

Case Report

Severe food-induced vasculitis in two children

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Food-induced vasculitis seems to be rare and is considered by some as controversial. The reported cases in the literature are few and mostly on adult patients. Described in this report are two children with severe vasculitis caused by specific foods. They were diagnosed at two separate allergy centers that have a special interest in food allergies. Case 1 was an 8-year-old girl with a 9-month history of cutaneous vasculitis with large joints involvement. Case 2 was a 23-month-old girl with an 8-month history of multiple hospitalizations for recurrent acute severe cutaneous and mucous membrane vasculitis with large joints involvement. In both patients, skin biopsy showed leucocytoclastic vasculitis. In neither of the patients could the symptoms be attributed to drug intake, infection, autoimmunity, or other systemic disease. Case 1 had a moderately elevated serum total immunoglobulin E (IgE) level and strongly positive skin test and radioallergosorbent test (RAST) to cow's milk and hen's egg, both of which were proven to be the cause by elimination-challenge tests. Case 2 had a slightly elevated serum total IgE level, but negative skin tests to foods, including chocolate that was suspected by the mother. Avoidance of chocolate resulted in remission, except following accidental ingestion of cocoa-containing products. These findings support the few previous reports on food-induced vasculitis, an entity that seems rare but may be more common than currently realized.

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You should keep an open mind, but not so open that your brain falls out.

Charles Sagar

Vasculitis, in general, is relatively uncommon and can be associated with several diseases (1). The hypersensitivity vasculitis (HV) group represents 17–29% of cases (2) and can be caused by a wide variety of exogenous and endogenous antigens, most commonly drugs and viral infections. HV affects mostly the skin and to a lesser extent the mucous membranes, and occasionally the joints or other organs. Histologically, there is

inflammation and necrosis of the wall of small blood vessels exhibited by endothelial swelling, perivascular polymorphonuclear cellular infiltrate, neutrophil fragmentation and nuclear debris, hence the name 'leucocytoclastic'. Often, there is extravasation of erythrocytes and fibrin deposits within and around the vessel wall. Immunofluorescence studies may demonstrate immune complex deposits in the blood vessel wall and, in some cases, the nature of the antigen and antibody involved may be identified. The prognosis is generally good, particularly when the offending antigen can be eliminated.

Food and food additives have been implicated in causing purpura or vasculitis in certain patients, mostly adults (3). However, a causal relationship did not receive wide acceptance, probably because of its rarity and the anecdotal

This paper is dedicated to the memory of Professor Luisa Businco who shared in the preparation of this manuscript before her death on December 1 1999.



Fig. 1. Cutaneous vasculitis caused by cow's milk and hen's egg in an 8-year-old Caucasian girl.

nature of most such reports. In this article, we describe two children with severe vasculitis related to specific food ingestion.

Case 1

An 8-year-old Caucasian female was referred for evaluation because of a 9-month history of recurrent eruption, sometimes associated with painful swollen joints. She was previously hospitalized several times and showed good response to systemic corticosteroid therapy. Her family history was negative for any similar condition or for significant atopy. The physical examination revealed reddish brown, palpable lesions on the thighs and legs, varying from 0.5 to 4 cm in diameter (Fig. 1). New lesions were bright red and older lesions were shades of brown or blue. There was also painful swelling of the ankles and knees. The rest of the physical examination was within normal limits. Laboratory evaluation showed normal complete blood count (CBC), erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), blood chemistry, urinalysis, serum protein electrophoresis, complement hemolytic assay (CH50), C3, and C4. Tests were negative for anti-streptolysin titer, rheumatoid factor, anti-nuclear antibody (ANA), cryoglobulins, lupus anticoagulant, anticardiolipin antibodies, circulating immune complexes, and hepatitis B antigens and antibodies.

The possibility of immunoglobulin E (IgE)-mediated hypersensitivity was explored. The total serum IgE level was moderately elevated (340 IU/ml). Skin-prick testing with common foods showed strongly positive reactions to



Fig. 2. Cutaneous and mucous vasculitis caused by cocoa in a 23-month-old African-American girl (published with permission).

cow's milk and hen's egg. A similar result was found by radioallergosorbent testing (RAST) for serum food-specific IgE antibodies (cow's milk class III and hen's egg class IV). A skin biopsy examination showed leucocytoclastic vasculitis. Strict avoidance of cow's milk and hen's egg resulted in complete remission within a few weeks, without any medication. With the family's consent, the patient was subjected to titrated double-blind placebo-controlled food challenges at 1-week intervals. A casein hydrolysate formula was used as a placebo and a vehicle for disguising each of homogenized cow's milk, lyophilized whole egg, and soybean formula. The casein hydrolysate and soybean formulas caused no adverse reactions. On the other hand, a few minutes after the administration of a cumulative dose of 105 ml of cow's milk, the child developed pruritus and urticarial rash. The rash did not respond well to oral antihistamine, and next day intra-muscular hydrocortisone was administered, with good response over several days. A similar reaction occurred following a challenge with lyophilized egg (cumulative dose 1,500 mg). Cow's milk and hen's egg were avoided and no relapses occurred during the 18-month follow-up.

Case 2

A 23-month-old African-American female was referred for evaluation of recurrent severe vasculitis that required multiple hospital admissions. Her first hospitalization was at 15 months of age when she had an upper respiratory infection, cough, and fever for a few days prior to admission. There was no history of drug exposure. Physical examination revealed moderate fever, erythematous macular rash, otitis media, mild conjunctivitis, and moderately swollen knees and elbows. Some of the skin lesions were described as having a clear center. She had normal CBC, differential white blood cell count (WBC), platelet count, coagulation studies, blood chemistry, urinalysis, chest X-ray, cold agglutinin titer, and a negative sepsis work-up. She was diagnosed as having erythema multiforme secondary to infection and was treated with ampicillin and prednisone, with resolution within 1 week. After 2 weeks of complete recovery, she developed sub-conjunctival and oral mucosal hemorrhage as well as petechial rash and numerous large purpuric lesions 1–3 cm in diameter on the face, trunk, and extremities (Fig. 2). Otherwise, she appeared generally well and had no significant fever. Again, laboratory evaluation was essentially normal. Prednisone therapy resulted in rapid recovery. The condition recurred three more times within a few months, exhibiting various combinations of marked cutaneous vasculitis, sub-conjunctival hemorrhage, large ecchymotic patches in the oral mucosa, gross rectal bleeding, and swollen joints. Results of her hematologic and immunologic studies were within normal limits, including complement, ANA, viral cultures, and bone marrow aspirate. Circulating immune complexes were not detected. Serum total IgE was slightly elevated at 49–58 IU/ml. A skin biopsy showed leucocytoclastic vasculitis.

Because of the sudden onset and course of each recurrence, HV was considered. Food allergy, specifically to chocolate, was suspected by the medical history. Percutaneous allergy skin tests with common foods, including chocolate, were negative. A trial of chocolate avoidance resulted in definite improvement, with only a few mild recurrences that the mother related to occasional chocolate ingestion. Because of the severity and multiple recurrences of the reaction, a challenge with chocolate was not performed. A trial of oral cromolyn, 100 mg three times a day, was associated with much milder and less frequent recurrences. Cromolyn administration continued for a few months at 50–100 mg three times a day,

with minimal relapses, then was discontinued. Strict avoidance of chocolate and cocoa was supposed to be maintained. Minor recurrences followed accidental ingestion of foods that contained chocolate or cocoa. A major relapse occurred in the form of large petechial spots in skin, oral mucosa, and conjunctivae, together with swelling of hands and feet, which the mother attributed to eating a piece of chocolate the night before. Again, it responded well to prednisone therapy.

Discussion

HV is predominantly mediated by a type III immunologic reaction (Arthus-type) in which the antigen combines with its specific antibody (predominantly of the immunoglobulin G [IgG] isotype) and complement to form circulating immune complexes. The latter deposit in the small blood vessels, particularly the post-capillary venules, and initiates vasculitis (4). In some cases, a type I (IgE-mediated) reaction may also be involved, causing increased vascular permeability and enhanced deposition of immune complexes and perivascular inflammation. It is not known whether IgE antibodies are incorporated in the immune complexes.

In this report, we discussed two children with typical clinical and histologic features of HV related to food ingestion. These children were identified at two separate large university allergy/immunology services with wide referral bases for evaluation of food hypersensitivity, which reflects the rarity of such a clinical entity (5,6). In both patients, the medical history, physical examination, and laboratory findings did not suggest autoimmune disorders, infections, or neoplastic disease. In case 1 the hypersensitivity was caused by cow's milk and hen's egg, as confirmed by blind-challenge testing, and case 2 had a strong temporal relationship to chocolate but was not intentionally challenged because of the multiple recurrences and severity of the reaction that was sufficiently alarming to require multiple hospital admissions. In fact, the last relapse was a major one and occurred after eating a piece of chocolate on the previous evening and thus may be considered a non-intentional challenge. It can be argued, however, that the offending antigen could be an additive rather than cocoa, even though no particular brand of chocolate was the culprit.

The prophylactic effect of oral cromolyn, at least partly, in case 2 is suggestive of involvement of gastrointestinal mast cell de-granulation. The protective effect of oral cromolyn in food allergy

has been reported, even for non-gastrointestinal manifestations (7–10). Oral cromolyn is widely used in Europe and several other countries, but in the United States its formal approval is for mastocytosis (11,12).

According to an early review by Winkelmann (13), between 1927 and 1951 there were nine reports (total of 22 patients) of food-related purpura, in patients 3–50 years of age. Those reports, however, were mostly anecdotal and lacked histologic and immunologic evaluations. Other case reports have provided a better documentation of the nature of vasculitis and its relationship to specific foods (14–16) or food additives (17–21). Lunardi et al. (22) described five patients (four female and one male), 13–45 years of age, with a history of allergy and cutaneous vasculitis of 1–13 years of duration, in whom double-blind challenges confirmed the offending agent to be: foods (two patients), food additives (two patients), and both (one patient). No patient had a relapse while on an elimination diet during the 2 years of follow-up.

It seems that critical data is accumulating, albeit slowly, to support the occasional involvement of food or food additives in some patients with episodic leukocytoclastic vasculitis. Despite being generally rare, such a causal relationship is probably more common than is currently realized. Multiple factors are responsible for this under-diagnosis, including the very low awareness level of its occurrence, lack of a specific laboratory test for it, difficulty in documenting it, negligence in its reporting, and obstacles in its acceptance for publication. Even though the condition is rare, its morbidity can be severe in certain patients, such as case 2 of this report who presented on a few occasions with very alarming acute gross rectal bleeding in addition to the remarkable vasculitis of the skin and mucous membranes and sometimes of the joints. It is by increasing the awareness of the medical profession of this disease entity that the possible offending food or food additive might be identified and the appropriate dietary management prescribed.

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