Case Report: Hematemesis could be An Unusual Presentation of Cow's Milk Protein Allergy in children in Egypt

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Cow's milk protein allergy (CMPA) is common in infants with variable clinical presentation including varied gastrointestinal manifestation. Cow's milk protein allergy chiefly, involving occurs in children below the age of 3 years, successful therapy depends on completely eliminating cow's milk proteins (CMP) from the child's diet. Ideally, with the replacement of hypo or an allergenic food. Symptoms suggestive of CMPA may be encountered in approximately 5 to 15% of infants emphasizing the importance of controlled elimination/milk challenge procedures. We report on an Egyptian male infant, who developed frequent attacks of hematemesis when begin to eat foods other than breast milk including cow's milk and its dairy products at the age of three months. Possible cow's milk protein allergy was suspected. Further diagnostic work-up was done including: Hb, hematocrit, MCV: iron, ferritin, CRP, occult blood in stools, antibodies to H-pylori and upper GIT endoscopy and biopsy from snip of duodenal mucosa. Measurement of serum cow milk protein specific IgE by radio allegro sorbent test (RAST) technique (immune CAP specific IgE method) and results revealed cow's milk protein allergy.

It is concluded that cow's milk protein allergy should be considered in cases of hematemesis presented in early infancy in infants who fed cow's milk early and that hematemesis should be added to the list of clinical presentation of CMPA.
hematemesis, mucous bloody diarrhea and chronic watery diarrhea, with endoscopic findings of acute and chronic gastritis (Yimyaem et al., 2003).

The long-term prognosis for the majority of affected infants is good, with about 80% naturally acquiring tolerance by the age of four years (Roberto & Di Costanzo, 2013). With remission rates of about 45-50% at 1 year of age, 60-75% at 2 years and 85-90% at 3 years (Host, 1994), gastrointestinal symptoms as frequent regurgitation, vomiting, diarrhea, constipation, blood in stool, iron deficiency anemia show a good prognosis (Host, 2002). It is interested for pediatricians to consider that other symptoms such as hematemesis could be an unusual presentation for CMPA, a high index of suspicion is required, as in our case to be put in consideration when managing such cases.

**Case Presentation**

Our case is an eight months old Egyptian boy, from Al Fayom city the second member of non-consanguineous marriage, suffered from recurrent attacks of vomiting of fresh blood for 2 months. He was exclusively breast feeding for 3 months of life without any maternal dietary restriction, after then, supplemented with tap water, yoghurt, cake, cereals, rice, potatoes, and fruits, he begins to developed recurrent attacks of diarrhea (4-5 times of loose stools / day) that was treated at home. At the age of 5 months he developed recurrent attacks of wheezy chest relieved by nebulized beta 2 agonist. Recurrent hematemesis after dairy milk supplementation was the relevant history for CMPA because it was previously reported by Yimyaem et al. (2003). One month later he developed severe attack of hematemesis for which upper GIT endoscopy which was done and revealed mild diffuse gastritis that was treated medically. This was followed by repeated attacks of hematemesis of moderate amount of fresh blood and melena during the next 2 months and severe iron deficiency anemia that required packed red blood cells transfusion, other history revealed no symptoms of other system involvement. Family history showed that the parents of the boy had no allergic rhinitis, itching to eggs or certain food, or atopic dermatitis, our patient was admitted to our hospital at 8 months for an attack of hematemesis. O/E: he appeared somewhat pale, but looks alert with fair activity and stable vital signs. His weight was 8.5Kg (at 50th centile), His length was 72 cm (at 75th centile) and head circumference 44 cm (at 25th centile).

His investigation revealed the following
* Microcytic hypochromic anemia (Hb 7.8 gm /dl, hematocrete: 29.7%, MCV:50.8 fl, MCH 16.5 Pg ).
* Decreased iron (serum iron: 17 µg/dl) and ferritin (serum ferritin: 4.7µg/dl).
* Negative CRP.
* Negative occult blood in stools.
* Negative antibodies to H-pylori, H-pylori IgG quantitative: 0.26u/ml (negative:<0.9, equivocal: 0.9-1.1, positive:>1.1). It was done by an immotile IgG serologic test for H-pylori chemiluminescent, two step immunometric assay (Siemens medical solutions diagnostic Los Angeles, CA 90045-6900 USA). Positive results greater than 1.1 IU/ml.
* Measurement of serum cow milk protein specific IgE was done by radio allegro sorbent test (RAST) technique (CAP method) the principle of the test based on that the suspected allergen is bound to an insoluble material and the patient's serum is added. If the serum contains antibodies to the allergen, those antibodies will bind to the allergen. Radio labeled anti-human IgE antibody is added where it binds to those IgE antibodies already bound to the insoluble material. The unbound anti-human IgE antibodies are washed away. The amount of radioactivity is proportional to the serum IgE for the allergen (Ten, 1995, WebMD, 2006) and results are scaled according to the following rating:

<table>
<thead>
<tr>
<th>RAST rating</th>
<th>IgE level (IU/ml)</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>&lt; 0.35</td>
<td>Absent or undetectable allergen specific IgE</td>
</tr>
<tr>
<td>1</td>
<td>0.35 – 0.69</td>
<td>Low level of allergen specific IgE</td>
</tr>
<tr>
<td>2</td>
<td>0.70 – 3.49</td>
<td>Moderate level of allergen specific IgE</td>
</tr>
<tr>
<td>3</td>
<td>3.50 – 17.49</td>
<td>High level of allergen specific IgE</td>
</tr>
<tr>
<td>4</td>
<td>17.50 – 49.99</td>
<td>Very high level of allergen specific IgE</td>
</tr>
<tr>
<td>5</td>
<td>50.00 – 100.00</td>
<td>Extremely high level of allergen specific IgE</td>
</tr>
</tbody>
</table>

According to the method of moderate level of serum specific IgE for cow milk protein was obtained: (1.35 IU/ml as compared to normal control level< 0.35 IU/ml), also specific phagocytic inhibition test for milk was found to be17% while the acceptable normal percentage is above 25%).
Histopathology

Upper GIT endoscopy was done, biopsy was performed from snip of duodenal mucosa with preserved villi and brush border. The biopsy specimen was fixed in formalin, embedded in paraffin, and stained with hematoxylin and eosin. The diagnosis was based on established histopathologic criteria.

Results

Results of endoscopic and histopathologic examinations of upper endoscopy demonstrated erythematous, erosive, and hemorrhagic mucosa of duodenum. Histopathologic analysis of biopsy specimens obtained from the duodenal mucosa showed preserved villi and brush border, there is moderate mixed chronic inflammatory cellular infiltration the mucosa, mainly lymphoplasmocytic. There is some eosinophils (about 10/HPF) and no increase in intraepithelial lymphocytes which diagnosed finally as mild non-specific duodenitis with some eosinophils.

According to Yu et al. (2013), Allergic Colitis (AC) under fibrotic endoscopic examinations has been diagnosed. The criterion for histopathologic diagnosis of AC in our case was based on the presence of five or more eosinophils per high-power field, normal value below 5 eosinophils per high-power field.

So the diagnosis of CMA was established, and all milk and milk products such as cheese, butter, ghee, butter milk cream, milk powder, whey, casein, and margarines which contain milk products was eliminated from maternal and infant diet for 4 weeks infant was discharged home for follow up after teaching the mother about dietary restriction, however he was re-admitted again with another attack of hematemesis that was found (from the history) to be related to maternal noncompliance to dietary restriction. Again maternal education regarding milk products was established and the baby was discharged and remained symptoms free.

Figure 1. Decision tree for the diagnosis and treatment of cow’s milk protein allergy (CMPA) in breastfed infants with mild to moderate symptoms (Adopted from: DeGreef et al., 2012).
Discussion

This case report showed that CMA can induce hematemesis in healthy infants which is rarely found, differential diagnosis of hematemesis in our case which were excluded by clinical history, examination and investigations, included suspension of infection (H-pylori infection which was excluded by H-pylori IgG antibodies), and / or others which was excluded by complete stool analysis and cultures, GERD, and congenital vascular malformation (which was excluded by upper endoscopy). Infection also was the most likely diagnosis that can be confused with CMPA (Urribarriet et al., 2011) but it was excluded by complete investigations (including CBC, ESR, CRP).

Because our patient came from rural area in which they depend on dairy milk products for both mother and infant and with early introduction of cow milk products which is homemade and daily consumed for nutritional or cultural reasons (Krüger & Malleyeck, 2009). This differential diagnosis should be considered.

Even in exclusively breastfed infants, CMPA is possible (de Greef et al., 2012; Vandenplas et al., 2007). The list of foods containing cow milk protein if the mother consume cow's milk or its products that should be eliminated from maternal and infant diets were described according to Zeiger et al. (1989).

The diagnosis of cow milk allergy in this patient was based on high level of IgE, pathological findings, which agree with Vandenplas (2007) who stated that diagnosis of CMPA is proved by laboratory and pathological diagnosis.

Also, clinical improvement after cow milk elimination, and exclusion of other suggested causes of hematemesis, but challenge test was not done due to poor compliance of parents. Challenge test should not be done earlier than 9-12 months after the elimination for confirmation diagnosis which is suggested by Vassilopoulou et al. (2008).

It is suggested that CMA induced duodenitis and allergic colitis is the cause of hematemesis in our case, Aanpreug & Atisook (2003) assumed that CMA induced gastritis was the most common cause of upper gastrointestinal hemorrhage in healthy infants among their researches.

The majority of children with early CMPA will eventually become tolerant to CMP by the age of 1 to 2 years up to 5 years when their mucosal immune system matures and they become immunologically tolerant of milk proteins (Vandenplas, 2007).

Learning Points/Take Home Messages

- Cow's milk protein allergy should be considered in cases of hematemesis presented in early infancy in infants who fed cow's milk early
- Hematemesis can be added to the clinical presentation of CMPA.

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