

# Multiple myeloma-associated skin light chain amyloidosis: A case of misdiagnosis

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**Abstract.** The present study reports the case of a 42-year-old male with multiple myeloma (MM)-associated skin light chain amyloidosis who presented with skin purpura as the initial symptom, which was misdiagnosis as Henoch-Schönlein purpura nephritis prior to admission to the Second Xiangya Hospital (Changsha, Hunan, China). The patient presented with purpura, papules petechiae and spontaneous ecchymosis, which was located scattered around the neck, chest and limbs, accompanied by a small amount of bleeding in the conjunctival and oral mucosa, and a swollen tongue. Upon laboratory examination, the serum immunological change showed increased serum immunoglobulin G and  $\lambda$  light chain levels, and a urine Bence Jones protein level of  $>1$  g/24 h. This was accompanied with an abnormal result for immunofixation electrophoresis, and positive staining with Congo red showing apple-green birefringence in skin biopsy specimens. Thus, the patient was diagnosed with MM-associated skin amyloidosis with the initial symptom of skin purpura. Following treatment with chemotherapy consisting of prednisone and bortezomib, the skin lesions markedly improved. The present study indicates that the presentation of skin purpura in systemic amyloidosis associated with MM may be an important aid in the diagnosis and direct treatment of this disease in the clinic.

## Introduction

Multiple myeloma (MM) is a clonal malignant disease of the plasma cells, characterized by the production of a monoclonal immunoglobulin, anemia, lytic bone lesions and renal failure (1). MM is divided into symptomatic, smouldering multiple myeloma and monoclonal gammopathy of

undetermined significance (2). Myeloma-associated amyloidosis is found in 12-15% of myeloma patients, among whom, 30% exhibit asymptomatic disease (3). The amyloid substance, which originates from immunoglobulin light chains (always of  $\lambda$  type) produced by myeloma cells, is deposited in various tissues, leading to organ dysfunction, affecting the heart, liver, kidney, nervous system and gastrointestinal tract (3,4). The diagnosis of MM-associated amyloidosis is confirmed based on positive amyloid tissue staining with Congo red and immunoglobulin light chain subtyping, evidence of a monoclonal plasma cell disorder and amyloid-related organ dysfunction (5). In addition, novel techniques are available for the early diagnosis, including immunofixation electrophoresis, bone marrow core biopsies with cluster of differentiation (CD)138 staining, and detection of the levels of circulating plasma cells, cytogenetic subtypes and abnormal plasma cell immunophenotype (2,3). Recent novel agents, including lenalidomide, bortezomib and dexamethasone combination therapy, demonstrate favorable tolerability for this disease. It has been reported that MM-associated amyloidosis is an independent high-risk prognostic factor, while a similar 1-year survival rate (~80%) has been found in amyloid light-chain (AL) amyloidosis patients with or without concurrent myeloma (1,3,6). MM-associated amyloidosis has complex and diverse clinical manifestations. Occasionally, the symptoms are not typical at the early stage of this disease, resulting in misdiagnosis. Cutaneous involvement, including macroglossia, purpura, petechiae and ecchymoses, are occasionally observed as elements among a constellation of signs, but rarely as the initial manifestation of systemic amyloidosis, particularly the myeloma-associated form (5,7). The current study presents a case of skin purpura with mucosal bleeding and hematuria as the first symptom, which was later diagnosed as MM.

## Case report

A 42-year-old male initially presented on December 15, 2013, with skin purpura and recurrent episodes of hematuria that had persisted for 6 months. The patient was diagnosed with Henoch-Schönlein purpura (HSP) nephritis at a local hospital and received prednisone (30 mg per day) for 3 months. Subsequent to treatment, the symptoms of purpura and hematuria persisted, so the patient was admitted to the Second Xiangya

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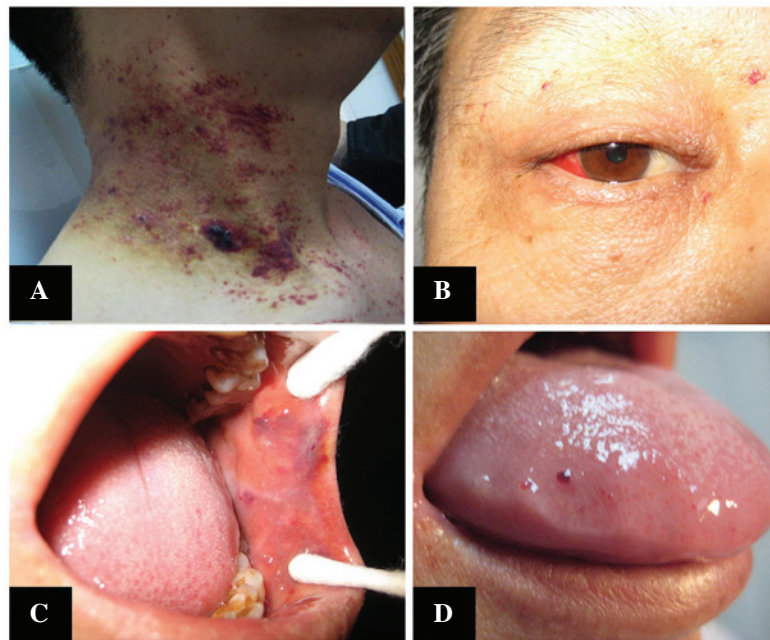


Figure 1. Distribution of skin purpura and the situation of the tongue. (A) Purpura distributed around neck. (B) Bulbar conjunctiva hemorrhage. (C) Petechia on the oral mucosa. (D) Petechia on the swollen tongue.

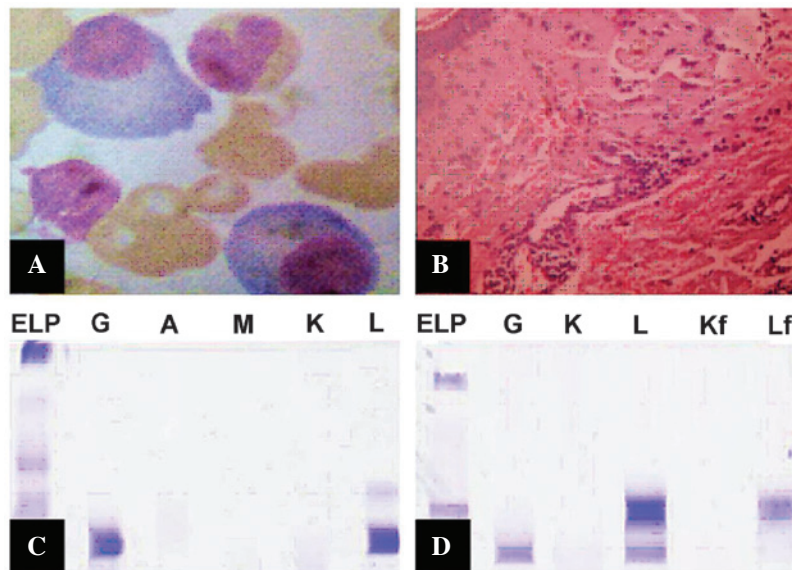


Figure 2. Laboratory test results. (A) Wright's-stained bone marrow aspirate smear showing the abnormal proliferation of plasma cells (x1,000 magnification). (B) Histopathological examination of the skin showing vascular endothelial cell proliferation and hemorrhage (hematoxylin and eosin stain; x200 magnification). Immunofixation electrophoresis of the (C) serum and (D) urine. ELP, positive immunofixation electrophoresis; Ig, immunoglobulin; G, IgG; A, IgA; M, IgM; K,  $\kappa$  light chain; L,  $\lambda$  light chain; Kf, free  $\kappa$  light chain; Lf, free  $\lambda$  light chain.

Hospital (Changsha, Hunan, China) on March 4, 2014, presenting with purpura, papules petechiae and spontaneous ecchymosis, which was located scattered around the neck, chest and limbs, accompanied by a small amount of bleeding in the conjunctival and oral mucosa, and a swollen tongue (Fig. 1). No itching, pain or oozing of the skin purpura was noted. In addition, the patient reported no dizziness, fatigue, bone pain, joint pain, hair loss, abdominal pain or fever. Blood tests to determine red blood cell (RBC), white blood cell, hemoglobin and platelet counts were normal, and renal function and the serum calcium level were also normal.

Urine analysis showed an abnormally high RBC count of 29,279.9/ $\mu$ l (normal range, 0-25/ $\mu$ l) and a negative result for protein in the urine. The coagulation tests (prothrombin time, activated partial thromboplastin time and fibrinogen level) were within normal limits. The serum albumin level was 30.9 g/l (reference range, 40-55 g/l), and tests for aspartate aminotransferase, alanine aminotransferase, total bilirubin and direct bilirubin for liver function were normal. Tests for human immunodeficiency virus, hepatitis B and hepatitis C were negative, but the erythrocyte sedimentation rate was 46 mm/h (reference range, 0-15 mm/h). Serum

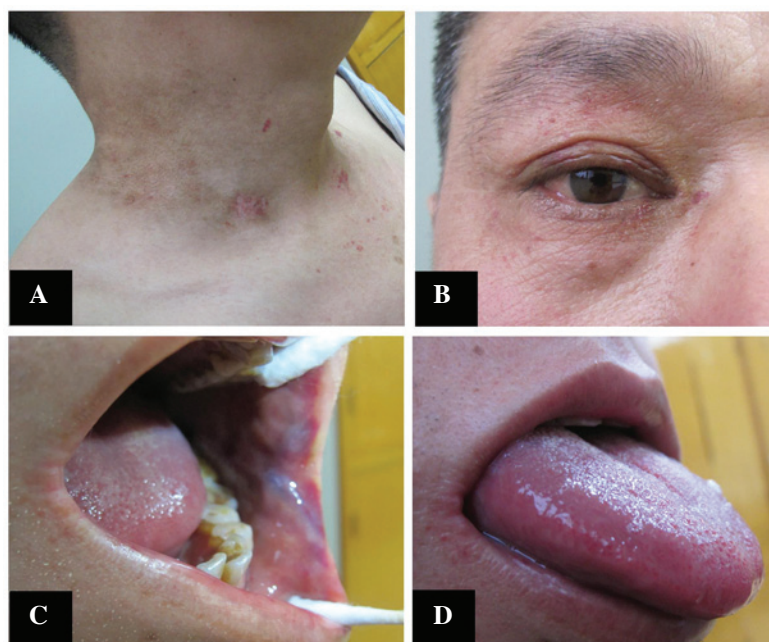


Figure 3. Changes visible on the (A) neck, (B) bulbar conjunctiva, (C) oral mucosa and (D) tongue following chemotherapy.

immunoglobulin (Ig) tests showed a high level of IgG at 21.60 g/l (reference range, 7.23-16.8 g/l), but a decreased level of IgA at 0.24 g/l (reference range, 0.69-3.82 g/l) and IgM at 0.16 g/l (reference range, 0.63-2.77 g/l). C3 and C4 were normal, while the level of serum  $\kappa$  light chain was 1.69 g/l (reference range, 5.98-13.29 g/l) and the level of  $\lambda$  light chain was 20.40 g/l (reference range, 2.80-6.65 g/l); the ratio of  $\kappa/\lambda$  was 0.08 (reference range, 1.47-2.95), and urine light chain analysis revealed a type of Bence-Jones proteinuria with a monoclonal increase in  $\lambda$  chain level (2.57 g; reference range, 0-0.02 g/l) and a normal level of  $\kappa$  chain. The  $\kappa/\lambda$  ratio was 0.02 (reference range, 1.47-2.95). In addition, serum protein electrophoresis was performed with the following results:  $\beta$ 2-microglobulin, 3.45 mg/l (reference range, 1-3 mg/l);  $\alpha$ 1 microglobulin, 2.03% (reference range, 2.8-5.6%);  $\alpha$ 2 microglobulin, 6.74% (reference range, 8.4-14.2%); and  $\gamma$  globulin, 31.3% (reference range, 11.5-25.7%). Other tests, including those for autoantibodies, such as anti-Sm anti-SSA, anti-SSB and anti-Jo-1 antibodies, were normal, as detected by an enzyme-linked immunosorbent assay kit (catalog no. 250402002-b; Changzhou Kelai Clinical Laboratory, Changzhou, Jiangsu, China) following the manufacturer's protocols. Factor VIII activity was normal. Echocardiography and X-rays of the chest, skull and pelvis were normal; bone-marrow biopsy revealed increased plasma cells accounting for 16% of the marrow cellularity. Examination of skin biopsy specimens demonstrated vascular endothelial cell proliferation in the small blood vessels, hemorrhage and a large overflow of red blood cells. In addition, positive staining with Congo red showing apple-green birefringence was observed under polarized light microscopy (Fig. 2). Furthermore, positive immunohistochemistry showed a positive reaction for  $\lambda$  light chain, and T cell markers (CD3, CD4, CD5, CD8 and CD43) were observed, as detected using rabbit polyclonal CD3 antibody (1:100 dilution; catalog no. ab5690), rabbit monoclonal CD4 antibody

(1:500 dilution; catalog no. ab133616), rabbit monoclonal CD5 antibody (1:250 dilution; catalog no. ab75877), rabbit polyclonal CD8 antibody with (1:200 dilution; catalog no. ab4055) and mouse monoclonal CD43 antibody (1:20 dilution; catalog no. ab89691) (all Abcam, Cambridge, UK), respectively. The specimens were negative for B cell marker proteins. Based on the history of plasmacytoma, the skin biopsy and the current presentation, a workup for MM [lipoarabinomannan (LAM)-IgG merge-free light chain-type]-associated skin light chain amyloidosis was initiated. Since the MM was accompanied by amyloidosis, indicating the disease was active (1), the patient was referred to an oncologist who began treatment with a VDT regimen as follows: In the induction of remission therapy, 1.3 mg/m<sup>2</sup> intravenous bortezomib on days 1, 4, 8 and 11; 20 mg daily intravenous dexamethasone on days 1, 2, 4, 5, 8, 9, 11 and 12, every 4 weeks for 4 cycles; and 100 mg thalidomide (daily). In addition, in post-remission therapy, 100 mg thalidomide (daily) was prescribed for 1 year. Following six courses of chemotherapy, the skin lesions markedly improved (Fig. 3). In January 2015, follow-up examination showed that the serum IgG level was 17.82 and the serum  $\lambda$  light chain level was 8.82 g/l, which were almost normal levels.

## Discussion

In the present case, the patient presented with skin purpura and hematuria, without proteinuria or clear bone destruction and anemia, which can be misdiagnosed as HSP nephritis. However, following treatment with prednisone for 3 months, the purpura and hematuria did not improve. HSP is a small-vessel vasculitis that affects the skin, joints, gut and kidneys. The feature of a rash in HSP presents as palpable purpuric vasculitis on the lower limbs spreading over the extensor surfaces to the buttocks and occasionally to the upper limbs, while skin lesions often occur on the lips, periorbital regions and eyelids of MM patients, accompanied

with macroglossia (8-10). Thus, the location of the purpura and skin biopsy is critical in differentiating between the diagnosis of MM-associated AL-amyloidosis and HSP. It is believed that skin purpura and lesions can also appear in autoimmune diseases and tumors, particularly in malignancies of the blood, such as MM. Therefore, further tests for serum immunological changes were performed in the present study, together with a skin biopsy. Increased serum IgG levels, as detected by serum Ig tests, increased  $\lambda$  chain levels, as detected by serum and urine light chain analysis, and a urine Bence Jones protein level of  $>1$  g/24 h was accompanied by an abnormal result for immunofixation electrophoresis, and positive staining with Congo red showing apple-green birefringence in the skin biopsy specimens. Thus the patient was diagnosed with MM-associated skin amyloidosis with the initial symptom of skin purpura.

AL amyloidosis is almost always associated with a plasma cell dyscrasia. In total, ~20% of amyloidosis is caused by MM, however, only 5-15% of patients with MM develop amyloid light chain deposits (11). A previous study reported a case of MM preceded by vascular purpura with cutaneous leukocytoclastic viscosity (12). It has also been reported that the purpura, papules, spontaneous ecchymosis and petechiae are occasionally the first and only sign of systemic amyloidosis (13). However, there have been no studies reporting MM (LAM-IgG light chain-type)-associated skin amyloidosis with skin purpura as the initial symptom. The present study discussed a case of MM-associated amyloidosis, in which the patient first presented with skin purpura and hematuria, without other systemic damage, and was thus misdiagnosed with purpura nephritis in the early stage. Furthermore, MM-associated AL amyloidosis also varies from other types of kidney disease, including chronic nephritis, where patients present with hematuria, proteinuria and anemia, which are usually observed in advanced stages of chronic nephritis. However, hypertension can also often be observed in chronic nephritis with impaired renal function. The mechanisms that cause intracutaneous bleeding may include abnormal M protein (14) and injury by tumorocellular infiltration or amyloidosis to the fragile vascular wall (15). Of course, these presentations of skin purpura are not specific to systemic amyloidosis associated with MM, but they may be an important aid to the diagnosis and direct treatment of this disease in the clinic.

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