



RECURRENT SKIN RASH IN A 61 YEAR OLD HOUSE WIFE

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<http://www.eaaci.net/site/content.php?l1=17&sel=400>*



Heidi, a 61 year old housewife, was referred from the department of orthopedic surgery for workup of a skin rash in the context of preoperative screening. She suffered since 3 months from recurrent red spots on the lower extremities. Therefore, colleagues from the referring department raised the suspicion of an underlying infection as a potential contraindication for elective menisectomy.

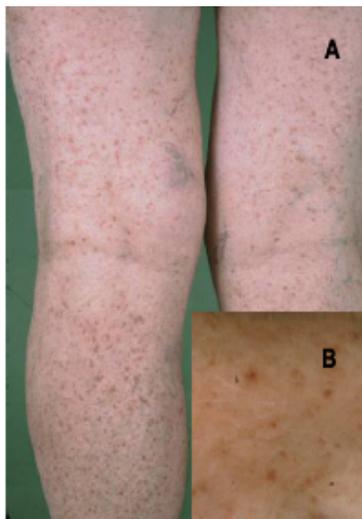


Figure 1A/B
Multiple erythematous macules and papules on the lower extremities

Heidi's medical history revealed autoimmune thyroiditis, treated with levothyroxin over 9 years, arterial hypertension treated with bisoprolol for 6 years and hyperlipidemia treated with pravastatin since 2 years. Additionally, she suffered from coronary heart disease and had been on 100 mg acetylsalicylic acid (ASA) for the last 9 years after coronary stent implantation. She denied asthma, hay fever, atopic eczema or other allergic diseases.

CLINICAL FINDINGS

Clinical examination showed multiple erythematous and hyperpigmented macules and papules on the dorsum of the feet, lower- and upper legs (Figure 1A/B). The remaining integument and further clinical examination showed no pathological findings.

Heidi's history and the clinical picture of palpable purpura lead us to the clinical diagnosis of allergic vasculitis.

HISTOPATHOLOGY AND DIAGNOSIS

HE staining showed neutrophilic infiltration in and around cutaneous vessels with leucocytoclasia. Based on these findings, the diagnosis of an allergic leucocytoclastic vasculitis was confirmed (Figure 2A/B).

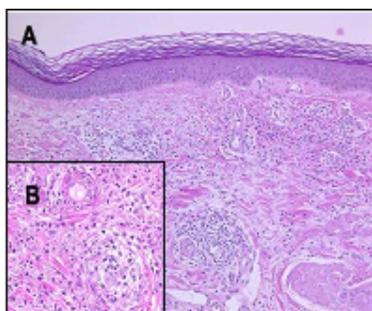


Figure 2A/B
A HE overview: Under an unchanged epidermis, a perivascular inflammatory infiltrate is reaching from the upper to the mid dermis.
B High power view showing inflammatory infiltration and necrosis of cutaneous vessels with formation of nuclear dust (karyorrhexis).

DIAGNOSTIC APPROACH

Taken the relatively recent history of 3 months of recurrent petechia, but the long term medication over 2-9 years, a drug induced vasculitis was considered unlikely. In the light of severe cardiac risk factors, the withdrawal of anticoagulation, antihypertensive- and lipid reducing medication was reserved as last stage in the diagnostic hierarchy. Instead, comprehensive vasculitis screening was performed immediately:

White and red blood cell count, coagulogram, routine chemistry and Hepatitis B/C serology were inconspicuous. Serum electrophoresis, screening for ANA and ANCA autoantibodies and cryoglobulinemia were negative. Also urine and stool examination, including parasitology and guaiac, showed no pathological findings.



During Heidi's stay in our department she developed an active relapse of palpable purpura. A detailed history was taken concerning the circumstances under which new purpuric lesions had occurred in the past. Heidi reported the ingestion of fruit salads preceding active rashes. Subsequent analysis of the ingested food preceding her last rash revealed a fruit salad containing apple, pear, banana and kiwi.

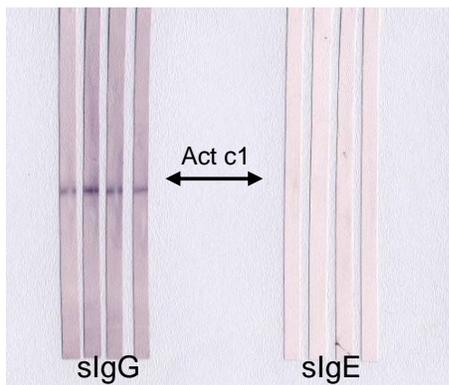


Figure 3

Fresh erythematous urticaria and macules on the abdomen 6 hours after ingestion of kiwi fruit.

Allergy screening showed a total IgE of 26.8 kU/ml (<100kU/ml) and no specific IgE was detected in a standard panel comprising seasonal, perennial and food allergens. Skin prick testing with aero- and food allergens and prick to prick testing with fruit suspected as elicitors of vasculitis, including apple, pear, pineapple, kiwi, melon and tomato were negative. Epicutaneous patch testing with standard allergens and ASA were negative as well.

To verify or rule out foodstuff as elicitor of vasculitis, Heidi was put on elimination diet and subsequently orally challenged to 40g of fresh fruits she consumed regularly, including apple, banana, kiwi and pineapple in an unblinded manner. 6 to 10 hours after consumption of kiwi she reproducibly developed an itchy rash consisting of confluent 3-5 mm urticaria on the legs, lower trunk and forearms with consecutive bleeding in the central part of the lesions (Figure 3). Western Blot analysis of a kiwi fruit extract with Heidi's serum showed IgG-, but no IgE-reactivity, corresponding to the major kiwi fruit antigen Act c1 (Figure 4). Despite plausible history of purpura following pineapple consumption, oral challenge was negative.



DIAGNOSIS

In the light of the patient's history, diagnostic findings and the reproducible induction of symptoms by oral provocation with kiwi, the diagnosis of "kiwi-induced allergic leucocytoclastic vasculitis" was established.

DIFFERENTIAL DIAGNOSIS

Based on the normal clinical-, serological- and pathobiochemistry findings, other forms of systemic vasculitis were excluded (Table 1)^{1, 2}. Also, common trigger factors of allergic vasculitis were ruled out (Table 2)^{1,2}.

Figure 4

Western blot analysis of kiwi extract with patient serum. IgG reactivity corresponding to kiwi major allergen Act c1 is observed, while no kiwi-specific IgE is detected.

**Table 1 - Differential Diagnosis of Purpura****A. Palpable Purpura**

Cutaneous necrotizing vasculitis, classical type
 Henoch-Schoenlein purpura
 Vasculitis associated with Sjogrens´ syndrome
 Vasculitis associated with myeloma
 Wegener's granulomatosis
 Churg-Strauss syndrome
 Microscopic polyangiitis
 Polyarteritis nodosa
 Mixed connective tissue disease
 (Meningococcal) sepsis
 Lymphoma
 Leukaemia
 Internal malignancies
 Cryoglobulinemia

B. Non-palpable Purpura

Hemorrhagic diathesis
 (hematologic/hepatic diseases)
 Thrombopenia
 Disseminated intravascular coagulation
 Vaskulopathia
 (e.g. amyloidosis, collagen defects like skorbut)
 Uremia

EVOLUTION AND FOLLOW UP

Heidi's therapy consisted of elimination diet with avoidance of the consumption of kiwi and pineapple. No recurrences of vasculitis were observed over a period of 3 years, while the purpuric lesions and hyperpigmentations resolved slowly over time.

DISCUSSION AND CONCLUSION

We were able to identify kiwi fruits as causal elicitors of allergic vasculitis in Heidi's case by repeated oral food challenge.

The presence of Act c1-specific IgG supports an allergen-specific process, but food-specific IgG antibodies are a frequent finding in healthy individuals. Strikingly, mainly dependent body regions like legs and feet were affected by vasculitis and therefore, the formation of IgG immune complexes with kiwi antigen and their deposition in dermal postcapillary venules was assumed as pathogenic process. The missing reaction to pineapple, despite positive history, is

probably caused by cross-reactions of the major pineapple antigen bromelain with Act c1, which share extensive sequence homologies (Figure 5). In case of cross reactivity, the amount of pineapple in oral provocation might have been too low or summative effects have failed to reach trigger value. Another, simple explanation is a possible co-ingestion of kiwi and pineapple.

Table 2 - Trigger Factors & Diseases Associated with Allergic Leucocytoclastic Vasculitis

Associated Diseases	Diagnostic Procedures
Bacterial, viral, fungal, parasitic infections	(e.g. pharyngeal smear, ASL, ADB for streptococcal infections)
Lupus erythematodes	ANA
Hemolytic anemia	RBC
Cryoglobulinemia	Cryoglobulins
Plasmocytoma	Immune electrophoresis
Morbus Hodgkin	Chest X-ray
Rheumatoid arthritis	Rheumatoid factor
Complement defects	C2, C3, C4
Hepatitis B/C	Hepatitis B and C serology
Serum sickness	History, circulating immune complexes
Food allergy	History, skin prick testing, elimination diet, oral food challenge
Drug allergy/ hypersensitivity	Skin Prick testing, i.c. testing, patch testing (including 6hrs.), (oral) provocation



About Vasculitis, Purpura and Food Allergy

ALLERGIC LEUCOCYTOCLASTIC VASCULITIS

The term vasculitis is defined as inflammation of blood vessels. Current classification schemes have been proposed by the American College of Rheumatology in 1990 and in the Chapel Hill classification from 1992, which integrate the size of affected vessels, as well as clinical and histopathological findings.^{5, 6} Based on current data, cutaneous vasculitis is associated with the following conditions: infection (15%-30%), inflammatory disease (15%-20%), drug intake (10%-15%), and malignancy (5-10%). In 45%-55% of cases, no underlying cause can be identified and therefore are classified as idiopathic.^{8,9}

HISTOPATHOLOGY AND PATHOPHYSIOLOGY

"Allergic leucocytoclastic vasculitis", which was diagnosed in Heidi's case, is a term delineated from "Cutaneous leucocytoclastic angiitis" defined by the Chapel Hill Classification and describes an angiocentric segmental inflammation, of small vessels of the skin, usually without internal organ involvement. Histological hallmarks are endothelial swelling and fibrinoid necrosis of postcapillary venules, with massive infiltration of neutrophils undergoing fragmentation of nuclei (karyorhexis, leucocytoclasia).⁷ The pathophysiology of allergic vasculitis starts with deposition of IgG or IgM immune complexes and fibrin in small vessels, mainly at regions with increased hydrostatic pressure. Complement activation by immune complexes leads to attraction of neutrophils, which disintegrate and release lysosomal enzymes and oxygen free radicals. Complement products (e.g. C5a) induce mast cell degranulation with release preformed mediators leading to stasis (histamine, serotonin) and *de novo* synthesis of proinflammatory cytokines and leukotriens like TNF- α or PGE₂, thus perpetuating the pathogenetic process.^{1,7}

CLINICAL FINDINGS

Acute clinical manifestations of allergic leucocytoclastic vasculitis range from urticae, over papules to vesicles and result in palpable purpura with superficial infarction or ulceration, mostly localized in dependent areas, regions of trauma or under tightly fitting clothes.¹ In recent Spanish studies, the frequency of conditions and drugs associated with leucocytoclastic vasculitis were analyzed (Table 3).^{8,9} Differences between populations and geographic regions can be assumed.

Table 3 - Prevalence of trigger factors in allergic vasculitis

Associated conditions/ trigger factors	% of patients
HCV	19.0
HBV	5.0
Other infections	4.0
Drug intake (e.g. penicillins, sulfonamides, quinolones, hydantoins, etc.)	10-24%
Underlying malignant neoplasm	10.0
Connective tissue disease	8.4
Inflammatory bowel diseases	2.5
Rheumatologic diseases	2.4
Behcet disease	2.0
Essential mixed cryoglobulinemia	1.3
Miscellaneous	3.0

REPORTED FOODSTUFF AS ELICITOR OF ALLERGIC VASCULITIS

Foodstuff is mentioned as possible elicitor of allergic vasculitis in reviews and textbooks of Dermatology and Allergy, but rarely considered in clinical practice and is reported only anecdotally in current literature:^{1, 7, 10} Eisenmann described 2 cases with purpura after oral provocation with rye bread and carrots.³ Also, cutaneous leucocytoclastic vasculitis with concurrent involvement of large joints after ingestion of cow's milk, hen's egg, and cocoa products were reported in two pediatric patients.¹¹ Besides food itself, also food additives



can provoke vasculitis, as documented by purpura associated with tartrazine and benzoate, with or without concurrent HCV infection and cryoglobulinemia.^{4, 12}

REPORTED FOODSTUFF AS ELICITOR OF OTHER FORMS OF PURPURA

Besides allergic vasculitis, idiopathic thrombocytopenic purpura (ITP) is another common cause of purpura, which can be caused by antibodies related to foodstuff as well. Reported foods causing ITP include cow's milk, sesame seeds and cranberry juice.¹³⁻¹⁵ Also, pathogen-derived toxins, such as shiga-like toxin produced by *E. coli* O157:H7 (and other toxin-producing strains) are capable of inducing hemolytic uremic syndrome which is - among others - characterized by purpura.¹⁶

DIAGNOSIS

Diagnosis of allergic leucocytoclastic vasculitis is based on patient's history, clinical examination and histopathology. Serology and diagnostic imaging should be used to rule systemic vasculitis. Bleeding disorders including thrombocytopenia and other forms of vasculitis have to be excluded (Table 1). Possible trigger factors of allergic vasculitis (Table 2, Table 3) should be evaluated thoroughly to allow specific therapy.⁷

THERAPY OF ALLERGIC LEUCOCYTOCLASTIC VASCULITIS

Therapy of allergic leucocytoclastic vasculitis should start with removal or causal therapy of trigger factors. To date no generally accepted gold standard for symptomatic therapy has been defined and almost no double-blind placebo controlled, prospective trials have been published. Topical treatment can be carried out with corticosteroid preparations, bed rest and gradient stockings are proposed as well.⁷ In more severe cases oral steroids (e.g. prednisolon 60-80mg for 3-5 days) or NSAID have been proposed for first line therapy. Second line therapies include colchicine, dapson, immunosuppressive agents, antimalarials and IVIg, whereas possible benefits of antihistamines are under debate.^{1, 2, 7}

VERIFICATION OF FOODSTUFF CAUSAL AGENT IN ALLERGIC VASCULITIS

Identification of causal agents in allergic vasculitis induced by foodstuff should combine approaches used for food allergies and vasculitis. Starting with comprehensive history, the possible elicitors should be narrowed down to a limited number of possible causes:¹⁷

- Food responsible for the reaction
- Quantity of the food ingested
- The length of time between ingestion and development of symptoms
- Whether similar symptoms occurred when the food was eaten previously
- Whether other factors, such as exercise were necessary for elicitation of symptoms
- When the last reaction to the food occurred

Skin prick testing and measurement of specific IgE should be carried out to evaluate an IgE-mediated process, but can also lead to flares of vasculitis mediated by immune complexes of other specificity. In addition, patch testing can give information on the relevance of suspected foodstuff or additives in food induced vasculitis.¹⁸ Absence of symptoms should be achieved in a diagnostic elimination diet, while the final proof of causality and verification of clinical significance can be accomplished by double-blind, placebo controlled food challenge.^{17, 19}



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Summary

We describe the case of a 61 year old woman who suffered from chronic recurrent allergic leucocytoclastic vasculitis with the clinical picture of palpable purpura. A comprehensive screening for the typical elicitors included infectious-, chronic inflammatory- or malignant disease and drug intake, but failed to provide a causal explanation for the vasculitic process. Finally, a relapse following the ingestion of a fruit salad allowed us the directed testing and verification of kiwi fruit as eliciting agent by oral provocation of our patient. Based on this finding, we recommend keeping foodstuff in mind as trigger factor for allergic leucocytoclastic vasculitis, especially in unclear cases which are classified as "idiopathic".

Keywords:

food allergy, differential diagnosis, immune complex vasculitis, pathophysiology, IgG



Assessment test

1. Which of the following statements is not true?

Palpable purpura is a frequent finding in:

- A. Mixed connective tissue disease.
- B. Polyarteritis nodosa
- C. Churg-Strauss syndrome
- D. Thrombopenia
- E. Henoch-Schoenlein purpura

2. Which of the following is a frequent cause of allergic leucocytoclastic vasculitis?

- A. Underlying malignant neoplasm
- B. Viral infections (e.g. Hepatitis B/C)
- C. Connective tissue disease
- D. Drug intake
- E. All of the above

3. A clinical manifestation of cutaneous vasculitis may include...

- A. Urticae
- B. Necrosis
- C. Papules
- D. Vesicles
- E. All of the above

4. Which is not considered a major player in the pathogenesis of allergic leucocytoclastic vasculitis:

- A. Neutrophils
- B. Endothelium
- C. Mast Cells
- D. Fibroblasts
- E. Immune complex deposition

5. For first-line therapy of allergic leucocytoclastic vasculitis have been proposed...

- A. Azathioprine
- B. Dapsone
- C. Cyclosporine
- D. Colchicine
- E. NSAID and glucocorticoids

6. Which class of drugs is not considered for second line therapy of allergic leucocytoclastic vasculitis?

- A. Antimalarials
- B. Colchicine
- C. Dapsone
- D. β -blockers
- E. IVIg



7. Foodstuff as elicitor of allergic leucocytoclastic vasculitis...

- A. ... should be considered is a possible cause in "idiopathic" cases.
- B. ... can be such different agents as rye bread, carrots, cow's milk, hen's egg or fruits.
- C. ... is a rare finding.
- D. All of the above

8. Which of the following is not regarded as trigger factor of allergic leucocytoclastic vasculitis:

- A. Fungal infections
- B. Hepatitis B
- C. Bacterial infections
- D. Alpha1-antitrypsin deficiency
- E. Hepatitis C