

Pediatric autoimmune disorders with gastrointestinal expressions: from bench to bedside

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Summary

The gastrointestinal (GI) tract may be involved in systemic autoimmune diseases or may be the target of organ-specific autoimmunity. Autoimmune enteropathy (AIE) is a rare disorder characterized by severe and protracted diarrhea, weight loss from malabsorption and immune-mediated damage to the intestinal mucosa, generally occurring in infants and young children, only rarely in adult. The salient histopathologic features of AIE are most prominent in the small intestine: villous blunting, crypt hyperplasia, mononuclear cell inflammatory expansion of the lamina propria with intraepithelial lymphocytosis, crypt apoptosis and absence of Paneth cells, goblet cells or both. Esophagus, stomach and colon are frequently also involved. Anti-enterocyte antibodies are identified in the majority of cases, and their presence, even if variable, can help confirming the diagnosis. The purpose of this review is to provide an overview of the latest immunological advances in AIE, as well as to offer a practical approach for histological diagnosis for 'general' pathologist.

Key words: autoimmune enteropathy (AIE), autoantibody, pediatric disease, autoimmune disease, small bowel, large bowel

Introduction

Autoimmunity is the aberrant reaction of immune system to human antigens (autoantigens). The triggers leading to recognition of own determinants, receptors, surface molecular cellular antigens as 'foreign', followed by activation of T and B lymphocytes, are unknown. The genetic background seems to play a limited role. The develop of autoimmune process include tissue infiltration with immunocompetent cells, overproduction of pro-inflammatory cytokines, and production of autoantibodies by plasmocytes ¹.

Gastrointestinal (GI) tract may be involved in systemic autoimmune diseases (systemic lupus erythematosus, inflammatory muscle disorders, vasculitis, etc.). The specific manifestations for each disease are influenced by the underlying autoimmune process, being either the initial presentation of these disorders or a complication of treatment ². Moreover, the GI tract may be the 'target' of organ-specific autoimmunity. In 1985, Unsworth and Walker-Smith ³ introduced the term "autoimmune enteropathy" (AIE) for cases of intractable diarrhea associated with the

Received and accepted: July 30, 2021
Published online: December 2, 2021

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Conflict of interest

The Authors declare no conflict of interest.

How to cite this article: Francalanci P, Cafferata B, Alaggio R, et al. Pediatric autoimmune disorders with gastrointestinal expressions: from bench to bedside. *Pathologica* 2022;114:32-39. <https://doi.org/10.32074/1591-951X-339>

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presence of circulating autoantibodies against the enterocytes with or without other autoimmune manifestations, in the absence of a primary immune deficiency. Although AIE primarily involves the small bowel, extent to esophageal, gastric and large bowel intestinal tract is very common (pan-gastrointestinal disorder). AIE is a disorders belonging to Childhood Enteropathies (CE), consisting in persistent unexplained diarrhea in children younger than 3 months. Other CE are: a) conditions related to defect of lipid trafficking; b) constitutive enterocyte disorders (microvillus inclusion disease and tufting enteropathy); c) congenital deficiency of intestinal endocrine cell⁴⁻⁵. AIE is probably the most frequent disorder among CE. Specific histopathologic findings of CE are summarized in Table I. Most cases manifest in males primarily with secretory diarrhea; a family history of other affected siblings, frequent extra-intestinal involvement and circulating autoantibodies to intestinal epithelial cells (enterocytes or goblet cells) are present⁶. The role of anti-enterocyte antibodies in monitoring AIE is not completely clear, as these autoantibodies could be present at the onset of clinical symptoms, after mucosal damage and disappear before the restoration of normal mucosa⁷. In addition, antibodies to enterocyte components at low titers have also been found in patients affected by other gastrointestinal disorders⁸. Intestinal biopsies may reveal a wide range of abnormalities, varying from normal villous architecture to villous atrophy, inflammation and/or increase crypt apoptosis. Patients may have concurrent, additional autoimmune gastrointestinal conditions, including autoimmune atrophic gastritis and lymphocytic colitis. A wide range of associated extra-intestinal conditions may also be seen in patients with AIE, including hypothyroidism, autoimmune hepatitis, arthritis, eczema, nephrotic syndrome and musculoskeletal manifestations⁹.

In this review, we focus on AIE with the aim of providing a clinical- pathological synthesis for reaching the diagnosis of autoimmune enteropathy. In particular, we emphasize the need of clinic-pathologic collaboration to reach the correct diagnosis within the spectrum of CE. In fact, establishing an early diagnosis is critical in reducing morbidity and improving long-term outcomes.

Clinical and laboratory aspects

CE cause severe chronic (> 2-3 weeks) diarrhea, unresponsive to dietary changes or elimination, often starting in the first week of life and malabsorption with fatal complications. A critical part of the diagnostic workup is represented by laboratory investigations, comprising a standard panel of blood chemistry tests including complete blood count, metabolic profile, inflammatory indices, serology and fecal cultural examinations. CE is suspected after the exclusion of other pediatric disorders causing the same symptoms, such as infections, VEO-IBD, congenital diarrheal disorders, refractory celiac disease, food allergies and infectious enteropathies¹⁰⁻¹². There is a great variation in clinical pictures: high-output diarrhea, malabsorption, growth failure and/or electrolyte abnormalities, sometimes requiring long term parenteral nutrition. Concurrently, additional autoimmune conditions and extraintestinal manifestations are present in the most severe disease. Serologic studies for anti-enterocyte and anti-goblet cells antibodies could be helpful in case of refractory diarrhea of unknown etiology in a child. However, their absence does not exclude the diagnosis⁶ and anti-goblet cell antibodies are not specific, as they may also be positive in celiac disease¹³.

Table I. Childhood enteropathies: differential diagnosis.

	Congenital enterocytedisorders			Congenital deficiency endocrine cells	AIE
	Defect of lipid trafficking	Microvillus inclusion	Tufting enteropathy		
Presentation	First 2 wks	First 2 wks	First 2 wks	First 2 wks	After 1 mth
Gene defect	MTP, HBL, CRD	MYO5b	EpCAM	NEUROG3	
Extraintestinal disease	Peripheral acanthocytosis	PFIC type 6	Dysmorphism Autoimmune diseases	Insulin-dep diabetes	Autoimmune diseases
Anti-enterocyte Ab	No	No	No	No	Yes
Villus atrophy	No	Yes	Variable	Variable	Variable
Surface epithelium	Normal (cytoplasmic vacuolization)	Absent brush border	Tufting	Normal	Variable
Lamina propria inflammation	No	Mild	Variable	Mild	Mild to severe

Genetic associated disorders

AIE appears to result from dysregulation of gut humoral and immune function¹⁴. Genetic mutations resulting in T-cell hyperactivation underlie two syndromic forms of AIE: a) Immune dysregulation: Polyendocrinopathy, Enteropathy, and X-linked (IPEX) syndrome, and b) Auto-immune phenomena: Polyendocrinopathy, Candidiasis, and Ectodermal Dystrophy syndrome (APECED).

IPEX is a rare recessive disorder caused by loss-of-function mutations in Forkhead box p3 (*FOXP3*), a transcriptional regulator required for normal development and function of regulatory T-cells (Treg)¹⁵. *FOXP3* is mainly expressed by CD4+CD25+ Tregs and controls their function and sustains their maintenance¹⁶. In IPEX patients, *FOXP3* mutations cause different degrees of Treg impairment, from complete absence of suppressive function and switching to effector phenotype, to partially preserved inhibitory effect¹⁷. Loss of *FOXP3* activity leads to immune hyperactivation in response to antigen stimulation and cellular injury via CD4+ effector T cells¹⁵. According to the type and site of *FOXP3* mutation, normal frequencies of CD4+CD25+CD127lowFOXP3+ Treg-like cells can be detected in the peripheral blood of patients, indicating that a population of dysfunctional Treg-like cells can originate from the IPEX thymus and reside in the periphery¹⁸. In IPEX syndrome, defective Tregs, incapable to adequately regulate cytokine production, switch to an effector phenotype, either Th2 or Th17, possibly contributing to the autoimmune damage¹⁹. Due to the fact that obvious relationship between site of mutation and Treg defects is still obscure, systematic functional and phenotypical study of Tregs from patients with immune dysregulation indicative of IPEX syndrome would provide support to confirm the diagnosis. As collateral result of *FOXP3* deficiency, B-cell tolerance is also compromised in IPEX: autoreactive B cells gather peripherally, due to impaired control of B-cell tolerance

checkpoints by defective Tregs, triggering the formation of tissue-specific autoantibodies, which can successively play a role in the clinical picture²⁰.

APECED is an autosomal recessive condition due to mutations in the AIRE gene encoding the autoimmune regulator protein. This protein plays a crucial role in immune tolerance, specifically in eliminating T cells that bind to self-antigens²¹. AIRE is implicated in the expression of tissue-restricted antigens (TRAs), i.e. tissue components that are only selectively expressed and do not possess ubiquitous localization. Such antigens are crucial for negative selection as they serve to the projection of the complete self-repertoire at the local site of negative selection and permit the destruction of all autoreactive T cells. APECED syndrome, therefore, implicates autoreactive T cells that evaded selection, alongside with autoantibodies²². AIRE plays a pivotal part in the maintenance of immune self-tolerance, by inducing the deletion of maturing self-reactive thymocytes and by producing Tregs that adequately kill autoreactive reactions exerted by self-reactive T cells in their periphery²³. Table II shows the comparison between non-genetic and genetic (IPEX and APECED) AIE.

Moreover, AIE can be associated with other primary immunodeficiencies such as common variable immunodeficiency (CVID) and hypogammaglobulinemia, the latter being the most commonly reported disorders. Some histologic features typically associated with AIE have been described in this context, such as increased basal apoptosis and depletion of goblet cells²⁴.

Pathophysiology of AIE

Immune tolerance is maintained by human leukocyte antigen (HLA) class II molecules, which are exposed on the surface of epithelial cells and present antigenic pep-

Table II. Comparison of non-genetic and genetic AIE.

	AIE (non-genetic)	AIE IPEX	AIE APECED
Disease name	Autoimmune enteropathy	Immunodysregulation Polyendocrinopathy Enteropathy X-linked Syndrome	Autoimmune Phenomena, Polyendocrinopathy, Candidiasis, and Ectodermal Dystrophy
Gene name	-	FOXP3	AIRE
Transmission	-	X-linked	Autosomal recessive
Association with other Autoimmune disease	Yes	Yes	Yes
Pathogenic mechanism	T-lymphocyte hyperactivation and Ab against enterocytes or goblet cells	T-lymphocyte dysfunction	T-lymphocyte dysfunction
Treatment	Immunosuppression	Immunosuppression, bone marrow transplant	Immunosuppression, hormone replacement

tides to T lymphocytes²⁵. In autoimmune enteropathy, aberrant expression of self-antigens on epithelial cells triggers CD4+ T lymphocytes, which produces downstream effects leading to the destruction of the enterocytes by means of apoptosis or other cytotoxic effects⁹. The contribution for T cell activation in the disease mechanism is supported by the efficacy of drugs such as cyclosporine in the treatment of autoimmune enteropathy²⁶. Autoantibodies directed against intestinal epithelial cells have also been found in the pathogenesis of autoimmune enteropathy and can be directed toward goblet cells, enterocytes, and the intestinal brush border. Autoantibodies directed against AE75, an intestinal antigen that exerts an important function in the integrity of tight junctions and cytoskeleton integrity, leads to enhanced intestinal permeability²⁷. These features increase the immunological response and are thought to contribute to the inflammatory enteropathy.

Tissue damage

Intestinal epithelium is a natural barrier between environmental and food antigens and cells of the mucosal immune system. In systemic autoimmune diseases, autoantibodies form immune complexes activating the classical complement cascade. This generates membrane attack complex formation and mucosal damage. In the small bowel, T lymphocytes, activated T cells, B cells, plasmoblasts and plasmocytes locally producing autoantibodies, infiltrate the mucosa moving from deep crypt level to the top of villi. Intestinal T lymphocytes could damage the enteric mucosae by exerting direct cytotoxicity against epithelial cells, causing enterocyte apoptosis with an antibody-dependent cellular cytotoxicity and through the secretion of lymphokines. Likewise, inflammation site under the epithelial layer is activated in sequential steps to develop and support chronic inflammation triggering tissue damage. IFN- γ and TNF, produced by activated T cells, activate macrophages and stimulate further production of TNF. This activation is associated with induction of epithelial cells apoptosis and damage to first defending cellular barrier. Moreover, high level of TNF facilitates maturation of stromal cells into myofibroblasts releasing metalloproteinases-tissue degrading enzymes^{1,9}.

AIE diagnosis

ENDOSCOPIC FEATURES

In AIE diagnosis, endoscopy has a crucial role, describing mucosal alteration and acquiring bioptic sam-

ples. Macroscopic aspect of AIE can vary from normal mucosa to hyperemia and ulcerations, with different distribution and intensity. It is mandatory to perform both upper GI endoscopy and colonoscopy, with multiple biopsies in each sites, even in presence of 'normal' mucosa.

SITE OF BIOPSY AND STAINS

Gastric (fundus, corpus and antrum), duodenal (levels I and II), distal ileum and colonic biopsies at every segment should be taken and sent for pathologic examination in separately coded vials. In the case of suspicion of congenital enterocyte abnormalities, one fragment should be sent for electron microscopy, while for lipid transport abnormalities an additional fresh piece of biopsy should be sent to pathology for lipid stains and/or for indirect immunofluorescence using patient's serum to detect the presence of anti-enterocyte antibodies²⁸. For histological examination, paraffin-embedded sections are cut at 3-4 μ m thickness and stained with hematoxylin and eosin. CD3 immunohistochemistry may be useful for a detailed count of intraepithelial T lymphocytes.

HISTOLOGY REPORT

The histopathology report should describe and grade following lesions (Tab. III)¹⁵:

- villous/crypt ratio, graded as normal, partial atrophy (villous/crypt less or = 1) or subtotal-total atrophy (villous/crypt < 1);
- goblet cells number, defined as normal, decreased or absent in glandular and surface epithelial cells;
- inflammatory component in the lamina propria, graded as normal, moderately or markedly increased;
- crypt epithelial apoptosis, reported if > 1 apoptotic figure per 10 crypts is observed;
- predominant type of inflammatory cells, such as lymphocytes, plasma cells, neutrophils or eosinophils;

Table III. Histopathological parameters.

Criteria	Grade
Villus atrophy	Normal-partial villus atrophy - subtotal total atrophy
Goblet cells	present-reduced-absent
Inflammatory infiltration	absent-mild-moderate-severe, IEL evaluated with CD3
Type of inflammatory cells	lymphocytes, plasma cells, neutrophils, eosinophils
Glandular pathological features	cryptitis, crypt abscesses, necrosis, apoptosis
Crypt epithelial apoptosis	> 1/10 crypts

- glandular alterations, such as crypt abscesses, partial or total atrophy and necrosis. The necrotic or apoptotic cells appeared as single-cell necrosis or clusters of necrotic cells.

The histological changes of AIE are rather variable. Based on predominant histological alterations, four pattern can be recognized: a) active chronic duodenitis, b) graft-vs-host disease-like pattern, c) coeliac disease-like pattern and d) enteropathy, the latter characterized by a depletion of intestinal goblet/Paneth cells along with the presence of anti-goblet/Paneth cell autoantibodies²⁹⁻³⁰.

Very suspicious for AIE histology alterations are: marked villous atrophy, crypt hyperplasia, a mixed inflammatory infiltrate of the lamina propria and extensive apoptosis in the crypts, similar to those noted in intestinal graft-versus-host disease. Depletion of goblet and Paneth cells, generally not observed in other inflammatory intestinal diseases, may address to a diagnosis of AIE. In contrast to coeliac disease with flat villi, intraepithelial lymphocytes tend to be relatively few in number³¹ (Fig. 1). A concomitant gastritis and crypt destructive colitis are present in the majority of cases⁷ (Fig. 2).

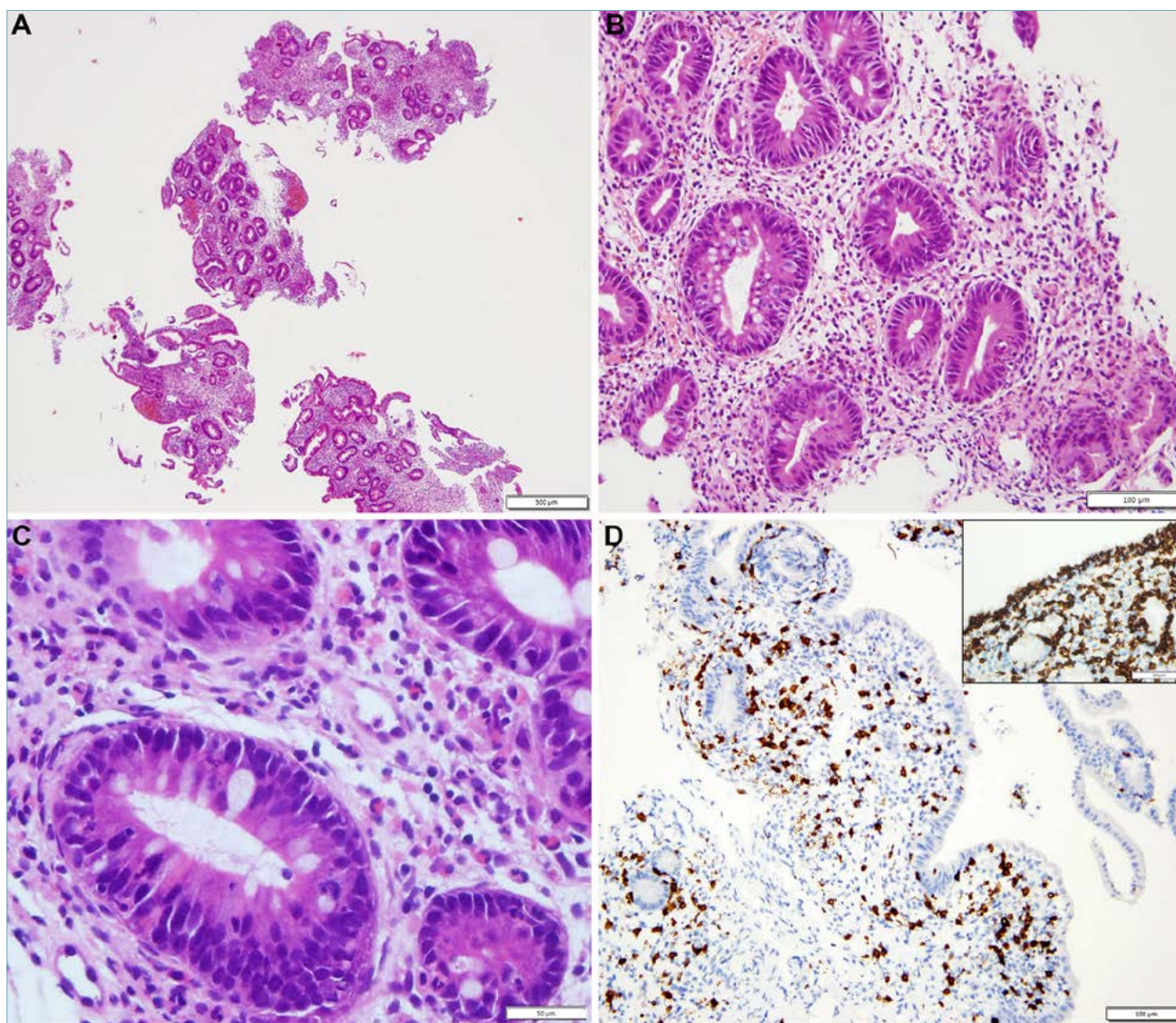


Figure 1. Duodenal biopsy from a 4-month-old boy with AIE. A) Marked mucosal crypt-destructive inflammatory infiltrate with villous atrophy (H&E, 4x). B) Significant reduction of goblet and Paneth cells (H&E, 20x). C) Increased basal crypt apoptosis (H&E, 40x). D) CD3 immunostaining shows few intraepithelial T-lymphocytes (20x), in the *inset* CD3 immunostaining in celiac disease displays > 25/10 T-lymphocytes/enterocytes (20x).

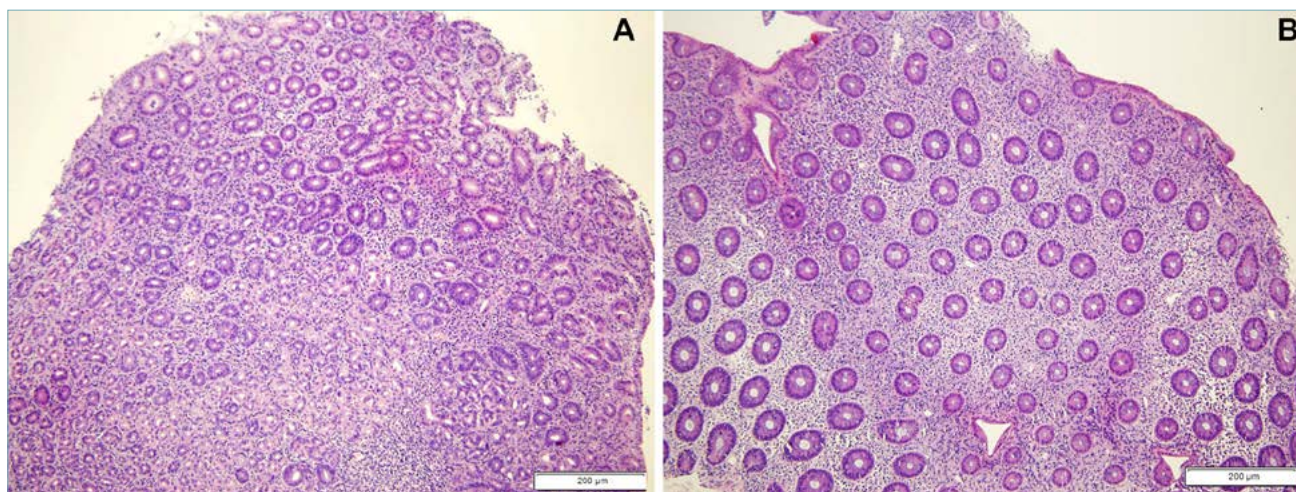


Figure 2. Gastric biopsy from a 4-month-old boy with AIE showing chronic gastritis (A, H&E, 10x) and chronic quiescent colitis (B, H&E, 10x).

On indirect immunofluorescence, positive fluorescent staining results in a linear pattern along the apex and baso-lateral border of the enterocyte (Fig. 3). The antibodies are predominantly IgG and have been described as complement-fixing, though IgM and IgA have also been described.

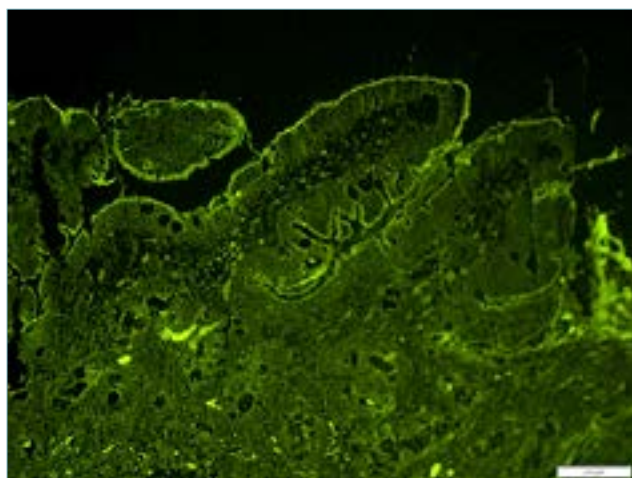


Figure 3. Indirect immunofluorescence using serum from a 4-month-old boy with AIE syndrome on frozen sections of normal human small bowel. There is diffuse linear staining along the apical border of the enterocytes all along the villi (20x).

Differential diagnoses

The differential diagnoses of pediatric AIE include other immune-mediated disorders, such as food sensitivity enteropathies (e.g. cow's milk intolerance and celiac disease)¹², VEO-IBD¹¹ and graft-versus-host disease⁵. In older patients, celiac disease is the first condition that should be ruled out, particularly refractory celiac disease which is a form no longer responsive to a gluten free diet³². Clinical and serological correlations are the cornerstone in this differential diagnosis. A high index of suspicion for AIE should be present when there is a severe inflammatory pan-enteric crypt destructive process with villous atrophy without significantly increased intraepithelial lymphocytes, with increased apoptosis in the base of the crypts and loss of goblet and Paneth cells. CVID may be distinguished in most cases by the relative paucity of inflammatory cells and the history of repeated infections.

Treatment

Management of autoimmune enteropathy includes:

- optimizing nutritional status (enteral and parenteral nutrition);
- anti-inflammatory drugs somministration (corticosteroids as first-line agents, second line agents such as calcineurin inhibitors, mycophenolate mofenil, azathioprine, anti-tumor necrosis factor agents, specific treatment like hematopoietic stem cell transplantation in special situations such as in

IPEX, abatacept in CTLA-4 deficiency, hormone replacement and immunosuppression in APS-1, immunoglobulin replacement for patients with hypogammaglobulinemia, etc.);

- close monitoring for complications of disease and for adverse effects of drugs critical to allow a better prognosis in these patients.

Conclusion

AIE in children, like adults, is a heterogenous disease characterized by severe and intractable diarrhea, immune-mediated damage to the GI and concurrent autoimmune-associated conditions. AIE most commonly presents in the small intestine with villous blunting, lamina propria expansion by mixed inflammation and neutrophilic cryptitis. Increased apoptosis can be associated and is a helpful feature when present. Intraepithelial lymphocytes are not increased as in celiac disease, even if a coeliac disease-like pattern may be identified. Histopathologic abnormalities outside the small intestine are recurrent and may facilitate recognition of this uncommon disease by the pathologist. AIE appears to be a *pan-gastrointestinal disorder*, frequently with multivisceral involvement, in which intestinal symptoms may be the initial manifestation of disease. More importantly, however, good clinico-pathologic collaboration is crucial for the differential diagnosis of childhood enteropathies and prompt initiation of appropriate therapy.

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