Différentes atteintes digestives de l'allergie aux protéines de lait de vache se présentant sous forme d'entéropathie exsudative

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"Différentes atteintes digestives de l'allergie aux protéines de lait de vache se présentant sous forme d'entéropathie exsudative "

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Résumé

Ce travail de thèse fait suite à un article soumis et accepté au « JPGN report » au sujet de l'allergie aux protéines de lait de vache (APLV). L'APLV est fréquente chez l'enfant et son diagnostic peut être difficile à poser notamment en raison d'une présentation variable avec différents symptômes et sévérité. L'article décrit quatre cas d'APLV de présentation sévère avec entéropathie exsudative. Au vu de la sévérité des présentations cliniques, ces patients ont bénéficié d'examens endoscopiques. Nous avons jugé intéressant de les présenter car il est rare en pédiatrie d'avoir des images macro- et microscopiques d'une allergie aux protéines de lait de vache. Nous pouvons constater qu'il n'y a pas d'atteinte pathognomonique et que ce processus peut atteindre n'importe quelle portion du tube digestif. De plus comme dit plus haut, les 4 cas présentent une entéropathie exsudative qui s'est manifestée par une hypoalbuminémie et hypogammaglobulinémie. Cette entité est rare en pédiatrie et la cause de la perte de protéines dans l'APLV reste peu claire.

En conclusion, l'APLV peut atteindre n'importe quel endroit du tube digestif avec une sévérité variable. L'absence de corrélation entre l'endoscopie et les résultats histologiques souligne l'importance d'une approche globale du patient présentant une possible APLV. Ce diagnostic doit être considéré chez tous les enfants présentant une hypoalbuminémie.

Introduction

Les allergies alimentaires sont fréquentes chez l'enfant et l'allergie aux protéines de lait de vache (APLV) est l'une des plus fréquente avec une prévalence de 2-3% (1) chez les enfants de moins de 1 an. Cette allergie concerne non seulement les enfants alimentés par un lait artificiel contenant des protéines de lait de vache, mais aussi les enfants allaités par une mère ayant un régime contenant des protéines de lait de vache. (1)

Différents types d'allergie

Il existe trois différents types d'APLV :1) IgE médiée avec des réactions immédiates dans les 2 heures suivant l'ingestion, 2) non-IgE médiée avec des réactions retardées entre 48h et une semaine après l'ingestion, et 3) la forme mixte. (1)(2)

Les réactions immédiates d'une allergie IgE médiée peuvent se manifester par une anaphylaxie, un urticaire aigu, un angiocœdème, un sifflement respiratoire, une toux, une rhinite, des vomissements, un œdème laryngé et/ou des difficultés respiratoires.(2)

Les allergies non-IgE médiées peuvent se manifester de différentes façons, par des vomissements, un reflux, des douleurs abdominales, des diarrhées, un refus alimentaire, des pleurs, une mauvaise prise pondérale, une hématochézie, une constipation, une anémie ferriprive, une entéropathie exsudative, ou par une dermatite atopique.(2)

L'APLV est plus fréquemment une allergie non-IgE médiée. Celles-ci sont catégorisées en 3 types en fonction de la zone atteinte.(3)

1.**Entérocolite induite par les protéines alimentaires** (food protein-induced enterocolitis syndrome (FPIES)) avec une atteinte de tout le tube digestif. La littérature décrit une forme aiguë et une forme chronique. La forme aiguë se manifestera par des symptômes systémiques qui peuvent être sévères, avec vomissements répétés 1-4h après l'ingestion, pâleur, choc

hypovolémique, léthargie. La forme chronique se manifeste par des symptômes principalement digestifs avec vomissements, distension abdominale, diarrhées, difficulté à prendre du poids, malabsorption, acidose métabolique.

Dans le cas de l'APLV il s'agit principalement de formes chroniques de FPIES, ceci en raison d'une exposition répétée aux allergènes.(3)(4)

2. **Entéropathie induite par les protéines alimentaires** (food protein-induced enteropathy (FPE)) avec une atteinte de l'intestin grêle. Celle-ci se manifestera par une malabsorption, diarrhées, vomissements, entéropathie exsudative et difficulté à prendre du poids.(3)(4)

3. **Proctocolite induite par les protéines alimentaires** (food protein-induced allergic proctocolitis (FPIAP)) avec une atteinte du côlon distal et rectum qui se manifestera par une hématochézie uniquement.(3)(4)

Diagnostic

Il n'y a pas d'examen complémentaire spécifique qui permet de poser le diagnostic, il s'agit d'un diagnostic clinique avec un test de provocation orale. En fonction de la suspicion clinique, allergie IgE-médiée ou non IgE-médiée, il s'agit d'effectuer une éviction des protéines de lait de vache durant respectivement 3-5 jours et 2-4 semaines. Si l'on constate une disparition des symptômes, il faut réintroduire des protéines de lait de vache. Le test est positif s'il y a récidive des symptômes à la réintroduction. A noter que le test de provocation orale sera fait sous surveillance plus ou moins rapprochée en fonction des symptômes présentés par le patient.(1)(3) Il y a la possibilité pour les allergies IgE-médiée d'effectuer un dosage des IgE spécifiques sanguins ou d'effectuer un Prick test cutané, mais un test de provocation orale sera toujours nécessaire pour confirmer le diagnostic.(1)

Il est important de penser aux diagnostics différentiels qui varient en fonction de la présentation clinique et de l'âge. Il s'agira de penser aux causes infectieuses, congénitales (diarrhées congénitales, déficit immun), aux maladies inflammatoires chroniques intestinales (MICI), à l'entérocolite nécrosante, aux troubles métaboliques, à l'insuffisance pancréatique, à la mucoviscidose, au reflux gastro-œsophagien, à la maladie de Hirschsprung, au volvulus, et à la fissure anale.(5)(6)

Physiopathologie

Les allergies alimentaires sont des réactions immuno-médiées. Elles sont dues à un manque ou à une perte de tolérance des aliments. Dans l'allergie aux protéines de lait de vache, les protéines sont reconnues comme une menace par le système immunitaire en particulier la caséine, l'α-lactalbumine et la β-lactoglobuline.(7)

Lors de réactions immédiates IgE-médiées, la protéine de lait est reconnue par les lymphocytes Th2 qui vont induire la production d'anticorps IgE spécifique par les lymphocytes B. Ceux-ci vont se lier aux mastocytes. Lors d'une réexposition les anticorps vont se lier aux protéines de lait de vache et déclencher une réaction immunitaire avec libération d'histamines et activation de cytokiniques.(7)(8) Ces réactions ont lieu dans les deux heures qui suivent l'ingestion. Les réactions non-IgE-médiées sont des réactions retardées. Le mécanisme est moins bien compris. Elles impliquent le système immunitaire innée et cellulaire avec l'activation des lymphocytes Th2, différentes cytokines et les éosinophiles créant de l'inflammation qui augmente la perméabilité intestinale. (5)(9-12)

Traitement

Le traitement consiste à effectuer un régime d'éviction (après avoir fait un test de provocation orale) des protéines de lait de vache. Pour ceci, il existe différentes possibilités. Les mères souhaitant poursuivre l'allaitement devront observer un régime strict sans protéines de lait de vache, donc sans produits laitiers et également sans lait de chèvre et de brebis, en raison de réactions croisées fréquentes. Il faudra être attentif aux apports calciques de la mère en ajoutant une supplémentation sous forme de comprimés qui contiennent 1g de calcium et 800UI de vitamine D avec l'aide d'une diététicienne. A noter qu'en cas d'échec, il est possible de faire une éviction du soja, ceci à nouveau en raison de la fréquence des réactions croisées.(2) Les laits thérapeutiques ont pour base des protéines de lait hydrolysées. La digestion des protéines dans le tube digestif se fait par plusieurs étapes d'hydrolysation. La protéine est scindée en gros peptides puis en plus petits peptides puis en acides aminés.(13) Lorsque la protéine est suffisamment hydrolysée, le corps ne la reconnait pas. Il n'y a donc pas de réaction. Chez les bébés nourris par lait artificiel, on débutera avec un lait dit extensivement hydrolysé à base de protéines de lait de vache. Ce lait contient des protéines de lait de vache hydrolysées et donc prédigérées sous forme de 80% de petits peptides et 20% d'acides aminés. Celui-ci est meilleur en goût et convient la plupart du temps. En cas d'échec de cette thérapie, de symptômes sévères (anaphylaxie, difficulté de prendre du poids) ou d'allergies multiples, il est préconisé d'introduire un lait à base de 100% d'acides aminés.(6)

A noter qu'il existe également des laits partiellement hydrolysés. Ces laits contiennent des gros peptides. Les protéines ne sont pas suffisamment hydrolysées pour le traitement de l'allergie aux protéines de lait de vache.(1)

Ci-dessous un tableau récapitulatif des différents laits hydrolysés :(7)

Type de laits	Protéines
Partiellement hydrolysé	Oligopeptides de taille jusqu'à 5000 daltons
Extensivement hydrolysé	Peptides jusqu'à une taille de 3000 daltons et acides aminés
Acide aminés	Acides aminés uniquement

Le lait de riz peut être considéré également à condition qu'il s'agisse d'une formule adaptée à l'âge de l'enfant. Le lait de soja est indiqué uniquement chez les plus de 6 mois en raison du risque de cross-réactivité chez les plus jeunes. Il est important d'essayer un lait à base d'acides aminés avant d'exclure une APLV. (1)(2)(14) Le lait sans protéines de lait de vache doit être poursuivi entre 6 et 12 mois d'âge. Si l'allergie est IgE médiée, ce lait sera administré plutôt jusqu'à 12-18 mois, avant réalisation d'un test de provocation orale sous surveillance et d'un dosage des IgE.(1) La diversification peut débuter, comme pour un enfant sans allergie, avec uniquement une éviction des PLV jusqu'à 9-12 mois d'âge ou au moins 6 mois après l'introduction du régime.(2) Une supplémentation en calcium et vitamine D sera nécessaire lorsque l'enfant prendra moins d'un litre de lait par jour.(7) Il est important de suivre l'enfant et sa croissance tous les 6 à 12 mois. L'APLV est une allergie qui se résout avec l'acquisition de la tolérance digestive, 50% des cas étant résolus à l'âge de 12 mois, et 90% à 6 ans.(2)(15)
Dans certains cas, l'APLV peut être sévère et se manifester par une entéropathie exsudative. Dans ces cas-là, des examens complémentaires seront effectuer pour exclure un déficit immunitaire, des diarrhées congénitales ou une MICI.

Entéropathie exsudative

L'entéropathie exsudative est une manifestation rare de plusieurs pathologies du système digestif et d'origine extra-digestive. Elle se manifeste par une perte de protéines par le tube digestif (albumine, immunoglobulines, céruloplasmine), entrainant des œdèmes avec possible ascite, épanchement pleural, épanchement péricardique, ainsi qu'une malabsorption des graisses et des vitamines liposolubles avec ou sans diarrhées.(16)(17)

Il existe 3 mécanismes :

1) Dilatation diffuse ou focale des vaisseaux lymphatiques d'origine congénitale par exemple la lymphangiectasie primaire intestinale. La dilatation induit une augmentation de la pression dans les lymphatique entrainant une perte de protéines. (9) Cette dilatation peut être secondaire à une autre pathologie notamment cardiaque par exemple une péricardite constrictive, une insuffisance cardiaque droite, une intervention de Fontan, une communication interauriculaire et une thrombose de la veine cave. (16) Ces pathologies ont en commun une anomalie du retour veineux dans le cœur droit. Le sang s'accumule dans le réseau veineux ce qui induit une augmentation de la pression veineuse puis de la pression dans le système lymphatique induisant une perte de protéine.
2) Atteinte inflammatoire avec érosion de la muqueuse intestinale et augmentation de la perméabilité de la muqueuse par exemple dans la maladie de Crohn.(9)(16)
3) Atteinte inflammatoire de la muqueuse sans érosion mais avec perméabilité des jonctions serrées, par exemple dans la maladie cœliaque.(9)

Une des méthodes diagnostiques est la clairance de l'alpha-1-antritrspysine dans les selles sur 24h.

L ’alpha-1-antitrypsine est une protéine synthétisée par le foie. Elle est présente dans le sang et en faible quantité dans les selles. Cette protéine n’est pas dégradée par le tube digestif et est éliminée par les selles. La clairance de 24h de cette protéine permet d’évaluer s’il y a une perte de protéines par le tube digestif. Si cette clairance est augmentée cela pose le diagnostic d’entéropathie exsudative.(18)

Certains centres utilisent la scintigraphie pour mesurer la perte de protéines (17). Cet examen évalue l’excrétion fécale de l’albumine marqués au 99mTc préalablement injectés par voie intraveineuse pour localiser le site de la perte de protéines.(19) Dans certains hôpitaux il est possible d’effectuer une lymphographie-IRM.(20) Ces examens ne sont pas utilisés en pédiatrie aux HUG. Pour le diagnostic différentiel de l’entéropathie exsudative, il est important d’exclure une perte de protéines d’origine rénale.

Concernant le traitement, celui-ci est principalement causal, et doit s’associer à une substitution des pertes intestinales et des carences vitaminiques.(16)(17)

Discussion

L’APLV, et principalement celle non-IgE médiée, peut se présenter avec une large palette de symptômes. Ceux-ci peuvent être sévères et mener à des examens complémentaires parfois invasifs chez le nourrisson et le jeune enfant. Cependant, les descriptions histologiques d’une APLV sont peu fréquentes et n’ont pas permis d’identifier des lésions pathognomoniques de cette pathologie. Dans cet article, nous décrivons 4 cas d’APLV de présentation sévère, ayant développé des signes d’entéropathie exsudative, avec hypoalbuminémie et hypogammaglobulinémie. Des examens complémentaires avec endoscopie digestive ont été réalisés pour exclure des diagnostics différentiels, notamment de type diarrhées congénitales,

déficit immunitaire ou MICI. De façon intéressante, les 4 cas présentaient des symptômes différents allant de diarrhées, d'une difficulté à prendre du poids à des œdèmes isolés. Les résultats endoscopiques et histologiques ont montré différentes atteintes le long du tube digestif de degrés de sévérité variés, mais la présence constante d'une éosinophilie tissulaire. Ceci confirme qu'il n'y a pas de pattern histologique pathognomonique et que l'atteinte peut intéresser toute portion du tube digestif. Malgré leur sévérité, un régime sans protéine de lait de vache a permis une amélioration clinique, ces 4 jeunes patients n'ayant pas présenté par la suite de signes de pathologies digestives durant la période de suivi entre 6 et 9 ans. Les PLV ont été réintroduites avec bonne tolérance après 12-15 mois d'éviction.

Cette petite série de cas démontre qu'il n'y a pas de signes biologiques ni d'examens complémentaires spécifiques de l'APLV, que le diagnostic reste clinique avec un test de provocation oral lorsque celui-ci est possible. Il convient de penser à une APLV devant une hypoalbuminémie d'origine extra-rénale.

Article

Cow's milk protein allergy with protein losing enteropathy under the scope

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Abstract

Objectives: Cow's milk protein allergy (CMPA) is very frequent in infants. Presentation is variable, and symptoms fluctuate in intensity. Diagnosis can be challenging as it is mostly clinical. In severe cases patients can present with anasarca secondary to protein-losing enteropathy (PLE). The exact mechanism underlying PLE is incompletely understood. Here we report four cases of severe PLE caused by CMPA warranting endoscopic workup in whom histological expression was characterized by variable features along the GI tract.

Methods: We report four cases of severe CMPA with PLE requiring extensive workup including endoscopy to exclude immune deficiency or congenital enteropathy. The different histological expressions along the GI tract are presented.

Results: The four cases were aged between 7 weeks and 2 years and presented with diarrhea, failure to thrive and/or edema. All four had severe hypogammaglobulinemia and hypoalbuminemia. Because of their severity, they underwent digestive endoscopy with biopsy. Histology ranged from the expected eosinophilia, observed in all cases, to severe mucosal atrophy with subtotal loss of colonic glands. We found alterations in the whole digestive tract. Correlation between endoscopy and histology was poor.

Conclusion: CMPA can affect any segment of the GI tract and the intensity of the histological findings varies among patients and localizations. Food protein allergy should be considered in infants and children with hypoalbuminemia.

WHAT IS KNOWN

- CMPA is essentially a clinical diagnosis with only rare histological descriptions
- Poor correlation between endoscopy and histology
- No pathognomonic endoscopical or histological findings

WHAT IS NEW

- PLE may be due to CMPA only
- Trial of CMP elimination as initial step
- CMP exclusion may allow for histological remission despite initial severe findings

Introduction

Cow's milk protein allergy (CMPA) is the most common food allergy in infants and young children, and can present with a diverse range of symptoms.[1] Immunological mechanisms in CMPA may be either IgE- and non-IgE-mediated: allergies to cow's milk protein (CMP) have in common symptom improvement after CMP elimination and symptom recurrence after CMP reintroduction.[1,2] Non IgE-mediated gastrointestinal food-induced allergic disorders (non-IgE-GI-FAs) include food protein-induced enteropathy (FPE), food protein–induced enterocolitis syndrome (FPIES) and food protein-induced allergic proctocolitis (FPIAP).[2] FPE predominantly affects the small bowel, while FPIES can affect the entire gastrointestinal (GI) tract and FPIAP affects the distal colon and rectum.[2]

FPIES and FPE most commonly present with vomiting, diarrhea, and failure to thrive (FTT).[1] FPIAP presents with bloody stools. In severe cases patients can present with anasarca secondary to protein-losing enteropathy (PLE) with an excessive loss of serum proteins (albumin, gammaglobulin) into the GI tract as seen in FPIES and FPE.[3] CMPA diagnosis is based on clinical features and symptom recurrence upon oral food challenge.[2] In rare cases, severe CMPA can raise concern for congenital enteropathy or immune deficiency indicating endoscopic workup. As endoscopy is rarely needed in general practice histological descriptions of CMPA are scant. The exact mechanism underlying PLE is incompletely understood. Here we report four cases of severe PLE caused by CMPA warranting endoscopic workup in whom histological expression was characterized by variable features along the GI tract. Withdrawal of the offending food led to disappearance of symptoms even in the most severe case.

Methods

Parental consent for publication was obtained. Our study did not require ethic committee approval. Clinical evaluation and follow-up, upper- and lower-endoscopy and histological

analysis were performed in all four cases at our institution between 2012 and 2016. However, the young age and clinical state of the patients did not allow for complete upper and lower endoscopy in all patients. Videocapsule endoscopy was performed in one patient.

Four to six 3-µm thick sections of formalin-fixed paraffin-embedded endoscopic biopsies were stained with hematoxylin-eosin (H&E). H&E staining is the standard stain, routinely performed by default in all histological analyses. Highlights general tissue architecture, cellular morphology, and inflammatory changes. Special stains were applied according to biopsy location (PAS (Periodic Acid-Schiff) in the duodenum and esophagus, modified Giemsa stain in the stomach). PAS stains mucins, glycogen, and basement membranes, useful for detecting goblet cells and mucosal integrity in the duodenum and modified Giemsa is used to identify Helicobacter pylori in the stomach. Lymphatics were highlighted by immunohistochemistry, using the mouse anti-human D2–40 immunostain (Dako, clone D2–40, 1:50). In selected cases, CD3 (Novocastra mouse monoclonal, clone 17C2; dilution 1:20), and CD20 (CellMarque mouse monoclonal, clone 1G12; dilution 1:20) were used to characterize T and B lymphocytes respectively.

Tissue eosinophil counts were performed on scanned H&E slides and were compared to the previously reported quantity of eosinophils in the gastrointestinal tract of children with no histological anomalies.[4,5] Peak counts of eosinophils were reported per high power field (HPF, 0.196 mm^2); eosinophilic infiltration was also reported as numbers of cells per square millimeter (eosinophils/mm^2).

Results

Main endoscopy and histology findings at initial presentation are summarized in Table 1, and patient characteristics in Suppl. Table 1.

Patient 1: a 4 month old breast-fed infant with diarrhea and vomiting

A four month-old boy, strictly breastfed from a mother ingesting cow's milk, presented with a history of non-bloody diarrhea for 12 days, postprandial vomiting and generalized edema. FTT was noticed for 2 weeks prior with a loss of 200gr in 2 weeks associated with a decrease in intake. The patient presented to our institution with anasarca. Laboratory results revealed severe hypoalbuminemia and hypogammaglobulinemia. Increased stool alpha-1-antitripsyn (A1AT) was indicative of protein loss in the stool. GI infection was ruled out and there was no proteinuria. Endoscopy showed mucosal edema in the duodenum, ileum and rectum. Histology showed normal architecture in all assessed locations (duodenum, ileum, and colon). Active inflammation was minimal, with rare neutrophils infiltrating the epithelium, in the duodenal bulb and the cecum. Eosinophils were increased in the lamina propria of the duodenum, descending colon, sigmoid, and rectum (Table 1)(Suppl. Fig. 1). The duodenum showed vacuolated enterocytes. Mild lymphatic dilatation was seen in the duodenal villous axis upon immunohistochemical evaluation (D2-40). Clinical improvement was observed within 10 days after initiation of parenteral nutrition (PN) followed by progressive introduction of an enteral nutrition with an extensively hydrolyzed formula. He had 12 months' elimination, and there was no symptom recurrence or evidence of enteropathy upon cow's milk protein (CMP) reintroduction. At the time of consent, Patient 1 was 6 years old and doing well.

Patient 2: a partially breast-fed 7 week old infant with bloody stools and vomiting

A 7 weeks-old girl presented with postprandial vomiting and persistent bloody diarrhea from the age of one month. She was breast-fed from a mother ingesting cow's milk and occasionally received infant formula since birth. She had developed FTT with weight stagnation since four weeks of life. As diarrhea persisted during fasting, parenteral nutrition was initiated. Clinical exam only showed moderate dehydration. Laboratory explorations revealed

hypoalbuminemia and hypogammaglobulinemia. Stool A1AT was not checked. GI infection was ruled out and there was no proteinuria. Endoscopy was macroscopically normal. Histological features were particularly striking in the colon, showing subtotal gland loss with surface epithelium dystrophy and rare neutrophilic infiltrate, edema, and increased eosinophils in the lamina propria (Fig. 1). A sparse lymphocytic infiltrate was mainly composed of CD3 positive T cells. The esophagus and stomach showed no architectural changes. The fundus showed increased lamina propria eosinophils and edema, and few apoptotic bodies (2 in 10 consecutive glands) (Table 1). Architecture was difficult to assess in the duodenum, but focal active duodenitis with a gland abscess was seen. Diarrhea resolved within 18 days of PN. Breastmilk with CMP was reintroduced while the patient was still on PN, and symptoms recurred. She was then started on extensively hydrolyzed formula. Because of the severe symptoms at presentation and of the histological findings, repeat endoscopy was performed one month after the initial biopsies. Upper gastrointestinal histology showed chronic active duodenitis, with partial villous atrophy, fused glands, and regeneration; apoptotic bodies were increased (up to 5 in 10 consecutive glands), and eosinophils were more numerous in areas with active neutrophilic duodenitis (Suppl. Fig. 2). Repeat endoscopy performed 11 months after the initial biopsies, revealed only mild surface epithelium dystrophy and rare bifid glands (Suppl. Fig. 3). Withdrawal of the offending food allowed for histological mucosal restoration. Lymphocytic infiltration was sparse in the lamina propria, and CD20 positive B lymphocytes were more numerous than the CD3 positive T cells. Duodenal architecture was restored, with only focal regenerative changes and lamina propria edema. Immunohistochemistry (D2-40) showed mild lymphatic dilatation. The patient remained asymptomatic after 15 months of CMP elimination, and CMP were reintroduced. At the time of consent, Patient 2 was 9 years old and doing well.

Patient 3: a 2 year- old "big cow's-milk drinker" with palpebral edema

A 27-months-old boy with a history of daily bilateral palpebral edema since the age of one year presented with a 2 month history of lower limb edema and no gastrointestinal (GI) symptoms. At time of diagnosis, the child was on an age-appropriate solid food diet and enjoying one liter of cow's milk daily. Clinical exam confirmed palpebral and lower limb non-pitting edema. Laboratory investigations revealed hypoalbuminemia and hypogammaglobulinemia. Stool A1AT was increased. GI infection was ruled out and there was no proteinuria. Video-capsule endoscopy revealed active bleeding, linear ulcerations alternating with pale zones throughout the small bowel, suggesting villous atrophy (Fig. 2A). Histology showed normal architecture, both in the upper- and lower-endoscopy specimens. Increased lamina propria eosinophils were seen in the stomach, reaching the numbers of 75/HPF in the antrum, whilst sparing the epithelium (Fig. 2B), in the duodenum, in the colon, and in the rectum (Table 1). Again, mild lymphatic dilatation was observed. Symptoms resolved within 8 days of initiating a CMP elimination diet and a partially hydrolyzed formula. As there was no recurrence of symptoms or evidence of enteropathy after one year of dietary elimination, CMP were reintroduced. At the time of consent, Patient 3 was 8 years old and doing well.

Patient 4: a baby with puffy eyes

A 13 month-old girl presented with a six day history of palpebral and lower limb pitting edema and a recent weight gain of 900gr without GI symptoms. At time of diagnosis, she was on an age-appropriate diet including cow's milk and other dairy products. Laboratory studies revealed hypoalbuminemia and hypogammaglobulinemia. Stool A1AT was increased. GI infection was ruled out and there was no proteinuria. Endoscopy was normal. Histology showed normal architecture in the upper gastrointestinal biopsies, with mild chronic pangastritis, but no activity or H. pylori infection; eosinophils were also increased in the

stomach, duodenum, sigmoid and rectum (Table 1)(Suppl. Fig. 4). Architecture was more difficult to assess in the left colon, due to crush artifacts, but appeared normal in the sigmoid and rectum. Mild lymphatic dilatation was observed in the duodenum. Clinical improvement was observed after 13 days with extensively hydrolyzed formula and CMP elimination diet. CMP were introduced when the patient had been symptom-free for 12 months. At the time of consent, Patient 4 was 6 years old and doing well.

Discussion

The four cases of CMPA presented herein were characterized by severe hypogammaglobulinemia and hypoalbuminemia. All the cases were non-IgE-mediated allergies, since the onset of symptoms is delayed. Mention of the presence of IgE in some patients is for information only (Suppl. Table 1). Two cases presented with FTT, both with proximal small bowel involvement on biopsy, suggesting that site of inflammation underlies clinical presentation to some extent. These two cases were diagnosed as FPIES. The other two patients came to medical attention at a later age, with no GI symptoms. They were diagnosed as FPE. All cases underwent endoscopy to assess for primary immune deficiency (PID). IgG, IgA and IgM levels normalized on a CMP elimination diet. In some cases, we have excluded beef and veal proteins as these foods may not be tolerated. Soy has been excluded because of the risk of cross-reactivity. In our cases, time of eviction was between 12 and 15 months depending on the child's clinical progress and the parents' wishes. All four children are well and asymptomatic at follow-up, none having developed symptoms consistent with inflammatory bowel disease (IBD). As median to long-term follow up of these children has been uneventful and there was no subsequent history of respiratory allergy, the final diagnosis was severe CMPA.

CPMA is a histological diagnostic challenge. These four cases suggest that CPMA with PLE can affect any segment along the GI tract, a feature that has not been clearly reported for two reasons: CPMA is most commonly a clinical diagnosis and (capsule-) endoscopy has been limited to older children. Taken together, this small case series yields a map of histopathologic presentation along the GI tract revealing varying degrees of regional involvement and disease severity.

The histological findings in CMPA vary along the GI tract. Jejunal villous shortening or a pathological villus-to-crypt ratio have been described.[2,6-10] When severe, CMPA may present with diffuse colitis and variable ileal involvement, with ulcers and crypt abscesses; in the distal duodenum and the jejunum, villous atrophy may be seen, together with increased numbers of lymphocytes, plasma cells, eosinophils and mast cells.[11,12] Endoscopy may show duodenal bulb nodularity[13] and biopsy may show lymphonodular hyperplasia in the duodenal bulb and colon.[14] These features were not observed in the four patients reported here. Isolated nodular lymphoid hyperplasia has been reported in older patients, without hypoalbuminemia or peripheral eosinophilia.[15] CMPA is in the differential diagnosis of very early onset intestinal bowel disease (VEO-IBD). In particular one of the histological patterns of VEO-IBD, the enterocolitis-like pattern, associates extensive villous atrophy in the small bowel. Although large-bowel mucosal architecture is preserved, edema and mucosal friability may lead to the detachment of the colonic epithelium.[16] We observed chronic active duodenitis with partial villous atrophy and regeneration in only one patient, while architecture was preserved in all other patients. This patient, depicted in Suppl. Fig. 2-3, showed severe colonic mucosa atrophy with near complete gland loss in the colon and increased apoptotic bodies at time of presentation, something which has been described in congenital immune deficiencie.[17] Although immune deficiency should be considered in the face of profound histological

alterations, empirically eradicating cow's milk protein from the diet is a practical first step for several reasons: CMPA is a frequent diagnosis, and eradication leads to rapid clinical improvement, serving as diagnostic and management orientation if clinical response is favorable. Of note, despite severe histological findings, endoscopy was normal in this case. Conversely, in another patient featured in Figure 2A, capsule video-endoscopy showed active bleeding with linear ulcerations and evidence of villous atrophy, findings that were not confirmed by histology. These two examples highlight the poor concordance between endoscopical and histological findings.

Tissue eosinophilia is expected in a food allergy.[18-20] Lamina propria eosinophilia was seen in one or more biopsy locations in all patients; in particular, all three patients with gastric biopsies displayed numerous eosinophils in the gastric lamina propria. Allergic conditions are documented in 58.9% of children with eosinophilic gastritis, and in 51.6% of children with eosinophilic gastroenteritis.[21] There are no clear cutoff values for eosinophilic infiltration. Winter et al. reported that finding >60 eosinophils per ten high power fields (HPF) in the lamina propria was highly specific for allergy-related proctocolitis.[22] These numbers were later confirmed by Odze et al.[23] In pediatric EGID, clear histological diagnostic criteria are established only for eosinophilic esophagitis, with in particular eosinophil counts defined as ≥15 per HPF. In contrast, the proposed eosinophil thresholds for eosinophilic gastritis (≥30/HPF in ≥5/HPF), eosinophilic gastroenteritis (≥50/HPF in the duodenum), and eosinophilic colitis (>50/HPF in the right colon, >30/HPF in the transverse and left colon) are less-well defined.[5,24] Moreover, to minimize heterogeneity across reports, recent studies recommend standardizing the reporting of eosinophilic infiltration density in cells/mm^2.[5] Therefore, the current thresholds still require further refinement to ensure consistency. Eosinophils also involved the epithelium, and the muscularis mucosae, in close association with lymphoid aggregates (data

not shown). The presence of <6 eosinophils/HPF on average however remains within normal range according to accepted norms.[4] Quantifying eosinophils in the lamina propria remains a challenge as numbers may vary with geographic location,[5] environmental, dietary, and seasonal causes among others.[25] Eosinophils as the main component of crypt abscesses are described in allergic coloproctitis.[22] In addition, acute neutrophilic infiltration was observed in two of the four patients presented here, with neutrophilic gland microabscesses in Patient N°2. Again, VEO-IBD should be considered in the differential diagnosis, since eosinophil-rich and mixed enterocolitis-like, eosinophil-rich patterns have been described in this setting.[26]

Unusual histological features have been reported in CMPA. First, rare examples of giant cell or granulomatous reactions are described in FPIAP;[27-29] obviously a differential diagnosis of Crohn's disease, immune deficiency, or infection needs to be considered in such cases. Second, a 7-month-old male presenting with clinical and histological features of abetalipoproteinemia was diagnosed with CMPA.[30] The suggestive histological findings consisted of cytoplasmic vacuolization (increased lipid droplets) of duodenal enterocytes, a feature also observed in Patient N°1. Similar findings are however also described with fasting and lipid-rich meals.

Finally, all 4 patients showed some degree of lymphatic duodenal dilatation, albeit mild and focal. PLE has been described in both FPIES and FPE, but the histopathology and the underlying mechanisms remain unclear. PLE can arise owing to different mechanisms: increased lymphatic pressure with lymphangiectasia, mucosal erosion, or a tight junction defect in an otherwise normal appearing mucosa.[31] In addition, increased intestinal permeability and fluid shifts secondary to local inflammation, and in particular to eosinophils, have been postulated to contribute to the pathophysiology of PLE in FPIES.[11] This concept is not novel as some of these mechanisms have in part been incriminated in IBD where inflammatory mediators interfere with lymphatic vessel function and alter lymph flow, leading to lymphangiogenesis

and lymphangiectasia, with increased mucosal edema and inflammation.[32,33] Extrapolating from the IBD literature, we postulate that one of the mechanisms of PLE in CMPA could also be increased lymphatic pressure secondary to mucosal injury and inflammation.

All in all, the cases presented herein suggest that there is no pathognomonic pattern of histological involvement, and that injury may arise anywhere along the GI tract, confirming the findings of others.[13,14] Allergen elimination allows for rapid and complete mucosal restoration in one case and total symptom resolution in all cases, including in severe cases. Finally, tissue eosinophilia is the norm, seemingly unrelated to clinical disease severity.

CPMA, especially non-IgE mediated, remains a diagnostic challenge for several reasons. First, it may present with a wide variety of symptoms ranging from isolated diarrhea/vomiting to FTT or edema. In severe cases, it may resemble congenital enteropathy with or without immune deficiency. Second, it is usually a clinical diagnosis, with no specific laboratory or imaging test. Therefore, although invasive, (capsule-) endoscopy may be a useful diagnostic tool for diagnosis in severe cases, or in cases where etiology is doubtful. PLE is a clinical diagnosis, combining diarrhea and/or edema with hypoalbuminemia. The source of protein loss can be confirmed using A1AT stool clearance after exclusion of renal protein loss.

Second, biological findings associated with CMPA are non-specific. For example, hypoalbuminemia and thrombocytosis could be due to acute inflammation. Leukocytosis is not the norm, as was not observed in this small series, and only one patient had documented peripheral eosinophilia, also commonly accepted to be suggestive of food allergy in general. Taken together, there is no specific blood marker of PLE due to CMPA. Clinical and biological response to CMP elimination and challenge remains an essential diagnostic tool.

Third, the complex and severe clinical picture may open the same differential diagnosis as the histological patterns to include immune deficiencies and eosinophilic gastrointestinal disorder. The severity of these four cases could indeed suggest an early IBD or a genetic disease. However, both their short-term and long-term course suggest that empirically removing CMP from the diet, is a pragmatic management method prior to exploring the possibility of rarer diseases.

While routine endoscopy is not required for the diagnosis of CMPA, (capsule-) endoscopy represents a safe diagnostic procedure in severe cases. It is noteworthy that none of the patients presented herein experienced endoscopy-related complications despite the theoretical infectious risk due to hypogammaglobulinemia and increased intestinal permeability.

Conclusion

CMPA can present with severe signs and symptoms and affect any segment of the GI tract. The lack of correlation between endoscopy and histological findings highlights the importance of a comprehensive approach to the patient presenting with possible CMPA. Food protein allergy should be sought in infants and children with hypoalbuminemia.

References

1. Koletzko S, Niggemann B, Arato A, et al. Diagnostic approach and management of cow's-milk protein allergy in infants and children: ESPGHAN GI Committee practical guidelines. *J Pediatr Gastroenterol Nutr*. 2012;55:221-9.
2. Labrosse R, Graham F, Caubet JC. Non-IgE-Mediated Gastrointestinal Food Allergies in Children: An Update. *Nutrients*. 2020;12.
3. Caffarelli C, Baldi F, Bendandi B, et al. Cow's milk protein allergy in children: a practical guide. *Ital J Pediatr*. 2010;36:5.
4. DeBrosse CW, Case J, Putnam P, et al. Quantity and distribution of eosinophils in the gastrointestinal tract of children. *Pediatr Dev Pathol*. 2006;9:210-8.
5. Koutri E, Patereli A, Noni M, et al. Distribution of eosinophils in the gastrointestinal tract of children with no organic disease. *Ann Gastroenterol*. 2020;33:508-515.
6. Yang M, Geng L, Xu Z, et al. Severe Food Protein-Induced Enterocolitis Syndrome to Cow's Milk in Infants. *Nutrients*. 2015;8.
7. Jarvinen KM, Konstantinou GN, Pilapil M, et al. Intestinal permeability in children with food allergy on specific elimination diets. *Pediatr Allergy Immunol*. 2013;24:589-95.
8. Iyngkaran N, Abdin Z, Davis K, et al. Acquired carbohydrate intolerance and cow milk protein-sensitive enteropathy in young infants. *J Pediatr*. 1979;95:373-8.
9. Kuitunen P, Visakorpi JK, Savilahti E, et al. Malabsorption syndrome with cow's milk intolerance. Clinical findings and course in 54 cases. *Arch Dis Child*. 1975;50:351-6.
10. Shiner M, Ballard J, Smith ME. The small-intestinal mucosa in cow's milk allergy. *Lancet.* 1975; 1:136-4.
11. Nowak-Wegrzyn A, Muraro A. Food protein-induced enterocolitis syndrome. *Curr Opin Allergy Clin Immunol*. 2009;9:371-7.
12. Fontaine JL, Navarro J. Small intestinal biopsy in cows milk protein allergy in infancy. *Arch Dis Child*. 1975;50:357-62.
13. Al-Hussaini A, Khormi M, Fagih M. Duodenal bulb nodularity: an endoscopic sign of cow's milk protein allergy in infants?. *Gastrointest Endosc.* 2012;75,2:450 - 453
14. Nowak-Wegrzyn A, Katz Y, Mehr SS, et al. Non-IgE-mediated gastrointestinal food allergy. *J Allergy Clin Immunol*. 2015;135:1114-24.
15. Machida HM, Catto Smith AG, Trevenen C, et al. Allergic colitis in infancy: clinical and pathologic aspects. *J Pediatr Gastroenterol Nutr*. 1994;19:22-6.
16. Parente P, Mastracci L, Vanoli A, et al. Pattern-based Histologic Approach in Very Early Onset IBD: Main Features and Differential Diagnosis. *Adv Anat Pathol.* 2022;29:71-80.
17. Washington K, Stenzel TT, Buckley RH, et al. Gastrointestinal pathology in patients with common variable immunodeficiency and X-linked agammaglobulinemia. *Am J Surg Pathol*, 1996;20:1240-52.
18. Lake AM. Food-induced eosinophilic proctocolitis. *J Pediatr Gastroenterol Nutr*. 2000;30 Suppl: S58-60.
19. Cervantes-Bustamante R, Pedrero-Olivares I, Toro-Monjaraz EM, et al. Histopathologic findings in children diagnosed with cow's milk protein allergy. *Rev Gastroenterol Mex*. 2015;80:130-4.
20. Sorea S, Dabadie A, Bridoux-Henno L, et al. Hemorrhagic colitis in exclusively breast-fed infants. *Arch Pediatr.* 2003;10:772-5.

21. Jensen ET, Martin CF, Kappelman MD, et al. Prevalence of Eosinophilic Gastritis, Gastroenteritis, and Colitis: Estimates From a National Administrative Database. *J Pediatr Gastroenterol Nutr*. 2016;62:36-42.
22. Winter HS, Antonioli DA, Fukagawa N, et al. Allergy-related proctocolitis in infants: diagnostic usefulness of rectal biopsy. *Mod Pathol*. 1990;3:5-10.
23. Odze RD, Bines J, Leichtner AM, et al. Allergic proctocolitis in infants: a prospective clinicopathologic biopsy study. *Hum Pathol*. 1993;24:668-74.
24. Koutri E, Papadopoulou A. Eosinophilic Gastrointestinal Diseases in Childhood. *Ann Nutr Metab.* 2018;73 Suppl 4:18-28.
25. Hoofien A, Salvatore O, Auth MKH, et al. A Quantitative Assessment of Mucosal Eosinophils in the Gastrointestinal Tract of Children Without Detectable Organic Disease. *Pediatr Dev Pathol*. 2022;25:99-106.
26. Parente P, Macciomei MC, Buccoliero AM, et al. Application of a pattern-based approach to histological diagnosis in very early onset IBD (VEO-IBD) in a multicentric cohort of children with emphasis on monogenic disease with IBD-like morphology. *Histopathology*, 2024;84: 440-450.
27. Dargent JL, Souayah H, Hainaut M. Granulomatous variant of allergic proctocolitis. *Histopathology*. 2009;55:758-60.
28. Raafat F, Castro R, Booth IW. Eosinophilic proctitis with giant cells: a manifestation of cow's milk protein intolerance. *J Pediatr Gastroenterol Nutr*. 1990;11:128-32.
29. Yamazaki K, Matsunami K, Kushima R, et al. Granulomatous Variant of Food Protein-Induced Allergic Proctocolitis. *JPGN Rep*. 2021;2:e062.
30. Cresoe S, Setya A, Beasley G, et al. Unusual Presentation of Cow's Milk Protein Allergy. *JPGN Rep.* 2022;3:e246.
31. Levitt DG, Levitt MD. Protein losing enteropathy: comprehensive review of the mechanistic association with clinical and subclinical disease states*. Clin Exp Gastroenterol.* 2017;10:147-168.
32. Zhang L, Ocansey DKW, Liu L, et al. Implications of lymphatic alterations in the pathogenesis and treatment of inflammatory bowel disease. *Biomed Pharmacother.* 2021;140:111752.
33. Van Kruiningen HJ, Hayes AW, Colombel JF. Granulomas obstruct lymphatics in all layers of the intestine in Crohn's disease. *APMIS*. 2014;122:1125-9.

Tables and figures

		Esophagus	Stomach	Duodenum	Ileum	Colon	Rectum
P1	Endoscopy	Normal	Normal	Edema	Edema	Normal	Edema
	Architecture	NA	NA	Normal	Normal	Normal	Normal
	Eosinophils	NA	NA	25/HPF, 97/mm^2	15/HPF, 37/mm^2	Caecum 11/HPF, 37/mm^2 Ascending 27/HPF, 87/mm^2 Transverse 15/HPF, 74/mm^2 Descending 31/HPF, 97/mm^2 Sigmoid 25/HPF, 67/mm^2	46/HPF, 137/mm^2
	Other	-	-	Rare PMNs, vacuolated enterocytes	-	Rare PMNs	-
P2	Endoscopy	Normal	Normal	Normal	NA	Normal	Normal
	Architecture	Normal	Normal	Non evaluable	NA	Major dystrophy, gland loss, vanishing glands	NA
	Eosinophils	*6/HPF, 9/mm^2	Antrum 26/HPF, 73/mm^2 Fundus 95/HPF, 269/mm^2	63/HPF, 195/mm^2	NA	Ascending 66/HPF, 209/mm2 Transverse 204/HPF, 393/mm2 Descending 144/HPF, 469/mm2	NA
	Other	-	Rare PMNs, rare apoptosis	PMNs, gland abscesses, apoptosis	-	PMNs in residual glands, apoptosis	-
E2, +1m	Endoscopy	Normal	Normal	Normal	NA	Normal	Normal
	Architecture	Normal	Normal	Chronic duodenitis, villous atrophy, gastric metaplasia	NA	Focal gland loss, dystrophy, regeneration	NA
	Eosinophils	0	Antrum 0	84/HPF, 157/mm^2	NA	Descending 119/HPF, 335/mm2	NA
	Other	-	Edema	Few PMNs, apoptosis	-	Few PMNs, apoptosis	-
E3, +11m	Endoscopy	Normal	Normal	Normal	NA	Normal	Normal
	Architecture	N		Regeneration, edema	NA	Dystrophic surface epithelium, bifid glands	
	Eosinophils	*2/HPF , 3/mm^2	Antrum 7/HPF, 12/mm^2 Fundus 5/HPF, 8/mm^2	21/HPF, 59/mm^2	NA	Descending 23/HPF, 100/mm^2	24/HPF, 67/mm^2
	Other	-	Edema	Edema	-	Rare PMNs, apoptosis, edema	
P3	Endoscopy	Normal	Normal	Normal	Alternance of linear ulcers and pale zones, villous atrophy, edema (vidéocapsule)	Edema	Normal
	Architecture	Normal	Normal	Normal	Normal	Normal	Normal
	Eosinophils	0	Antrum 75/HPF, 144/mm^2 Fundus 36/HPF, 222/mm^2	90/HPF, 191/mm^2	76/HPF, 173/mm^2	Caecum 60/HPF, 225/mm^2 Ascending 63/HPF, 186/mm^2 Transverse 38/HPF, 213/mm^2 Descending 56/HPF, 117/mm^2 Sigmoid 28/HPF, 107/mm^2	32/HPF, 125/mm^2
	Other	-	-	-	-	Apoptosis	-
P4	Endoscopy	Normal	Normal	Normal	NA	Normal (*left colon only*)	Normal
	Architecture	NA	Normal	Normal	NA	Normal	Normal
	Eosinophils	NA	Antrum 12/HPF, 29/mm^2 Fundus 20/HPF, 49/mm^2	46/HPF, 185/mm^2	NA	Descending 14/HPF, 34/mm^2 Sigmoid 20/HPF, 59/mm^2	28/HPF, 68/mm^2
	Other	-	-	-	-	-	-
Ref Eo#	DeBrosse et al. [4]	0.03±0.10/HPF	Antrum <8 (1.9±1.3/HPF) Fundus <9 (2.1±2.4/HPF)	<26 (9.6±5.3/HPF)	<28 (12.4±5.4/HPF)	Caecum 15.4 (10.2-18/HPF) Transverse colon 16.3±5.6/HPF Sigmoid <42 (8.3±5.9/HPF)	<32 (8.3±5.9/HPF)
	Koutri et al. [5]	0/HPF, 0/mm^2	2 (1-3/HPF), 10.2 (5.1-15.3/mm2)	12 (6.3-15/HPF), 61.2 (31.9-76.5/mm2)	12 (9.6-15/HPF), 61.2 (31.9-76.5/mm2)	Caecum 15.4 (10.2-18/HPF), 78.4 (51.9-91.8/mm2) Ascending 13.5 (12.8-17.5/HPF), 68.9 (65.1-89.3/mm2) Transverse 13 (8-19/HPF), 66.3 (40.8-97.1/mm2) Descending 13 (9.3-15/HPF), 66.3 (47.2-76.5/mm2) Sigmoid 8 (5.1-11/HPF), 40.8 (26.1-56.1/mm2)	5 (1.9-7.8/HPF), 25.5 (9.8-40/mm2)

Abbreviations: HPF: high power field (x400; 0.196 mm2); PMN: polymorphonuclear neutrophil; NA: no data available; Ref Eo#: reference numbers of eosinophils: median (interquartile range)
In red: increased eosinophilic infiltration, according to ≥1 ref.

Table 1: Main endoscopy and histology findings at initial presentation *NDA: no data available; HPF: high power field

	Clinical presentation		Albumin nadir (n 35-48g/l)	IgG Nadir (g/l)	IgE specific	Platelets (n 168-392G/l)	CMP Eviction duration	Other eviction	CMP re-introduction	Interval between CMP eviction and clinical remission
Case	**Age**	**Presenting symptoms**								
1	4m	Hydrops Non-bloody diarrhea 6/d	12	0.34 (n 2.8-9.9)	Negative	259	12m for milk 7m for beef, veal, soy	Beef, veal, soy	At 16m	10d
2	7w	Bloody diarrhea 8/d	21	1.76 (n 5.6-15.4)	Negative	562	15m	Gradual food introduction fruit > vegetable > gluten	At 17m	18d
3	2y	Palpebral and lower limb edema, non-pitting	15	0.98 (n 3.7-11.7)	Positive	799	12m for all	Beef, veal	At 3y	8d
4	13m	Palpebral and lower limb edema, pitting	20	0.54 (n 4.1-12.1)	Negative	703	12m	No	At 2y	13d

CMP = cow's milk protein; y = years, m = months, w = weeks, d = days, n = normal range

Suppl. Table 1: Patient characteristics

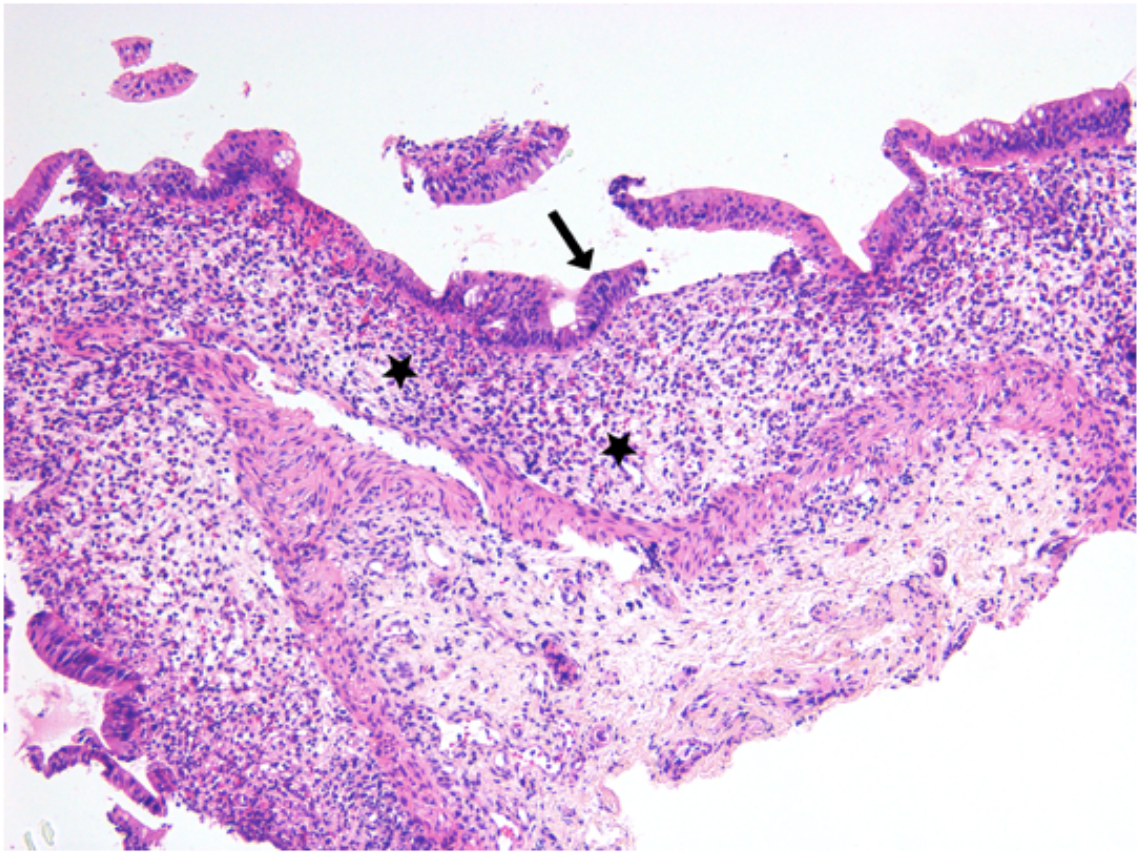


Figure 1: Histological findings in case N°2, at 8 weeks of age. The transverse colon shows complete gland loss, surface epithelium dystrophy (arrow) with mucin depletion, and edema and inflammation in the lamina propria. Up to 95 eosinophils (as seen between the 2 stars) were counted per high power field (HPF, x400) (Hematoxylin & Eosin, H&E, x100).
Findings in the duodenum, and major improvement of the colon histological findings are provided in Supplemental Figure 1 and 2.

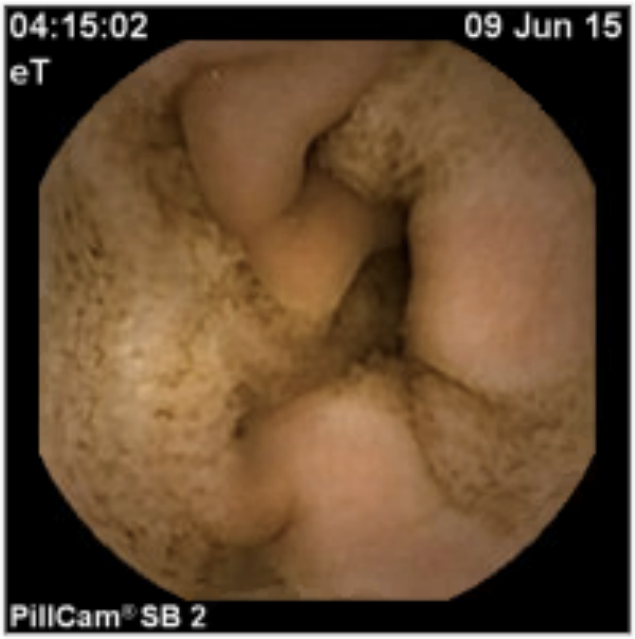


Figure 2A: Video-capsule endoscopy revealed active bleeding, linear ulcerations alternating with pale zones throughout the small bowel, suggesting villous atrophy

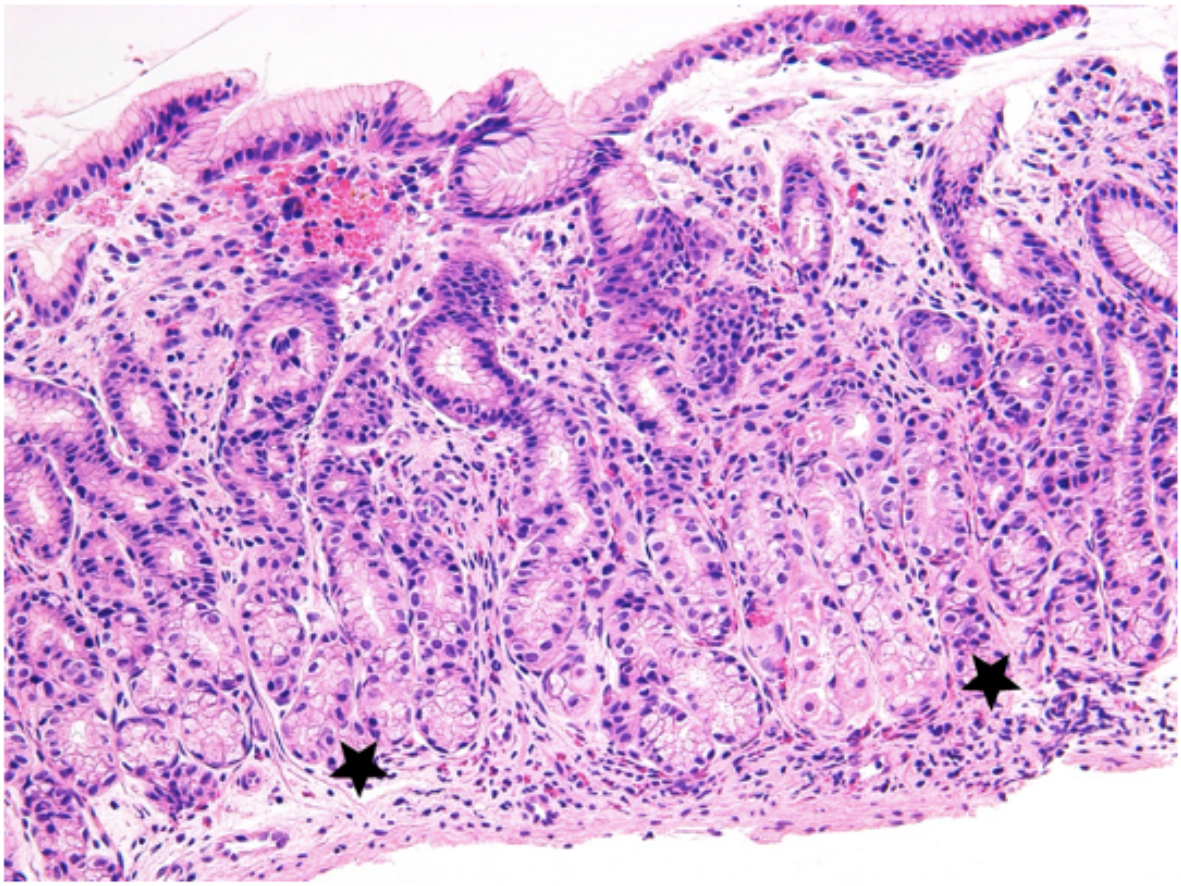
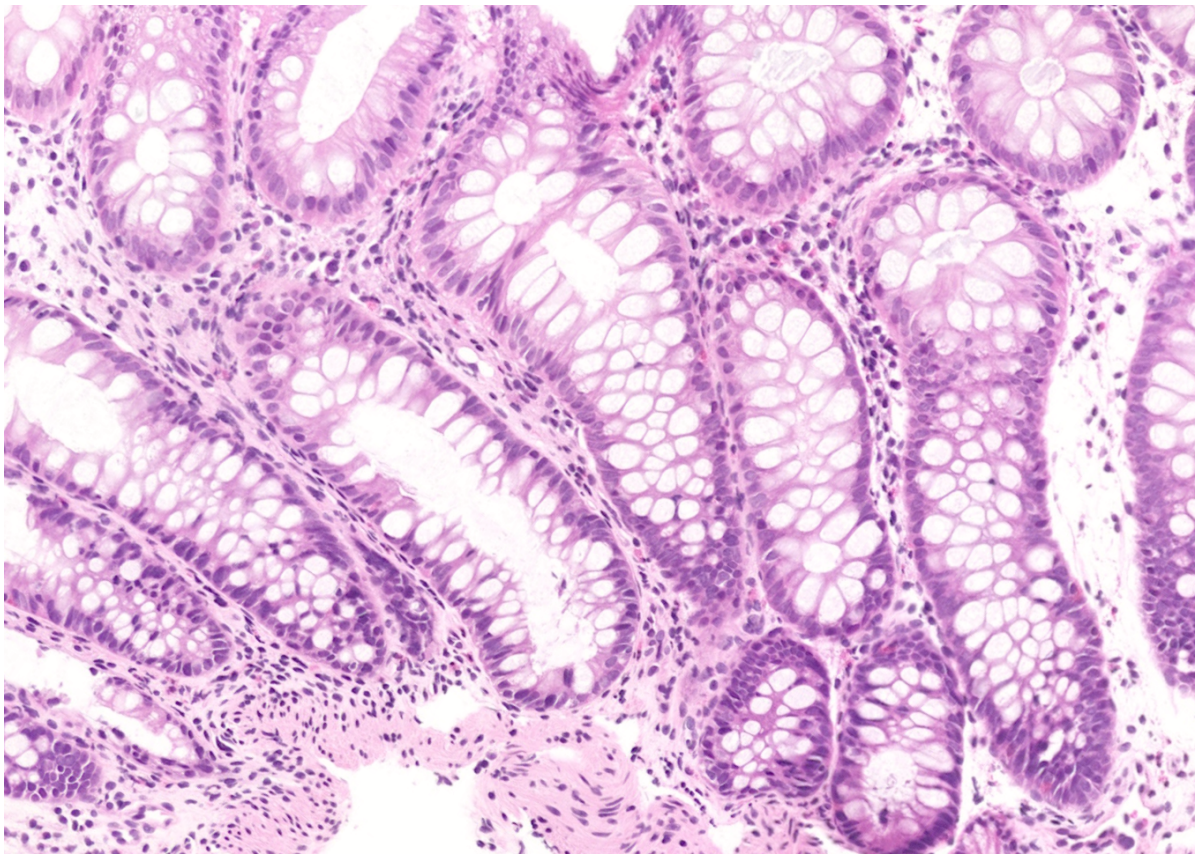
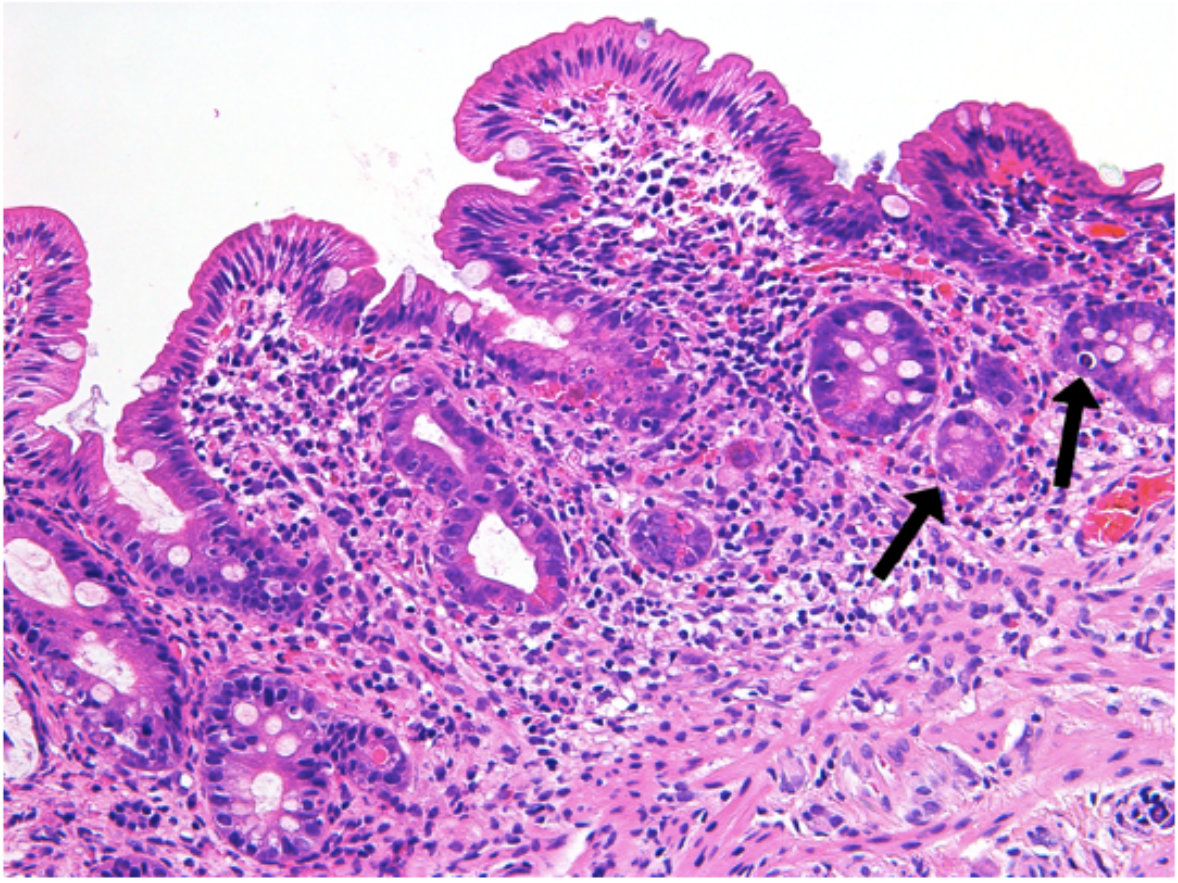


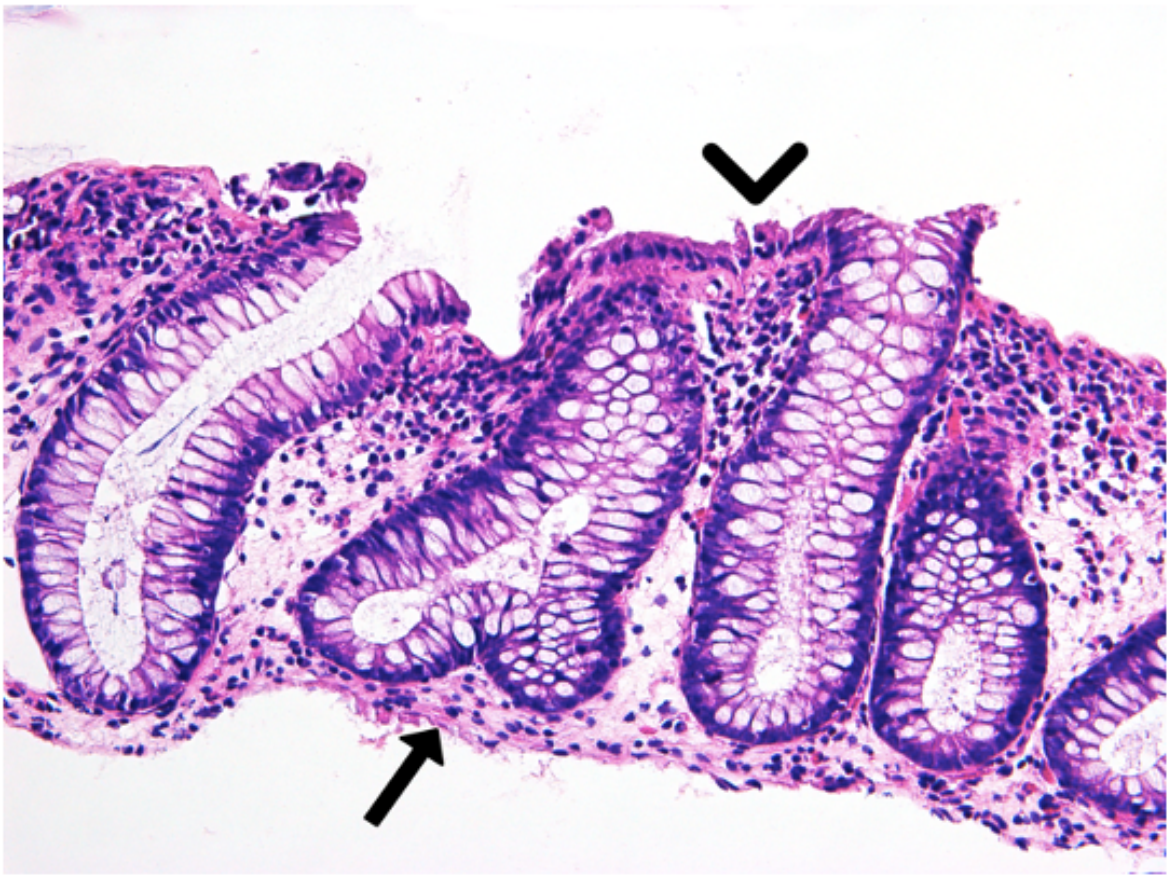
Figure 2B: Histological findings in case N°3. The antral mucosa shows intact architecture. Increased eosinophils are seen in the lamina propria (area between the 2 stars), sparing the epithelium (H&E, x200).



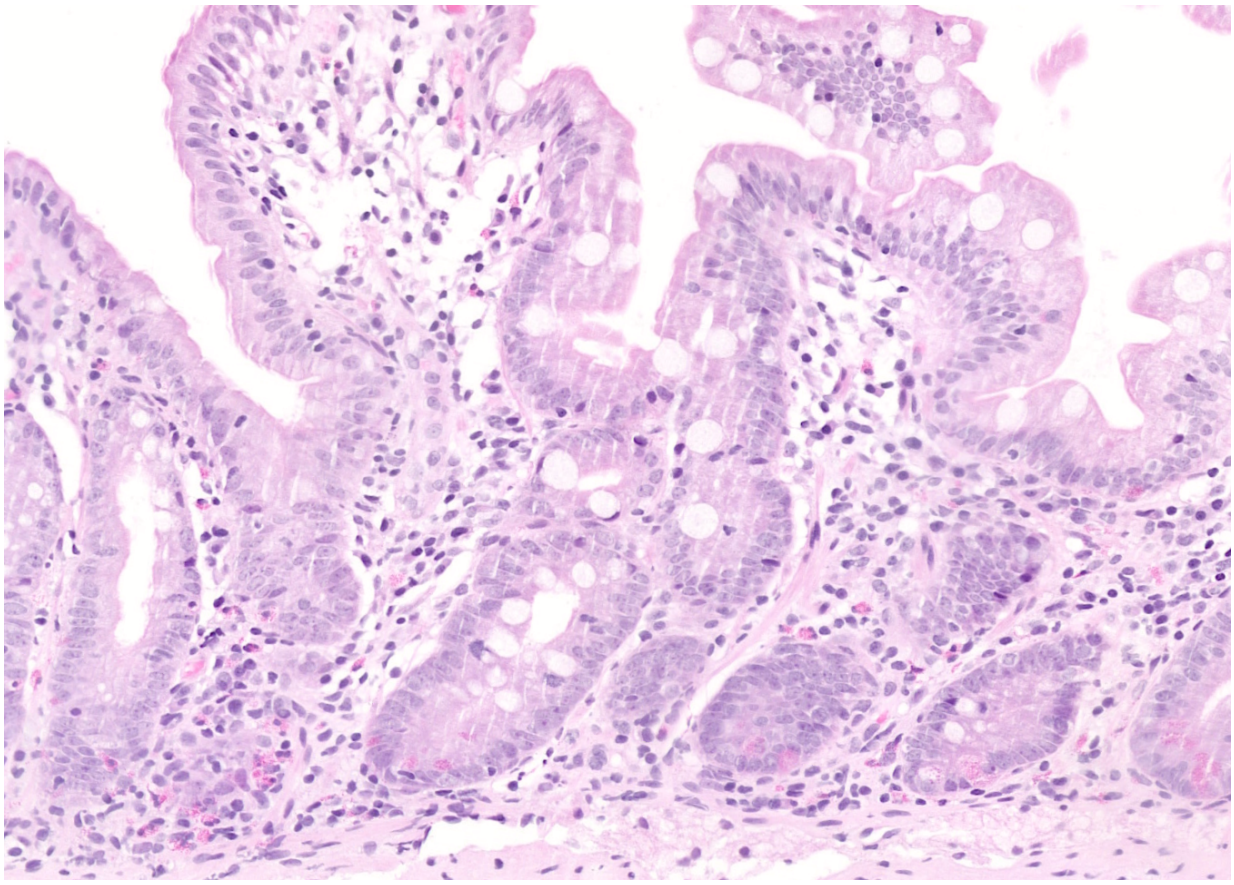
Suppl. Fig. 1: In patient N°1, histology of the rectal biopsy showed no architectural anomalies (H&E). An increased number of eosinophils was observed in the lamina propria, reaching 48 per high-power field (HPF) and 137/mm2, exceeding the normal reference range of <32 (8.3±5.9/HPF) and 25.5 (9.8-40/mm2).



Suppl. Fig. 2: In patient N°2, at 12 weeks of age, chronic active duodenitis was seen, with partial villous atrophy, mucin depletion, regeneration and increased apoptosis (arrows). Lamina propria eosinophils forming small aggregates were more abundant (maximum 65 eosinophils/HPF) in areas with neutrophilic infiltration (H&E, x200).



Suppl. Fig. 3: At 13 months of age, colon architecture has markedly improved in patient N°2, with only rare bifid glands (arrow), and mild degrees of surface epithelium dystrophy (arrowhead) and lamina propria edema. Eosinophil numbers dropped to 15 per HPF maximum in the lamina propria (H&E, x400).



Suppl. Fig. 4: In patient N°4, there were no architectural changes (H&E). Again, increased eosinophil numbers were seen in the lamina propria. In the duodenum, numbers reached 46/HPF and 185/mm2 (reference range of <26 (9.6±5.3/HPF) and 61.2 (31.9-76.5/mm2)).

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Bibliographie

1. Koletzko S, Niggemann B, Arato A, Dias JA, Heuschkel R, Husby S, et al. Diagnostic Approach and Management of Cow's-Milk Protein Allergy in Infants and Children: ESPGHAN GI Committee Practical Guidelines. J Pediatr Gastroenterol Nutr. août 2012;55(2):221-9.
2. Caffarelli C, Baldi F, Bendandi B, Calzone L, Marani M, Pasquinelli P, et al. Cow's milk protein allergy in children: a practical guide. Ital J Pediatr. 2010;36(1):5.
3. Labrosse R, Graham F, Caubet JC. Non-IgE-Mediated Gastrointestinal Food Allergies in Children: An Update. Nutrients. 14 juill 2020;12(7):2086.
4. Nowak-Węgrzyn A, Katz Y, Mehr SS, Koletzko S. Non–IgE-mediated gastrointestinal food allergy. J Allergy Clin Immunol. mai 2015;135(5):1114-24.
5. Nowak-Wegrzyn A, Muraro A. Food protein-induced enterocolitis syndrome. Curr Opin Allergy Clin Immunol. août 2009;9(4):371-7.
6. Sampson HA. Food allergy. Part 2: Diagnosis and management. J Allergy Clin Immunol. juin 1999;103(6):981-9.
7. Vandenplas Y, Broekaert I, Domellöf M, Indrio F, Lapillonne A, Pienar C, et al. An ESPGHAN Position Paper on the Diagnosis, Management, and Prevention of Cow's Milk Allergy. J Pediatr Gastroenterol Nutr. févr 2024;78(2):386-413.
8. Pratelli G, Tamburini B, Badami GD, Lo Pizzo M, De Blasio A, Carlisi D, et al. Cow's Milk: A Benefit for Human Health? Omics Tools and Precision Nutrition for Lactose Intolerance Management. Nutrients. 22 janv 2024;16(2):320.
9. Sampson HA. Food allergy. Part 1: Immunopathogenesis and clinical disorders. J Allergy Clin Immunol. mai 1999;103(5):717-28.
10. Michelet M, Schluckebier D, Petit LM, Caubet JC. Food protein-induced enterocolitis syndrome – a review of the literature with focus on clinical management. J Asthma Allergy. juin 2017;Volume10:197-207.
11. Zhang S, Sicherer S, Berin MC, Agyemang A. Pathophysiology of Non-IgE-Mediated Food Allergy. ImmunoTargets Ther. déc 2021;Volume 10:431-46.
12. Fujita H, Meyer N, Akdis M, Akdis CA. Mechanisms of Immune Tolerance to Allergens. In: Ring J, Darsow U, Behrendt H, éditeurs. Chemical Immunology and Allergy [Internet]. S. Karger AG; 2012 [cité 1 mars 2025]. p. 30-8. Disponible sur: https://karger.com/books/book/2758/chapter/5793910
13. Gaudichon C, Benhaddou S. Physiologie de la digestion des protéines et de l'absorption des acides aminés et déterminants de la digestibilité protéique. Médecine Mal Métaboliques. déc 2024;18(8):648-55.
14. Vandenplas Y, Brough HA, Fiocchi A, Miqdady M, Munasir Z, Salvatore S, et al. Current Guidelines and Future Strategies for the Management of Cow's Milk Allergy. J Asthma Allergy. oct 2021;Volume 14:1243-56.
15. Cresoe S, Setya A, Beasley G, Gonzalo DH, Chan A. Unusual Presentation of Cow's Milk Protein Allergy. JPGN Rep. nov 2022;3(4):e246.
16. Braamskamp MJAM, Dolman KM, Tabbers MM. Clinical practice: Protein-losing enteropathy in children. Eur J Pediatr. oct 2010;169(10):1179-85.
17. Levitt D, Levitt M. Protein losing enteropathy: comprehensive review of the mechanistic association with clinical and subclinical disease states. Clin Exp Gastroenterol. juill 2017;Volume 10:147-68.
18. Amiot A. Gastro-entéropathies exsudatives. Rev Médecine Interne. juill 2015;36(7):467-73.
19. Kallel F, Amouri A, Hamza F, Charfeddine S, Guermazi F. Apport de la scintigraphie à l'albumine marquée dans les entéropathies exsudatives : à propos de deux cas. Médecine Nucl. oct 2009;33(10):671-3.
20. Arrivé L, Azizi L, Lewin M, Hoeffel C, Monnier-Cholley L, Lacombe C, et al. MR Lymphography of Abdominal and Retroperitoneal Lymphatic Vessels. Am J Roentgenol. nov 2007;189(5):1051-8.