



Case Report

A Case Report and Review of the Literature: A Case of AA Systemic Amyloidosis Presenting as Abdominal Mass and Multisystem Dysfunction

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Abstract

Gastrointestinal mass lesions involvement in AA amyloidosis is a rare condition, and the diagnosis of gastrointestinal amyloidosis presenting as a mass is often delayed and underdiagnosed. Here, we report the case of a 62-year-old woman who was referred to our department for nephritic syndrome and renal dysfunction. She reported a progressive anemia and numbness of limbs 4 years previously, loss of appetite and weight loss for 1 year. Her medical history included pulmonary tuberculosis and thoracic vertebrae tuberculosis. The interesting thing is that a mass in her left lower abdomen was found for 1 year, and her diagnosis was considered as a digestive system tumor for this mass. But through pathological examination of renal and the abdominal mass biopsies, she was diagnosed as AA systemic amyloidosis finally. In the condition of absence tumor and autoimmune disease, the AA amyloidosis in this patient may be secondary to tuberculosis infection. The clinical manifestations of systemic amyloidosis are varied and lack of specificity, therefore it is often misdiagnosed or missed. In addition to typical symptoms of multiple systemic dysfunction, the most special thing in this patient is the abdominal lump with amyloid substance in. This is a rare clinical manifestation, which is easily to be misdiagnosed as a tumor and delaying treatment. Therefore, tissue biopsy for these patients timely, through pathology and special staining, can contribute to early diagnosis of systemic amyloidosis, and reduce and delay the occurrence of complications of this disease.

Keywords: Abdominal mass; A 62-year-old women; Amyloidosis; Tuberculosis

Introduction

Systemic amyloidosis caused by extracellular accumulation of amyloid, which can involve varied organs and tissues, and damaging their structure and function. This protein was already discovered by some scholars in 1985, and it cannot be absorbed because of the abnormal folding into a fibrous structure containing β fold [1]. Amyloid can involve multiple systems and can also involve local tissues, therefore, the clinical manifestations of diversity and lack of specificity. So, it is difficult to diagnose this disease only by clinical manifestation. However, this protein shows a specific expression in Congo red staining, which will be red under the light microscope and be apple green under polarized light after stained with Congo red. Therefore, Congo red dye is a simple and effective methods to recognize amyloidosis [2]. At present, amyloidosis is mainly divided into 6 types in clinical,

including primary amyloidosis (AL), secondary amyloidosis (AA), hereditary amyloidosis, dialysis-related amyloidosis, organ-specific amyloidosis and senile amyloidosis [1]. Among them, AL amyloidosis is the most common type [3], it often occurs in patients with multiple myeloma and primary amyloidosis [4]. And AA amyloidosis is less common, which is caused by increased serum amyloid A(SAA), an acute-phase protein response to inflammation and also contain the β -folding lamellar structure, deposition in tissues [1,4,5].

AA amyloidosis is often secondary to some autoimmune disease, chronic inflammation or tumor [6-9], tuberculosis as a chronic inflammation can also cause AA amyloidosis, especially in developing country [10,11]. The incubation period, from Mycobacterium tuberculosis infection to appear the symptoms of amyloidosis in the corresponding tissues and organs, can be as short as several weeks or years [11]. Through retrospective analysis of clinical and pathological datas from this case of AA amyloidosis treated in our hospital, we find the special things is

that this patient had a history of tuberculosis, next she was found to have a mass in her left lower abdomen for a long diarrhoea, and then misdiagnosed as tumour, but finally diagnosed as AA amyloidosis. This mass is very uncommon, and there are no similar reports have been reported in the literature. For that reason, we analyzed and summarized this case based on literature, aiming at improving the early prevention and treatment of AA amyloidosis.

Case Presentation

A 62-year-old female, a Chinese, was admitted to department of nephrology, Xiangya Hospital, Central South University on May 16, 2016. Her chief complaint was numbness of limbs and anemia for 4 years, anorexia for 1 year and edema of both lower extremities for 8 months.

She began to have limbs numbness in 2012, but she did not go to the hospital until 4 years later. After examination, finding mild small cell hypopigmentation anemia (Hb 94g/L) and increased platelet and normal number of white blood cells in her blood examination, serum albumin was decreased(30.7g/L) and globulin was elevated(56.5g/L), and electromyogram (EMG) showed peripheral neuropathy. Then she was treated with Vitamin B1, vitamin B6, Mecobalamin Tablets and Escitalopram, but there is no significant improvement in symptoms after treatment. The patient had anorexia and weak, nausea and occasional vomiting after eating, alternation of diarrhoea and constipation since February 2015. After examination, showing moderate small cell hypopigmentation anemia (Hb71g/L), blood albumin was significantly lower than before(17.5g/L) and globulin was increased(59.6g/L), blood light chain showed immunoglobulin κ was 19.1g/L and immunoglobulin λ was 11.5g/L and κ/λ ratio was 1.66, immunofixation electrophoresis was negative, fecal occult blood test was positive, the examination of rheumatism and lupus erythematosus were both negative. Gastric mucosal congestion and swelling under the gastroscopy. Colonoscopy found intestinal mucosal congestion and swelling, texture crisp and easy to touch bleeding. Abdominal computerized tomographic scanning(CT) found a lump (size was 60×47mm) in her left lower abdomen, and it is not clear boundaries with the surrounding bowel, considered it might be a low grade malignant tumor. At that time, the doctor advised her to do a further examination, but the patient refused. She began to have mild edema in the lower limbs from 2016, then she came to our hospital for an outpatient clinic. The examination showed elevated serum creatinine (fluctuate between 250 $\mu\text{mol/l}$ to 280 $\mu\text{mol/l}$), 24 hours urinary albumin was 5.92 g, the bone marrow cytology examination showed active bone marrow proliferation and iron deficiency. Finally, she was admitted to our department of medical treatment in August 2016. Since 2014, her weight has fallen by 5 kilograms. The patient was diagnosed with pulmonary tuberculosis and tuberculosis of thoracic vertebra in June 2011, and had taken anti-tuberculosis treatment for 1 year.

She has reviewed after 1 years of treatment of tuberculosis, the results of examination are normal. Physical examination revealed normal body temperature, normal breathing, normal pulse and normal blood pressure, short and thin, anemia appearance, mild pitting edema of lower limbs, the sensation of the extremities is decreased, the muscle strength and muscle tension of limbs are normal, and the nerve reflex is normal.

The laboratory examination data of the patient in our hospital were as follows. Blood routine examination showed white blood cell $4.7 \times 10^9/\text{L}$, red blood cell $2.56 \times 10^{12}/\text{L}$, haemoglobin 56g/L, platelet $605 \times 10^9/\text{L}$. Iron metabolism examination revealed ferritin was 29.9 $\mu\text{g}/\text{L}$, serum iron was 1.8 $\mu\text{mol}/\text{L}$, serum total iron binding capacity was 33.8 $\mu\text{mol}/\text{L}$, transferrin was 1.34g/L and transferrin saturation was 5.33%. Serum albumin was 18.3g/L, globulin 44.8g/L, creatinine 258 $\mu\text{mol}/\text{L}$ (normal value 53-132.6 $\mu\text{mol}/\text{L}$), blood glucose, aminotransferase and myocardial enzymes were all normal. 24-hour urine protein quantitative was 4.09g. Serum light chain test showed that immunoglobulin κ was 5.67g/L and immunoglobulin λ was 4.08g/L and κ/λ ratio was 1.39. Immuno fixed electrophoresis of blood and urine were negative. Bone marrow cytology examination showed bone marrow proliferation was active and without abnormal proliferation of plasma cells. C reactive protein was 42.3mg/L, and erythrocyte sedimentation rate was 120mm/h. CA 19-9 was 6.52KU/L. The examinations of rheumatism and lupus, autoantibody spectrum, immunization test, PPD skin test, T-SPOT and tuberculosis antibody, hepatitis B, hepatitis C and syphilis were all negative. Renal ultrasonography showed the size of double kidneys(left was 91×45mm, right was 97×47mm) were normal and parenchyma disease (level B). Abdominal ultrasonography revealed a substantial and heterogeneous mass (47×32×38mm) in her left retroperitoneal, and retroperitoneal multiple lymph node enlargement (the size of the biggest one is 13×7mm). Furtherly, abdominal CT still revealed a lump (the size was 5.1×3.4cm) in her left lower abdomen (Figure 1). Colonoscopy showed that the mucosa of sigmoid colon and rectum was hyperemia and edema, and vascular texture was disorder, the diagnosis was erosive colitis. Then she took the renal biopsy, the diagnosis of electron microscopy was amyloidosis nephropathy maybe (Figure 2). In HE staining under light microscopy, the volume of the glomeruli is significantly increased, a large number of unstructured mass in red dye were deposited in glomerular mesangial area and capillary wall, and no cell proliferation (Figure 3). The Congo red stain in renal tissue was positive (Figure 4), the result of oxidizing Congo red stain was negative (Figure 5). As AA amyloidosis can caused by chronic inflammation and tumor, in order to clarify the reason why the patient get diarrhea and relationship between the abdominal mass and amyloidosis, we made a colonic mucosal biopsy for the patient. Then colonic mucosal pathological result was chronic inflammation of rectal mucosa with deposition of amyloid in HE staining (Figure 6), and

the Congo red staining was positive (Figure 7). Then, in order to define the nature of the abdominal mass, she made a biopsy of it under the guidance of B ultrasound, and the pathological examination revealed that a large number of plasma cells and lymphocytes infiltration, with calcification and suspected amyloidosis under the light microscope (Figure 8), and the Congo red staining was positive (Figure 9). Next, to determine the type of amyloidosis, we examined the renal biopsy tissues using immunofluorescence to test amyloid A, finding all of the tissue was positive (Figure 10). Based on the above examination data, the diagnosis of AA systemic amyloidosis is clear, and the abdominal mass and multiple system symptoms are all caused by this disease.



Figure 1: Abdominal CT. There is an oval mass in her left lower abdomen (the white arrow show), its size is 5.1×3.4cm, its boundary is clear, its density is roughly well-distributed, and there are some scattered calcification in it, it is obvious enhancement after enhancement, the CT value of plain scan is 49HU, the CT value after enhancement is 104HU.

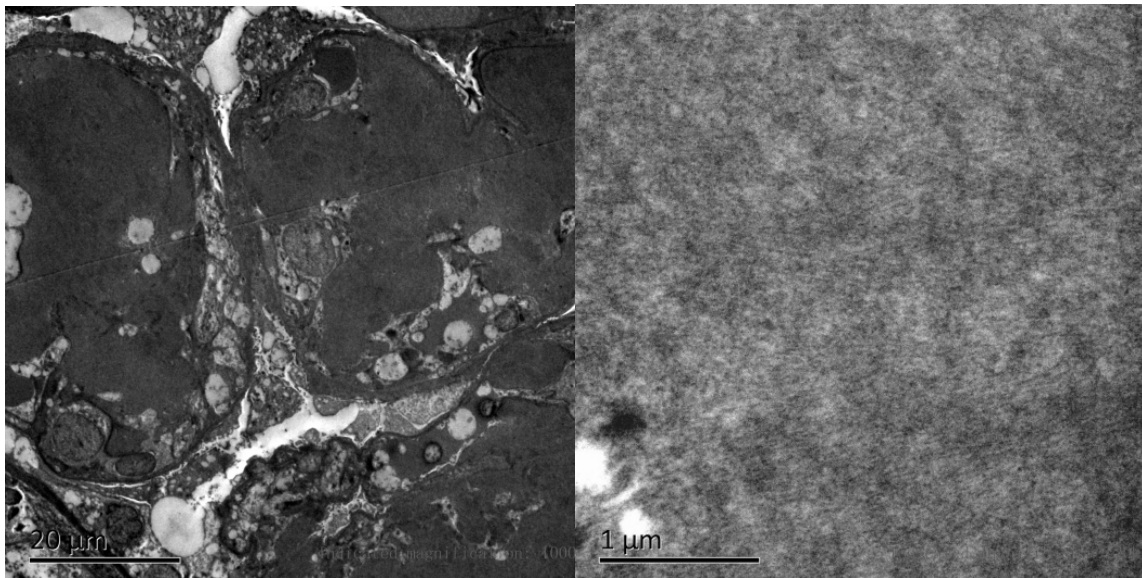


Figure 2: The electron microscopy of renal tissue. There are massive clumps of filamentous (may be amylin, the diameter is about 10nm) in glomerular mesangial matrix and segmental basement membrane, the matrix is broadening.

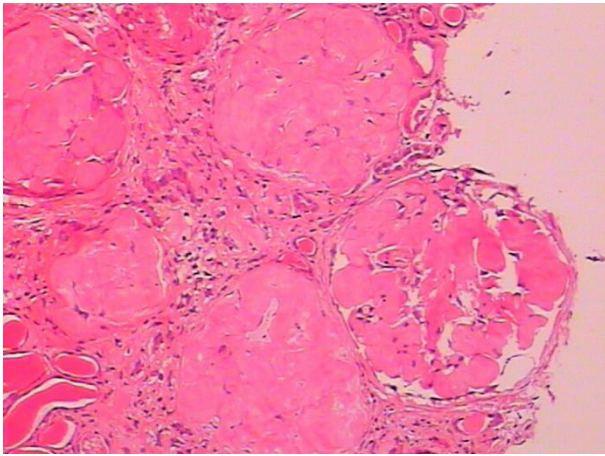


Figure 3: The renal tissue section with HE staining of nodular glomerulosclerosis.

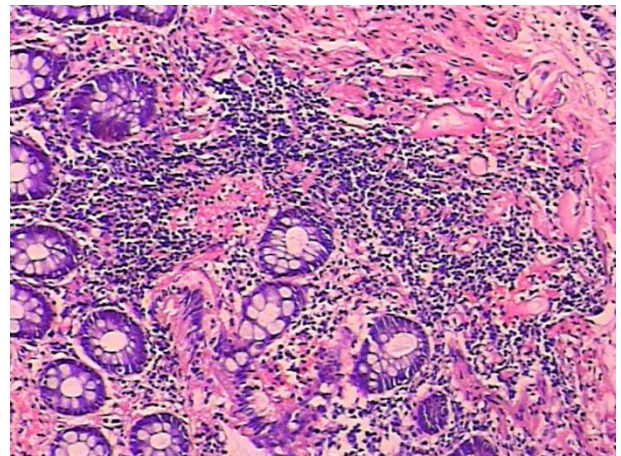


Figure 6: HE staining of colon mucosa biopsy section. There are a lot of inflammatory cell infiltration and amyloid deposition in rectal mucosa.

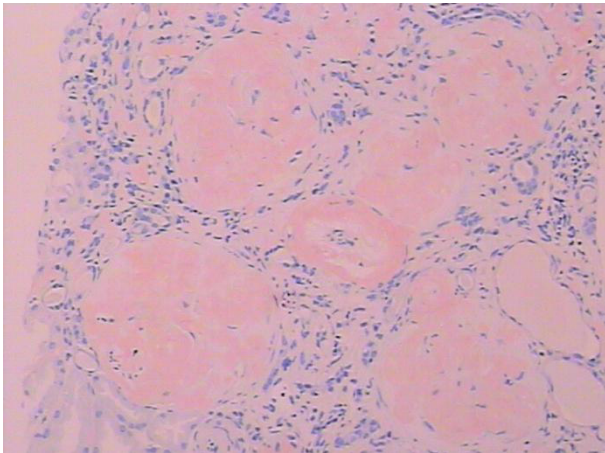


Figure 4: The renal tissue section with Congo red staining is positive.

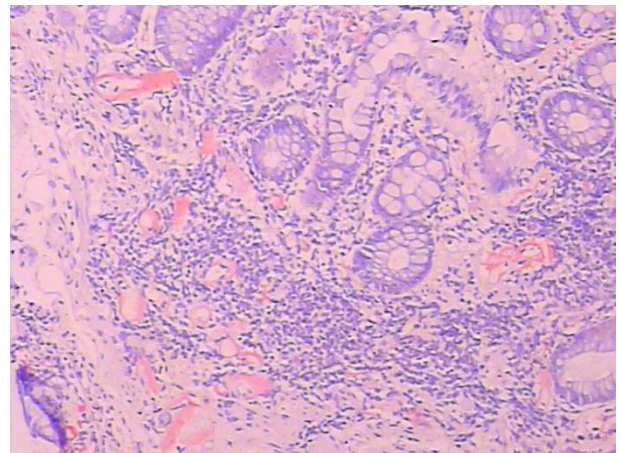


Figure 7: The rectal mucosa with Congo red staining is positive.

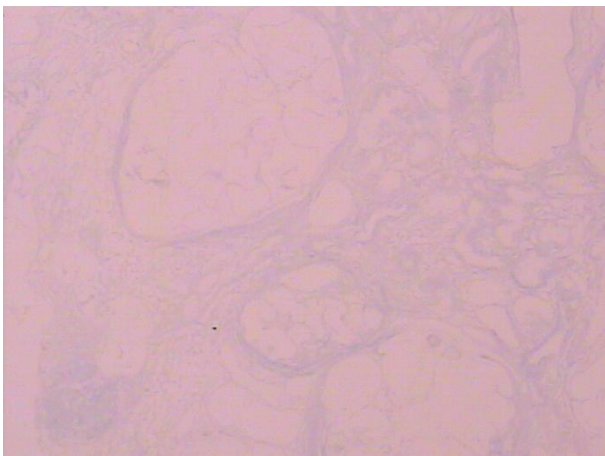


Figure 5: Pathological section of renal biopsy to oxidize Congo red staining, when pre-treatment in the renal section by potassium permanganate, the Congo red staining is negative.

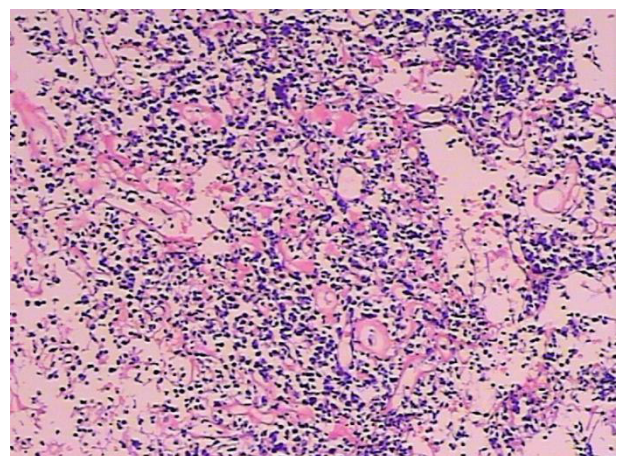


Figure 8: The mass tissue section with HE staining. There are a large number of plasma cells and lymphocytes infiltration, with calcification and suspected amyloidosis under the light microscope.

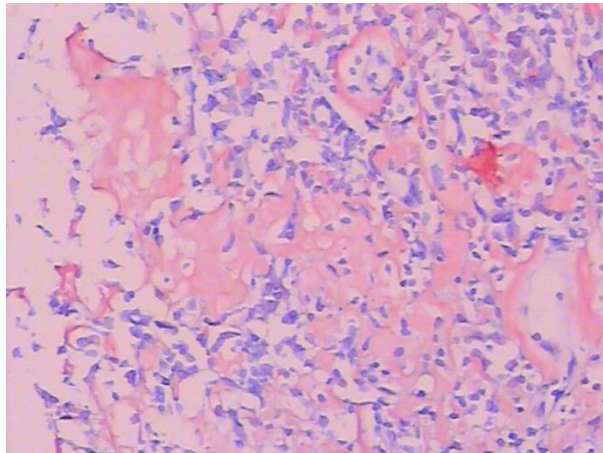


Figure 9: The mass tissue section with Congo red staining is positive.

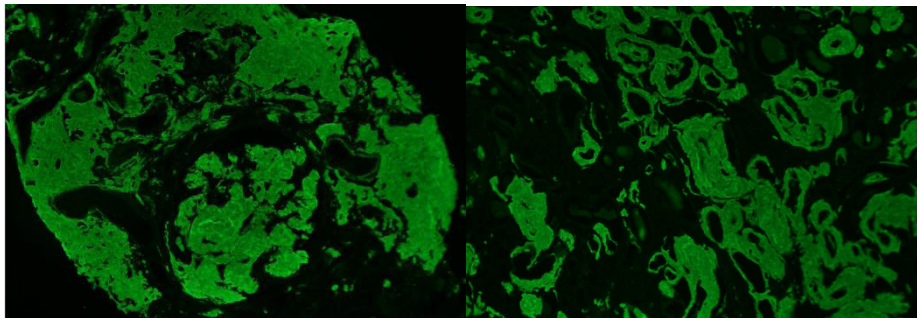


Figure 10: Immunofluorescence staining of amyloid protein A (green) is positive in pathological sections of renal biopsy.

We reviewed the patient's medical history, she had tuberculosis of the lungs and thoracic vertebrae 5 years ago, after diagnosed as tuberculosis for 1 year she appeared numbness of limbs and anemia, and appearance of gastrointestinal symptoms such as nausea, vomiting, diarrhoea and constipation appeared gradually 4 year later, and showed renal structural and functional abnormalities 5 years later. The patient was diagnosed as AA systemic amyloidosis by biopsy of renal tissue, colonic mucosa and abdominal mass, excluded the tumor, and she has no symptoms of autoimmune diseases and the autoantibodies are all negative, so excluded autoimmune diseases also, therefore combined with her medical history of tuberculosis before her illness, we thought that AA systemic amyloidosis is the most likely cause by tuberculosis. The patient had completed tuberculosis related examination on admission, and the results were all normal and had no evidence showed abortive tuberculosis. Therefore, after the diagnosis was clear, the patient was treated with colchicine and other symptomatic treatment, like compensating albumin, correcting anemia, and neurotrophic therapy. After treatment, the patient with edema, anemia and numbness of limbs symptoms gradually improved. Her renal function also improved and proteinuria obviously decreased.

Discussion

Amyloidosis is a rare disease, and its morbidity is 0.005%-0.009% per year worldwide [10]. Although AL amyloidosis is the most common type, AA amyloidosis is also not rare in developing countries. The common cause of AA amyloidosis is autoimmune disease, such as rheumatoid arthritis, ankylosing spondylitis, inflammatory bowel disease, etc. But in developing countries, AA amyloidosis secondary to tuberculosis is also a common cause [10,11]. At present, effective treatment for tuberculosis has been achieved, so tuberculosis induced amyloidosis is also gradually decreasing, however, in India, this is still the most common cause of secondary amyloidosis [12]. Even in Turkey, secondary amyloidosis caused by tuberculosis accounted for 10% [13]. Secondary amyloidosis caused by tuberculosis, symptoms of amyloidosis can occur as early as 2-4 weeks after tuberculosis infection and can also occur after some years of tuberculosis infection [11]. This patient's earliest symptom was limb numbness occurred one year after the diagnosis of tuberculosis, we deduced that amyloidosis was first involved peripheral nerve, and then gradually involved in the digestive and urinary systems to appear

symptoms of amyloidosis, therefore, the most likely primary disease is pulmonary and thoracic tuberculosis infection.

AA amyloidosis is caused by increased serum amyloid A, an acute-phase protein response to inflammation, which can be deposited in extracellular tissue and cause different clinical manifestations. Kidney is the most commonly involved organ in amyloidosis, and often manifested as massive proteinuria or even nephrotic syndrome, renal insufficiency, and it is very unusual that AA amyloidosis doesn't involve the kidney [3]. In some rare cases, it can appear renal diabetes insipidus or Fanconi syndrome, due to amyloid deposition in the peri-collecting duct tissue or proximal tubular cells [2]. Thus, patients with chronic inflammation appears to have massive proteinuria should be suspected of having AA amyloidosis. Liver and spleen are also frequently involved, and often expressed as hepatosplenomegaly, jaundice, anorexia and steatorrhea [14]. Amyloidosis involving the digestive tract is also common, and can present as macroglossia, gastrointestinal dysfunction, haemorrhage of digestive tract and malabsorption syndrome, but the common symptoms are diarrhoea, marasmus and anorexia. Amyloidosis can also involve nervous system to cause peripheral neuropathy and abnormal sensation [3,14,15]. Infiltration of soft tissue by amyloid can appear carpal tunnel syndrome, macroglossia, enlargement of the salivary glands, submandibular soft-tissue infiltration and enlargement of the salivary glands [3]. The heart is also the most common involved organ, and it can cause heart failure and arrhythmia, which is the common cause of death in amyloidosis, but in AA amyloidosis heart is rarely involve [3].

Organ dysfunction caused by amyloidosis tends to be irreversible, therefore it is important to detection and treatment in an early time to prevention and control of this disease. But the clinical manifestation of amyloidosis is various and lack of specificity, so early identification of suspicious patients with amyloidosis is very important. For the elderly are a high risk group for amyloidosis, heart and kidney are the two most common organs of amyloidosis involvement, if there is heart failure, arrhythmia, proteinuria or renal insufficiency for unknown reasons, we should consider the possibility of amyloidosis. Finding evidence about deposition of amyloid is important, which often need tissue biopsy to prove, such as renal biopsy, skin biopsy, fat biopsy, rectal biopsy, ect. Because of common staining is easy to be misdiagnosed and missed diagnosis, it is necessary to further clarify the pathological section of suspicious patients by Congo red staining and electron microscopy. When pretreatment in the section by potassium permanganate, the Congo red staining is negative in AA amyloidosis, therefore oxidized Congo red staining can preliminarily distinguish AA amyloidosis and AL amyloidosis, but the accurate classification can be made by immunofluorescence or immunohistochemistry [16]. Nowadays, there is also a new technique to help sensitively diagnose and type amyloidosis,

especially in problematic cases, it is the LMD/MS technique or laser microdissection combined with mass spectrometry [3,9,17]. Accurate typing can find the direction of primary disease, and guide the clinical treatment of amyloidosis [3,4].

Currently there is no special treatment for amyloidosis, for AA amyloidosis, mainly using the treatment of primary diseases and reduce SAA production, supportive treatment for damaged organs, so as to achieve the purpose of delaying the progress of the disease. For patients with tuberculosis treatment with anti-tuberculosis therapy, and Tumor Necrosis Factor(TNF) inhibitor for rheumatological disorder, Interleukin-1(IL-1) inhibitor for auto-inflammatory disorder can improve the outcome [3,18]. In some patients with AA amyloidosis that underlying inflammatory disorder can't be characterised, can response to specific inhibition of interleukin (IL) 1 or IL-6 [3]. It is reported that eprodisate, a negatively charged sulfonated small molecular weight substances, can inhibit formation of amyloid A, and has been used in phase 3 [3]. Colchicine is effective for patients with familial Mediterranean Fever(FMF) and AA amyloidosis secondary to FMF, so it is usually used for these patients [19,20]. However, AA amyloidosis caused by other reasons treatment with colchicine also received good effect [21,22]. So, we treated this patient with colchicine and other symptomatic treatment, finally her symptoms and renal function have improved, and proteinuria has decreased obviously.

Patients with amyloidosis can have various clinical manifestations, the patient in this case not only presented typical symptoms of kidney, digestive tract, blood system and peripheral nerve involvement, but also finding a lump in her abdomen which made up of amyloid, a very rare manifestation, which is easy to misdiagnose as a tumor and delay the patient's prompt treatment. Amyloidosis involves the heart can cause sudden death in serious circumstances, and involves kidney can cause kidney dysfunction, and these lesions are often irreversible, therefore, the delay in diagnosis and treatment is serious and aggravates the burden of treatment. So, in clinical work, we should be vigilant to various clinical symptoms and special manifestations presented by amyloidosis. Especially in the process of receiving elderly patients for treatment, if the diagnosis is uncertain, it is very important to make a biopsy or add Congo red staining to exclude amyloidosis. This article reports this rare case of amyloidosis to provide reference for clinical workers.

Compliance with Ethical Standards

Funding: This study was funded by National Natural Science Foundation of China (81270786).

Conflict of Interest: All authors declare that they have no conflict of interest.

Ethical approval: All procedures performed in studies involving human participants were in accordance with the ethical standards

of the ethics committees of Xiangya Hospital of Central South University and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent: Informed consent was obtained from the participant included in the study.

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