An infant with colitis

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Clinical Protocol

Six-month old male child, presented to the OPD with a history of bleeding per rectum. Symptoms had started at around 3.5 months of age. The child used to pass loose or semi-formed stool mixed with blood almost every time he defecated (4-8 times/day) Occasionally there was some mucus too. There was also a history of intermittent non – bilious vomiting. There was no bleeding from any other site, no fever or constipation. No history of recurrent infections, wheezing or atopy.

This child was first by order of birth of a non-consanguineous marriage. He was born pre-term (35 weeks) with a birth weight of 1.75 Kg. There was no family history of allergies or inflammatory bowel disease. The child was developmentally normal.

He was on mixed (breast milk + formula feed) since the early neonatal period. Complementary feeding had just been introduced.

He had been treated with oral/ IV antibiotics/ probiotics before he presented to us but there was no response. He had also been given a trial of 7 days of a milk/ milk product free diet (was fed a soy formula) but there was no response.

On examination, the child weighed 4 kg. (- 4.00 z), and height 60 cm. (-3.42 z). The child appeared lethargic. Pallor was present. There were no clubbing or lymphadenopathy. Skin was apparently normal.

Abdominal examination revealed no distension or hepatosplenomegaly. Perianal examination was normal, with no fissure or tag seen.

The investigations with their results are enumerated in Table 1.

Table 1. Investigations

Investigation	Result
Hemoglobin(> 11.5 g/dL)	9.7 g/dL
Total Leukocyte Count (4000 – 11000/ mm^3)	6400/mm^3
Differential Leukocyte Count (N/L/E/M)*	28/52/11/6
Platelet count(150000 – 400000/ mm^3)	440000/ mm^3
Peripheral blood smear	Microcytic hypochromic anaemia
Erythrocyte Sedimentation Rate (< 20 mm/hr)	25 mm/hr
Albumin(3.5 – 5.5 g/dL)	3.5 g/dL
AST/ALT(< 40 U/L)	24/29 U/L
C – Reactive Protein (< 6 mg/dL)	19.6mg/dL

*N – Neutrophil, L – Lymphocyte, E – Eosinophil, M - Monocytes

Discussion

The infant's history *i.e.* presence of loose stools with blood and mucus is suggestive of colitis. Colitis in children can have multiple causes such as infection, inflammatory bowel disease, allergic, ischemic/ vascular or colitis secondary to immune deficiency disorders. The approach to a child with colitis would be to first narrow down the differentials based on the age of the child. The causes of colitis in children stratified according to the age of the child are tabulated in Table 2.

Table 2. Common causes of colitis categorized by different age groups

Age	Cause of Colitis
Neonates and infants	Necrotizing enterocolitis* Food protein induced allergic proctocolitis Hirschsprung associated enterocolitis Primary immunodeficiency disorders Infectious colitis Infantile onset inflammatory bowel disease
2-6 yrs	Infectious colitis Henoch-Schönlein purpura Acquired immunodeficiency disorders Early onset inflammatory bowel disease Colitis in GSD 1b
>6yrs	Infectious colitis including Tubercular & *C. difficile* colitis Pediatric onset inflammatory bowel disease Vascular-ischemic colitis (associated with rheumatologic disorders) Collagenous colitis Eosinophilic colitis

*To be considered only in preterm infants (rarely term infants with predisposing factors like sepsis, cardiac disease etc.) in the first few weeks of life.

The index case is an infant and clinical features of the causes of colitis in an infant are listed in Table 3.

Food protein induced allergic proctocolitis is the most common cause of rectal bleeding in infants occurring in around 2-5 % formula fed infants. (1,2) Our patient was exposed to cow milk protein since early infancy. However, there are a few unusual points - the presence of severe failure to thrive, raised inflammatory markers and lack of response to a week-long trial of a milk – free diet being unusual.

An infectious cause per se is unlikely given the protracted course and lack of response to antibiotics. However, it is possible in the setting of an underlying immunodeficiency disorder. Even though there is no history of recurrent infections in this child it is a possibility as a child with an immunodeficiency may initially present with just an isolated GI infection. (3) Amongst the primary immunodeficiencies, in patients with common variable immunodeficiency (CVID) chronic colitic changes have been reported in 20 – 38% patients. (4) Colitis is also

Table 3. Common causes and clinical features of colitis in an infant

Cause of colitis	Clinical Features	Diagnosis suggested by
Hirschsprung associated enterocolitis (HAEC)	Presenting either before or after definitive surgery for HD, abdominal distension and explosive diarrhea, along with emesis, fever, lethargy, and even shock	Intestinal 'cut-off sign' on abdominal X-ray - 74% sensitivity & 86% specificity
Primary immunodeficiency disorders	A history of bacterial or fungal infections with unusual organisms, or unusually severe and recurrent infections with common organisms	Lymphocytopenia neutropenia Abnormal low serum immunoglobulin levels Low B-cell and T-cell lymphocyte subsets Defective oxidation burst in neutrophils by NBT or DHR
Infectious colitis	Acute onset of watery or bloody diarrhea, abdominal pain and fever	Stool examination and culture
Food protein induced allergic proctocolitis	Bloody stools in a well-appearing infant	Allergen elimination and challenge procedure
Infantile (and toddler) onset inflammatory bowel disease	YOUNG AGE onset Multiple family members, consanguinity Autoimmunity Thriving failure Treatment with conventional medfails Endocrine concerns Recurrent infections or unexplained fever Severe perianal disease Macrophage activation syndrome Obstruction and atresia of intestine Skin lesions, dental, hair abnormalities Tumors (Acronym - YOUNG AGE MATTERS MOST)	Diagnostic ileocolonoscopy, histopathology.

*NBT – Nitroblue tetrazolium dye reduction *test*, DHR – Dihydrorhodamine

frequent in patients with chronic granulomatous disease (CGD), affecting 11% to 17% of patients. Other rarer primary immunodeficiency disorders (Severe combined immunodeficiency, Wiskott–Aldrich syndromes *etc.*) may also present with colitis. (5)

Infantile onset inflammatory bowel disease (IBD) comprises around 1% of all IBD patients and it presents and behaves quite differently from the disease that develops in older children or adults. The course of the disease is generally more severe. In up to approximately 25% of these patients, not only do they have IBD, but they also have an underlying immunodeficiency, autoinflammation disorder or epithelial barrier defect (monogenic disease). Our child does have some (young age of onset, failure to thrive) features listed in Table 3. Considering the symptoms and elevated inflammatory parameters (elevated CRP, thrombocytosis) it should be kept as a possibility.

HAEC would not be considered as there is no clinical setting for the same.

To sum up, the clinical possibilities were – allergic colitis, primary immunodeficiency disorders and inflammatory bowel disease.

Course in the hospital

The child was evaluated keeping in mind the possibilities that were narrowed down on the basis of the history. The child's HIV serology was negative, T & B lymphocyte subsets and immunoglubulin profile was normal [IgG – 864 mg/dL (Normal-309-1573), IgA-84 mg/dL(Normal-22-98),IgM-59 mg/dL(Normal -3.7-89)] and NBT Normal.

A proctosigmoidoscopy was performed which showed an edematous mucosa with nodularity and diffuse superficial ulceration (Figure 1a). Occasional apthous ulcers were also seen (Figure 1b). Biopsies were obtained and sent for histopathological evaluation.

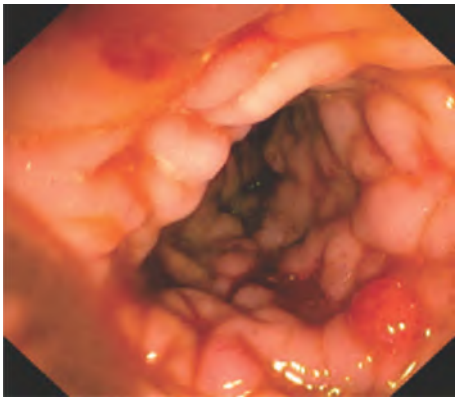

Figure 1a. Endoscopic image showing edematous mucosa with nodularity.

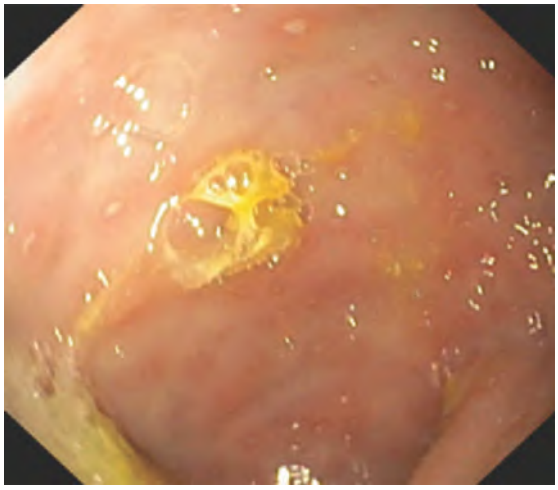

Figure 1b. Endoscopic image showing apthous ulcers

Histopathology Protocol (Figure 2)

There are multiple fragments and local denuded epithelium with surface mucodepletion. The lamina propria showed dense infiltrate of eosinophils. No crypt architectural distortion, granuloma, pigment laden macrophages, parasites or viral inclusions. The features were suggestive of allergic colitis.

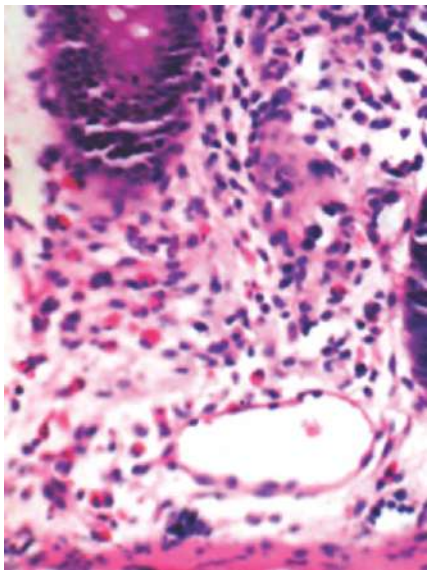

Figure 2: The rectal mucosal biopsy show edema and prominent eosinophils (>15 eosinophils/ HPF) in the lamina propria. (H&E X 200)

Discussion on histopathology

The salient histopathological features of the clinical possibilities are tabulated in Table 4.

Our patient shows a dense eosinophilic infiltrate (>15/HPF) in the absence of features of other disorders hence suggesting allergic colitis. The number of eosinophils on biopsies in patients with allergic colitis is a question of debate. Previous studies have suggested a diagnostic criteria of eosinophilic infiltration in the lamina propria of ≥ 6/HPF. (8, 9)

Table 4. Salient histopathological features of the causes of colitis in an infant

	Histopathological features
Common variable immunodeficiency (CVID)	Histopathologically, CVID is a great mimic. Features that may be seen include absence or paucity of plasma cells (evident in approximately two thirds of patients).(6) Apoptosis is much more common as compared to IBD A preponderance of eosinophils in the inflammatory infiltrate is NOT seen.
Chronic granulomatous disease (CGD)	Sharply defined aggregates of epitheloid histiocytes surrounded by a cuff of dense lymphocytic inflammation. Inflammatory cells consist mostly of degranulating eosinophils, large pigment laden macrophages & lymphocytes with paucity of neutrophils(7)
Inflammatory Bowel Disease	Moderate to severe chronic architectural changes Increased apoptosis, eosinophils in lamina propria and crypts.
Infectious colitis	Superficial ulcers with exudates, cryptitis with abscesses and increased cellularity of lamina propria with predominant neutrophils and lymphocytes
Food protein induced allergic proctocolitis	Focal eosinophilia (>6 eosinophils/HPF) in the lamina propria of one or two crypt regions or eosinophilic proctitis (focal eosinophilia and eosinophilic infiltrates in the muscularis mucosa and/ or eosinophilic crypt abscess)

Follow – up

The child was then put on a diet free of milk and milk products which included rice – dal, mashed fruits and vegetables etc. No milk substitute formula was used. Iron and calcium supplements were given.

Child gradually responded. After 2 weeks the blood and mucus subsided completely. Stool frequency reduced and the child started gaining weight.

At the last follow – up at 1.5 years of age the child weighed 10.4 Kgs (- 0.61 z-score). Anaemia had subsided and the child was gaining milestones appropriate for age.

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Food Protein induced allergic proctocolitis (FPIAP) commonly presents in infancy with most affected children presenting with symptoms by 6 months of age. Onset is rare after 12 months. It is typically manifested with rectal bleeding in well-appearing infants during the first months of life accounting for up to 60% of healthy infants with rectal bleeding. (10) Onset is usually insidious, with a latent period after introduction of the food as was seen in our child. It is typically caused by cow's milk and soy proteins and exclusively breast-fed infants may also develop clinically significant FPIAP via dairy protein transfer into human breast milk. Failure to thrive (FTT) is characteristically absent. (10)

So then why did our child have FTT? FPIAP is a part of a group of non–IgE-mediated gastrointestinal food-induced allergic disorders which also includes food protein–induced enterocolitis syndrome (FPIES) and food protein–induced enteropathy (FPE). FPIES is on the severe end of the spectrum with patients presenting with repetitive vomiting, pallor, a raised CRP and lethargy.(10,11)Chronic FPIES can lead to failure to thrive. FPE presents with protracted diarrhea, intermittent vomiting and FTT. These are all separate clinical entities but have many overlapping clinical and histologic features and at times may co - exist. (10,11) Our child presented with rectal bleeding, FTT, vomiting and a raised CRP, suggesting a possible mixed phenotype. (11) Though we didn't carry out a duodenal biopsy it is conceivable that the child had the presence of a co-existing enteropathy. The salient differences between the three types of non–IgE-mediated gastrointestinal food-induced allergic disorders are tabulated below.(Table 5)

A diagnostic elimination diet to see if symptoms improve suggests the diagnosis. Definitive diagnosis requires an oral food challenge test, however it is barely required in clinical practise. Milk protein should be avoided for up to four weeks (minimum of two weeks) until there has been a clear improvement in symptoms. A proctosigmoidoscopy and rectal biopsy is indicated only if there are atypical features or non-responsiveness to treatment. In our child we decided to go ahead with a procto-sigmoidoscopy because of the presence of protracted bleeding, failure to thrive and anaemia. Aphthous ulcers (small discrete ulcers with surrounding erythema and normal intervening mucosa) are suggestive of FPIAP. However, these findings are neither sensitive or specific. In our child the concomitant presence of diffuse loss of vascular pattern and superficial ulcerations raised the possibility of an inflammatory bowel disease but there were no suggestions of the same on histopathology.

FPIAP has a favourable prognosis, as most children will outgrow their allergy. The management comprises of the avoidance of cow's milk and cow's milk products. If the mother is exclusively breastfeeding, she should be advised to exclude all cow's milk and cow's milk products from her diet. The choice of cow's milk substitute should take into account the age of the child, the severity of the allergy. If the child is being formula fed, they should be tried with an extensively hydrolysed formula (eHF). Hydrolyzed formulae are those where the proteins have been hydrolyzed in order to remove allergenic epitopes. Soy formulae can be considered where eHF may be considered unaffordable. Soy formula is well tolerated by most individuals with Cow Milk Protein Allergy (CMPA). However, it is to be remembered that around 10-20% of children with CMPA may also have allergy to Soy. (10,12) Our child had not shown any response to week-long trial of

Table 5. Differences Between Non–IgE-Mediated Gastrointestinal Food-Induced Allergic Disorders

	FPIES	**FPIAP**	**FPE**
	Dependent on age of exposure to antigen; usually 1 d to 1 y	Days to 6 mo	Dependent on age of exposure to antigen; CM and soy up to 2 y
Family history of atopy	40% to 70%	Up to 25%	Unknown
Symptoms			
Emesis	Prominent, repetitive	Absent	Intermittent
Diarrhea	Severe	Mild	Moderate
Bloody stools	Severe	Prominent	Rare
Edema	Severe	Mild, infrequent	Moderate
Shock	15%	Absent	Absent
FTT	Moderate-to-severe in patients with chronic FPIES	Absent	Moderate
Laboratory findings			
Anemia	Moderate	Mild, infrequent	Moderate
Hypoalbuminemia	Acute	Mild, infrequent	Moderate
Acidemia	Might be present	Absent	Absent
Leukocytosis	Prominent	Absent	Absent
Thrombocytosis	Moderate	Mild	Absent
Peripheral blood eosinophilia	Absent	Occasional	Absent
Natural history	Varies by population, CM tends to resolve by age 3-5 y	Majority resolve by age 12 mo	Most cases resolve in 24-36 mo

FPIES - food protein–induced enterocolitis syndrome, FPIAP - food protein–induced allergic proctocolitis, FPE - food protein–induced enteropathy, CM – Cow's Milk

soy milk suggesting possible concomitant soy allergy too. Hence, we chose to avoid soy. In children with severe symptoms or intolerance to eHF, one may use an amino acid formula. As these formulas are expensive and as our child was already beyond 6 months of age we chose to put him on a semi – solid/ solid milk free diet and did not use any commercial formula. The unequivocal response clinched the diagnosis.

As cow's milk is the major source of calcium in infant diets, children on milk exclusion diets are at risk of a deficient calcium intake and should be supplemented.

Cow's milk allergy will resolve in the majority of children. Individuals should be reassessed at 6–12 monthly intervals from 12 months of age to assess for suitability of reintroduction. Most children with non-IgE mediated CMPA will develop tolerance by 5 years of age (13,14)

To conclude, FPIAP is the commonest cause of colitis in an infant. In children with atypical features one should evaluate for other possible etiologies and carry out a proctosigmoidoscopy.

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