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CASE REPORT

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A patient with Behcet's disease and IgA nephropathy in China

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Abstract

Background Behcet's disease (BD) is an inflammatory disorder of unknown cause that is characterized by recurrent oral aphthous ulcers, genital ulcers, uveitis, and skin lesions. Local vasculitis can cause damage to the visceral system, but it is rare in kidney patients, especially those with IgA nephropathy (IgAN). In China, a small number of related cases have been reported. Here we present a case of co-occurrence of BD and IgAN.

Case presentation : An 18-year-old female who presented with a history of recurrent oral ulcers was found ten years ago. Four years later, the patient presented with reddish nodules on the skin of both lower limbs and then presented with vulvar ulcers. This patient was clinically diagnosed with Behcet's disease after left calf skin biopsy and presented severe proteinuria and hematuria during this period. IgAN was diagnosed after percutaneous renal biopsy. The patient was treated with hormonal, anti-inflammatory, immunomodulatory, kidney protective, and protein-lowering urine agents. After 3 years of follow-up, the patient reappears oral ulcers, reddish nodules on the skin of both lower limbs and renal dysfunction.

Conclusions BD is less common in China and is clinically prone to missed diagnosis and misdiagnosis. BD with IgAN is rarer. We should regularly pay attention to the routine urine and renal function of BD patients for early detection and treatment and to prevent further progression of the disease.

Keywords Behcet's disease, IgA nephropathy, Biopsy, Renal

Background

The etiology of systemic variant vasculitis in Behcet's disease (BD) is unknown and involves the skin, mucous membranes, joints, eyes, arteries, veins, nervous system or gastrointestinal system [1]. Local vasculitis can cause lesions of the visceral system, but kidney sufferers are rare, especially with IgA nephropathy (IgAN). Previous research showed that [2] glomerulonephritis or focal proliferative glomerulonephritis, and amyloidosis seem to be the most common type of renal lesion in BD, which includes minimal change disease, proliferative glomerulonephritis, rapidly crescentic glomerulonephritis, renal amyloidosis and IgAN. Despite there is still controversy over whether IgAN is primary or secondary in patients with BD, the co-occurrence of BD and IgAN is of interest. Nephrotic syndrome secondary to amyloidosis has been documented in recent years. The co-occurrence of BD and IgAN has been reported in only a few patients. This article reports 1 patient with co-occurrence of BD and IgAN. Combined with a previous literature review, this case will further improve the clinical understanding of this disease.

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Case presentation

An 18-year-old female who presented with a history of recurrent oral ulcers was found ten years ago (Fig. 1A and B). Four years later, the patient presented with reddish nodules on the skin of both lower limbs (Fig. 1C). The patient subsequently presented with vulvar ulcers. Left calf skin biopsy was conducted at another hospital. The left calf skin biopsy showed the dilation and congestion of blood vessels in the superficial to middle layers of the dermis, red blood cell exudation. Some blood vessel walls become thickened and damaged, lymphocytes and tissue cells also produce an infiltrate around blood vessels (Fig. 1D). Immunofluorescence staining for IgA (Fig. 1E) and Congo red staining revealed negative staining in the skin (Fig. 1F). This patient was clinically diagnosed with BD and presented severe proteinuria and hematuria during this period. At the same time, urinalysis showed urinary protein +++ and urine occult blood ++++ from external hospital.

Then, the patient sought medical attention at our hospital. Laboratory examination such as the urine and microscopic analysis, urine microprotein test, and kidney function tests were conducted (Table 1). Urinalysis showed protein++and blood+++, and the sediment contained 25 white blood cells per microliter, 33 red blood cells per microliter. Laboratory studies revealed the following results: urinary transferrin, 14.600 mg/L; urine α1 microglobulin, <6.35 mg/L; urine β2 microglobulin, <0.183 mg/L; trace albumin, >250 mg/L; urea, 4.18 mmol/L; Creatinine 55μmol/L; Urea/creatinine ratio, 18.82; glomerular filtration rate, 131 ml/min/1.73m^2.

At the same time, kidney puncture biopsy was performed, and 23 glomeruli were found (Fig. 2A). Light microscopy revealed cellular crescents in three glomeruli including 1 small cellular crescent and 2 small fibrous-cellular crescents. Otherwise, 1 glomerular show necrotizing lesions: disrupted capillary wall, fibrinoid deposit, 5 glomeruli arterioles reveal leucocytes infiltration that consist of a few lymphocytes, plasma cells and individual neutrophils. Tubules are intact with absence of atrophy, and no associated interstitial fibrosis. Interlobular arterioles show vasculitis lesion. Congo red staining is negative, renal amyloidosis is not observed (Fig. 2B). Periodic acid-silver methenamine (PASM) staining indicated segmental proliferation of mesangial cells and increase of mesangial matrices accompanied by a small cellular crescent (Fig. 2C). CD3 immunostaining showed vasculitic lesion of interlobular arterioles (a few T lymphocytes infiltration in the interlobular arterioles) (Fig. 2D). Immunofluorescence was positive for C3c (2+), IgA (2+), IgM (segmental 2+), while C1q, Fibrin, IgG are negative, in all 23 glomeruli (Fig. 2E and data not shown). Electron microscopy indicated well-delineated mesangial electron dense deposits (EDDs) are identified, and no EDDs are seen in the glomerular capillary basement membrane. Among the 23 glomeruli, 2 glomeruli exhibit normal cellularity and intact capillary tufts architecture. The epithelial cells show foot processes fusion. Based on the above facts, the final pathological diagnosis was IgAN (local hyperproliferative glomerulonephritis). Oxford Classification: M0E1S0T0C1.

The patient was treated with hormonal, anti-inflammatory, immunomodulatory, kidney protection, and protein-lowering urine agents. After 3 years of follow-up, the patient reappears oral ulcers, reddish nodules on the skin of both lower limbs and abnormal results of urine routine analysis renal dysfunction. Routine blood, urine, liver and kidney function tests were performed during this period. (Table 2).

Discussion and conclusions

The incidence of BD is regional, with a high incidence in Turkey, Iran, Iraq and other places along the ancient Silk Road. China is also a country with a high incidence of BD, but research on BD in China is lacking. Professor Guan began to pay attention to BD and conducted clinical research more than 20 years ago. They summarized its epidemiological characteristics, developed a series of concepts from diagnostic processes and treatment strategies to clinical prognosis, and redefined BD. BD is a form of vasculitis of unknown etiology is characterized by a variety of clinical manifestations and usually affects young adults. Oral ulcers is the most common first symptom, and gradually accompanied by vulvar ulcers, nodular erythema and other skin mucosal diseases, selective ophthalmitis, intestinal ulcers, aortic valve regurgitation, venous thrombosis, aneurysms, arterial stenosis, arthritis and hemocytopenia.

BD was first classified into 8 clinical phenotypes: skin mucosal BD, eye BD, intestinal BD, heart BD, blood vessel BD, nerve BD, blood BD and joint BD [3]. The patients have repeated oral ulcers as the first symptom, followed by pale red nodules on the skin of both lower limbs, accompanied by pain in both the knee joints and ankles, followed by vulvar ulcers. In this case, the left calf skin biopsy showed that the dilation and congestion of blood vessels in the superficial to middle layers of the dermis, leading to red blood cell exudation. Some blood vessel walls become thickened and damaged, lymphocytes and tissue cells also produce an infiltrate around blood vessels. The basic characteristic of BD is vasculitis. So, the diagnosis of BD of this case is accurate.

According to the diagnostic/classification criteria of ICBD for BD [4], a score≥4 indicates BD. The ICBD for this patient was 5, so the clinical diagnosis was BD. During this period, the patient developed severe proteinuria

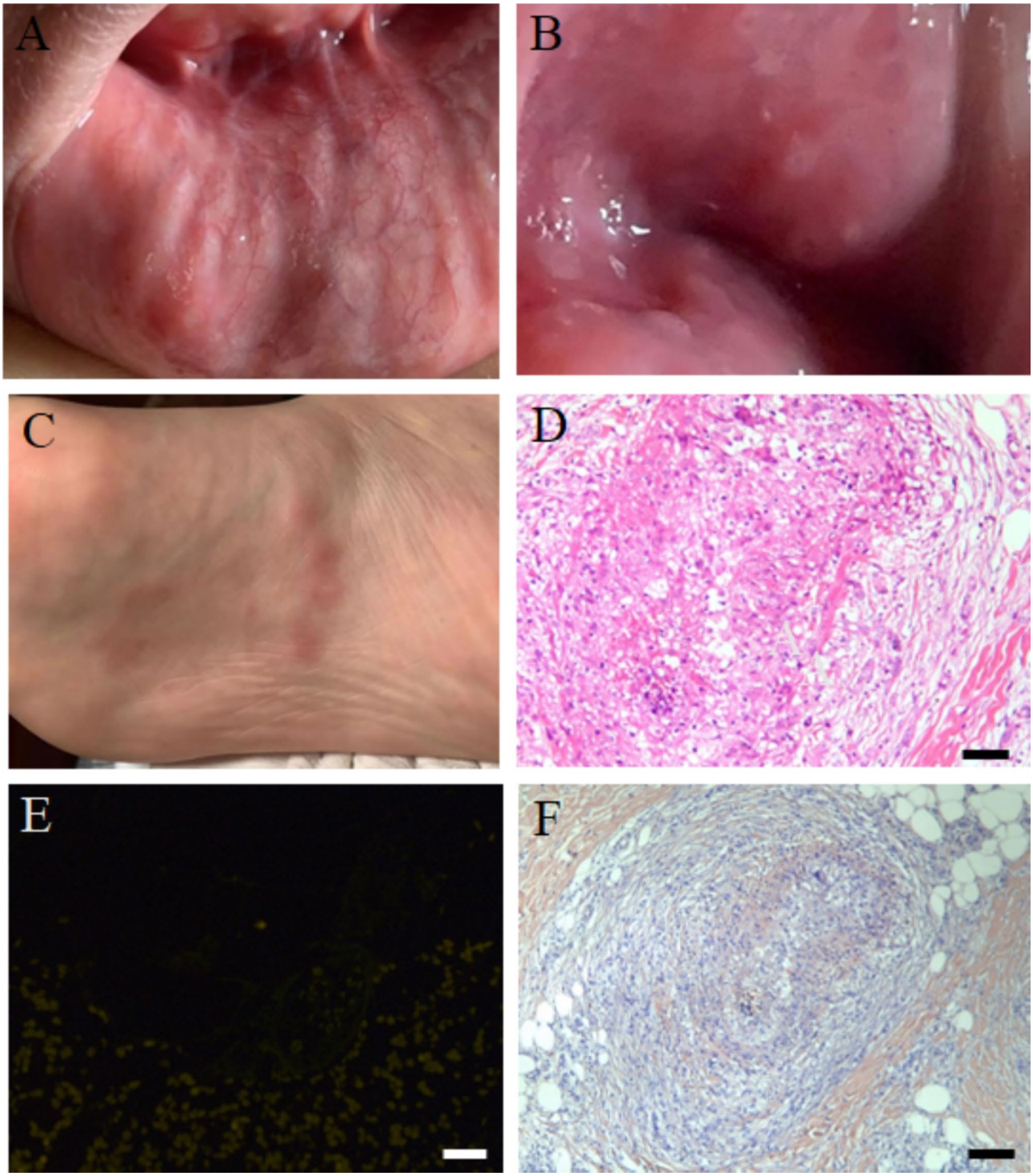

Fig. 1 Findings of physical examination and left calf skin biopsy. (**A**) Ulcers on the lower lip. (**B**) Ulcers on the buccal mucosa. (**C**) Reddish nodules on the skin in the sole of the foot. H&E staining (**D**), immunofluorescence staining for IgA (**E**) and Congo red staining (**F**) of left calf skin biopsy. The left calf skin biopsy showed the dilation and congestion of blood vessels in the superficial to middle layers of the dermis, red blood cell exudation. Some blood vessel walls become thickened and damaged, lymphocytes and tissue cells also produce an infiltrate around blood vessels. Immunofluorescence staining for IgA and Congo red staining revealed negative staining in the skin. Scale bar, 50 μm

Table 1 Laboratory data

Urine routine and microscopic examination		Urinary transferrin	14.600 mg/L
Urine occult blood	3+	Urine α1 microglobulin	< 6.35 mg/L
Urinary protein	2+	Urine β2 microglobulin	< 0.183 mg/L
WBC	25/μL	Trace albumin	> 250 mg/L
RBC	33/μL	Kidney function	
Urine glucose	-	Urea	4.18 mmol/L
Urine bilirubin	-	Creatinine	55μmol/L
Urine ketone body	-	Urea/creatinine ratio	18.82
Urine microprotein test		glomerular filtration rate	131 ml/min/1.73^2
IgG	20.400 mg/L		

and hematuria, and IgAN was diagnosed after percutaneous renal biopsy. Combined with the above medical history and pathogenesis, the patient was finally diagnosed as the co-occurrence of IgAN with BD. Altay et al. [5] reported 2 patients with BD combined with IgAN. Zheng [6] et al. reported that there are 16 kidney-related diseases among 618 patients with BD, accounting for 2.6%. Two of them had pathological features of IgAN after renal biopsy.

At present, although the pathogenesis of BD and its associated kidney disease is not clear, some studies [7, 8] believe that genetic factors and immune abnormalities play important roles in the occurrence and development of BD. Various immune cells and cytokines, especially autoimmune regulatory T cells (Tregs) and auxiliary T cells type 22 (Th22), play a role in the immune pathogenesis of BD. The dose at which BD causes nephropathy is currently unclear. Some studies have shown that [9] the amount of circulating immune complex produced by abnormal T cells is related to the occurrence and development of micropathogenic glomerulopathy (MCD) in patients with BD. Overexpression causes the disappearance of MCD-related foot cells and proteinuria [10, 11]. Based on the above research, we believe that the abnormal function of T cells and their overexpression by IL-13 may also be related to the occurrence of IgAN in patients with BD, but further research is needed.

The prognosis of the co-occurrence of IgAN with BD is relatively optimistic, while only a few patients experience renal failure. The patient we reported was treated with hormonal anti-inflammatory, immunomodulatory, kidney protection, and protein-lowering urine. After 3 years of follow-up, the patient reappears oral ulcers, reddish nodules on the skin of both lower limbs and renal dysfunction. It has been reported [5, 12] that BD secondary to nephropathy can be relieved in some patients, but some studies have shown that the disease can further progress. Some patients developed from IgAN II to stage IV 2 years later.

Here we present a case of co-occurrence of BD and IgAN. Immunofluorescence staining was negative for IgA in the left calf skin biopsy. But Granular deposits of IgA (2+) was found in mesangial areas of renal biopsy. So, attributing this case to secondary IgAN is inappropriate. Based on this, we believe that it is a co-existence relationship between BD and IgAN. At present, it cannot be ruled out that BD patients may develop primary IgAN, including this case. IgAN is one of the most common types of glomerulonephritis, which can occasionally occur in patients with BD. BD is a chronic, recurrent autoimmune or inflammatory disease based on vasculitis, which can lead to various types of glomerulonephritis. Comparing the immunological characteristics of these two diseases, there may be a relationship between IgAN and BD, but we cannot rule out simple coincidences. After renal biopsy, IgAN was found in this patient, but we cannot explain the sequence and causal relationship between BD and IgAN. Therefore, further research is needed to investigate the pathogenic correlation between BD and IgAN.

Due to the hidden symptoms or intermittent attacks of BD with renal injury, it is easy to misdiagnose, which may be one of the reasons for the long-term neglect of BD syndrome with renal injury. Therefore, for such patients, attention should be given to routine urinary parameters, blood creatinine levels and clearance rates to detect renal lesions as early as possible and prevent the occurrence and development of disease.

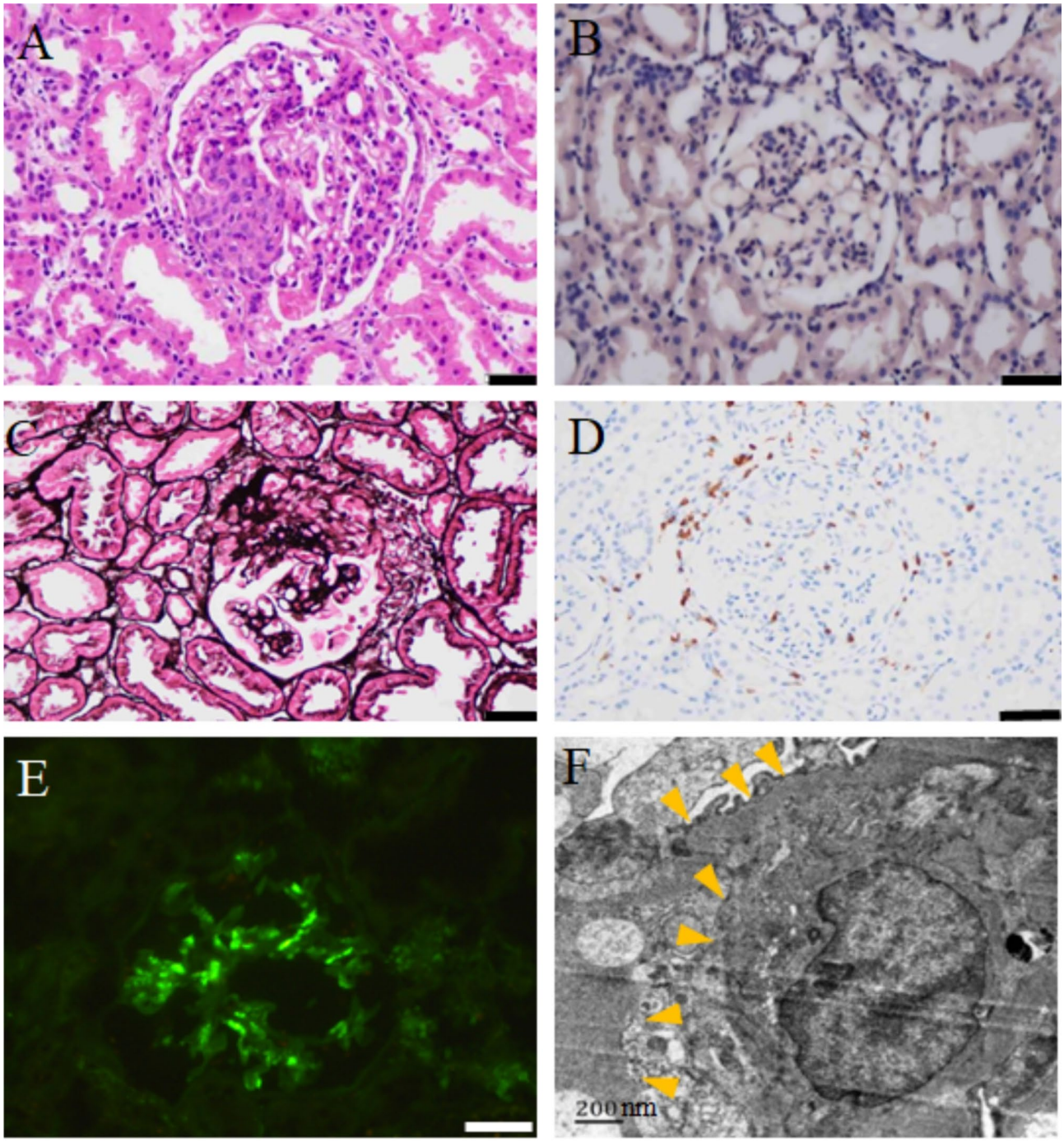

Fig. 2 Histopathological examination, immunostaining and electron microscopy of the renal biopsy. (**A**) H&E staining showed necrotizing lesions, disrupted capillary wall, fibrinoid deposit and extravasation of lymphocytes, plasma cells and individual neutrophils. (**B**) Negative result of Congo red staining revealed renal amyloidosis is not observed. (**C**) Periodic acid-silver methenamine (PASM) staining indicated segmental proliferation of mesangial cells and increase of mesangial matrices accompanied by a small cellular crescent. (**D**) CD3 immunostaining showed vasculitic lesion of interlobular arterioles (a few T lymphocytes infiltration in the interlobular arterioles). (**E**) Immunofluorescence staining revealed granular deposits of IgA show within the mesangial area. (**F**) Electron microscopy indicated electron-dense deposits were found in the mesangial area. Scale bar, 50 μm

Table 2 Laboratory data

Urine routine and microscopic examination		Urine bilirubin	-
Urine occult blood	3+	Urine keton body	-
Urinary protein	1+	Kidney function	
WBC	13/μL	Urea	3.8 mmol/L
RBC	137/μL	creatinine	45μmol/L
Urine glucose	-		

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12882-024-03748-y.

Supplementary Material 1

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Author contributions
Liao and Hong wrote the main manuscript text, Wang and Su prepared Figs. 1 and 2(A-D), Gan prepared Fig. 2(E-F), Hu Guided the article and provided ideas. All authors have read and agreed to the published version of the manuscript.

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Data availability
The datasets used and/or analysed during the current study available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate
Not applicable.

Consent for publication
The patient agrees to use the data and pictures in the article for publication, please refer to the figure below. All of the participants were informed and agreed to publish the manuscript.

Competing interests
The authors declare no competing interests.

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