

Allergic vascular purpura

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An instance of nonthrombocytopenic vascular purpura is reported due to tartrazine sensitivity. There were no abnormal hematologic findings present. Possible pathogenetic mechanisms involved in this condition are discussed.

Nonthrombocytopenic vascular purpura has been reported to be caused by allergy to drugs, insects, and inhalants.¹⁻¹¹ We wish to report an instance of vascular purpura resulting from sensitivity to a food additive, namely, tartrazine (yellow No. 5 dye).

CASE REPORT

Patient M. W. H., a 22-year-old married Caucasian female nurse, was first seen by us in 1968 through the courtesy of Dr. Philip Blank. She had been troubled for the previous five years with acute intermittent bouts of profuse bleeding manifested by one or more of the following: menorrhagia, purpura, and/or bleeding from the ear, nose, gums, and bowel. These episodes were often accompanied by chills and fever. The bleeding was sufficiently severe at times to require hospitalization and blood transfusions.

There was no family history of bleeding. Past medical history was contributory only for bronchial asthma, perennial allergic rhinitis, and hay fever. Clinically significant positive intracutaneous tests were obtained to pollen, house dust, and molds but not to milk. There was no temporal correlation between these allergic respiratory manifestations and the bleeding episodes.

Physical examination revealed a young woman in distress only during the episodes of severe bleeding when her temperature ranged from 100° to 102° F. and her pulse and respiratory rate were increased. Blood pressure was 116/60. Purpuric lesions were found distributed on various body skin areas (Figs. 1 to 3). On one occasion bleeding into the soles of her feet was observed. No telangiectasia was present. Bleeding was seen at times in the ear canal and mucous membranes of the mouth, nose, and posterior pharynx. Cardiorespiratory examination was negative. Examination of the abdomen revealed no organomegaly or abdominal masses. Pelvic and rectal examination were normal except during the periods of bleeding. Neurological findings were unremarkable.

Extensive and repeated laboratory studies were carried out in 1968, 1969, and 1970 in various laboratories with essentially normal results. These included urinalyses and blood chemistry determinations such as creatinine, electrolytes, and serum protein electrophoresis. Bone marrow studies, multiple lupus erythematosus (LE) cell preparations, antinuclear factor, skeletal muscle, and skin biopsies were negative. Stools were markedly positive for occult blood during the active stage of the disease. Agglutination tests for *S. typhosa* (H), *S. paratyphi*, *S. schottmuelleri*, and *Brucella* were negative. Cold agglutinin titer was 1:32; antistreptolysin-O titer was 110 Todd units without rise. Serology was non-reactive. Gastrointestinal x-ray studies were negative. X-rays of the chest and sinuses and the electrocardiogram were normal. Intravenous pyelogram was negative. Blood cultures were sterile. Cervical scrapings were negative.

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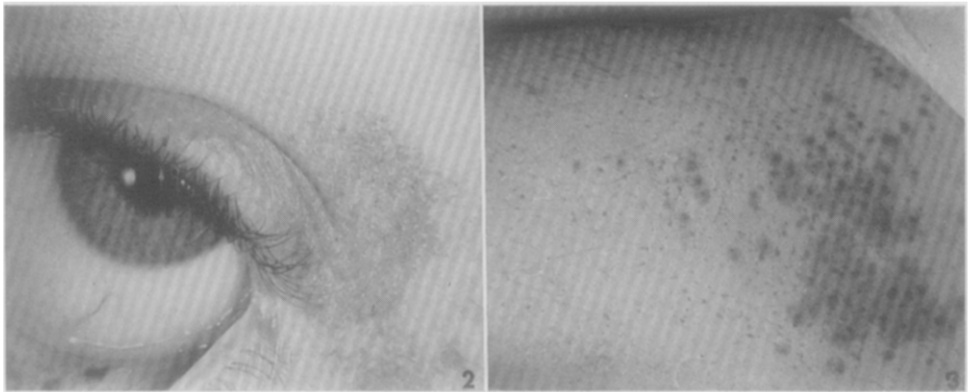


FIG. 1. Petechiae and purpura on mucous membrane of the mouth.

Hemostatic studies, carried out in the laboratory of Dr. Jessica Lewis, Department of Medicine, University of Pittsburgh, showed the following to be normal on three occasions: bleeding time (Duke and Ivy), tourniquet test, clotting time (glass and silicone), clot retraction, clot lysis, serum prothrombin time (SPT), prothrombin time (PT), recalcification time, partial thromboplastin time (PTT), plasma thrombin time (PL-T), and thromboplastin generation test (TGT). Recalcified plasma clots did not lyse in 5M urea. Also within the normal range were assays of factors I, II, V, VII, X, VIII, and IX. Platelet counts were between 200,000 and 216,000 per cubic millimeter. Platelet glass adhesive indices were normal. On three occasions the patient's platelets aggregated normally on addition of ADP (adenosine diphosphate, 0.001M), and on two of three tests aggregation was normal with added collagen.

Food diaries were instituted in January, 1968, in order to determine whether the ingestion of foods had any causal relation to the bleeding. The patient thus discovered that the ingestion of butter or margarine was invariably followed by bleeding. Provocative tests carried out with feeding butter or margarine always brought on bleeding into the skin and episodes of epistaxis with chills and fever which lasted for one to five days. Similar exacerbations were not precipitated by the ingestion of other dairy products. Further investigation revealed that tartrazine (FD&C yellow dye No. 5) is the food color additive in butter and margarine. Double-blind studies using coded capsules containing the dye or placebo precipitated bleeding in each and every instance only when the patient ingested dye-containing capsules. Scratch-patch tests were carried out with the dye in a 1:1,000 and later in a 1:100 dilution. No immediate wheal and flare reaction was obtained. However, there appeared at the test site in 24 hours a delayed response which consisted of erythema, induration, vesiculation, and petechiae occasionally accompanied by mild epistaxis and bleeding from the ears. Skin tests on controls were negative. Passive transfer tests (P-K tests) using the patient's serum and increasing concentrations of a solution of tartrazine were negative.

The Ouchterlony plate technique was employed for the determination of precipitins in the patient's serum against tartrazine, FD&C No. 5 dye. The center well contained the serum



FIGS. 2 and 3. Petchiae and purpura on various skin areas.

and the peripheral wells contained a 2 per cent solution of the dye. There were no demonstrable precipitin bands over a period of 7 days.

Furthermore, *in vitro* investigations failed to reveal that tartrazine (yellow No. 5) was toxic to this patient's platelets. The dye was prepared in concentrations of 1, 0.1, 0.01, and 0.001 per cent. The addition of $\frac{1}{20}$ part of these concentrations of the dye to normal or the patient's blood did not affect the subsequent clot retraction or SPT, PT, PTT, PL-T, or TGT.

Platelet-rich plasma from the patient and a normal individual was incubated with $\frac{1}{40}$ volume of the one per cent dye for 20 minutes with constant motion (in a platelet aggregometer, Chrono-Log Co.). No clumping or aggregation was observed, and subsequent addition of ADP produced normal aggregation in both samples.

DISCUSSION

The patient reported in this communication gave a history of repeated attacks of bleeding into the skin and from various mucous membranes. These episodes were related to the ingestion of foods containing tartrazine (FD&C yellow dye No. 5).

Various conditions were considered in differential diagnosis. A diagnosis of von-Willebrand's disease (hereditary vascular purpura or vascular pseudo-hemophilia) was made at one time elsewhere because of one suggestively abnormal factor VIII finding. This disease is characterized^{1, 2} by a prolonged bleeding time, a low antihemophilic globulin (AHG), low platelet adhesiveness, and a dominant autosomal hereditary history. This diagnosis was excluded because none of these findings was present on our own repeated examinations. The diagnosis of classical Schönlein-Henoch purpura was also considered. However, the abdominal pain, erythema, urticaria, serous effusions, renal and joint manifestations, and eosinophilia usually associated with this disease were absent in our patient.¹²⁻¹⁴

In a discussion of the pathogenesis of bleeding, it is desirable to consider the factors which normally control bleeding and then speculate on possible immunogenic causes. Bleeding is controlled by the coagulation components, the platelet factors,³ and the vascular component, i.e., the endothelium. As indicated above, we found no evidence of any coagulation or platelet abnormality. This then is essentially a vascular purpura associated with increased capillary fragility and permeability.

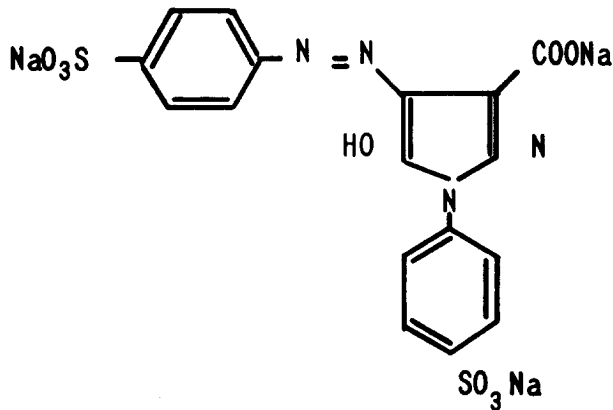


FIG. 4. Chemical formula of tartrazine (FD&C yellow No. 5). Trisodium salt of 3-carboxy-5-hydroxy-1-sulfophenyl azopyrazole, an aniline dye.

Instances of bleeding resulting from allergy to various substances have been reported. Snyder⁶ described a case of nonthrombocytopenic vascular purpura due to the ingestion of coffee occurring in an atopic individual who showed no abnormal hematologic findings. Many drugs, including quinine, belladonna, mercury, penicillin, meprobamate, aspirin, chloral hydrate, phenacetin, and oxytetracycline, have been reported to produce nonthrombocytopenic vascular purpura.^{1, 2, 5, 11} We¹⁰ have reported nonthrombocytopenic vascular purpura accompanying a serum sickness type of penicillin reaction in three patients who had no abnormal hematologic findings. The purpura subsided upon cessation of penicillin therapy.

Experimentally, vascular purpura has been produced^{4, 5} by injecting dogs or guinea pigs with rabbit antisera against dog or guinea pig vascular endothelium. Stefanini and Mednicoff⁴ obtained precipitin reactions using sera of patients with anaphylactoid purpura and extracts of human aorta.

Tartrazine (FD&C yellow No. 5) is a pyrazole derivative (Fig. 4). It is the trisodium salt of 3-carboxy-5-hydroxy-1-sulfophenyl azopyrazole, an aniline dye. It includes heterocyclic rings and acidic groups. It is unfortunate that the Food and Drug Administration, while certifying some 11 coal-tar dyes, does not require packages to indicate the presence of the dye on the labeling. Artificial colors in foods and drugs may cause atopic reactions, such as bronchial asthma.¹⁵ Urticaria has been reported from tartrazine (yellow No. 5) coloring agent following ingestion of Deronil, Decadron, or Paracortol tablets.

Lockey and Draude^{16, 17} have called attention to the presence of yellow No. 5 (tartrazine) in a great variety of products, including dry drink powders, carbonated beverages (Tang), colored candy, as a dye used for identification of solutions of drugs, in coloring drug capsules, and tablets such as Deronil, dexamethasone (Decadron), and prednisolone (Paracortol), toothpastes, cosmetics, hair-waving and hair-rinsing products, face powders, and many other articles.

The bleeding in this case was caused by the ingestion of tartrazine. The question then arises as to the pathogenesis of this bleeding. The completely negative hematologic studies here reported reveal no evidence of a toxic effect or of a hematologic disease responsible for the purpura. The presence of an atopic background in this patient does not necessarily imply an atopic or immunologic basis for her condition. Indeed, direct intracutaneous tests with the dye did not yield a wheal and flare reaction. Passive transfer tests were negative. The delayed positive skin test (scratch-patch test) was probably induced because of the local reaction on blood vessels. And yet, it is possible, though exact proof is lacking, that the dye, tartrazine, may in this case act as a hapten bound covalently to a protein carrier, such as the endothelial cells of small blood vessels. Circulating antibodies formed to this conjugate, it is postulated, react with the antigenic component of the endothelium or with an antigen which has become closely associated with the endothelium which is in constant contact with the circulating plasma. The complement system is then activated, leading to lysis of these cells. This results in increased blood vessel permeability, which in turn is responsible for the purpura and bleeding. Alternatively, circulating antigen-antibody complexes related to the dye might be deposited on the vascular endothelium. As is true of all allergic reactions, there is an acute onset on exposure, in this case the ingestion of the dye. Complete recovery occurs upon its withdrawal. Re-exposure causes reappearance of the bleeding, and the extent of the bleeding is dose dependent. The positive scratch-patch tests and provocative tests lend further weight to this supposition. However, Samter and Beers¹⁸ suggest the possibility that, as in the case of aspirin sensitivity, this dye may produce a direct stimulation of certain vulnerable peripheral chemoreceptors.

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