

CASE REPORT

Neutrophilic, urticaria-like erythema associated with immunoglobulin A monoclonal gammopathy of undetermined significance

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ABSTRACT

A 70-year-old-male had suffered from non-pruritic, erythematous eruptions on the trunk for 3 months without any general symptoms. The individual lesions lasted for several days. Laboratory investigation showed marked elevation of serum immunoglobulin A (2235 mg/dL) with monoclonal gammopathy (IgA κ -type). Monoclonal gammopathy of undetermined significance was diagnosed. Histopathological examination of the eruption revealed diffuse neutrophilic infiltration with leukocytoclasia in the dermis. There was no vasculitis. Treatment with antihistamines alone was not effective. Diaphenyl sulfone (DDS) at 75 mg/day dramatically improved the skin lesions. A similar case of urticarial erythema associated with IgA myeloma has been previously reported. We suggest that neutrophilic, urticaria-like erythema associated with IgA monoclonal gammopathy may be regarded as a new entity.

Key words: diaphenyl sulfone, immunoglobulin A, monoclonal gammopathy, neutrophils, urticaria.

INTRODUCTION

Monoclonal gammopathy of undetermined significance (MGUS), formerly known as benign monoclonal gammopathy, is a nomenclature described by Kyle in 1978.¹ This diagnostic term is a hematological condition characterized by the presence of serum M protein with a γ -globulin concentration less than 3 g/dL, less than 10% of plasma cells in the bone marrow, absence of or a small amount of M protein in the urine, and no radiographic or laboratory evidence of lytic lesions, anemia, hypercalcemia or renal insufficiency.² Immunoglobulin (Ig)A gammopathy including myeloma is known to be closely connected with neutrophil-related dermatoses including subcorneal pustular dermatosis,³ urticarial vasculitis⁴ and erythema elevatum diutinum.⁵

We describe a patient with long-lasting, non-pruritic, urticaria-like erythema associated with underlying IgA MGUS.

CASE REPORT

A 70-year-old Japanese man visited us with non-pruritic, erythematous lesions on the upper abdomen of 3 months' duration. The individual lesions lasted from 3–5 days. He had not noted any general symptoms including fever and bone pain. Physical examination revealed multiple, indurated erythemas with hemorrhagic components which measured 1–5 cm in diameter, localized on the anterior chest and upper abdomen (Fig. 1). No dermographism was observed. Laboratory investigation showed mild anemia with a red blood cell count of $356 \times 10^4/\mu\text{L}$.

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Figure 1. Clinical view. Several indurated urticaria-like erythemas on the anterior chest and upper abdomen.

and a normal white blood cell count of $5100/\mu\text{L}$ (54.5% neutrophils). The serum Ig levels demonstrated markedly elevated serum IgA concentration at 2235 mg/dL ($n = 110\text{--}410$). Serum IgG levels were low (576 mg/dL; $n = 870\text{--}1700$), and IgM and IgE were within normal limits (93 mg/dL and 6 mg/dL, respectively). Total protein was 7.4 g/dL. Liver enzymes and serum creatinine levels were almost normal. Antinuclear antibody and anti-DNA antibody were negative. CH50 was 54.1 U/mL ($n = 28\text{--}36$). Interleukin-6 as a growth factor for myeloma was 2.5 pg/mL ($n = <4.0$). Serum protein electrophoresis revealed monoclonal gammopathy (IgA κ -type). Bence-Jones protein in the urine could not be detected. A radiographic examination revealed no punched-out lesions of the bones. Bone marrow aspiration revealed that the proportion of plasma cells was 11%. Blood G-band MM/PL showed no chromosome aberration. Accordingly, IgA MGUS was diagnosed.

A skin biopsy specimen exhibited a diffuse, not perivascular, neutrophilic infiltration with a few eosinophils in the dermis showing marked edema (Fig. 2a,b). There was leukocytoclasia and extravasation of erythrocytes but no evidence of vasculitis. Toluidine blue and alcian blue stains showed a few mast cells in the edematous stroma. Atypical infiltrated cells including myeloma cells were not observed.

Antihistamines such as olopatadine and epinastine alone were not effective for the skin lesions. Diaphenyl

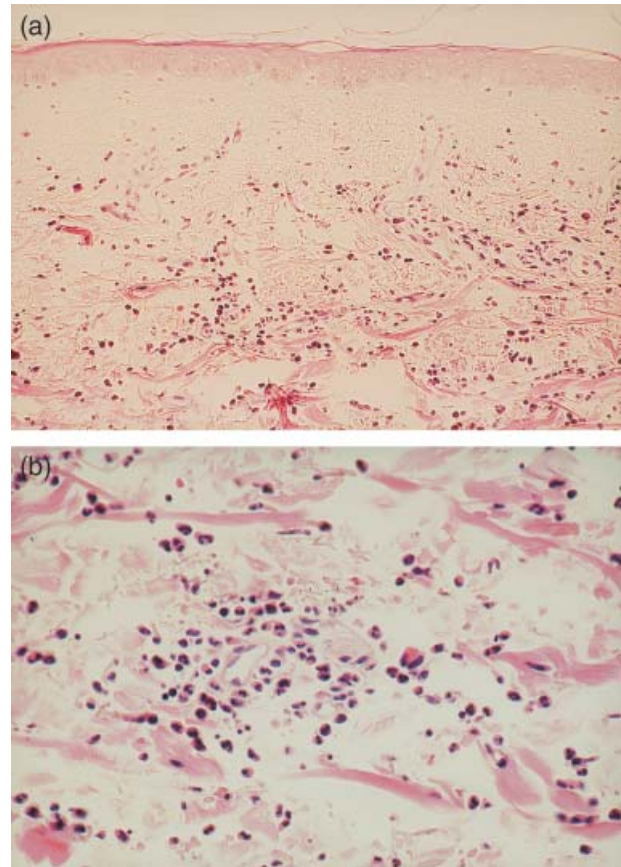


Figure 2. (a) Histological view. Inflammatory cell infiltration and marked edema are seen in the dermis. (HE stain, original magnification $\times 100$). (b) Higher magnification. Diffuse neutrophilic infiltration with leukocytoclasia and a few eosinophils are observed in the dermis. There is no evidence of vasculitis. (HE stain, original magnification $\times 200$).

sulfone (DDS) at 75 mg/day cleared the skin lesions in 1 week. In contrast, serum IgA was increased up to 3155 mg/dL. The urticarial and hemorrhagic erythemas relapsed when DDS was reduced to 25 mg (Fig. 3). An increased dose of DDS (75 mg/day) markedly improved the skin eruption followed by brownish pigmentation. Because of increased serum IgA levels (3476 mg/dL) and progression of anemia ($256 \times 10^4/\text{mm}^3$, Hb 8.4 g/dL), chemotherapy including 8 mg/day melphalan and 40 mg/day prednisolone was started based on the consideration of the transformation from MGUS to myeloma. Although anemia was improved, the urticaria-like erythema with purpura relapsed and exacerbated at lower doses of DDS (50 mg/day) during the



Figure 3. Numerous urticaria-like erythema with marked hemorrhagic components relapsed on the anterior chest and abdomen at a lower dose of diaphenyl sulfone (25 mg/day).

chemotherapy. Increased doses of DDS (75 mg/day) promptly resolved the skin lesions.

DISCUSSION

The present case was characterized by non-pruritic, urticaria-like erythema with individual lesions lasting 3–5 days associated with MGUS. The histological features demonstrated diffuse neutrophilic infiltration with leukocytoclasia in the dermis. However, it was different from neutrophilic urticaria because neutrophilic urticaria histologically presents neutrophil infiltration without leukocytoclasia and vasculitis in the dermis, and it responds to antihistamine therapy as well as ordinary urticaria.⁶ Urticarial vasculitis can be excluded by the absence of vasculitis or perivascular cell infiltration, and general symptoms

such as fever, arthralgias and abdominal pain. Accordingly, the clinical and histological features of the present case were too unusual to be categorized to ordinary urticaria or classical urticarial vasculitis.

The present case revealed monoclonal gammopathy (IgA κ -type); however, there was no punched lesions of the bone, elevated serum calcium or Bence-Jones protein in the urine. The percentage of plasma cells in bone marrow was 11%, indicating borderline MGUS/myeloma. MGUS may potentially evolve into multiple myeloma. We considered the present case as MGUS evolving into IgA myeloma. The chemotherapy of melphalan and prednisolone did not inhibit the activity of the skin lesions.

The association of unusual urticarial rash and monoclonal gammopathy is known as Schnitzler's syndrome.⁷ This rare disorder consists of chronic, non-pruritic, urticarial rash with tissue neutrophilia in the dermis, intermittent fever, bone pain and the association of monoclonal IgM gammopathy. A similar association has been previously described between urticarial erythema and IgA myeloma by Zhang *et al.*⁸ They reported a Japanese patient of non-pruritic, persistent, wheal-like erythema with IgA myeloma who had no general symptoms. Histological examination revealed leukocytoclasia as well as perivascular leukocytic infiltration in the dermis.

The relationship between IgA gammopathy and the skin eruption is unknown. Complementary activation by large amounts of IgA may contribute to the development of the neutrophilic, urticaria-like erythema.⁸ From a review of published work of similar cases, including urticarial vasculitis and urticarial erythema with IgA myeloma as well as Schnitzler's syndrome, the coexistence of urticarial lesions and monoclonal gammopathy suggests a significant association between urticaria-like erythema and IgA MGUS in the present case.

The present case, as well as a case report by Zhang *et al.*,⁸ seem to be identical; slightly or non-pruritic, long-lasting, urticaria-like erythema without any general symptoms. Histological features revealed neutrophilic infiltration and leukocytoclasia without vasculitis. These clinicopathological findings might be regarded as intermediate between urticaria and urticarial vasculitis in a disease continuum.⁹

We suggest that neutrophilic, urticaria-like erythema associated with IgA MGUS and myeloma may be

regarded as a new entity. Further accumulation of similar cases is needed to clarify the relationship between urticaria-like erythema and IgA MGUS or myeloma and to establish it as a new entity.

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