Clinical and Experimental Dermatology 1993; 18: 441–444.

Malignant atrophic papulosis. A report of two cases with altered fibrinolysis and platelet function

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Accepted for publication 16 *November* 1992

Summary

Malignant atrophic papulosis is a systemic vaso-occlusive disorder characterized by typical skin lesions. We report two new cases with impairment of blood fibrinolytic activity and alterations in platelet function. The first case showed an increase in plasminogen activator inhibitor-1 (PAI-1) activity, and the second case had a decrease in platelet aggregation induced by adenosine diphosphate and adrenaline but normal with collagen. The impairment of blood fibrinolytic activity and platelet aggregation may have pathogenic and therapeutic implications in malignant atrophic papulosis.

Malignant atrophic papulosis (MAP) or Köhlmeier-Degos' disease is a rare systemic, vaso-occlusive disorder of unknown cause. The disease is characterized by the development of typical skin lesions and multiple gastrointestinal infarctions. The course is usually inexorable, and the majority of patients die within a year of the onset of the disease,[1,2] although some patients have benign forms and survive for more than 10 years.[3]

The pathogenesis of the widespread vascular lesions characteristic of this disorder is not clear. This paper presents two new cases of MAP, emphasizing haemostatic alterations as possible causative factors. The first patient died, and the second one is still alive 8 years after diagnosis.

Case reports

Case 1

A 36-year-old male was first seen in 1982 with non-confluent, asymptomatic, erythematous papules on the abdomen. Within a few days, the lesions developed a porcelain centre surrounded by a telangiectatic rim (Fig. 1). The lesions then spread to the proximal third of the upper extremities. The palms and the soles were spared.

In January 1984, the patient felt precordial pain. In August, he began to experience diffuse abdominal pain. On physical examination there were necrotic and ulcerated lesions with an excavated border on the skin. Laboratory tests showed a normal complete blood count, erythrocyte sedimentation rate, immunoglobulins, CH50 and complement fractions. Abnormal results included: SGOT of 40 U/l (normal up to 30 U/l), SGPT of 60 U/l (normal up to 30 U/l) and hypoalbuminaemia, albumin of 2·6 g% (normal $3{\cdot}9 \pm 0{\cdot}6$ g%). Antinuclear antibodies were negative.

The chest X-ray showed bilateral pleural effusions, the abdominal CT scan demonstrated ascites and echocardiography showed a pericardial effusion. Laboratory examination of the pleural fluid was consistent with a transudate and the microbiological studies (Gram stain, Ziehl–Neelsen stain and cultures) were all negative. Arteriography showed various degrees of stenosis in the small and medium calibre branches of the inferior mesenteric artery with areas of hypoperfusion in the colon (Fig. 2). The histopathological study of one white, atrophic, lesion showed a wedge-shaped area of necrosis of the dermis covered by a markedly atrophic granular layer associated with slight hyperkeratosis. Within the necrotic area, the collagen, as a result of necrobiosis, had a homogeneous and smudged appearance. At the lateral margins of the lesion, perivascular and periadnexal mononuclear infiltrates were seen. In the deep dermis, the walls of some blood vessels were surrounded by a lymphocytic infiltrate with endothelial alteration and fibrinoid necrosis of the wall. The clinical and histopathological findings have allowed us to establish the diagnosis of MAP.

Screening tests of primary haemostasis and coagulation, including protein C and antithrombin III determinations were normal. No electrophoretic abnormalities of fibrinogen and plasminogen were detected. The fibrinolytic studies[4] showed an increase in plasminogen activator

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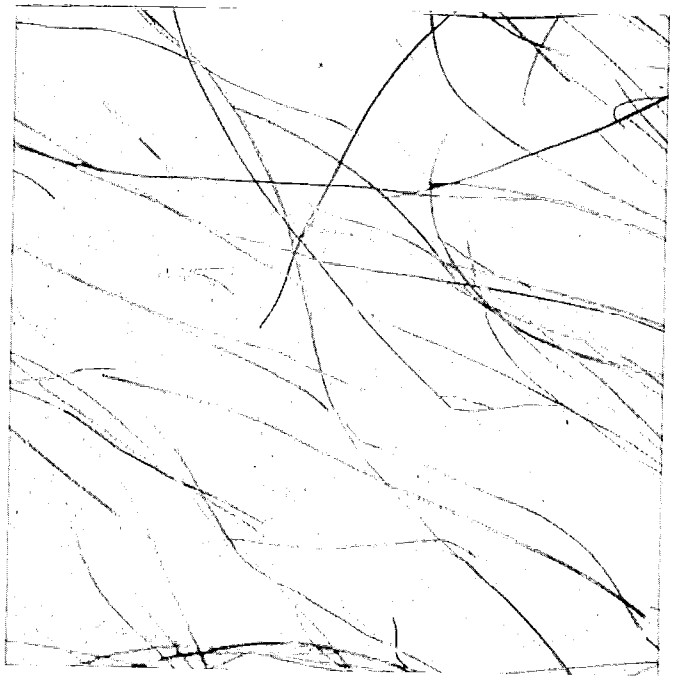

Figure 1. Lesion with a porcelain centre surrounded by a telangiectatic rim (case 1).

Figure 2. Arteriography showing stenosis in the small and medium calibre branches of the inferior mesenteric artery with areas of hypoperfusion in the colon.

inhibitor-1 (PAI-1) activity 3·9 U/ml (normal 2·2±0·2 U/ml (Table 1). Platelet aggregation induced by adenosine diphosphate (ADP), collagen and adrenaline was normal.

In spite of treatment with cyclophosphamide, cyclosporin A, plasmapheresis and intravenous prostacycline, the patient's condition worsened and he died in November 1984.

Table 1. Fibrinolytic parameters in the patients and controls. Mean±s.d.

	Patient 1	Patient 2	Controls ($n=10$)
EFA (U/ml)			
Before occlusion	0·4	0·3	0·3±0·1
After occlusion	4·3	1·2	4·0±3·2
tPA (U/ml)			
Before occlusion	0·08	0·12	0·1±0·03
After occlusion	0·9	0·22	0·8±0·4
PAI-1 (U/ml)	3·9	1·9	2·2±0·2

EFA, euglobulin fibrinolytic activity;
tPA, tissue plasminogen activator;
PAI-1, plasminogen activator inhibitor.

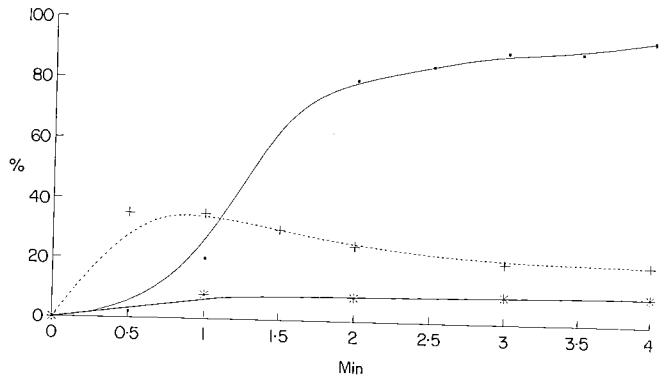

Figure 3. Collagen (■), ADP (+), and adrenaline (*)-induced platelet aggregation in case 2.

The autopsy revealed multiple infarcts and ischaemic ulcers in the small intestine, colon, stomach, spleen and the liver. There were bilateral pleural effusions, as well as, a zone of liquefaction in the grey substance of the frontal lobe.

Case 2

A 17-year-old male first noted, in 1984, asymptomatic outbreaks of non-confluent, erythematous papules with white, atrophic, centres, localized on the abdomen, back and proximal one-third of the extremities. A few months after the appearance of the cutaneous lesions, he had mild abdominal pain associated with the ingestion of food. The following investigations were normal: full blood count, liver function tests, CH50, complement fractions, antinuclear antibody titre and circulating immune complexes (CIC). The histopathological study of one cutaneous lesion was similar to that in case 1. Based on the clinicopathological findings a diagnosis of MAP was made.

Screening tests for primary haemostasis indicated the absence of ADP and adrenaline-induced platelet aggregation but normal platelet aggregation with collagen was observed (Fig. 3). Protein C and antithrombin III were within normal limits. A venous occlusion test showed a poor fibrinolytic response with a decrease in tissue plasminogen activator (tPA), 0·22 U/ml (normal, $0{\cdot}8 \pm 0{\cdot}4$) with normal PAI-1 levels (Table 1).

The patient is still alive without treatment. Some papules with a central, porcelain, white scar and telangiectatic rim occasionally appear on the trunk.

Discussion

The aetiology of MAP remains unknown. Absence of CIC and negative results on direct imunofluorescence tests in most patients with MAP make an autoimmune mechanism unlikely.[5] Other authors, however, have described lymphocyte-mediated necrotizing vasculitis[6] and vasculitis with leucocytoclasis.[7] At the present time there is little question that some form of vascular damage exists in MAP, although no agreement has been reached about the nature of such changes.

The endothelial damage appears to be fundamental to an explanation of the thrombotic phenomena, which is mediated by alterations in coagulation and fibrinolytic mechanisms.

Cunliffe *et al.*[8] suggested that decreased fibrinolytic activity either in blood or in local vascular endothelium plays an important role in disorders of small blood vessels. Black *et al.*[9] observed complete loss of fibrinolysis around small blood vessels in the centre of the earliest papules and prolongation of euglobulin lysis time. However, it was demonstrated that fibrinolysis is preserved around the necrotic zone.[10] Furthermore, impaired blood fibrinolytic activity in MAP has been reported.[11,12] These findings suggest a disturbance in endothelial function which leads to an impairment of the normal fibrinolytic activity. It is not possible to say whether these changes in endothelial function or fibrinolytic activity are primary or secondary manifestations of the pathogenesis of MAP.

The studies performed in our patients indicate a decrease in the fibrinolytic potential (Table 1). The first patient showed an increase in PAI-1 activity. In the second patient there was a decrease in tPA, which probably reflects an alteration in tPA release from the vascular endothelium.

tPA derived from endothelial cells can convert plasminogen to plasmin with subsequent clot lysis. The capacity to release tPA can be assessed by venous occlusion of the arms or injection of vasoactive drugs, etc. Seventy per cent of patients with severe thrombo-embolic disease showed an impaired capacity to release fibrinolytic activity into the circulation in response to such stimuli. Defective fibrinolysis resulting from alterations in tPA can occur through: (a) congenital deficiency; (b) defective release of tPA; or (c) increased plasminogen inhibitors.[13] Congenital tPA deficiency is extremely rare and is inherited as an autosomal dominant disorder.[14] Oral contraceptive use has been reported to cause decreased tPA release from the endothelium. Elevated PAI-1 activity has been found in plasma from patients with venous thrombosis, Gram-negative sepsis and other conditions that predispose to fibrin clot formation.[13,15] Aside from a local defect in the fibrinolytic activity in the zones where microscopic damage occurs,[9] our data indicate the existence of a deficit at systemic level.

Contrary to previously reported cases,[16,17] our second patient presented with decreased platelet aggregation induced by ADP and adrenaline. This abnormality of platelet function was confirmed by repeated examination over 6 years, excluding drug interference. To our knowledge this is the first case of a patient who has this laboratory finding. Whether decreased platelet aggregation is a compensatory mechanism for decreased blood-fibrinolytic activity, or an independent phenomenon is not yet known.

So far, there is no satisfactory treatment for MAP. Antiplatelet agents such as aspirin and dipyridamole appear to be effective in the treatment of MAP associated with platelet function abnormalities.[16,17] Because defective fibrinolysis, whether primary or secondary, seemed to be important in the pathogenesis of MAP treatment with stimulators of fibrinolytic activity were tested. Phenformin and ethyloestrenol have resulted in cessation of the appearance of new lesions in one patient[18] but was not effective in the other.[19] Anisoylated plasminogen streptokinase activator complex (APSAC), tPA and urokinase are other therapeutic alternatives that should be considered in patients who present with multiorgan symptoms.

We conclude that the impairment of blood fibrinolytic activity and platelet aggregation may have implications for the pathogenesis and treatment of MAP and thus fibrinolysis and platelet function should be assayed in these patients.

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