Minimal change disease in HIV combined with monoclonal gammopathy of uncertain significance: a case report and literature review

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Case Report

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Abstract

Previous studies have shown a significant increase in monoclonal gammopathy (MG) prevalence in patients with human immunodeficiency virus (HIV). HIV and MG both can cause renal injury and have attracted increasing nephrologists' attention. To date, there has been a lack of relevant studies on the renal pathology of HIV combined with MG. Here, we report a case of a newly diagnosed HIV patient with co-morbid MG and subsequent or concurrent massive proteinuria whose renal biopsy showed minimal change disease (MCD). After a period of administration of highly active antiretroviral therapy (HAART), HIV viral RNA was undetectable in plasma, along with complete remission of the nephropathy. However, there was no significant effect on MG.

Introduction

Monoclonal gammopathy (MG) includes a heterogeneous group of diseases ranging from monoclonal gammopathy of undetermined significance (MGUS) to multiple myeloma (MM), characterized by clonal proliferation of plasma cells. MGUS is defined by the presence of serum monoclonal protein with an M-spike less than 3g/dl and plasma cells in the bone marrow less than 10%, which does not fulfill the hematological criteria for malignancy. In the meantime, not accompanied by hypercalcemia, renal insufficiency, anemia and lytic bone lesions.[1] In 2012, monoclonal gammopathy of renal significance (MGRS) was proposed, a renal injury secondary to the monoclonal protein based on MGUS.[2] There are various risk factors for MGUS, such as age, male sex, black race, pesticide exposure, family history of MGUS and prior bacterial or viral infections.[3] At present, there are few documented studies about MG in human immunodeficiency virus (HIV) patients. Most of the studies were consistent. HIV-infected individuals have an increased MGUS prevalence compared to the general population.[4–6] There is only one different view that the prevalence of MGUS among our local HIV-positive veterans is comparable to that of the general population.[7] The exact mechanism is not clear and needs more investigation. HIV infections and their associated immune dysregulation may predispose individuals to MG.

Minimal change disease (MCD) accounts for 10–15% of adults who present with nephrotic syndrome.[8] MCD is often idiopathic but may occur secondary to infections, neoplasms, allergies, drugs and other glomerular diseases. Few studies evaluated renal lesions associated with MG in patients undergoing renal biopsy. Renal disease in HIV patients was first described in 1984.[9] It can vary from systemic and local renal infections, renal involvement by neoplasm, glomerular disease, tubulo-interstitial disease and vasculitis. A variety of glomerulopathy could be observed in patients infected with HIV. HIV-associated nephropathy (HIVAN) has been characterized as the most common cause of renal failure in HIV patients, and its typical histopathological was collapsing focal segmental glomerulosclerosis (FSGS). The other common form of renal impair is HIV immune complex kidney disease (HIVICK), which is described as immune complex deposits in the capillary loops and mesangium, mesangial cell expansion, tubulointerstitial inflammation, including immune complex glomerular disease (membranous nephropathy, membranoproliferative, and mesangial proliferative glomerulonephritis), IgA nephropathy and lupus-like proliferative glomerulonephritis.[10–12]

A few studies demonstrated MCD in HIV patients, let alone in HIV patients with MG. Here, we put forward a case of a patient infected with HIV whose serum protein electrophoresis revealed MG, with a kidney biopsy showing MCD. To our knowledge, this is the first case report study of renal pathology in HIV-infected patients with MG.

Case Presentation

A 61-year-old Chinese male presented fatigue, nausea and vomiting for four days, was found to have severe proteinuria at the local hospital, then transferred to our hospital for further treatment. He often catches a cold and therefore takes nonsteroidal anti-inflammatory drugs frequently. He was no history of hypertension, diabetes or renal disease. His family history was negative. On admission, the physical examination revealed a blood pressure of 137/69mmHg, a temperature of 36.0°C, a heart rate of 70/min, and a respiratory rate of 18/min. No organomegaly was noticed. Other signs were normal.

After admission, His white blood cell count was $1.8x10^9$ cells/L, hemoglobin was 132g/L, the platelet count was $42x10^9$ cells/L and absolute neutrophil count was $0.47x10^9$ cells/L. His absolute lymphocyte count was $1.04x10^9$cells/L. CD4 count was $0.18x10^9$/L and CD19 count was $0.79x10^9$/L. His albumin (Alb) was 2.82g/dL, globulin was 3.78g/dL, serum creatinine (SCr) was 0.99mg/dL and blood urea nitrogen (BUN) was 21.2mg/dL. Immunoglobulin (Ig) A was 76mg/dL, IgG was 3170mg/dL and IgM was 227mg/dL, respectively. Serum sodium 140mmol/L, potassium 3.56 mmol/L, calcium 2.08mmol/L phosphorus 0.9mmol/L and bicarbonate 21.5 mmol/L were within reference ranges. Complement 3 (C3) and 4 (C4) level was 0.58 g/l and 0.21 g/l. light-chain kappa was 24.3mg/ml and light-chain lambda was 3.23mg/ml. Antineutrophil cytoplasmic antibodies (ANCA) and anti-phospholipase A2 receptor (PLA2R) antibodies were negative. Antinuclear antibodies (ANA) titre1:100. Serological tests for viral were performed: cytomegalic virus IgM was negative and IgG was positive, Epstein-Barr virus IgM was negative and IgG was positive. HIV, syphilis antibody and Treponema pallidum antibody (TP-Ab) were all negative. Hepatitis B surface antigen and hepatitis C antibodies were negative. The antigen and antibody of coronavirus disease 2019 (COVID-19) were negative. The urinary protein level is 3.79g/d, and 49.6% is 24h-urine microalbumin. Ultrasound indicated enlargement of multiple lymph nodes, including cervical, inguinal and retroperitoneal regions. We are highly suspect of hematological malignant tumors, particularly lymphoma. Thus, we carried out a further comprehensive examination.

Serum protein electrophoresis suggested an M spike of 2.34g/dL. The result of serum immunofixation electrophoresis presented monoclonal IgG kappa. Lymph node biopsy indicated small B cells atypical hyperplasia. Bone marrow aspiration showed granulocytosis, megakaryocytic hyperplasia, 4% atypical lymphocytes, and 1.5% mature plasma cells. X-rays of the skull and pelvis showed no significant bone destruction. Echocardiography and abdominal ultrasound were normal. We performed CT scans. No focus suspicious for lymphoma, myeloma or infection. MGRS was suspected, but other glomerular diseases accompanied by MGUS could not be excluded. Therefore, a renal biopsy was performed for diagnostic verification and further analysis. Light microscopy (LM) revealed that 2 of 22 glomeruli were globally sclerosed. Other glomeruli were moderate mesangial expansion, accompanied by mesangial cell

proliferation and mesangial matrix accumulation. The tubular exhibited focal vacuolization. Tubular atrophy and interstitial fibrosis were slight, and the intima of the vessels was moderately thickened. (Fig. 1)

Congo red staining for amyloid was negative. Direct immunofluorescence (IF) examination of frozen renal tissue was negative for IgG, IgA, IgM, C3, C4, C1q, fibrin, kappa and lambda light-chain. The electron microscopy reported diffuse podocyte foot-process effacement. The glomerular basement membrane was normal in thickness and ultrastructure. The immuno-electron microscopy of renal tissue was negative. The histiocytes did not contain any crystal inclusions. No electron-dense substance was observed in the glomerular, tubular or renal interstitial immune. These findings were consistent with a diagnosis of MCD ultimately. (Figure 2)

Because of the low level of platelets at admission and nephrotic syndrome (NS), we treated with intravenous methylprednisolone (40mg per day) for six days at first. WBC, PLT and kidney function were recovered. Since there is no direct evidence that MG causes kidney damage, thus, it confirmed the diagnosis of MGUS with MCD. He had clinical signs such as fatigue, anorexia and weight loss (2 months loss of 5 kilograms), combined with abnormal laboratory: granulocyte deficiency, increased IgG and elevated light-chain kappa. We perform a detailed and comprehensive screening for infections, allergies and tumors again. At this time, his HIV antibody was positive and was further confirmed by western blot. His HIV-1 viral load was $9.3x10^4$IU/mL at the time of diagnosis. His CD4 count was $0.18x10^9$/L and his CD19 count decreased to $0.12x10^9$/L simultaneously. According to these findings, we made the diagnosis of MCD in MGUS with HIV-1 infection.

After a period of administration of highly active antiretroviral therapy (HAART), the patient showed good compliance, and the treatment was well tolerated without clinically significant side effects. The patient was followed up for 18 months until now, HIV viral RNA was undetectable in plasma, along with serum creatinine decreased to normal and urine protein turned negative. CD4 count rises from $0.18x10^9$/L to $0.44x10^9$/L (normal range $0.2x10^9$/L to $1.82x10^9$/L). However, there was no significant effect on IgG and the level of κ light-chain.

Discussion And Conclusion

Although the patient suffers from nephrotic syndrome, his renal puncture pathology did not provide sufficient evidence to support the diagnosis of MGRS. We considered it insufficient to conclude that MG caused his renal injury. Therefore, his diagnosis was determined to be: HIV combined with MGUS and MCD.

We presented the first case report of renal pathological findings in an HIV-infected patient with MGUS. Interestingly, the initial consequence of the HIV antibody was a false negative, which may sometimes lead to a delay in the diagnosis. The hook effect is a phenomenon whereby an extremely high amount of the total analyte may cause an inappropriately low result. It is frequently observed in experiments due to

the inappropriate proportion of antigens and antibodies. Antigen-antibody reactions can lead to an antigen or antibody excess, resulting in falsely decreased results and potential misdiagnosis.[13] In our case report, sandwich lateral flow immunoassays are limited at high antibody concentrations by the hook effect, leading to a false negative result.

MGUS is prevalent in nearly 5% of the population above 70 years old, and the percentage is remarkably higher in older individuals.[14] Plenty of evidence indicated that MGUS might progress to multiple myeloma (MM), other malignant plasma cell disorders and lymphoma. Approximately a quarter of patients with MGUS will develop MM within 20 years of diagnosis.[15] The majority of studies concluded that HIV infection is positively associated with MG. Only one study showed no significant difference in the incidence of MUGS between HIV and normal subjects.[7] The prevalence of MGUS among the general population and HIV-infected patients are 0.15% and 2.5%, respectively.[16] There is very little data and uncertainty regarding the incidence and natural history of MGUS patients with HIV. HIV infection could be implicated in the development of monoclonal gammopathy (MG), but the mechanism remains unclear. HIV itself is not only associated with hypergammaglobulinemia but also is a risk factor for MGUS. The pathophysiology is complex and related to the progressive loss of CD4 lymphocytes, abnormal function, nonspecific polyclonal B-cell activation, and chronic immune system stimulation by several antigens or pathogens.[17] The progressive depletion of infected CD4 lymphocytes is a crucial event in the context of HIV infection, as well as systemic immune activation and dysregulation.[18] The chronic expansion of B cells in HIV infection, with subsequent impaired B cell maturation, results in the lymphoid follicular formation, reactive lymph nodes, autoimmune disorders and B cell malignancies. In addition to being stimulated by HIV directly, other viral antigenic may also play a causative role in the development of MG by different mechanisms. The Epstein-arr virus may infect and stimulate B cells, impair their function, leading to malignant transformation of lymphocytes. Expression of the Epstein-Barr nuclear antigen-2 gene induces the expression of CD21 and CD23 B cell surface antigens, leading to B cell expansion in turn.[19] HCV infection is a well documented risk factor for MG, mixed cryoglobulinemia, autoimmune disorders, and lymphomas. The increased risk of monoclonal protein in the context of immunosuppression after organ transplants further indicates that immune deficiency may also play an essential role in the pathogenesis of MG among HIV patients.[20] The prevalence of MGUS is significantly higher in newly diagnosed young HIV patients. Therefore, MGUS can be used as an indicator for routine screening tests for HIV. In the meantime, HIV-infected patients with MUGS should be reassessed yearly to alert the occurrence of plasma cell malignancies. MG in HIV-infected individuals is more likely to occur at a younger age, which often disappears with antiretroviral treatment (ART).[21, 22] Several studies revealed that highly active antiretroviral therapy (HAART) results in a significantly M-protein decrease, as well as an improved patient outcome.[23–25] HAART effectively lowers the HIV load, then reduces B cells stimulated by HIV or other viral antigenic, which would be associated with a reduction in M-protein level. However, there was no significant change in the M protein in our case, maybe concomitantly present in a patient without a direct causal relationship between the two. Perhaps the follow-up was not long enough to observe his M-protein changes. However, it is necessary to closely monitor the M-protein levels during the follow-up to be alert for the development of MGRS or even hematologic malignancy.

Up to now, there are few reports on MG with MCD. Ribas[26] reports three cases of MG with podocytopathy: two patients were diagnosed with MCD, one is MM and the other is Waldeström macroglobulinemia. In MGRS, monoclonal immunoglobulins and their fragments can cause renal disease by direct deposition in renal tissue or interference with the complement or coagulation system.[27]There was no direct evidence of MG-related nephropathy in this case report. We made the HIV patient the diagnosis, MCD combined with MGUS. Among MGUS patients with kidney disease, diabetic nephropathy and focal segmental glomerulosclerosis were the most common lesions, and MCD ranked fifth with 7.3%. Nonetheless, the conclusion suggested MGUS patients did not have renal disease related to hypergammaglobulinemia.[28] A retrospective study in 2020 included a total of 160 MG patients who underwent renal puncture biopsy, and these patients were divided into MGRS lesions and Non-MGRS lesions.[29] No MCD was found in 64 patients with MGRS, while only one MCD was found in 96 patients with Non- MGRS lesions. Several hypotheses can be formulated on how MG triggers MCD. Glomerular injury may be caused indirectly through immune-mediated. A T cell process ignited by the MG might lead to podocyte injury.[30]

HIV causes kidney injury through different pathways, including lesions directly related to HIV gene expression in the kidney and those related to co-morbidities, drug effects, immune dysregulation and co-infections.[31] MCD is one of the rare types of pathology in HIV Individuals. A retrospective study in 2012 included 88 HIV-infected patients presenting with a biopsy-proven glomerular disease, with MCD accounting for 4.5%.[32]Another retrospective study that included 949 HIV individuals showed that MCD accounted for only 1.05% of all biopsy pathologies.[33] It has been suggested that chronic HIV infection may trigger immune disturbances, promoting podocyte dysfunction.[33] The mechanism of podocyte injury induced by HIV is also unclear. Current guidelines recommend HIV Individuals accompanied by nephropathy as an indication for initiation of combined ART irrespective of CD4 + lymphocyte count. [35] Several studies have demonstrated that ART improves kidney diseases, such as HIV-associated nephropathy, HIVICK and HIV-associated thrombotic microangiopathy.[36, 37] In the context of ART, angiotensin-converting enzyme (ACE) inhibitors or angiotensin-receptor blockers (ARBs) and/or prednisone may be added.[31] In a French retrospective study, eight patients were identified over 16 years. Based on ART treatment, 6 cases were treated with hormones as first-line treatment and 2 cases were in spontaneous remission. After a median follow-up of 20 months, all patients were in remission (complete in 5 cases). [38] In our case, we were given a short six days steroid hormone treatment for granulocyte deficiency. HAART was then given and during our follow-up, complete remission of the kidney disease was observed with no further recurrence. Therefore, we have reason to believe that HIV is maybe closely related to MCD. Furthermore, this patient had a history of taking NASID. It should be considered whether it is the contributions to MCD. Drug-induced MCD is certainly not wholly excluded.

In conclusion, there is no case report about HIV combined with MCD and MUGS. We speculate that MCD may be associated with HIV in our case. However, for MGUS, longer follow-up surveillance is needed to demonstrate the relationship between the three further.

Declarations

Ethics approval and consent to participate

This study was conducted according to the guidelines laid down in the Declaration of Helsinki. Informed consent was obtained from the patient described in this report.

Consent for publication

Written informed consent was obtained from the patient for the publication of this case report.

Availability of data and materials

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

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

Jingzhen Li contributed to the conception of the study;

Jingzhen Li and Xing Su contributed significantly to analysis and manuscript preparation;

Jingzhen Li and Miao Chen performed the data analyses and wrote the manuscript;

Beiyan Bao and Lingxia Ouyang helped perform the analysis with constructive discussions.

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Figures

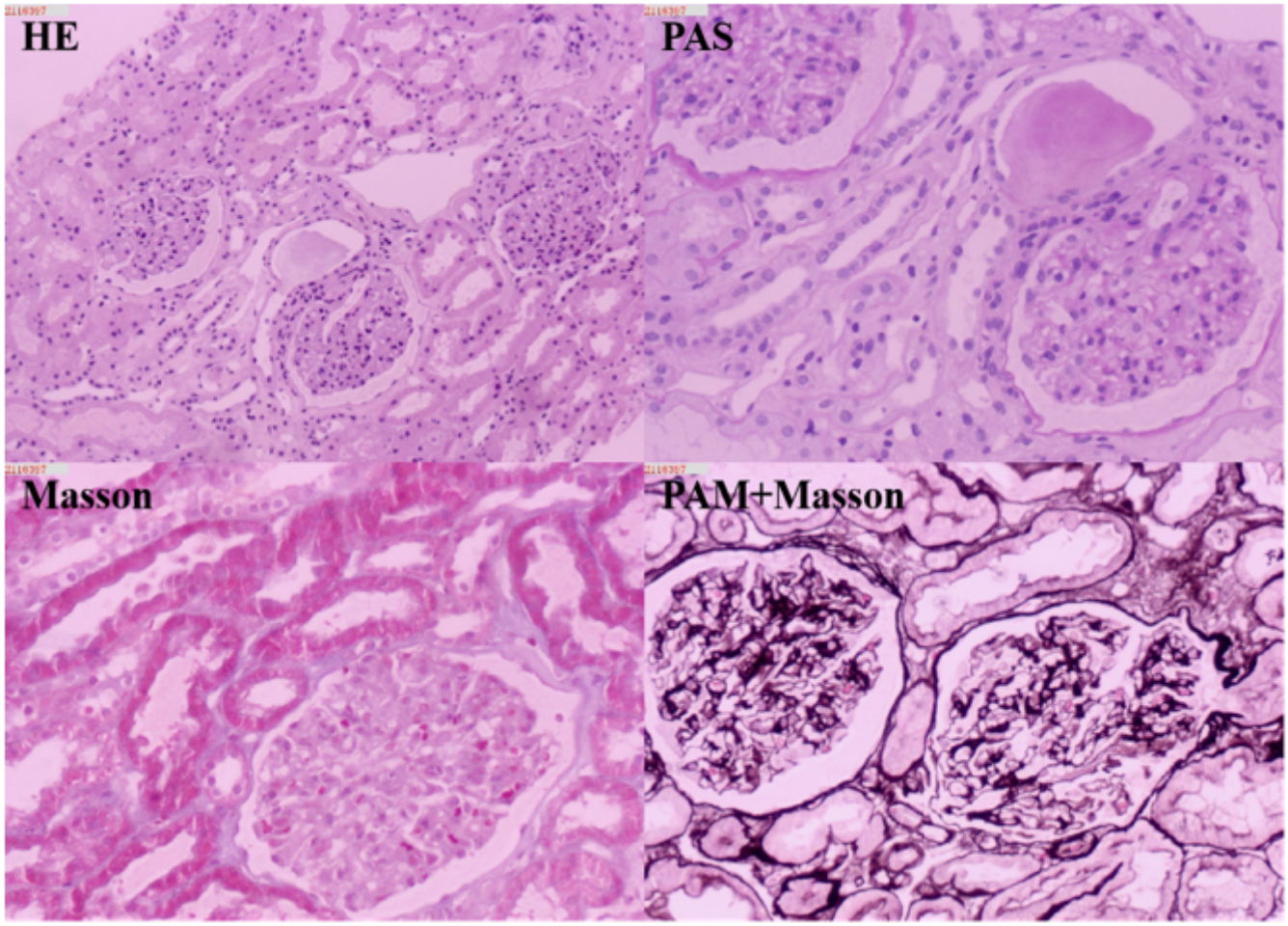

Figure 1

Histological features of the renal biopsy under the light microscope

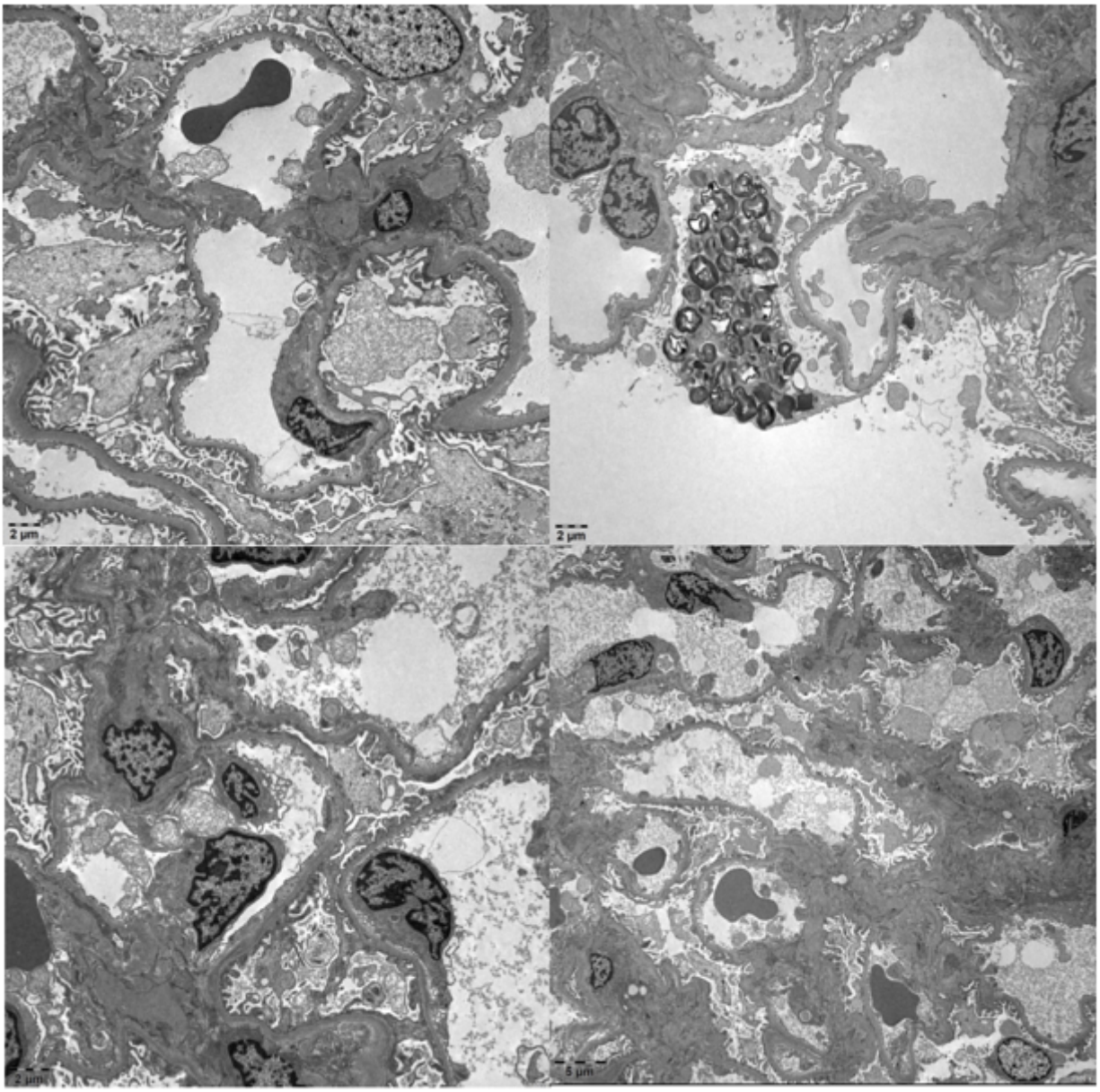

Figure 2

Histological features of the renal biopsy under the electron microscope