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Case Report

Milk Protein Allergy

Cow's Milk Protein Allergy in an Infant - A Case Report

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Abstract: Cow's milk protein allergy (CMPA) is a common condition of food allergy in babies, and it is encountered in children with an incidence of 2% to 7.5% estimated in the first year of life. Breast-fed and formula-fed babies can present with CMPA symptoms, and it's essential to diagnose CMPA to avoid the repercussion of overdiagnosis or underdiagnosis. A one-year-old female child complained of fresh blood in her stools for two days which was painless. She was on breast milk and complimentary feeds, and her nutritional status was normal. she had been through 7 similar episodes of easy blood in stools from 4 months of age. She was treated with IV antibiotics and initially suspected of colitis, and investigations were not done. There was no family history of allergy, atopy, or asthma. On examination revealed pallor, vitals stable, and systemic examination were normal. Complete blood count shows low HB, peripheral smear shows microcytic anaemia, CRP-negative. Stool for occult blood positive. Faecal calprotectin was negative. USG Abdomen - normal, USG Endoscopy -Normal, Colonoscopy showed Oedematous mucosa of the terminal ileum and prominent villi with erythema, sigmoid, and rectum revealed erythematous with erosion with prominent Pit pattern. Biopsy- From sigmoid and rectum showed increased eosinophils in lamina propria. Hence the child was diagnosed to have Cow's milk protein allergy. The mainstay treatment includes avoiding Cow's milk consumption for four weeks - 6 months' post-diagnosis. In that instance, breastfeeding mothers should be advised to avoid milk and milk products during breastfeeding.

Keywords: Cow's milk protein allergy, complimentary feed, breastfeeding.

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1. INTRODUCTION

CMPA is common among infants and is caused due to the allergen beta-lactoglobulin (β-lg), casein, and alpha-lactalbumin[1]. The incidence of CMPA in children under one year of age is around 2 - 7.5% in western countries, whereas, in India, the incidence is 1.5 – 3%.[2-3] Although familiar, it's often confused with systemic infection. Manifestation starts around six months when the infants are introduced to cow's milk. However, in exclusively breastfed infants, CMPA is due to maternal consumption of milk products, resulting in the secretion of β-lg in breast milk. The allergic reaction that manifests could be of three types: IgE mediated, Mixed IgE and non-IgE mediated. [4] Most prevalent type of food allergy is CMPA typically impacts the paediatric population, particularly infants. Excessive usage of cow's milk as a replacement for human milk has increased the prevalence of this illness. When a child has CMPA, their body reacts because it cannot recognise one or more of the casein, alpha-lactalbumin, or beta-lactoglobulin proteins found in cow's milk.[5] The symptoms of a CMPA typically appear within the initial months of infancy. IgE-mediated or non-IgE-mediated conditions can both be used to describe CMPA. Mixed IgE and non-IgE CMPA refer to some CMPA cases that exhibit both IgE and non-Ige features. The IgE-mediated response is a typical allergy response that results in prompt physiological reactions. Once after exposure, within a few hours, the infant may exhibit symptoms in the skin, oropharynx, upper and lower respiratory tracts, gastrointestinal tract, and cardiovascular system. The agents responsible for these reactions are cow's milk proteins, such as casein, β-lactoglobulin, α-lactalbumin, serum albumin, and immunoglobulin. A sensitization phase and an activation phase constitute Ig-E-mediated CMPA. IgE antibodies against cow's milk proteins are released during sensitization and bind to the surface of mast cells and basophils in anticipation of the following exposure to milk from cows. [6] The activation phase begins in subsequent exposures when the IgE antibodies already linked to basophils and mast cells bind to the allergenic epitopes of casein, lactoglobulin, or -lactalbumin. This results in the release of inflammatory mediators, which ultimately show up as CMPA's clinical symptoms. Non-IgE-mediated CMPA has a variety of postulated explanations, but its processes are less well understood. [7] Milk's two main proteins are casein (around 80%) and secondary whey proteins (20%). Casein, the vital milk protein in fraction to produce higher sensitivity in people, is one of the leading milk proteins. Calcium phosphate-micelle complexes make up most of the phosphate-conjugated milk protein casein. Four varieties of casein exist: casein alpha series one and series 2, beta, gamma, and kappa casein all play important roles in the body. Secondary proteins are a cluster of globular proteins with a relatively balanced distribution of acidic, basic, hydrophobic, and hydrophilic amino acids. Beta-lactoglobulin and alpha-lactalbumin are essential whey proteins that account for roughly 70–80% of all whey proteins. IgE, serum albumin, lactoferrin, lactoperoxidase, and protease-peptones are additional whey proteins that should be addressed. The composition of cow's milk includes 11.6 mg/dl of alpha s1 casein and 3.0mg/dl, whereas both are absent in breast milk. Both of these proteins are absent in breast milk[8-9] In this study, we discuss a case of an infant diagnosed with Cow's milk protein allergy.

2. CASE REPORT

2.1. Presenting complaints

A one-year-old female child complained of painless fresh blood in her stools for two days at a frequency of 6-7 episodes per day. She was fed with both breast milk and complementary feeds. Her nutritional status was normal.

2.2. History of present illness

Since four months of age, she had been through 7 similar episodes of painless blood in her stools. Still, she was only treated with IV antibiotics as colitis was suspected, and further investigations were not done.

2.3. Medical and Family history

There was no family history of allergy, atopy, or asthma. Her development was expected, and she was immunized as per National Immunization Schedule with no optional vaccines given.

2.4. Physical examination

On examination, she appeared pale, her vitals were within normal limits and systemic examination was normal.

2.5. Laboratory tests

Routine blood investigations showed decreased haemoglobin (10.5gm/dl), and the peripheral smear was suggestive of microcytic hypochromic anaemia. C - reactive protein was negative, and Liver Function Test and Prothrombin Time – International Normalised Ratio were average. Total serum IgE was elevated (54.12). Stool complete analysis was positive for occult blood, and faecal calprotectin was negative.

2.6. Imaging studies

The child was initially diagnosed with colitis; however, antibiotics did not improve symptoms. Therefore, a medical gastroenterologist's opinion was sought, and a UGI endoscopy and colonoscopy were done. While UGI endoscopy findings were normal, Colonoscopy revealed oedematous mucosa of the terminal ileum and prominent villi with erythema, as shown in figure 1. In addition, the ileocecal valve showed a well-known pattern; the sigmoid colon and rectum were erythematous with erosions and prominent pit patterns, as shown in figure 2. Therefore, a biopsy was taken from the rectum and sigmoid colon and was sent for histopathological analysis, which shows increased eosinophils in lamina propria (15/HPF).

2.7. CMPA- Clinical reasoning

At this point, a differential diagnosis of Cows Milk Protein Allergy (CMPA) or Inflammatory bowel disease (IBD) was considered. On further probing, the history revealed that the child had not taken cow's milk or any other milk product. However, the mother consumed milk products throughout the breastfeeding period. This could have likely resulted in the child presenting with episodes of loose stools, suggesting a diagnosis of CMPA rather than IBD.

2.8. Management and follow-up.

The mother was advised to continue breastfeeding and avoid milk and milk products for herself and the child. As a result, the child improved symptomatically, and the frequency of loose stools gradually reduced and eventually stopped. The child was also started on oral iron supplements and multivitamins for the anaemia. On follow-up after six months, the child was symptom-free, and her anaemia was corrected. However, subsequent repeat sigmoidoscopy showed resolution of colitis, as shown in figure 3.

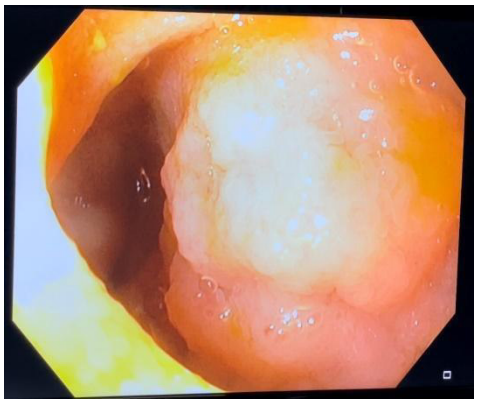

Fig.1 Terminal ileum showing oedematous mucosa, prominent villi with erythema

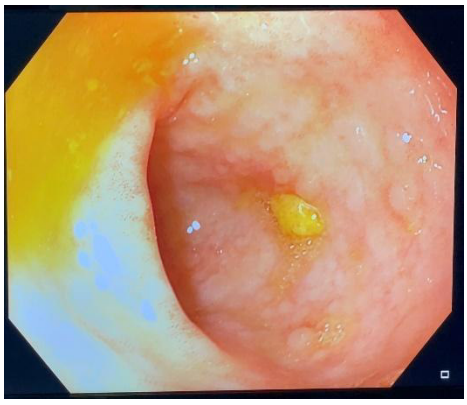

Fig.2 sigmoid colon showing prominent pit pattern

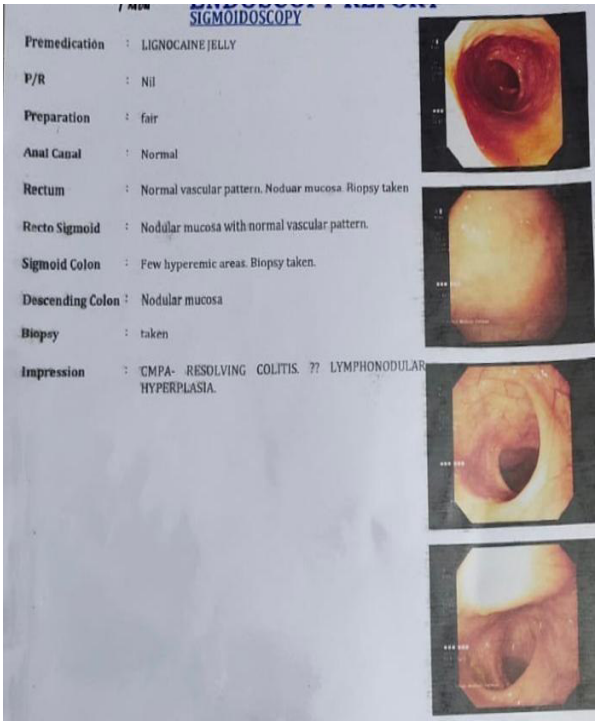

Fig.3 Repeat sigmoidoscopy showing resolving colitis

3. DIAGNOSIS OF CMPA

Diagnostic Testing could show IgE-mediated, cell-mediated, and mixed responses can occur during CMPA. Many young children and newborns with CMPA will not have serum-positive IgE levels. Within 2 hours of ingesting an allergen, an IgE-mediated response typically causes an acute reaction. A late reaction would be a symptom of a particle response and would happen two days to 1 week after exposure to an allergen. If the only symptoms are gastrointestinal, a cell-mediated reaction is more likely. CMPA caused by an IgE response typically presents with gastrointestinal, integumentary, and respiratory symptoms. [10] A clinical suspicion of CMPA may be confirmed by the clinical diagnostic procedure. Implementing an oral food challenge under the supervision of a healthcare professional to look for an acute response is the best model for diagnosing CMPA. Other testing techniques include a skin prick test, where a wheal measuring more than 6 mm in infants under the age of 2 is deemed positive, or a particular IgE test using a blood sample, where a value of five kilounits per litre or more in children under two is considered positive. Both procedures have a CMPA predictive ability of 95% or above.[11] These two tests, in combination with a favourable history and physical exam, can identify CMPA, which directs to appropriate treatment (Fig 4)

4. TREATMENT PLAN

Absolute abstinence from any supplies having cow's milk protein is the only effective treatment for CMPA. A thoroughly solubilized procedure is the primary alternative for babies with a low risk of anaphylaxis. As a first line of protection, the amino acid method should be given to infants at a high risk of anaphylaxis rather than a formula that has been substantially solubilised.[4] When a baby with CMPA, soy milk formula shouldn't be given to infants younger than six months. Mothers who are lactating should be persuaded to continue the practice and to cut off milk and milk-based derivatives from their diet entirely. This can be complex, calls for thorough instruction on checking the ingredient list and potential milk-hidden items, and may even call for a reference to a certified dietician. [11] The mother should receive mentoring that covers different options for obtaining calcium and maintaining balanced nutrition, excluding milk components. Recovery from the infant's symptoms should be apparent within two to four weeks, but it may be noticeable as soon as 3 to 5 days.[10] Laboratory tests should be performed to check albumin levels and haemoglobin for protein leakage and anaemia from blood passed with stools in severe cases of CMPA. An amino acid formula might be indicated to correct hypoalbuminemia and anaemia effectively. The mother could keep breastfeeding but also scrape out soy and eggs from her diet when symptoms are chronic and improve but do not diminish.[12] If symptoms persist, consulting with a licensed dietitian to put the mother on a non-allergenic diet until the baby's symptoms are entirely under control, followed by gradually resuming foods one after another as the baby tolerates them, is recommended. It is essential that the mother is given adequate nutritious food for her and the baby fed by her and that the risks and advantages of pursuing breastfeeding vs switching to an amino acid formula are considered. Blood in the stool can be a concerning symptom for mothers. Therefore, reassuring them that the infant is well and being checked for issues is essential. However, albumin and haemoglobin levels should be checked if a modest amount of blood is found in the faeces. The baby should be moved to an amino acid formula if they have low albumin levels, anaemia, or stunted or delayed growth. Infants who received Lactobacillus GG had considerably fewer hematochezia than infants who were simply on a thoroughly solubilized formula. If a probiotic like Lactobacillus is given to the newborn with CMPA, it could improve symptoms. Pancreatic enzymes are given to the mother to dissolve milk protein further before the baby consumes them.[14] By the age of 1, around 50 per cent of children diagnosed with CMPA will develop resilience to cow's milk protein; likewise, gradually, the child develops a tolerance for milk-based proteins to almost 90 per cent by age 6. Once milk and its derivatives are completely abstained from the diet, restoring the diet can be started in small amounts one by one after 4-6 months from the time of complete elimination. Throughout 3 to 5 days, the milk should be progressively reintroduced. Start with tiny doses of hydrolyzed cow's milk formula and increase the daily dosage. Infants who have begun eating solids ought to be exposed to food items that include baked milk or a small quantity of milk derivative, and then the milk content should therefore be gradually increased.[6,15]

5. DIFFERENTIAL DIAGNOSIS

The alternative diagnoses that are more likely to be identified include anal fissure, infectious colitis and food protein-induced colitis due to the expansion of hematochezia due to the child's age, the onset of symptoms, and clinical presentation. The most prevalent aetiology of colitis in the young population is infectious colitis, which can affect newborns and originate from viral, bacterial, or parasite causes. Infectious colitis frequently presents with abrupt onset of fever, nausea, cramps or abdominal pain, frequent passing of stools in a day, and in a few cases, blood in the stool might also be seen. The history and physical assessment are frequently used to arrive at a diagnosis, although stool sample cultures can also be used to confirm the diagnosis.[16] Unknown in their aetiology, anal fissures are most prevalent in newborns under one year of age. Having difficulty emptying the bowel (complaints of pain in passing stools) and having bright red coloured blood in the faeces on the toilet tissue or in the diaper are noted. A diagnosis is established by visually inspecting the anus while pulling the skin firm to make any potential lacerations visible. At around one to three weeks of age, breastfeeding and formula-fed newborns may experience food protein-induced colitis, which manifests as diarrhoea, vomiting, and blood and mucus in the stool. Blood streaks and mucous in stools that emerge before six months in an ordinarily healthy infant are typical indications of milk hypersensitivity.[17] Additionally, CMPA could cause symptoms in other bodily systems, such as rhinitis or wheezing in the respiratory system or rashes, hives, or atopic dermatitis in the skin as observational symptoms. The likelihood of the CMPA being IgE-mediated increases if these signs are evident.[18]

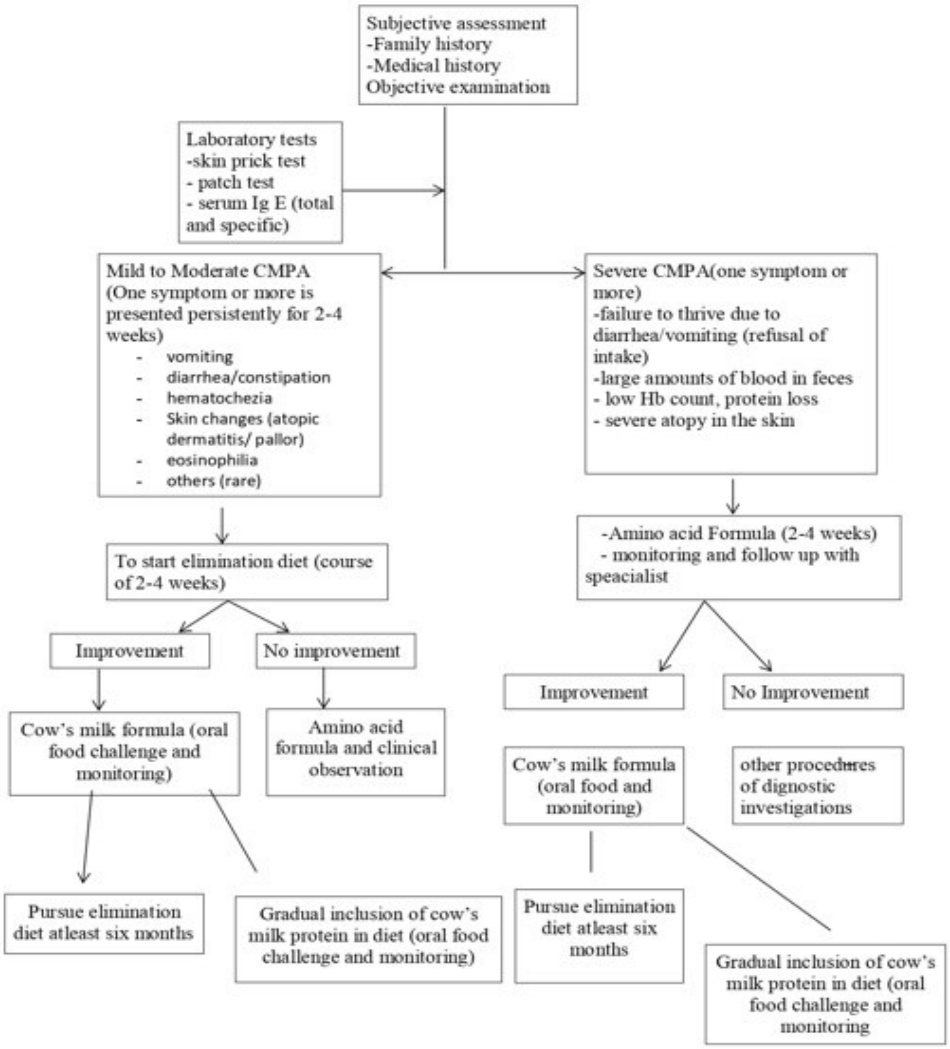

Fig 4 : Diagnosis and management of CMPA flow chart

6. DISCUSSION

The most common allergens causing CMPA are beta-lactoglobulin (β-lg), casein, and alpha-lactalbumin. The protein fractions in milk with the percentage of sensitization are Beta-lactoglobulin 66-82%, Casein 43-60%, Alpha albumin 41-43%, Bovine Serum Globulin 27%, Bovine Serum Albumin 18%. The cow's milk protein allergy is often confused with lactose intolerance, a non-immune-mediated reaction. A study in 2019 in turkey by Sackesen et al. showed that IgE-mediated reactions generally occur immediately, within minutes to hours after ingestion. Reactions can vary from mild to life-threatening anaphylaxis was not the presenting complaint in this child. Casein and whey are the milk proteins responsible for IgE-mediated milk allergy. Mixed IgE and non-IgE mediated have cell-mediated and humoral mechanisms and usually present with acute or chronic symptoms.[19] The non-IgE mediated CMPA or Food protein-induced enterocolitis syndrome is primarily seen in infants.[20] They typically present with severe vomiting and diarrhoea within 2-4 hours of ingestion. In some severe cases, it may cause profound dehydration, lethargy and shock. Food protein-induced proctitis/proctocolitis usually manifests by six months of age and is characterized by occasional diarrhoea with blood streaked mucous, which was seen in this child. Food protein-induced enteropathy presents protracted diarrhoea during the first nine months of life, within weeks after the introduction of the allergic food. The children with this condition present with failure to thrive, and some children present with malabsorption; however, this child had no symptoms of such.[21, 22] Heiner syndrome, a rare disease due to hypersensitivity to cow's milk, can cause acute or chronic respiratory disease in infants and young children.[23] These children usually present with failure to thrive, respiratory symptoms (recurrent cough, wheezing, nasal congestion and hemoptysis), gastrointestinal symptoms (vomiting, diarrhoea, colic, hematochezia) and anaemia. These children can also present with gastroesophageal reflux disease symptoms due to eosinophilic esophagitis, which does not respond well to conventional treatment.[24] A study published by Liu XY, Huang XR(2020) also strongly supported the fact that Heiner syndrome should be worth considering in any young child who has an unexplained chronic pulmonary infiltrate, respiratory failure, and evidence of CMPA, even though the chief complaint of the patient is hematochezia and not focused on the respiratory system. Exclusively breastfed children may also present with CMPA if enough of the cow's milk protein is transmitted to the child through breast milk. A study done in the United Kingdom by J. Gomes-Belo et al. showed that The diagnosis could be made by taking allergy-specific history and specific details regarding presenting symptoms which should include: age of onset, speed of the onset, quantity of milk consumed, frequency of the symptoms following milk consumption, the severity of the reaction, maternal diet in breastfed infants, family history of atopy, and any response to elimination and

reintroduction, and maintaining a food diary will be helpful in the clinical diagnosis. Investigations include skin prick test for CMPA, total blood IgE and specific IgE (RAST) for CMP. [25, 26] The gold standard for diagnosis is a Double-blind placebo-controlled oral food challenge (DBPCFC), which is not feasible in most clinical practice. Diagnosis can be made after observing the response of eliminating Cow's milk from the diet for 2-6 weeks.[25, 27] If the symptoms resolve and reintroduction of the cow's milk causing reoccurrence of symptoms will confirm the diagnosis of CMPA. The treatment involves avoiding consuming Cow's milk for four weeks - 6 months' post-diagnosis. In breastfed infants, the mother should be asked to refrain from milk and milk products throughout the breastfeeding period. The clinical history is an important step in the diagnostic process. It involves a thorough medical interview that covers the following key points: a description of the foods that cause allergic reactions, symptoms (onset, course, episodes, frequency, and replication), dietary information (formula-fed or breastfed), history of other foods that have been removed effectively, and treatment, comorbidities associated from birth or any time after birth.[27, 28] To substantiate diagnosis, an oral food challenge must be conducted if it is practical when these tests are negative. The prick test and IgE observation in serum are typically not carried out till the baby is about one to two years old since they can frequently result in false-negative in infants. These two tests may be required in uncommon circumstances where it is unclear what an infant is allergic to. Any other system symptoms are typical of food allergies provocative of IgE response. Removal of cow's milk products in the baby's food or the mother's diet for about 2-4 weeks becomes diagnostic if monitored. Oral food challenges cannot be carried out.[4] It is crucial to consider other potential allergies if symptoms don't subside and there is no possible exposure to milk.[29-30] In A study published by Vandenplas et al., for children below two years of age, extensively hydrolyzed or amino acid-based formulas can be used. Soya milk in diet should be avoided in younger children < 6 months as the phytates in the milk hinder the absorption of minerals in the diet. The Cow's milk protein allergy is seldom permanent, most children grow out of the CMPA by 2-3 years (70%) of age, and milk can be slowly introduced to the diet. Even though there is no specific time to reintroduce milk into a child's diet, a dietitian's opinion should always be sought.[31]

7. CONCLUSION

Cow's milk protein allergy (CMPA) in young children might be often confused with infections and may result in the unwarranted use of antibiotics. A clear nutritional history and high clinical suspicion are required to diagnose this condition. Early clinical diagnosis is the key to a better prognosis in these patients to exclude the allergic agents from daily sustenance.

8. AUTHORS CONTRIBUTION STATEMENT

Dr Jana Sababathi conceptualized and gathered the data with regard to this work. Dr Sundari S and Dr Jacquilyne Kharlukhi analyzed the case. Necessary inputs were given towards the design of the manuscript. Finally, all authors discussed the case report and results and contributed to the final manuscript.

9. CONFLICT OF INTEREST

Conflict of interest declared none.

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