagnosed during the work-up evaluation of IDA, emphasizing the important contribution of gastric *corpus* histopathology findings to a definitive diagnosis.

MATERIALS AND METHODS

We performed a descriptive, observational case-series study of five cases of pediatric AIG retrospectively collected from clinical files covering a 6-year period (2006-2011).

Diagnosis was suggested during investigation of IDA [Hemoglobin (Hb) < 2 SD for age and sex and serum ferritin < 15 ng/mL], refractoriness to oral iron therapy for at least 6 mo, and requirement for intravenous iron therapy. Upper endoscopy confirmed the presence of *corpus* atrophic gastritis and positive anti-parietal cell autoantibodies (PCA). At least three gastric biopsies were collected from each patient (gastric *fundus*, *corpus*, and *antrum*). Duodenal mucosa biopsies were also obtained. Cultural examination for *Helicobacter pylori* (*H. pylori*), according to standard methodology^[20], was performed in all cases.

Formalin-fixed (10%), paraffin-embedded tissues from *antrum* and *corpus* biopsies were processed according to conventional histological technique. Serial sections (4 μm) were stained with hematoxylin-eosin (HE), Giemsa staining for *H. pylori*, and Periodic acid-Schiff/Alcian blue staining at pH = 2.5 to confirm the presence of intestinal and pseudopyloric metaplasia (antral-like mucosa obtained from anatomically-collected *corpus* mucosa). Degree of active and chronic inflammation was scored on a scale of 0 to 3 (0 = none, 1 = mild, 2 = moderate, and 3 = intense) according to the updated Sidney system^[21]. As gastrin cells are absent from *corpus* mucosa, gastrin immunostaining was performed in all cases (indirect method with polymer detection system peroxidase/DAB) were performed for gastrin (polyclonal antibody, 1:1800 dilution, A0568, DAKO®), to ensure that the biopsied tissue was obtained from *corpus*. ECL-cell hyperplasia in the gastric *corpus* was also evaluated in all cases using chromogranin A staining (polyclonal antibody, 1:350 dilution, Invitrogen®). Results were scored as normal, linear, or nodular hyperplasia, using the modified Solcia classification^[22]. According to this classification, linear ECL-cell hyperplasia is characterized by a linear sequence of at least five ECL-cells lying inside the basement membrane of glands. The diagnosis requires at least two such lines

Table 1 Demographic, clinical and laboratorial characterization of autoimmune gastritis patients

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Mean \pm SD
Patient Data						
Age (yr)	14.75	16	14.1	16.1	7.25	13.6 \pm 2.87
Gender	M	F	M	F	F	-
Ethnicity	African	African	Caucasian	Caucasian	Caucasian	-
Personal History	-	-	Type I Diabetes	-	-	-
Familial History	Mother (sarcoidosis, multiple myeloma)	Mother (breast cancer), Uncles (type I diabetes)	Mother (breast cancer)	Mother (autoimmune thyroiditis)	Mother (autoimmune thyroiditis)	-
Symptoms	Dyspepsia	Dyspepsia	-	-	-	-
Laboratorial Data						
Hemoglobin (g/dL)	9.1	10.7	9.7	9.9	8.5	9.56 \pm 0.71
Serum ferritin (ng/mL) (Ref: 7-140)	4.5	5.6	4.1	2.9	3.2	4.06 \pm 0.96
Vitamin B12 (pg/mL) (Ref: 200-835)	-	509	236	618	-	454 \pm 160
Gastrin (pg/mL) (Ref: < 100)	106	479	548	32	800	393 \pm 286
PGI/ PGII (Ref: > 1.0)	1.68	0.9	2.07	1.09	1.04	1.36 \pm 0.46
PCA	(+)	(+)	(+)	(+)	(+)	-
IFA	(-)	(-)	(-)	(-)	(-)	-
TPO/Tg-Ab	(-)	(-)	(-)	(+)	(-)	-

PCA: Parietal-cell antibody; IFA: Intrinsic factor antibody; TPO/Tg-Ab: Anti-thyroid antibodies.

per linear millimeter of mucosa; micronodular ECL-cell hyperplasia is defined by the presence of micronodular clusters of five or more ECL-cells not exceeding 150 μ m in size.

To characterize mucosal inflammatory infiltrate, *corpus* biopsy immunostaining with anti-CD3 antibody (polyclonal A0452, DAKO[®]), anti-CD20 antibody (Clone L26, M0755, DAKO[®]), anti-CD68 antibody (Clone PG-M1, A0452, DAKO[®]), and anti-gastrin (polyclonal, A0568, DAKO[®]) was performed. All positively-marked cells were counted (epithelium, crypt, and *lamina propria*) at 40x magnification; results were expressed as number of immunostained cells per field. Sections were independently evaluated by two experienced pathologists. Clinical data concerned age, gender, ethnic background, past medical history, familial history, and laboratorial data at admission. These included iron status evaluation (Hb, ferritin), serum B12 vitamin levels, serum gastrin, serum pepsinogen I, pepsinogen II, respective ratio (PG I /PG II), and autoimmune profile [PCA, intrinsic factor auto-antibodies (IFA), anti-thyroglobulin and/ or anti-thyroid peroxidase autoantibodies (TPO/Tg-Ab) and anti-transglutaminase auto-antibodies (TgA)]. *H. pylori* serology was further included. Other potentially contributing causes of anemia were excluded, namely gastrointestinal blood loss, nutritional deficiency, menstrual losses, inflammatory bowel disease, and celiac disease. No patient was under any pharmacological treatment, including anti-secretory therapy.

Descriptive statistical analysis was performed (mean, median, SD, minimum, and maximum).

RESULTS

The five patients included in this report had a mean age of

13.6 \pm 2.8 years and a male:female ratio of 2:3. Three patients were Caucasian and two were of African origin. Regarding past medical history, one girl had type I diabetes and the rest were previously healthy. Familial history was positive for autoimmune thyroiditis (two mothers), multiple myeloma (MM) and sarcoidosis (one mother), breast cancer (two mothers), and type I diabetes (two uncles of one child). No patient had major gastrointestinal symptoms (Table 1).

Laboratorial values on admission included: mean Hb = 9.5 \pm 0.7 g/dL; mean serum ferritin = 4.1 \pm 0.9 ng/dL; mean serum gastrin = 393 \pm 286 pg/mL (4/5 had hypergastrinemia) and the PG I /PG II ratio below 1 in only one patient. Serum B12 vitamin levels were normal in the three patients in whom it was performed (Table 1). Laboratory values were otherwise normal including liver and kidney function tests.

All patients bar one had negative IgG for *H. pylori*. By definition, all children had positive PCA; none had positive IFA. TPO/Tg-Ab were positive in the sole patient with autoimmune thyroiditis and none had positive TgA (Table 1).

Esophagogastroduodenoscopy showed slight nodular duodenitis in two patients and fold softening in the other two patients.

Histological findings included the presence of a diffuse and moderate to intense mononuclear infiltrate composed of lymphocytes and plasma cells in the lamina propria (Figure 1, Table 2). In all cases, patchy oxyntic gland mononuclear cell infiltration was evident, with moderate to severe atrophic gastritis in four patients (Figure 2) and mild atrophic gastritis in one (younger patient). In *corpus* mucosa, intestinal and pseudopyloric metaplasia were observed in one and three patients, respectively. All biopsies were negative for *H. pylori*, both in Giemsa staining and

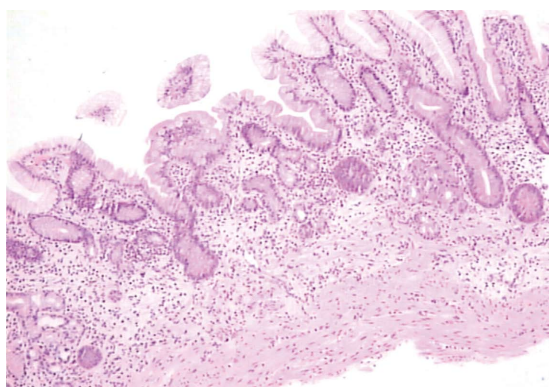


Figure 1 Gastric antrum mucosa (hematoxylin-eosin staining) with chronic atrophic gastritis and moderate-to-intense inflammatory infiltrate.

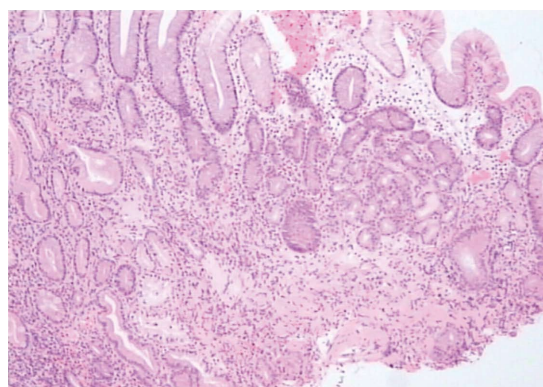


Figure 2 Gastric corpus mucosa: Loss of oxyntic cells and the presence of pseudo-pyloric metaplasia.

Table 2 Gastric biopsies immunostaining counts for T lymphocytes, B lymphocytes, and macrophages

	CD3		CD20		CD68	
	Patients ¹ (range)	Control ²	Patients (range)	Control	Patients (range)	Control
L. propria	204.4 (108-284)	66 -	40.6 (16-73)	8		
Epithelium	77.6 (16-143)	6	0	0		
Crypts	170.2 (77-355)	17	0	0		
Overall	-	-	-	-	50.8 (16-119)	9

¹Patients: Results expressed as mean number (and range) of stained cells per power field (× 40); ²Control: Histologically normal corpus biopsy.

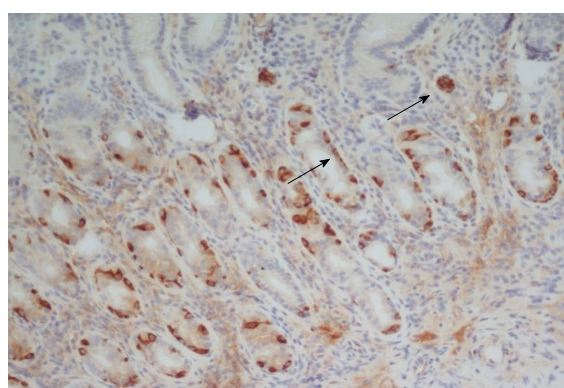


Figure 3 Chromogranin A staining of gastric corpus mucosa from a patient with autoimmune gastritis. Note the linear and nodular (arrows) hyperplasia of endocrine cells.

cultural examination.

Characterization of *corpus* mucosa inflammatory infiltrate showed that it was mainly composed of T lymphocytes (CD3+) rather than B lymphocytes (CD20+) or macrophages (CD68+). Gastrin immunostaining of *corpus* biopsies was negative in all cases, indicating that the biopsies concerned the oxyntic mucosa (data not shown). Furthermore, chromogranin A staining at *corpus* showed linear ECL-cell hyperplasia in 4/5 patients and micronodular ECL-cell hyperplasia in 3/5 cases (Figure 3). Duodenal biopsies showed no major abnormalities in any of the patients.

DISCUSSION

AIG is recognized as a very rare condition in childhood^[13,14], but due to its asymptomatic course in the majority of the patients, it may remain underdiagnosed at a young age. In this report, we studied five youths with a diagnosis of AIG presenting as IDA. Though this association has recently been highlighted in the adult population, it has rarely been reported in pediatric patients.

IDA is a common condition in childhood^[23], and its refractoriness to oral iron therapy should suggest a range of gastrointestinal pathologies, including celiac disease.

This entity was excluded in our patients. Although iron absorption is also known to be impaired in the setting of gastric hypo/achlorhydria, gastric atrophy is usually not considered a frequent etiological factor for IDA in the pediatric age group. In adult patients with IDA and no major gastrointestinal symptoms, it has been previously reported that 20% had gastric atrophy associated with hypergastrinemia and positive PCA^[24]. Moreover, Hershko *et al.*^[25] reported that AIG is 4-6 times more frequent in patients with unexplained IDA than celiac disease. Although pernicious anemia is considered the classic hematological presentation of AIG, further studies have highlighted IDA as a precocious manifestation of this gastric condition^[10,11]. Hershko *et al.*^[25] compared patients with macrocytic anemia and patients with IDA to show that the former were much younger, and the mean globular volume of erythrocytes, ferritin, and gastrin increases with age as cobalamin levels decrease^[9]. In our report, all patients bar one (a seven year old girl) were adolescents and diagnosed as having AIG during investigation for refractory IDA, thus reinforcing the hypothesis of IDA as an early manifestation of AIG. On the other hand, it can't be assumed that AIG is the only etiologic factor, as IDA in fertile woman may incur menstrual loss^[10,26]. Although in the present study intravenous iron therapy and follow-

up data were not included, it is well recognized that periodical replacement of iron stores in these patients is necessary.

Although serum gastrin levels were increased in three of our patients in the present study, the PG I /PG II ratio was low in only one patient. The different disease course time, as well as lesser histological involvement, should be taken into account in patients of a young age compared to those in adulthood.

Lahner *et al*^[27] have recently reported, PCA and IFA sensitivity of 81.5% and 37%, respectively, in adults. It is not surprising that all our patients had positive PCA and negative IFA, as it has been argued that the positivity of IFA increases with age and the duration of the disease^[28], and eventually some patients will develop IFA at later stages.

It has been clearly established that a CD4+ T cell response to the H/K ATPase beta-subunit, in particular, is essential for the initiation of autoimmune gastritis^[29]. Thus, the immunopathology of autoimmune gastritis is due to a disruption of the mucosal immune response, potentially involving Treg cells, rather than a direct depletion of the end-stage parietal and zymogenic cells^[29]. According to the frequent association of AIG with other autoimmune diseases, we report the case of one girl with a previous diagnosis of type 1 diabetes and another case with positive TPO/Tg-Ab without clinical manifestations. There was also a strong familial history of autoimmunity in three patients (type 1 diabetes in the uncles of one girl and autoimmune thyroiditis in the mothers of two girls). Previous studies showed that type 1 diabetes^[30,31] and autoimmune thyroiditis^[19,32,33] may be associated with positive PCA and AIG at young ages.

Segni *et al*^[19] reported an incidence of PCA in patients with autoimmune thyroid disease reaching 21%, with atrophic gastritis in 5/18 patients submitted to endoscopy. Interestingly, all our patients had both positive PCA and *corpus* atrophic gastritis. This underlines the need to screen patients with autoimmune conditions for AIG.

Concerning histopathological features, we noticed that in all of our patients (with one exception) there was a moderate to severe gastritis with intense inflammatory infiltrate (T lymphocytes predominance, as expected), intestinal and/or pseudo-pyloric metaplasia, and ECL micronodular or linear hyperplasia. Micronodular hyperplasia is generally combined with linear hyperplasia and is typically found in patients with autoimmune chronic atrophic gastritis in association with higher levels of serum gastrin^[22].

The importance of a firm histological diagnosis of AIG should be emphasized, which requires a representative number of gastric mucosal samples (*antrum*, *corpus*, and *fundus*) due to the focal nature of the process^[4,34]. It is also essential to topographically localize mucosal biopsies in order to ensure that the gastritis process is localized to the *corpus* and *fundus* (negative immunohistochemistry for G cells).

The association of *H. pylori* with AIG is a controver-

sial issue. Although AIG is not classically associated with *H. pylori* active infection, this agent had been advocated by some authors as a trigger for the development of the autoimmune process in the gastric mucosa^[35-37].

According with this, no culture was positive and only one of our patients had positive IgG serology for *H. pylori*, which was compatible with past infection. These findings are consistent with previous reports that did not find an association between AIG and *H. pylori* infection^[38]. Finally, concerning the issue of cancer risk, endoscopic surveillance of AIG every 5 years has been suggested^[39].

In conclusion, our study aimed to further contribute to a better characterization of the clinical expression of AIG at a pediatric age, as well as highlighting IDA as a precocious hematological manifestation and the diagnostic contribution of a careful immunohistological evaluation. Furthermore, in the setting of personal and/or familial history of autoimmune disease, the importance of taking AIG into account and including PCA in the autoimmune screening panel is emphasized.

COMMENTS

Background

Autoimmune gastritis is a very rare entity in patients of a young age. Although classically associated with pernicious anemia in adulthood, recent studies have reported its presentation as an iron-deficiency anemia.

Research frontiers

Pernicious megaloblastic anemia is a well-known complication of autoimmune gastritis. The association of this digestive disease with iron deficiency anemia in young patients and the mean globular volume evolution throughout life in autoimmune gastritis patients has currently been highlighted.

Innovations and breakthroughs

Autoimmune gastritis is classically seen as a disease of the elderly, manifesting as pernicious anemia. This study describes five cases of this disease in children and adolescents, which was diagnosed in the setting of refractory iron deficiency anemia.

Applications

Refractory iron deficiency anemia could be a manifestation of autoimmune gastritis in young patients and this diagnosis should be considered, after the exclusion of more frequent etiologies, particularly in the setting of a personal or familial history of other autoimmune diseases.

Terminology

Autoimmune gastritis - atrophic gastritis restricted to the *corpus* associated with the presence of autoantibodies against the parietal cell proton pump H+/K+ adenosine triphosphatase. Refractory Iron Deficiency Anemia - Anemia (Hb < 2 SD for age and sex) due to iron deficiency (serum ferritin < 15 ng/mL), refractory to oral iron therapy for at least 6 mo and a requirement for intravenous iron therapy.

Peer review

The inflammatory infiltrate in the gastric mucosa should be identified by immunohistology with antibody markers minimally for T cells, B cells, and macrophages. The characteristics of the gastric glandular atrophy should be documented by immunostaining for parietal cells by antibody to these cells in order to assess for any loss of these cells from the gastric mucosa; the hypergastrinemia supports the loss of these cells. The presence of metaplasia should be assessed by immunostaining for mucin.

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