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Polycythaemia rubra vera and water-induced pruritus: blood histamine levels and cutaneous fibrinolytic activity before and after water challenge

H.K.STEINMAN, A.KOBZA-BLACK, T.M.LOTTI*, L.BRUNETTI*, E.PANCONESI* AND M.W.GREAVES

Institute of Dermatology and St John's Hospital For Diseases of the Skin, Homerton Grove, London, U.K. and *Instituto di Clinica Dermosifilopatica del l'Universita degli Studi di Firenze, via Alfani, 37-50100 Firenze, Italy

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SUMMARY

We studied blood histamine activity (HA) and cutaneous fibrinolytic activity (CFA) in a patient with polycythaemia rubra vera (PRV) and water-induced pruritus, before and after water exposure. The results suggest that the water-induced itching in PRV is associated with an increase in HA. In addition, markedly increased levels of CFA were found both before and after water exposure. These findings have been previously reported in patients with aquagenic pruritus (AP) but not in patients with PRV. As the water-induced itching in PRV and AP share many common features, these findings suggest that the pathophysiology of the water-induced pruritus in these two conditions may be similar.

Generalized pruritus is a common and characteristic symptom of polycythaemia rubra vera (PRV), occurring in approximately 50% of cases.[1,2] The itching is often exacerbated by bathing or showering, and in some cases water contact induces nearly intolerable pruritus. Thus, itching in PRV often closely resembles that of aquagenic pruritus (AP).[3,4] In many cases, the pruritus subsides with control of the polycythaemia. However, there is no clear relationship between the degree of pruritus and the severity of the disease, and approximately 20% of patients continue to experience itching despite adequate reductions in their red blood cell mass.

The pathogenesis of the pruritus is not known. Gilbert, Warner and Wasserman[2] reported that 66% of their patients with untreated PRV had elevated blood and urine histamine levels as opposed to only 7% of their patients with treated PRV. Greaves *et al.*[3] reported raised levels of blood histamine in patients with AP following water exposure, and Lotti *et al.*[5] reported increased cutaneous fibrinolytic activity (CFA) in an AP patient following water challenge. We

Correspondence: Howard K.Steinman, M.D., University of California, San Diego School of Medicine, Division of Dermatology (H-811J), 225 West Dickinson Street, San Diego, CA 92103, U.S.A.

report the results of blood histamine and CFA determinations in a patient with PRV and water-induced pruritus, before and after water exposure.

CASE REPORT

The patient, a 55-year-old man, developed PRV in 1970, which was effectively treated with regular venesections and occasional courses of oral busulphan therapy. In 1976, he began to experience intense skin discomfort on contact with water, which he described as like sharp pins pricking his skin. The discomfort occurred irrespective of water temperature or salinity and began within 1–5 min of water contact. After drying, it remained intense for approximately 30 min and completely subsided within 1 h. The discomfort would begin on his thighs and legs and then spread to his trunk and arms. Localized application of water to his skin induced discomfort at the site of contact. The pruritus was not associated with observable skin lesions but did induce extreme emotional irritability. He had a history of chronic idiopathic urticaria since 1981, which had almost completely subsided by the time of the present study. Previous evaluation had excluded the presence of any physical urticarias, including aquagenic urticaria. Therapy with H1 histamine antagonists had failed to relieve the pruritus. Oral ferrous sulphate therapy, 325 mg three times daily, resulted in significant symptomatic improvement, but had to be discontinued due to an unacceptable rise in his red blood cell mass.

Physical examination was normal except for the presence of three cutaneous urticarial wheals and hepatosplenomegaly. Laboratory investigations gave the following results: haemoglobin 15·4 g/dl, packed cell volume 52%; platelet count 146×10^9/l; white blood cell count $12{\cdot}2 \times 10^9$/l (82·5% neutrophils, 10% lymphocytes, 2·5% monocytes and 1% basophils); serum iron 4 μmol/l; total iron-binding capacity 69 μmol/l; total bilirubin 30 μm/l; alkaline phosphatase 143 IU/l; aspartate transaminase 27 IU/l. The following investigations were negative or normal: serum electrolytes, urea, calcium and phosphate, thyroid stimulating hormone, T_3, T_3 resin uptake, euglobulin lysis time, VDRL, TPHA, hepatitis B surface antigen, chest X-ray and electrocardiogram.

METHODS

Blood histamine assay

Venous blood samples were obtained using an indwelling canula in an antecubital vein. A baseline blood sample was obtained, and the patient was then immersed to his upper chest in tap water at 38°C for a period of 5 min. Blood samples were obtained at 5 min intervals until 40 min after first exposure to water, and then at 10 min intervals up to 90 min. 100 min after first exposure to water the patient was immersed a second time to his upper chest in the tap water bath at 38°C and blood samples were obtained at 5 min intervals for an additional 30 min. Each blood sample was assayed for histamine-like activity immediately after it was obtained using the cascade superperfusion assay of Vane,[6] modified as described by Lawrence *et al.*[7] Briefly, two superfused longitudinal strips of guinea-pig ilea were used, the second with the H1 antihistamine, mepyramine, added. The contractile responses, which were blocked by mepyramine on the second guinea-pig ileum, were considered to be due to histamine.

Cutaneous fibrinolytic activity

In a separate experiment, CFA was assessed before and after water exposure in the patient and a control subject matched for age and sex. All skin samples were obtained from the left upper arm

using a 6 mm circular punch biopsy. After obtaining the initial skin samples, the patient and the control subject were immersed to their upper chests in tap water at 40°C for 10 min. This resulted in moderate pruritus in the patient but no pruritus in the control subject. The second skin biopsies were then obtained, sampling an area of symptomatic skin in the case of the patient. The skin specimens were washed in phosphate buffered saline for 5 min, then quick frozen using liquid nitrogen. They were then cryostat sectioned into slices 6 μm in thickness and processed using Todd's autohistographic technique,[8] modified to obtain constant tissue and fibrin film thickness.[9,10]

RESULTS

The measurements of the patient's blood histamine activity (HA) over time are shown in Figure 1. At rest, the HA was < 1·0 ng/ml. Immediately after the 5 min bath, the HA rose to 1·8 ng/ml. Itching was first noted 10 min after the onset of water exposure and lasted for 35 min. HA continued to increase to a maximum value of 6·5 ng/ml 90 min after the beginning of water exposure, at which time the patient was exposed to a second 5 min water bath. The patient again experienced pruritus 10 min after the beginning of water exposure, which lasted for approximately 35 min. The HA was 9·2 ng/ml 10 min after the beginning of the second water challenge (110 min from first exposure). The patient's HA rose to 10 ng/ml 30 min after the second water exposure, at which time the study was stopped.

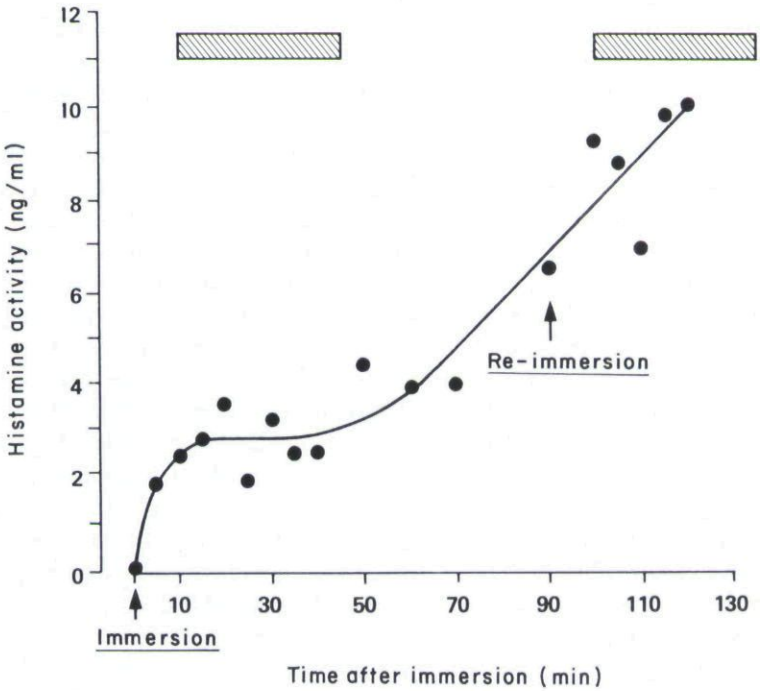

FIGURE 1. Blood histamine activity in a patient with polycythaemia rubra vera and water-induced pruritus, before, during and after water immersion. ● Histamine activity; ▨ onset and duration of itching

The results of CFA determinations showed a greater degree of CFA in the PRV patient relative to the control both before and after water challenge. However, no observable increase in CFA was noted in either the patient or control after water challenge. CFA was determined by dividing the surface area of the sectioned skin sample by the surface area of the overlying fibrin film lysis. Before and after water exposure, the fibrin film lysis in the patient's specimens extended beyond the borders of the skin sample, CFA in both specimens being 0·4. In the control subject, small areas of fibrin film lysis were localized primarily over dermal blood vessels, CFA being 1·5 in both specimens. Fibrinolysis was abolished when skin specimens from the patient were treated with epsilon-amino-caproic acid prior to exposure to the fibrin film, suggesting that the increase in fibrin film lysis was due to an increase in plasminogen activator activity.[11]

DISCUSSION

Pruritus is a common feature of PRV, occurring in up to 50% of untreated patients.[2,12,13] It is usually characterized by a generalized, often severe, prickling skin discomfort that develops within minutes of water contact and lasts for 15–60 min. In some patients, the pruritus is nearly intolerable, and these patients may resort to regional sponge bathing or avoid bathing altogether. In many patients, the pruritus occurs only after a hot bath or shower, but in some patients contact with water at any temperature will induce discomfort. The pruritus may be somewhat temperature dependent, as many patients can diminish the severity of their symptoms if they prevent skin cooling after warm water contact. Moreover, some patients note pruritus after getting into a cold bed or on being exposed to cold ambient temperatures. In many cases, the pruritus subsides with control of the polycythaemia, but there is no clear relationship between the severity of the polycythaemia and the degree of the pruritus. Up to 20% of patients continue to experience generalized pruritus despite adequate control of the underlying disease.

Iron deficiency has also been proposed as a cause of PRV-related pruritus, and it has been reported that almost all PRV patients have some degree of iron deficiency on the basis of measurements of bone marrow iron levels.[14] Salem *et al.*[15] reported in an uncontrolled trial that supplementary oral iron therapy greatly reduced or eliminated pruritus in all six of their patients with PRV and iron deficiency. Our patient also noted significant relief of pruritus with oral iron therapy, but, as with three of Salem's patients, iron therapy had to be discontinued due to an unacceptable rise in the patient's red blood cell mass. The mechanism by which iron deficiency might induce pruritus or by which oral iron therapy might ameliorate it is not known.

Elevated levels of blood and urine histamine in patients with uncontrolled PRV were reported by Gilbert *et al.*[2] In their study, 22 of 33 (67%) patients with uncontrolled PRV had raised levels of blood histamine as opposed to only 2 of 30 (7%) patients with controlled PRV. 52% of the uncontrolled PRV patients complained of pruritus as opposed to 20% of controlled patients. It is not specified whether the blood samples were obtained from patients during attacks of water-induced pruritus, nor is it indicated whether the samples were obtained while the patients were experiencing pruritus. The results of the present study suggest that increases in HA in patients with PRV may be correlated with the onset of pruritus, and that these increases may be induced by water contact. The patient presented in this report had normal levels of blood histamine when he was asymptomatic, prior to water exposure, but markedly raised levels of blood histamine following water challenge and the onset of generalized pruritus. Increased HA in association with the onset of water-induced pruritus has not been previously reported in

patients with PRV but has been previously shown in patients with AP,[3] a condition that in many respects manifests itself in an identical manner to the water-induced pruritus of PRV.[3,4]

Although raised blood HA may be associated with the pruritus of PRV, it is unlikely that histamine is the sole mediator of the itching. H_1 histamine receptor antagonists are generally of little value in the treatment of the pruritus. Fjellner and Hagermark[13] have proposed that serotonin and prostaglandin E_2 (PGE_2) act as mediators of pruritus in PRV. They showed in a double-blind, cross-over study that aspirin decreased the pruritus to a greater degree than did placebo in 15 of 17 symptomatic PRV patients. Aspirin is both an inhibitor of prostaglandin synthesis and an inhibitor of platelet aggregation, and platelet aggregation results in the release of serotonin. PGE_2 is also known to lower the threshold of human skin to histamine-induced itching.[16]

The results of CFA determinations in our patient indicate that markedly elevated levels of CFA were present both at rest and following water exposure, and that the increase in CFA may be due to increases in plasminogen activator activity. Although the significance of these findings is not known, similar findings have been observed in patients with AP[5] (Lotti *et al.* unpublished observations). Wheals induced by the intradermal injection of histamine have been shown to cause increases in CFA.[17] Thus, the observed elevation of fibrinolytic activity may be a secondary phenomenon.

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