THE ROLE OF PATHOLOGIST TO GUIDE THE DIAGNOSIS IN A CASE OF RECURRENT BLOODY DIARRHEA IN A YOUNG CHILD

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Abstract

Introduction: Primary eosinophilic gastro-intestinal disorders represent a specific group of inflammatory diseases characterized by the presence of eosinophilic infiltrates of the digestive wall. These disorders are classified into eosinophilic esophagitis, gastro-enteritis and colitis, the last one being the rarest described. *Objectives:* This paper presents a case with eosinophilic colitis in a 3 years old boy which was considered at the onset as Crohn's disease due to common clinical manifestations and similar endoscopic findings, along with an initial inconclusive histopatological interpretation of the biopsy sample. *Case presentation:* Young male, without significant postnatal medical history, at the age of 3 years old presented an episode of acute bloody diarrhea without fever. The investigations performed at the local county hospital, including colonoscopy, established the diagnosis of Crohn's disease. Oral systemic corticosteroids were initiated. After tapering the doses, the symptoms reappeared. The case was addressed to our University Hospital for further investigations. Upon admission, the child didn't present relevant changes at clinical examination. Inflammatory tests were negative, with moderate peripheral eosinophilia, increased total IgE serum level, increased level of specific IgE antibodies against casein/lactalbumin/beta-lactoglobulin. Fecal calprotectin was increased, colonoscopy showed disseminated aphtoid lesions separated by normal mucosa from descendent colon to cecum. Histopathological examination revealed inflammatory infiltrates composed by lymphocytes/eosinophils (~ 30 eosinophils/field). We sustained the diagnosis of eosinophilic colitis associated to cow's milk proteins allergy. After dairy exclusion, with systemic corticosteroids and leukotriene inhibitors, the evolution was favorable. *Conclusions:* A number of pediatric disorders may present similar clinical manifestations with Crohn's disease: infectious enterocolitis/cow's milk protein allergy/eosinophilic colitis. Fecal calprotectin and colonoscopy examination don't have maximum accuracy for differential diagnosis. Histopatological examination is the most specific tool for defining the diagnosis.

Key words: eosinophilic colitis, Crohn's disease, colonoscopy, biopsy

Introduction

During the last few years the incidence of inflammatory bowel diseases (IBD) has risen among the pediatric population. The negative impact upon the normal growth and development process increased the interest of pediatrics specialists towards this pathology. Many other chronic pediatric enteropathies can have similar clinical symptoms as Crohn's disease: cow's milk protein allergy, eosinophilic colitis, intestinal tuberculosis, celiac disease, cystic fibrosis, recto-sigmoid juvenile polyps.

Primary eosinophilic gastro-intestinal disorders represent a specific group of inflammatory diseases characterized by the presence of eosinophilic infiltrates of the digestive wall. These disorders are classified into eosinophilic esophagitis, gastro-enteritis and colitis, the last one being the rarest described. Eosinophilic colitis is a heterogeneous entity with a bimodal distribution of age of onset and can be presented as an acute diarrheal disease in infants and young children, or as a recurrent colitis in teenagers. Pathogenesis of primary eosinophilic colitis is partially elucidated, being incriminated IgE mediated food allergy to certain food proteins or delayed type allergy non IgE mediated and T lymphocyte associated. (1)

Given the nonspecific symptoms, most commonly abdominal pain, constipation/diarrhea and rectal bleeding that are associated with eosinophilic colitis, the lack of distinctive clinical findings and its relapsing-remitting course made the examination of colonic biopsy the golden standard for diagnosis. Eosinophils are easily visible in routine haematoxylin-eosin (HE) stained paraffin embedded sections and can be assessed semi-quantitatively. At present, no consensus has been reached on the histological criteria required to make the diagnosis of eosinophilic colitis.(2)

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There is no consensus over its diagnosis and management and uncertainty is compounded by the use of the same term to describe an idiopathic increase in colonic eosinophils and an eosinophilic inflammatory reaction to known aetiological agents such as parasites or drugs. In patients with histologically proven colonic eosinophilia, it is important to assess the underlying causes and to integrate the medical history of the patient with clinical and laboratory data.(3)

Eosinophils respond to stimuli, including trauma, infections and allergens, by degranulating to release inflammatory mediators including leukotrienes, vasoactive intestinal polypeptide, tumour necrosis factor and interleukins. Eosinophils density in the colon is increased in various disorders including food allergy, parasitic infections and IBD, but in some patients no underlying gastrointestinal pathology is identified and in these cases a diagnosis of primary eosinophilic colitis can be made.(4)

Since tissue eosinophils are increased in many chronic inflammatory conditions, there is a potential for misdiagnosis of early IBD as eosinophilic colitis. In contrast to IBD, the architecture of the colonic crypts in eosinophilic colitis is normally preserved. In doubtful cases with prominent eosinophils, especially if symptoms worsen, rebiopsy after several months may be necessary to exclude IBD.(5)

Case report

The authors present the case of a 3,5 years old child, male patient, who has been admitted for diarrhea and stools with blood streaks (3-4/day) without having fever.

The child comes from a young, healthy couple from rural environment. He was borne at term, weighting 3600 grams. The child was vaccinated according to the national programme, he has been breastfed until 2 years of age and, the complementary feeding has been properly initiated at the age of 6 months old.

As past medical history, at 3 years old, the child presented the first episode of acute diarrhoea with blood streaks, without fever and he was hospitalised at the local County Hospital, Paediatric Ward. After running a set of investigations, infectious enterocolitis was ruled out, Colonoscopy was performed and the endoscopist described redness and small ulcers disseminated form the sigmoid level until the cecum area.Ileo-cecal valve and terminal ileum were normal. Biopies were taken. The histopathological examination showed inflammatory infiltrate consisting predominantly of plasma cells, lymphocytes and several eosinophils, micro abscess with massive necrosis and frequent macrophages. The conclusion was: pancolic Crohn's disease. Oral systemic corticosteroids were initiated. After tapering the doses, the symptoms reappeared and the case was addressed to our University Hospital for further investigations.

Clinical examination upon admission showed normal somatic development for his age - weight 16 kg, height 97 cm. There weren't any relevant changes at clinical examination except the digestive system: painful abdomen at palpation, diarrhea with streaks of fresh blood. There was not liver or spleen enlargement.

The laboratory tests showed normal parameters for total blood count except moderate peripheral eosinophilia (12% eosinophils). Inflammatory tests were negative. Liver and renal tests were normal. Blood coagulation parameters were normal. Assessment of serum immunoglobulines levels IgA, IgG and IgM were within normal values for age. We found increased total serum IgE level, increased level of specific IgE antibodies against casein/lactalbumin/beta-lactoglobulin and egg white. Fecal calprotectin level was increased. We ruled out infectious causes of enterocolitis. Intestinal tuberculosis was also ruled out by performing Quantiferon test that was negative. We ruled out congenital immunodeficiency, celiac disease, cytomegalovirus (CMV) and human immune deficiency virus (HIV) infection.

The laboratory results are summarized in table 1.

Abdominal ultrasound showed normal aspect.

In case of a pediatric patient with recurrent bloody diarrhea considered as steriod dependend Crohn's diseases according to previous endoscopic assessment along with an initial inconclusive histopatological interpretation of the biopsy sample, endoscopic re-assessment become mandatory.

In such a case it is important to integrate clinical and medical history data with laboratory tests and histopathological results. Good clinical status with normal development, along with peripheral eosinophilia, increased total IgE serum level and elevated specific IgE against dietary proteins must drown attention to any clinician to the diagnosis of cow's milk proteins and egg white allergy that could mimic IBD in a young child. The association of IgE mediated alimentary allergy with eosinophilic colitis is well known and the histopathologic report must guide the diagnosis.

We performed upper endoscopy and we repeated the colonoscopy taking multiples biopsies samples from this patient.

Upper endoscopy showed esophagus, stomach and duodenum with normal endoscopic appearance. Colonoscopy showed rectum and sigmoid with normal mucosa. From descending colon to the cecum there were aphtoide lesions/small ulcerations, separated by normal mucosa and there was inflammation of ileo-cecal valve. Serial biopsies were taken.

Figure 1 shows endoscopic aspect of the descending colon.

Histopatological examination showed lymphocytic and eosinophilic infiltrate in the lamina propria (~ 30 eosinophils/field). Glandular architecture was preserved with normal appereance. PAS stain showed no microbial colonies/parasites.

Figures 2 and 3 show histopathological images with dense eosinophilic infiltrate especially in the descending colon.

Table 1: Laboratory results.

Hemoglobine Erytrocytes	12.5 g % 4327000/mmc	Inflammatory tests	ESR=10 mm/h CRP=0.40 mg/l Fibrinogen=2 g/l
Leukocytes Formula	7600/ mmc Sg=21% Ly=62% Eo=12% Mo=7%	Bleeding time Coagulation time INR APTT	2 min 3 min 15 sec 1 35 sec
Platelets	225000/mmc	Iron level	12 µmol/l
Blood gases level	pH = 7.37 pCO2 = 32.3 mmHg, BE = -2 mmol/l HCO3 = 22 mmol/l	Serum elektrolytes	Na=140, K=4.16, Ca= 2.75, Cl=102 mmol/l
Proteinemia	60,6 g/l	Glicemia	4 mmol/l
ELFO	Albumines = 64.3%, α1=2.1%, α2=9.9%, β=10%, γ=13.7%	Immuno-globulines serum level	IgA = 0,71 g/l IgG = 14,37 g/l IgM = 2,04 g/l
Liver function	GPT = 25 U/l GOT = 37 U/l Gamma GT = 42 U/l Alkaline phosphatase = 215 U/l	Stool analysis	Stool cultures: negative Rotavirus/Adenovirus Antigen: negative Clostridiun Difficile stool toxin A/B: negative Coproparasitologic exams: repeated negative Coprochemical exam: stool pH = 6, starch, muscle fibers, fat: absent Fecal calprotectin > 60 mg/g (Cal-Detect kit)
Renal function	Ureea =1.25 mmol/l Creatinine=62 µmol/l	Other tests:	IgA anti tissue transglutaminase and anti-endomisium antibodies = negative Quantiferon test = negative IgM/IgG CMV antibodies = negative HIV test = negative
Total serum IgE level	425 IU/ml (normal values < 60 IU/ml)	Elevated specific IgE against casein, alpha lactoglobulin, beta lactoglobulin and egg white (class 2 and 3).	

APTT: activated partial thromboplastin time, INR: international normalized ratio, CMV:cytomegalovirus, HIV: human immune deficiency virus.

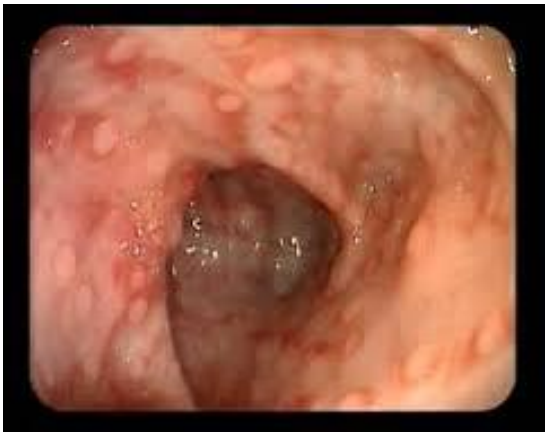

Figure 1: Endoscopic aspect of descending colon with multiple aphtoide lesions separated by normal mucosa.

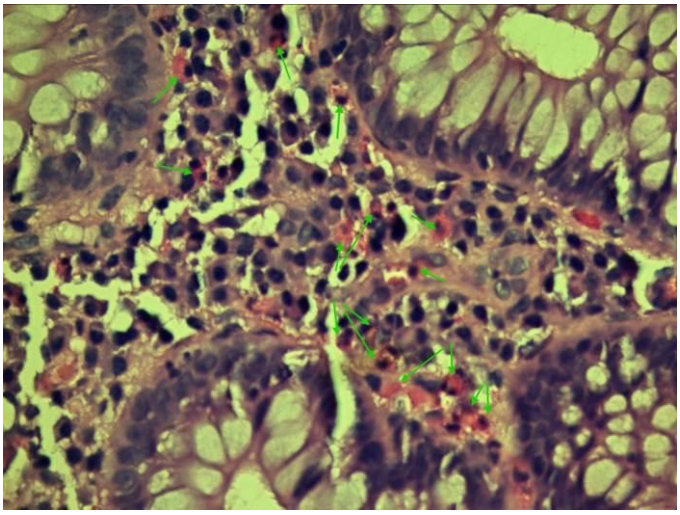

Figure 2. Descending colon biopsy, MOx200, HE staining. Lymphocytic and eosinophilic infiltrate in the lamina propria.

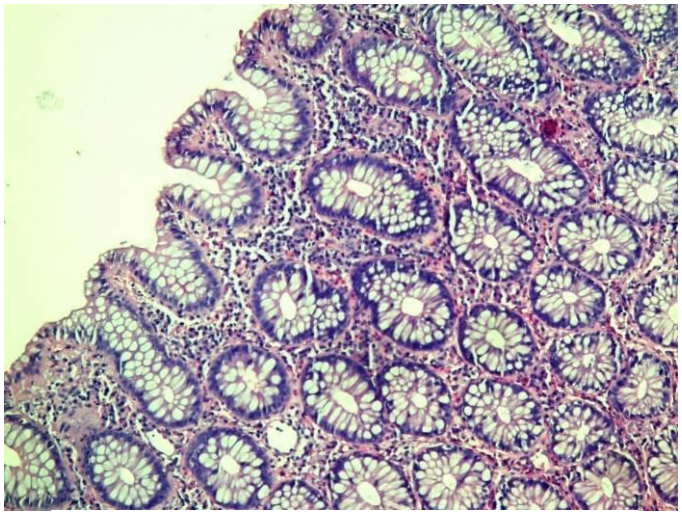

Figure 3: Transverse colon biopsy, MOx100, HE staining. Lymphocytic and eosinophilic infiltrate in the lamina propria. Normal glandular architecture.

The massive eosinophilic infiltrate in the colonic mucosa along with peripheral eosinophilia and increased total and specific IgE serum level guided the diagnosis to eosinophilic colitis associated to cow's milk proteins and egg's white allergy in this case.

In order to achieve symptoms resolution, an important part of the treatment consists in diet. In this case, we excluded dairy and egg's white from the child's diet and we recommended a semi-elemental formula based on extensive proteins hydrolysates. The medication consisted in systemic oral corticosteroids - Prednisone 1 mg/kg/day, 4 weeks, with progressive withdrawal, aminosalicylates - Mesalazine 50 mg/kg/day, leukotriens inhibitors: Montelukast 5 mg/day, antihistamines - Aerius 2.5 ml/day and probiotics.

During hospitalization, the evolution was favorable, with disappearance of rectal bleeding and normalization of stools. After corticosteroids tapering, the child remained in good clinical condition, the somatic development was within normal ranges. There were no relapses, under semi-elemental formula and exclusion diet, along with mesalazine and leukotriene inhibitors for 1 year as maintenance therapy. The child was complaint to the diet and medical treatment. The prognosis is favorable on long-term, with the possibility to recover tolerance to allergenic foods after the age of 5-6 years according to some authors. (6)

Discussions

Eosinophilic colitis was first described in 1936 and the term first appeared in the literature in English in 1959 (7), (8). In 1985 Naylor and Pollet reviewed 22 cases of eosinophilic colitis: no common aetiology was identified, though food allergies, drug reactions, and parasites were reported in several cases.(9)

Drugs reported to cause colonic eosinophilia include nonsteroidal anti-inflammatories, tacrolimus, rifampicin, carbamazepine. Particular attention should be paid to the temporal relationship between drug administration and symptoms and colonic eosinophilia should not be attributed to a drug reaction without adequate clinical-pathological correlation.(10)

In 1990, the publication of a series of thirteen cases of allergic colitis that had initially presented before two years of age, identified a specific subtype of eosinophilic colitis: a treatable disorder of early childhood that was caused by food allergy (usually to eggs, milk, or soya) and was of limited duration, typically remitting entirely with an appropriate exclusion diet. (11)

Eosinophilic colitis has been described in association with eosinophilia elsewhere in the gut using the term eosinophilic gastrointestinal disorder. However, evidence linking eosinophilic colitis with eosinophilic infiltration elsewhere in the gut is lacking: a recent review of eosinophilic gastrointestinal disorder concluded that eosinophilic colitis has a different pathophysiology and is probably best regarded as a separate entity. (12)

According to some reports, there is the possibility to diagnose an overlap syndrome between eosinophilic colitis and IBD in children. One study has described Crohn's colitis with a heavy eosinophilic infiltrate as eosinophilic-Crohn overlap colitis.(13) Pensabene et al found a higher overall colonic eosinophil density in children with IBD compared to those with food allergies (14), which suggests that it may not be possible reliably to diagnose eosinophilic colitis in the presence of inflammatory bowel disease, especially Crohn's disease, where eosinophils are typically more numerous than in ulcerative colitis. (15) Patients with eosinophilic colitis may show peripheral eosinophilia and there is a statistically significant association between colonic eosinophil density and elevated total serum IgE levels.(16) It has been proposed that gut eosinophilic disorders are IgE-

mediated through the high-affinity receptor FcepsilonRI. (17)

The onset of food protein-induced enterocolitis, especially cow's milk protein allergy, appears usually in the first year of life. In the case presented above, there are no details about symptoms during infancy regarding history of atopy or digestive manifestations of cow's milk protein allergy. From his medical past history, we found out that the child has been breastfed for 2 years. This fact could induce a degree of oral tolerance and could delay the onset of proteins' allergy in this case.

We rejected the first established diagnosis of Crohn's disease at this young patient due to histology result in the first place, along with missing clinical and laboratory findings characteristic to Crohn's disease as: failure to thrive, anemia, inflammatory syndrome. This patient presented in a good clinical state, with normal somatic development for his age, without anemia, signs of intestinal malabsorption or inflammatory syndrome. Peripheral eosinophilia and increased total serum IgE level along with elevated specific IgE against cow's milk proteins represent important markers for the diagnosis of eosinophilic colitis associated to cow's milk protein allergy. Moreover, the histopatological examination didn't reveal any granulomas and it showed normal glandular architecture that could ruled out Crohn's disease. In contrast to IBD, the architecture of the colonic crypts in eosinophilic colitis is normally preserved. Another argue that could rule out Crohn's disease in this case is the favorable evolution of this patient without relapsing after corticosteroids withdrawal, following exclusion diet, semi-elemental formula and leukotriene inhibitors as maintenance therapy.

Colonic eosinophilia may be a significant finding in some symptomatic individuals but there has been no consistency regarding the cut-off point above which eosinophil density should be regarded as increased, the region of colon to be assessed, or the number of microscopic fields examined. Several studies have reported geographic variation in eosinophil density in the normal colon. A detailed study on endoscopic material from normal colon carried out by DeBrosse found a gradient of eosinophil density from ascending colon to rectum from 20/field to 8/field, respectively. (18) As eosinophil density varies with site, it would be important to set a limit for each site or to use a mean value across the whole colon in order to diagnose eosinophilic colitis.

In addition to counts of total eosinophil density, some studies have assessed degranulation as an indicator of eosinophil activation. It is possible to observe degranulation

in routinely stained sections and to grade it semi-quantitatively; however, it is not known if the trauma of biopsy could provoke degranulation of otherwise inactive eosinophils. (19) The uncertainty over the diagnosis of eosinophilic colitis emphasises the need for proper clinical-pathological correlation.

Conclusions

A number of pediatric intestinal disorders may have similar clinical findings as Crohn's disease: infectious enterocolitis, cow's milk protein allergy, eosinophilic colitis, malabsorption syndromes, celiac disease etc.

Fecal calprotectin and colonoscopy don't have maximum accuracy for differential diagnosis, histopathology is defining for diagnosis.

Eosinophilic colitis is often under-diagnosed. Colonic eosinophilic infiltration can be parceled, imposing the need for serial biopsy sampling for diagnosis.

In patients with histologically proven colonic eosinophilia, it is important to search the underlying causes and to integrate clinical status of the patient with medical history data and laboratory tests.

The lack of distinctive clinical symptoms or laboratory anormalities associated with eosinophilic colitis imposed to establish the diagnosis by examination of colonic biopsies. There is no consensus over its diagnosis and management. In the future it will be necessary to standardize the diagnosis of eosinophilic colitis by establishing clear histological criteria, including a limit of colonic eosinophils above which the diagnosis will be made.

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