Thrombocytosis as an overt sign of cow's milk allergic proctocolitis

To the Editor,

Cow's milk protein allergy is the most common food hypersensitivity and can affect predominantly the gastrointestinal tract, causing discrete entities namely allergic proctocolitis, food protein induced enterocolitis syndrome (FPIES), or food protein induced enteropathy.[1]

Their diagnosis remains clinical as they are non-IgE mediated immune responses.[1] However, there are some non-specific laboratory findings, such as leucocytosis and thrombocytosis, in clinically compatible cases of FPIES.[2,3] Relevant observations have not been made in children with allergic proctocolitis.

We, herein, present three exclusively breast fed infants, with allergic proctocolitis due to milk protein, in whom remarkable thrombocytosis drew our attention.

A 40-day-old boy was admitted to the hospital because of blood-streaked-stool or mucous mixed with blood in the stool, of nine days duration. The infant was born after an uneventful full-term pregnancy and delivery. He was exclusively breast fed since birth. The second day of the disease he was evaluated by his paediatrician who suggested elimination of milk products from the mother's diet, with some improvement but without, however, complete resolution of the bloody stools.

The patient was a healthy alert infant with body weight of 4.4 kg (50th percentile) and body height of 60 cm (95th percentile). His physical examination revealed an audible murmur which was attributed to ventricular septal defect and eczematous lesions of the face. Liver was palpable 1.5 cm below the respective costal margin. From the family history, a paternal history of allergic rhinitis was elicited.

The laboratory investigation showed the following: Hb 11.6 gr/dl, Ht 34.2% MCV 79.4 fl, white blood cells 14960/mm^3 (neutrophils 18%, lymphocytes 71%, monocytes 6% and eosinophils 5%), platelets 647,000/mm^3, PT 11.5 sec, INR 0.96, aPTT 25.25 sec. The biochemical parameters, as well as, the serum proteins and immunoglobulins included were all within the normal range. Microscopic stool examination did not reveal leucocytes or eosinophils. Stools were haemoglobin positive and cultures disclosed normal flora while stool antigen for adenovirus and rotavirus were negative.

Allergy evaluation with Rast to cow's milk was negative. Based on the clinical manifestations, the child was diagnosed with food-induced allergic proctocolitis and the mother was put on a diet free from milk, soya, nuts, fish and egg. The child showed improvement in the amount of visible blood but he has not been free from symptoms for 18 days. The mother was initially reluctant to discontinue breast feeding and therefore she was advised to continue to be on an elimination diet and to give her baby amino-acid-based formula, whenever he needed it. The infant accomplished symptoms clearance as soon as the mother discontinued breast feeding and the child was put exclusively on a baby amino-acid-based formula. The platelet count was 349,000/mm^3 one day before the patient's discharge from hospital.

A 3.5-month-old girl, born at term, was admitted to the hospital because of bloody stool since the age of two months. She was exclusively breast fed without any restrictions of the maternal diet. Ten days prior to admission milk products were eliminated from her mother's diet without noticing, however, any improvement in the rectal bleeding of the baby. The infant's history was positive for eczema during the first month of life. On admission she appeared well with a weight of 8.4 kg (> 97th percentile) and a height of 65 cm (97th percentile). The clinical examination was unremarkable. The laboratory investigation revealed the following: Hb 11.7 g/dl, Ht 34.3%, MCV 77fl, white blood cells 13,450/mm^3 (neutrophils 35%, lymphocytes 53%, monocytes 7%, eosinophils 2%), platelets 729,000/mm^3, PT 13.3 sec, INR 1.12, APTT 30.1. The biochemical parameters, including total serum proteins and immunoglobulins, were within the normal range. Microscopic stool examination did not reveal leucocytes or eosinophils and a smear was positive for occult blood. Culture was negative for common pathogens including ova and parasites. Specific IgE antibodies to cow's milk (Rast) were negative.

The infant remained in good health during her hospitalisation without, however, showing significant improvement with regard to the rectal bleeding despite the fact that the mother was put on an elimination diet from milk and soy products, nuts, fish, and egg. Rectocolonoscopy showed macroscopic lesions compatible with colitis whereas the histological examination of biopsy specimens was consistent with allergic colitis. Based on these results and on the fact that the symptoms persisted despite the strict diet of the mother, the infant was put on amino-acid based formula with resolution of rectal bleeding, whereas the platelet count was decreased to 370,000/mm^3.

A four-month-old boy was admitted to the hospital with blood streaked stools since the first month of age. The infant was exclusively breast fed and dietary products were eliminated from mother's diet at the age of one month after the onset of symptoms without, however substantial response. The laboratory investigation was within the normal range with the exception of platelets which were 630,000/mm^3 and the SGOT which was 120 U/L. The patient underwent a rectal biopsy at the age of four months, which showed chronic inflammation with eosinophil infiltration compatible with allergic disease. The infant was then put on amino-acid based formula with a good response.

Visible rectal bleeding, even in the form of blood streaked stools, in otherwise healthy infants is an alarming symptom and requires investigation. It is important to assess whether a relevant case should be aggressively evaluated for an emergency underling aetiology or it is reasonable to defer extensive work-up. Cow's milk protein allergy, causing allergic proctocolitis, has been considered among the common causes of bloody stools in infants.[1] This reaction is not IgE-mediated and with the exception of rectal biopsy there are no other tests of high diagnostic validity

to support its occurrence.[4] It should be emphasised that allergic proctocolitis, in contrast to FPIES, is not uncommon among exclusively breast fed infants, as was the case in our patients. The persistence of bleeding in our patients, despite the restrictions of maternal diet, could be attributed to the difficulty to remove all sources of milk protein allergens from the diet.

There is not a non-invasive supportive test for this entity and diagnosis relies on clinical history, elimination diet and exclusion of other medical causes.[1] However, recently thrombocytosis was observed in the majority of children with FPIES.[2] To the best of our knowledge our patients are the first cases which are described with allergic proctocolitis and thrombocytosis. It should also be mentioned that thrombocytosis has been observed in patients with inflammatory bowel disease[5] but not in those with diarrhoea due to infectious gastroenteritis.[5] However, inflammatory bowel diseases are not met in infancy.

While primary thrombocytosis is rare in childhood, its secondary form occurs frequently.[6] By definition, platelet counts above $450x10^9/l$ are considered elevated whereas thrombocytosis < $700x\ 10^9/l$ is classified as mild.[6] The estimated incidence of secondary thrombocytosis is 6-15% among hospitalised children and mild thrombocytosis accounts for 72-86% of these cases.[6] Although viral and bacterial infections have been considered as the most common causes of secondary thrombocytosis,[6] this was not the case in our patients as no infectious agents were implicated with the appropriate work up. Infectious agents should always be excluded in children presenting with symptoms of allergic proctocolitis before proceeding with elimination diets.

Furthermore, our patients did not have any tissue damage such as anal fissures, a condition that should be also differentiated from allergic proctocolitis. All our patients were older than 30 days, as it is known that the thrombocytosis susceptibility is higher during the neonatal period.[7] They all had haemoglobin and haematocrit within the normal range and therefore thrombocytosis could not be a reflection of haemoconcentration or iron deficiency anaemia.

We therefore assume that mild thrombocytosis of our patients were attributable to the allergic proctocolitis due to milk protein allergy. Recently, Mehr et al.[2] showed that 63% of 66 episodes of FPIES were characterised by thrombocytosis. Similar findings were found in a cohort study performed by Hwang et al.[3] However, in the latter study, the elevation of the platelets count in children with FPIES was not significant in comparison with children with similar symptoms attributable to infection or other causes.

As far as the mechanism is concerned, it has been suggested that interleukin-6 induces megakaryopoiesis by stimulating hepatic thrombopoietin (TPO) production.[8] An inverse relationship between platelet count and TPO exists in healthy subjects.[9] A notable exception is represented by reactive thrombocytosis where levels of TPO higher than expected have been detected.[10] Interleukin-6 induces an increased expression of hepatic TPO mRNA and consequential thrombocytosis.[10] We postulate that interleukin-6 is secreted in response to the immune-inflammatory process of allergic proctocolitis. The duration of symptoms prior to the admission would allow increased megakaryocytosis and therefore thrombocytosis.

In conclusion, allergic proctocolitis may be quite persistent in breast fed infants even after an appropriate strict elimination diet was followed by the mother. Thrombocytosis may be an additional feature of this immuno-inflammatory condition.

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Allergy to curry: case report[☆]

To the Editor,

In recent years, the increasing use of spices has resulted in a rise of allergic reactions to them, especially in atopic patients. Curry is a mixture of several seeds such as coriander, onion, curcuma, caraway, cumin or mustard. Most of them belong to the Umbelliferae family.[1] Contact dermatitis, the oral allergy syndrome and some cases of anaphylaxis are the most reported allergic reactions to these allergenic sources.[2–5] Various pollen-food syndromes (PFS) have been described in pollinic patients, many of them produced by panallergens, but curry has never been included in them. However, some of the spices present in curry powder (parsley, caraway or coriander) have been reported as hidden allergens and cross-reactivity with mugwort pollens have been described (The celery–mugwort–spice syndrome).[6]

We describe a 45-year-old woman with rhinoconjunctivitis through May, June and September. She referred several episodes of papular lesions and pruritus in mouth mucosa, itching and erythema in face, palms and neckline immediately after eating several meals containing curry spices. No apparent relationship with other ingredients of the culprit meals as chicken, cous-cous or rice was suspected. The symptoms did not return when the patient ate the same meals cooking without curry. Skin prick test was positive to extracts from curry and coriander (Bial-Arístegui, Bilbao, Spain) (Fig. 1) as well as to pollens from *Platanus acerifolia*, *Artemisa vulgaris* and *Chenopodium album* (ALK-Abelló, Madrid, Spain). It was negative to other curry components: curcuma, mustard, cinnamon, onion, garlic, fennel, ginger, black pepper, laurel, nutmeg, cardamom and clove (Bial-Arístegui, Bilbao, Spain) and pollens from *Olea europaea*, *Cupressus arizonica*, *Plantago lanceolata* and *Dactylis glomerata* (ALK-Abelló, Madrid, Spain). Serum specific IgE was determined by EAST technique (enzyme allergo sorbernt test). Solid-phase was obtained by coupling the extract solution (10 mg/mL) to the 6-mm diameter CNBr-activated paper discs, as described by Ceska and Lunqvist.[7] EAST was performed following the manufacturer's instructions (Specific IgE EIA kit HYTEC HYCOR Biomedical Ltd. UK), and values equal to or higher than 0.35 kU/L were considered positive. Serum specific IgE against extract from three different types of curry powder were 1.3, 1.9 and 2.2 kU/L, respectively. Serum specific IgE measurements to three different types of curry powder were 1.3, 1.9 and 2.2 kU/L, respectively. Among the species of the Umbelliferae family, it resulted positive to aniseed 2.2, dill 1.2, caraway 1, fennel 1.3, cumin 0.5 and coriander 0.5 kU/L. It was negative to parsley, celery and carrot.

The molecular mass of the IgE binding protein was calculated by SDS–PAGE immunoblotting. SDS–PAGE was carried out according to the method of Laemmli,[8] 12.5% and 4% were used for separating and stacking gel, respectively. The samples were prepared in 0.125 M HCl–Tris pH 6.8, 0.1% SDS, 5% β-mercaptoethanol at 100 °C for 5 min. When immunoblotting was performed, proteins were electrophoretically transferred to polyvinylene difluoride membrane (PVDF) and after membrane blocking with 5% dry skim milk (1 h at 37 °C), they were incubated with patient's serum (16 h at 4 °C); after washing they were incubated with peroxidase-conjugated mouse Anti-human IgE (Є-chains specific) (SouthernBiotech, USA), and detected by the chemioluminescence method as recommended by the manufacturer (ECL-Plus; Amersham Pharmacia Biotech). When immunoblotting inhibition was carried out patient serum was preincubated with the inhibition phases at 1 mg/mL (overnight at 4 °C). The IgE-binding pattern observed by immunoblotting with three types of curry powder and different spices were similar. The molecular masses of the IgE-binding bands ranged from 30 and 92 kDa (Fig. 2). Cross-reactivity was studied by means of IgE-immunoblot inhibition assay, revealing allergenic relationship between curry and cumin or cilander and between curry and pollens from *A. vulgaris*, *P. acerifolia* and *C. album* (Fig. 3).

We present a case of immediate hypersensitivity to curry powder in an atopic patient. Skin prick test and specific IgE were positive to the spices of the Umbelliferae family present in curry as well as to pollens from the following families: Compositae, Platanacea and Chenopodiaceae.

The existence of specific IgE against common panallergens from pollens and plant-derived foods is a widely accepted and experimentally supported explanation for some of the allergenic relationships detected. Some of the responsible cross-reactive molecules for the development of PFS in weed pollinosis have been described in detail as profilin, LTPs, and high MW allergens and/or glycoallergens.[9]

Pollens from the Compositae family (*Artemisia*),[9,10] Chenopodiacea[9] and Platanacea pollens[11] have been described as a cause of PFS with different fruits (e.g. banana, melon) but allergies to spices have never been associated to Platanaceae or Chenopodiacea pollens.

In this study we found in vitro cross-reactivity with clinical implications among food spices belonging to Umbelliferae family and pollens from the Compositae family (*A. vulgaris*), the Platanacea (*P. acerifolia*), and the Chenopodiaceae (*C. album*), due to allergens with molecular masses between 30 and 97 kDa.

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