

SHORT REPORTS

Chronic Lymphatic Leukaemia, Malignant Melanomas and Mosquito Hypersensitivity

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Chronic lymphatic leukaemia (CLL) has been found to be correlated to other primary malignancies in a considerable number of cases (6). Especially skin cancers are overrepresented. In 1967 Berg (2) published a study in this field. He took into consideration the many pitfalls inherent in retrospective epidemiological studies of skin cancers, but found previously reported correlations between CLL and skin cancers of different types to be real.

Attempts to explain this correlation in modern immunological terms have been few (3). A case with simultaneous occurrence of CLL, malignant melanomas and hypersensitivity to mosquitoes is presented here as it might be of help in interpreting this puzzling correlation.

CASE REPORT

The patient is a retired forestry officer, born in 1905. In 1972 the diagnosis of CLL was established. He then had only a very slightly elevated peripheral leukocyte count (15 000 per mm³) but 75% lymphocytes in the differential count. Sternal marrow aspirate was consistent with CLL. This malignancy has remained in a very quiescent stage, leaving the patient in good general health and not requiring

therapy at any time since the time of diagnosis. In 1972 he also had an episode of herpes zoster. In connection with this illness he first noted exaggerated reactions to mosquito bites (*Culex pipiens*). This was very surprising as he had spent a great deal of his professionally active time outdoors in forests sometimes very rich in mosquitoes. He had never experienced more than the usual short period of itching after a bite. Now the reactions to bites gradually became more and more persistent, more oedematous and erythematous. In 1974, despite very restricted exposure to mosquitoes, the reactions became even more pronounced and at times real bullae appeared about 3 to 5 hours after the bite. These bullae reached a size of several centimetres and were filled with clear fluid. They soon ruptured, leaving encrusted scars healing with slight hyperpigmentation but as a rule without signs of bacterial infection. At that time he was first referred to a dermatologist. It proved impossible to accomplish the proposed natural hyposensitization by exposure to single mosquitoes as the reactions were severe. In the summer of 1975 a black nodule was noted in the skin over the left scapula. Clinically it was very strongly suspected to be a malignant melanoma. This diagnosis was confirmed histologically. A wide excision was made. No axillary lymph nodes were palpable. Early in 1976 another malignant melanoma was diagnosed, behind the left ear, and was excised.

INVESTIGATION PROCEDURE

In November 1975 the following investigations were carried out (normal values within parentheses): WBC 18 500 per mm³ with 63% lymphocytes (<10 000 with $\leq 45\%$ lymphocytes). IgG 16.2/l (5-15), IgA 2.8 (0.5-3), IgM 0.52 (0.4-1.7), IgE 585 ng/ml (20-500).

T and B cells in peripheral blood were determined by means of E rosettes and surface membrane immunoglobulin markers respectively (5). The T cells comprised 46% and the B cells 52%. The latter figure is clearly elevated ($\leq 20\%$). Phytohaemagglutinin (PHA) stimulation of peripheral lymphocytes was performed with several dilutions and with autologous or pooled homologous sera in the culture medium. Cultivation time was 3 days. The

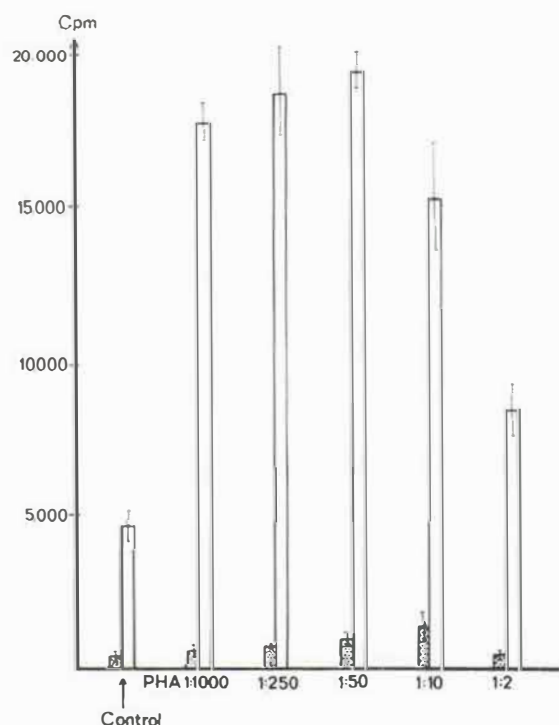


Fig. 1. Lymphocyte transformation as a response to stimulation by phytohaemagglutinin (PHA). The values are given as counts per minute (cpm) $\pm$ standard deviation. The responses to various dilutions of PHA with pooled homologous sera in the medium are within normal limits (open bars). Autologous serum exerts a pronounced inhibitory effect (stippled bars).

uptake of tritiated thymidine was measured in a liquid scintillation counter as counts per minute. The results are shown in Fig. 1. The stimulation in the pooled homologous sera was within normal limits. In autologous serum there was an almost total absence of stimulation of DNA synthesis by PHA. The chemotactic response of granulocytes to casein was normal. The melanin metabolite 5-S-cysteinyl-dopa was measured on two occasions (November 1975 and February 1976). No increased excretion of this metabolite was found, a fact indicating absence of metastases. (The determinations were kindly performed by Professor Rorsman, Department of Dermatology, Lund, Sweden.)

Intracutaneous tests with a mosquito extract from Vitrum, Stockholm, Sweden, and with purified protein derivate of tuberculin (PPD) yielded the following results:

	Prick test	i.c. injection
Mosquito extract 15 min	—	++ ¹
Mosquito extract 48 hours	3×4 mm	8×10 mm
PPD 2 tuberculin units 48 hours	Not done	10×12 mm

DISCUSSION

This patient developed CLL, hypersensitivity to mosquitoes and malignant melanomas in this order. It seemed possible that the CLL might be the cause of the ensuing diseases. It has been shown (8) that CLL is a B cell leukaemia and it is believed to be a monoclonal disease (4). This indicates one possible way of explaining the hypersensitivity state. The lymphoid B cell clone proliferating in this patient gives rise to immunoglobulins which react with mosquito antigen and give the immediate reactions found in the intracutaneous tests. The IgE levels are, as a rule, depressed in CLL (10). The postulated production of reaginic antibodies against mosquitoes in our patient might explain the slight increase found in his IgE level. The nature of the delayed reactions is not clear. The clinical picture was that of an ordinary reaction of tuberculin type. However, a mixed humoral and cell-mediated reaction or an Arthus reaction of moderate degree cannot be ruled out.

The cell-mediated immunological reactions evidently seemed to work well in this patient in certain respects. Thus he had a positive tuberculin test and PHA stimulation in homologous serum was within the expected limits. The suppression of this stimulation by autologous serum as shown in Fig. 1 is worth nothing. Evidently his serum contains inhibitory factor(s) which render the T cells almost incapable of responding to PHA. The same phenomenon is found even in atopic patients (1). This could mean that the immunological surveillance is defective. This in turn facilitates the survival and proliferation of tumour cell lines, in our patient manifesting themselves as malignant melanomas. The nature of this factor or factors is unknown in the present case. It has been shown, however, that antibodies and antigen-antibody complexes, for instance, may have this effect (7). In the discussion of IgE-mediated allergy a defect in the function of suppres-

¹ Equivalent to histamine 0.1%, 0.1 ml.

tor T cells has been suggested as a possible basic mechanism (9). On the basis of animal experiments these authors suggest that the ordinary balance between the B cells producing immunoglobulins and the T cells suppressing this production is disturbed in this type of allergy. This model could be applied to our patient too. The functional defect of the T cells when exposed to autologous serum could render them incapable of regulating the immunoglobulin production and it also could make their immunological surveillance function less efficient.

The interpretations suggested in this report are obviously hypothetical. Nevertheless, it is an attempt to reveal possible links between an unusual clinical picture in a patient and certain disturbances in his immune system.

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A Haemorrhagic Bullous Eruption of the Hands Caused by Phenylbutazone: A Report of 3 Cases

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Abstract. Three patients developed a haemorrhagic eruption on the hands after taking phenylbutazone. The reaction appeared within two weeks of taking the drug and is probably an allergic capillaritis. All patients showed generalised capillary fragility with a positive Hess test which became negative within a week of stopping the drug. A mechanism is suggested for the development and distribution of the blisters.

Key words: Bullous eruption; Phenylbutazone; Purpura

Skin manifestations of drug reactions caused by phenylbutazone and its analogues are not uncommon. They may present as a general exfoliative dermatitis, erythema multiforme, or toxic epidermal necrolysis (1) and may even prove fatal (2). More commonly they present as morbilliform, maculopapular, or urticarial eruptions (4, 12). Purpuric and haemorrhagic eruptions have also been reported. These may be secondary to thrombocytopaenia (7) or non-thrombocytopaenia secondary to angiitis (6, 13).

This present communication describes three cases of phenylbutazone sensitivity presenting as non-thrombocytopaenic purpura with distinctive bullous haemorrhagic lesions on the hands.

Case 1

A 60-year-old engineer reported to the Casualty Department with a three-day history of large haemorrhagic blisters on the hands. He had not suffered from skin trouble previously and was otherwise well. However, one week previously, whilst at work, he had suffered a minor sprain of the right wrist. He was given phenylbutazone 200 mg t.d.s. by his general practitioner, to be taken for one week. He was taking no other medication.

On examination, the eruption was found remarkably symmetrical on both hands. There were tense blood blisters between all the fingers, over the palmar surface of the proximal phalanges, and some extension to the dorsum of the terminal phalanges. The largest blisters were seen particularly between the thumb and first finger