A Case of Primary Systemic Amyloidosis and Type 2 Diabetes Presenting with Nephrotic Syndrome and Recurrent Periorbital Purpura

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ABSTRACT

The clinical manifestations of primary systemic amyloidosis with the involvement of a variety of organs, such as the kidney, heart, peripheral nervous system, liver, and so forth, are varied, complicated and nonspecific. The mucocutaneous manifestations, sometimes as the symptom in the early stages of disease, may provide an important clue for the diagnostic suspicion. Here we described a case of primary systemic amyloidosis with the history of Type 2 diabetes mellitus (T2DM) for nine years who had recurrent periorbital purpura in the initial stage, followed by nephrotic syndrome. The diagnosis was primary systemic amyloidosis finally determined by electron microscopy of renal pathology.

Keywords: Electron microscopy, nephrotic syndrome, primary systemic amyloidosis, recurrent periorbital purpura, renal biopsy, T2DM

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INTRODUCTION

Amyloidosis is a group of disorders that result from the extracellular deposition of amyloid protein in tissues or organs, leading to morphological changes and dysfunction (1, 2). Amyloidosis can be organ-limited or systemic (3), and systemic amyloidosis is classified into primary, secondary and familial. Primary systemic amyloidosis, also known as amyloid light chain (AL) amyloidosis, may be idiopathic or myeloma-associated. The clinical manifestations of systemic amyloidosis are varied depending on the tissues or organs involved, early clinical features may be nonspecific and complicated. Kidney, heart, vessels, liver, gastrointestinal tract, peripheral nerves, autonomic nervous system, skin, and respiratory system are the most commonest affected organs. Amyloid light chain amyloidosis presenting with nephrotic syndrome is difficult to be identified from other kidney diseases without renal biopsy, such as diabetic kidney disease. Skin involvement may be seen in AL amyloidosis, and between 29% and 40% of patients with systemic amyloidosis develop mucocutaneous disease (2, 4, 5). However, skin damage as the first and mainly symptom of AL amyloidosis is relatively rare.

Herein, we present a patient with Type 2 diabetes mellitus (T2DM) presenting with recurrent periorbital purpura and nephrotic syndrome was finally determined with AL amyloidosis by electron microscopy of renal pathology that illustrates the importance of electron microscopy in the diagnosis of AL amyloidosis in early stage, but also represents a good example of AL amyloidosis presented with the initial symptom of periorbital purpura often present a diagnostic challenge for the nephrologists.

CASE REPORT

A 57-year old man was diagnosed with Type 2 diabetes nine years ago. Treatment with insulin was started with a good clinical control of glucaemia. He complained of recurrent facial ecchymosis around his eyelid, mouth and subconjunctival haemorrhage for more than one year, which was aggravated when he rubbed eyes or had a bad cough. He was diagnosed with telangiectasis and received the treatment of stanozolol, prednisone and leucogen without improvement. Three months ago, he observed the moderate pitting oedema over both lower limbs. Urinalysis showed proteinuria 4+ and 24-hour protein (24 HTP) 8.26 g; liver and kidney function were normal and he was admitted to our hospital. The patient denied any familial history of cutaneous lesions and kidney diseases and he had no past medical history.

Physical examination on admission indicated that the blood pressure was normal. There was no lymphadenopathy and general physical examination of heart, lung and abdomen revealed normal findings. Skin examination revealed large bilateral periorbital purpura (Fig. 1A) and blood blisters were found under the buccalmucosa and on the tongue (Fig. 1B–C) without rash or petechiae on trunk and limbs. Moderate pitting oedema was found over both legs.

On initial laboratory testing, complete blood count, electrolyte panel and liver and renal function test were normal. Coagulation profiles, bleeding time, clotting time, blood clot retraction test, capillary fragility test and platelet count were normal. Serum albumin was 25.0 g/L. 24HTP and chemistry data upon admission are shown in Table 1.

Table 1: Results of laboratory tests during twenty days of disease course

	Day 1	Day 10	Day 20
Hb (g/L)	141	137	144
PLT ($X10^9$/L)	93	107	103
Alb (g/L)	21.0	19.4	18
PT(s)	11.5	10.1	10.9
APTT(s)	26.2	22.9	10.9
INR	1.04	0.95	0.99
PAG (ADP)	73%（69–88）		
PAG (Epi)	44.0% ↓ (78–88)		
PAG (AA)	27.0% ↓ (74–99)		
24hMTP (g/24h)	11.56	14.49	--
KAP (g/L)	4.56↓ (6.98–13.00)		
LAM (g/L)	3.34↓ (3.80–6.50)		
KAP/LAM	1.37↓ (1.50–2.56)		
NKAP (g/L)	0.9310↑ (<0.02)		
NLAM (g/L)	2.4000↑ (<0.05)		

Note: Hb, haemoglobin; PLT, platelets; Alb, albumin; PT, prothrombin time; APTT, activated partial thromboplastin time; 24hMTP, 24-hour urine protein; KAP, serum KAPPA light chain; LAM, serum LAMBDA light chain; NKAP, urine KAPPA light chain; NLAM, urine LAMBDA light chain; PAG (ADP), platelet maximum aggregation rate of 5 uM ADP, PAG (Epi), platelet maximum aggregation rate of 5 uM epinephrine; PAG (AA), platelet maximum aggregation rate of 0.5 mM arachidonic acid.

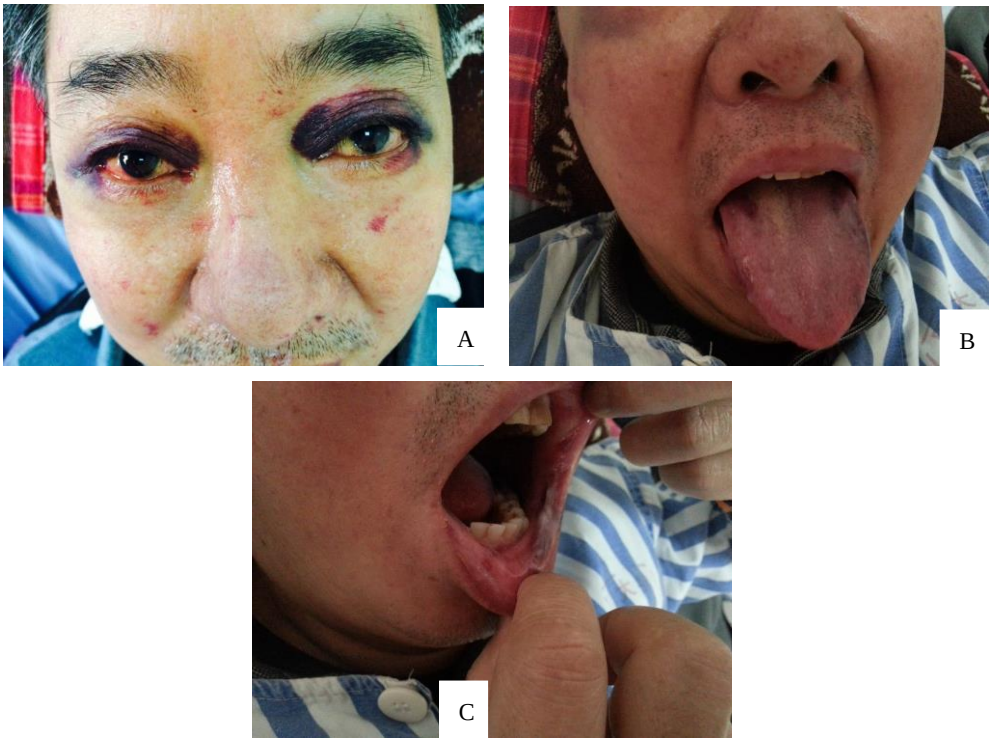


Fig: 1. (A) Facial ecchymosis and periorbital purpura (raccoon eyes); (B–C) Blood blisters were under the buccal mucosa and on the tongue.

Blood clot retraction test, antineutrophil cytoplasmic antibody (ANCA), anti-glomerular basement membrane antibody (anti-GBM), anti-dsDNA antibody, complement, immunoglobulin, and other immunological examination were not presented abnormally. Serum protein electrophoresis was negative. Urinary immunofixation electrophoresis showed the urinary monoclonal lambda (λ) light-chian and free lambda light-chian were increased.

Cardiac ultrasonography showed slightly enlarged left atriumand ventricles with normal ejection fraction rate electromyography (EMG) showed peripheral neurogenic lesion in both lower limbs. The bone marrow biopsy revealed the proliferation of bone marrow cells was normal, fundus photograph showed multiple microaneurysms, which was diagnosised diabetic retinopath.

A renal biopsy (Fig. 2) showed minor glomerular lesions and no global or segmental sclerosis. The glomerular basement membrane was vacuolar degeneration and segmental broadened. Some light staining substance seemed to be deposited in the basement membrane.

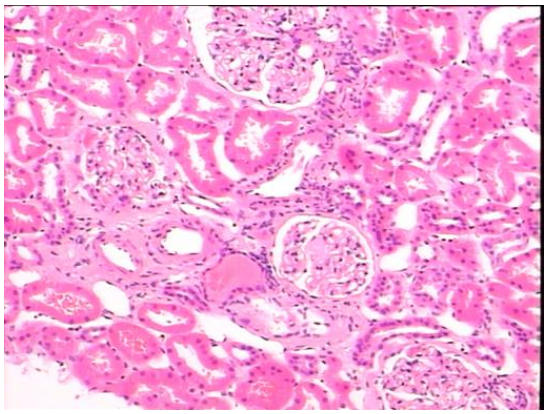
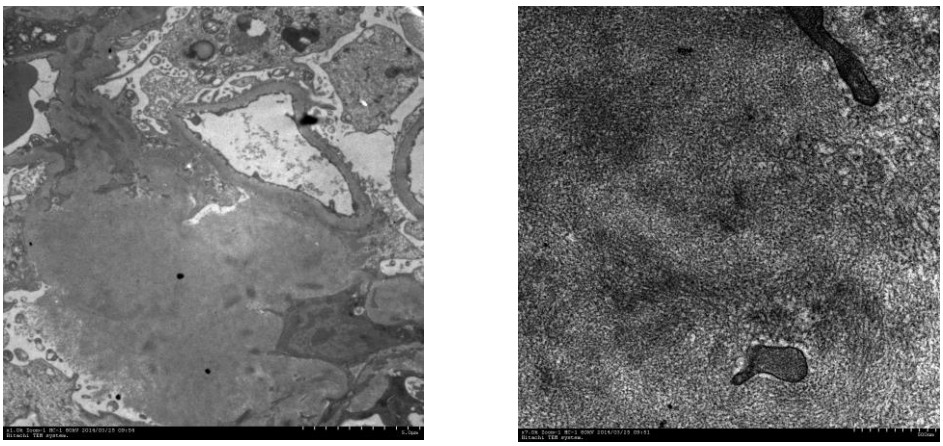


Fig: 2. Glomerulus image showing renal amyloidosis.

Congo red staining was positive in focal areas. The electron microscopic observation showed focal segmental mesangial region expanded and mesangial matrix was hyperplasia. A small amount of amyloid fibers which have a diameter of 10 to 20 nm were arranged disorderly in the mesangial area (Fig. 3 A-B). These findings were consistent with the early stage of renal amyloidosis.

Then the patient was diagnosed with T2DM and primary systemic amyloidosis, and his kidney, heart, peripheral nerves and skin were involved.



A B

Fig: 3. (A–B) Glomerulus image showing renal amyloidosis by electron microscopy observation.

DISCUSSION

While nephrotic syndrome with or without renal insufficiency, congestive cardiomyopathy, peripheral neuropathy and hepatomegaly are the most common clinical manifestations when primary systemic amyloidosis is diagnosed. Proteinuria is one of the common symptoms in the early stages of amyloidosis. Gertz *et al* (6) showed that 84% of the patients had symptoms of 24HTP over 1 g, and it was the primary cause of patient deaths. Systemic amyloidosis is usually

misdiagnosed, because clinical symptoms vary dramatically depending on the location of the amyloid protein deposition. Because our patient had a nine-year history of T2DM, for nephrologists, we must identify the proteinuria whether caused by diabetic kidney disease (DKD). Renal biopsy is necessary for making definite diagnosis of DKD, in the present study, 45.5% of patients with DM were histologically diagnosed with non-DN (7, 8). Histological analysis showed that patients with DKD had significantly more severe tubulo-interstitial and vascular damage than those with other renal diseases (9). In our patient, abnormally elevated lambda light chains and renal biopsy helped to confirm the diagnosis of primary systemic amyloidosis.

The clinical manifestations of primary systemic amyloidosis are varied, complicated and non-specific. Fatigue, weight-loss and other non-specific symptoms are manifested in the beginning of primary systemic amyloidosis (10). Usually, skin lesions as the first major symptom seen in primary systemic amyloidosis are relatively rare, whereas the skin lesions are usually atypical. Cutaneous manifestation depends on the site of amyloid protein deposition (2). Purpuric rash mainly located on the face, neck, eyelids, nose and around the orbit and mouth was the most common manifestation, which can be misdiagnosis for medical personnel unfamiliar with it.

Bilateral periorbital purpura (raccoon eyes) which is common in head trauma or domestic violence is a specific symptom of AL amyloidosis (11). Periorbital haemorrhage was caused by accumulation of amyloid protein on the subcutaneous capillary wall, which makes the capillaries fragile. There are several important factors attributing to the cause of haemorrhage. Amyloid deposition in the vessel wall and perivascular space cause amyloid angiopathy, leading to vascular fragility and the dysfunction of vasoconstriction. Because of light chains increase the

affinity with clotting factors, which can not play roles in blood coagulation. When the patient with haemorrhage who had a normal fibrinolytic system did not lack clotting factors, platelet function should be considered. Fragile capillaries can burst after some actions, like coughing, sneezing and valsalva maneuver (12–14). These lesions are also likely to occur in the skin folds, such as the eyelids, armpits, anus and so on. Meanwhile, lips and buccal mucosa also can be involved.

By haematoxylin and eosin (HE) staining, a small amount of light staining substances deposited in kidney tissue was found which was easily ignored by pathologist inexperienced and we could not distinguish between amyloidosis and early diabetic nephropathy damage clearly.

Meanwhile, the small amount of light staining substances made the Congo red staining and light chain staining to be positive difficultly. Initially, we identified the diagnosis of early-stage amyloidosis by electron microscopy. By electron microscopy, we can see the characteristic amyloid fibers. These fibers have a diameter of 10 to 20 nm, a length of 30 to 100 nm, stiff and no branches, showing irregular arrangement and these fibers are often deposited in the mesangial region, glomerular basement membrane, small blood vessel walls and renal interstitial. When severe glomerulosclerosis occurs, amyloid has been difficult to prove with Congo red staining, or in the early-stage of amyloidosis, there is a small amount of amyloid deposition in the organization. In these situations, electron microscopy observation may be the most important, or even the only pathological diagnosis based on. Therefore, the electron microscopy observation has important diagnostic value of renal amyloidosis.

The patient had been misdiagnosed for two years. In addition to massive proteinuria, the most prominent symptom of our patient is intracutaneous haemorrhage. In the course of primary

systemic amyloidosis, spontaneous or interventional treatment-related haemorrhage can be seen in nearly 1/3 of patients and the purpuric rash is more commonly seen. Unexplained recurrent purpura, petechiae prompt the possibility of systemic amyloidosis. With a special stained histopathological examination, the correct diagnosis can be made earlier. Pathological diagnosis is considered the gold standard, but after kidney or liver biopsy, individual patients may have fatal massive haemorrhage. Therefore, we can consider abdominal subcutaneous fat, salivary glands, rectal biopsy which are less risky as the first examination.

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