Int J Clin Exp Med 2019;12(7):9491-9494
www.ijcem.com /ISSN:1940-5901/IJCEM0088260

Case Report

Myeloid bodies in a patient with membranous nephropathy: a case report and literature review

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Received September 14, 2018; Accepted March 12, 2019; Epub July 15, 2019; Published July 30, 2019

Abstract: Aim: Myeloid bodies, known as laminated electron-dense inclusions, are characteristic of Fabry disease, but are occasionally in focal segmental glomerular sclerosis. However, it has not been found in other nephropathies. Methods: Here, a case is reported with myeloid bodies in hepatitis B virus-associated membranous nephropathy. Results: The present patient, a 47-year-old male, presented with hypoalbuminemia, and massive proteinuria without hematuria. Laboratory tests were positive for hepatitis B surface antigen, hepatitis B e antigen and hepatitis B core antibody, with HBV-DNA of 1.09E+05 IU/ml. Renal biopsy revealed atypical MN. Additionally, myeloid bodies were found by electron microscopy. The α-galactosidase A (α-GLA) gene was normal. The manifestations were gradually alleviated with antiviral therapy alone. Conclusion: This is the first case report with myeloid bodies in HBV-associated membranous nephropathy (MN) without Fabry disease. Myeloid bodies in renal biopsy specimens should be interpreted with caution.

Keywords: Myeloid body, membranous nephropathy, fabry disease, hepatitis B virus

Introduction

Fabry disease is a rare monogenic disorder that is inherited in a recessive X-linked manner [1]. Mutations in the α-galactosidase A (α-GLA) gene cause deficiency in or absence of α-GLA, leading to lysosomal accumulation of glycosphingolipids, especially globotriaosylceramide, in various organs such as the kidney. The characteristic feature of renal involvement is the presence of laminated electron-dense inclusions, known as myeloid bodies, which are detected by electron microscopy. The diagnostic gold standard is genetic analysis.

Myeloid bodies are identified in the epithelial and mesangial cells of a focal segmental glomerular sclerosis patient without Fabry disease [2], but have not been reported in other nephropathies. Herein, the first case with myeloid bodies in renal biopsy is reported in a paitent who was diagnosed with HBV-associated membranous nephropathy (MN) without Fabry disease.

Case presentation

A 47-year-old male was admitted to our hospital for edema of both lower limbs lasting 3 months. In the last month, he complained of gradually-worsening gastrointestinal discomfort, including nausea, vomiting and abdominal pain. He denied any family history of genetic disorders and reported that his parents were healthy, 80-year-old individuals. Except for the both lower limb edema, his physical examination on admission was unremarkable.

The following laboratory results were obtained: hypoalbuminemia (23 g/L), proteinuria (4 g/24 h) without hematuria, hypo-complementemia (complement3 (C3) 0.54 g/L), hepatitis B surface antigen (HBsAg) and e antigen (HBeAg) and core antibody (HBcAb) positivity, and 1.09E+05 IU/ml hepatitis B virus (HBV)-DNA. Other measurements, including renal function, hepatic function, lipids, immunoglobulin (Ig) A, M and G, lupus-related antibodies, and anti-neutrophil cytoplasmic antibodies, were normal or negative. Ultrasonography showed a normal renal size and structure.

Renal biopsy was performed. Under light microscopy, 15 glomeruli were counted, among which adhesions to Bowman's capsule were observed in 5. The podocytes were slightly swollen. The glomerular basement membrane

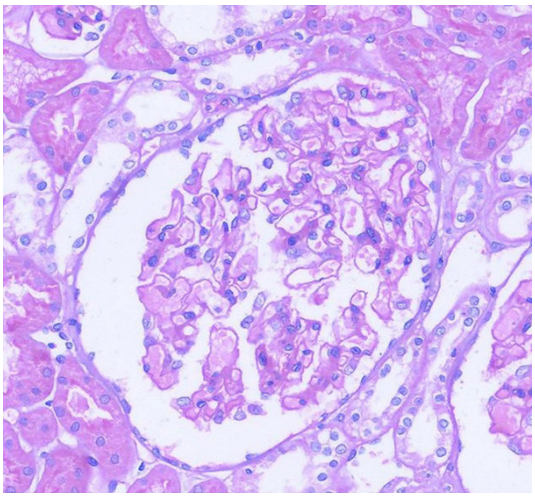

Figure 1. Hematoxylin and eosin staining in glomeruli: The glomerular basement membrane showed vacuolar degeneration and was focally thickened, with no spikes visible (HE, × 40).

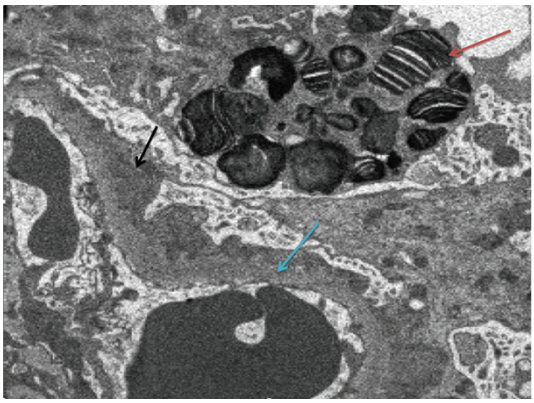

Figure 2. Electron microscopy findings: A small quality of myeloid bodies (red arrow) was observed in podocytes. The glomerular basement membrane (blue arrow) appeared irregularly thickened, with subepithelial electron-dense deposits visible (black arrow) (× 10000).

showed vacuolar degeneration and was focally thickened without visible spikes. Sub-epithelial deposits were observed by Masson's trichrome staining. The tubule, interstitium, and vessels were virtually normal (**Figure 1**). Immunofluorescence showed granular mesangial staining for Ig G (+++) and C3 (+++), but IgA, IgM, C1q, FRA, HBsAg, and HBcAg were negative. Electron microscopy revealed diffuse foot process effacement, an irregularly thickened glomerular basement membrane, and slight mesangial expansion with electrodense deposits under the epithelium and within the mesangium and paramesangium (**Figure 2**). Additionally, myeloid bodies were found in a small number of podocytes, which is characteristic of Fabry disease. To confirm Fabry disease, genetic analysis was conducted. However, Fabry disease was excluded because no abnormality in the patient's α-GLA gene was identified.

Considering the high titer of HBV-DNA, single antiviral therapy (Entecavir 0.5 mg per day, po) was administered, and HBV-DNA became undetectable (<5.000E+02 IU/ml) three months later. Thereafter, 24-urine protein excretion declined from 3.42 g to 0.391 g, and his serum albumin level increased from 23.6 g/L to 38 g/L within 1 year.

Discussion

Fabry disease, also called angiokeratoma corporis diffusum, was first described independently by a German dermatologist, Johannes Fabry, and an English dermatologist, William Anderson, in 1898 [3, 4]. Globotriaosylceramide can accumulate in a wide variety of cells, such as vascular endothelium, cardiac, skeletal, and smooth muscle, and renal cells, causing a spectrum of symptoms that include acroparesthesias, hypohidrosis, angiokeratomas, telangiectasias, cornea verticillata, cerebrovascular lesions, cardiac disorders and renal dysfunction [5]. For most male patients, α-GLA activity is decreased or undetectable, whereas enzyme activity is in the normal range in females and a few males because of random X chromosome inactivation. Accordingly, molecular genetic testing for GLA mutation is the most reliable diagnostic approach [6].

All types of kidney cells can be involved, including podocytes and endothelial, mesangial, and tubular cells, with podocytes being predominantly affected. As a result, patients may present with glomerular and tubular disorders. The characteristic sign is diffuse deposition of myeloid bodies by electron microscopy and enlarged podocytes with abundant, finely vacuolated cytoplasm due to lipid inclusion. Symptoms often emerge during childhood and adolescence, and glomerular manifestations follow a course similar to that of diabetic nephropathy, involving early hyper-filtration, massive proteinuria, and progressive deterioration of renal function. Proteinuria is the most common symptom, and untreated patients usually

develop end-stage renal disease in their 50s [7, 8].

In the current patient, myeloid bodies were found in podocytes. However, he was not diagnosed with Fabry disease for the following reasons. First, the patient had no family history, extra-renal organ involvement or other symptoms. Second, no foam cells were observed by light microscopy, and only a few myeloid bodies were detected by electron microscopy. Third, GLA gene mutations were not detected.

Other diseases may involve lamellar lipid inclusion; for example, silicon nephropathy and Niemann-Pick disease have both been reported to have similar inclusions [9]. Additionally, some drugs can cause these bodies, such as (hydroxy) choroquine, amiodarone and aminoglycosides. These drugs can be sequestered in tissues (the liver, spleen, lungs, and kidneys), allowing for lysosomal trapping and inhibition of key lysosomal enzymes and contributing to identical ultrastructural features [10, 11]. The patient was not exposed to silicon or the aforementioned drugs and also lacked Niemann-Pick disease-specific manifestations.

MN is characterized by a uniform thickening of the glomerular capillary wall due to diffuse subepithelial localization of immune aggregates. It can be idiopathic and, in a minority of patients, appears to be related to antigens or environmental agents derived from various sources, such as drug therapy, malignancy, systemic lupus erythematosus and HBV. For HBV-associated renal disease, diagnosis is important because therapy with glucocorticoids and cytotoxic agents, which are common therapies for the idiopathic MN, may not be beneficial in patients with HBV-associated renal disease and may lead to HBV replication reactivation, hepatitis flares, and liver failure if used without antiviral therapy. The current patient was seropositive for HBV-Ag (HBsAg, HBcAb, and HBeAg), without another identifiable cause for renal disease (negative autoantibodies, no history of drug therapy and no malignancy upon general imaging examination). Therefore, HBV-associated MN were suspected, which is differentiated from idiopathic MN based on the following clues [12]: first, HBV-MN is often associated with hypo-complementemia; second, HBV-MN frequently has atypical pathological manifestations, including mesangial hyper-cellularity, endocapillary [13], and transitional features between MGN and membranoproliferative glomerulonephritis (MPGN) types I and III [14, 15], and immunopathologic or ultrastructural evidence of mesangial immune complex deposition [16]. In contrast, deposits are observed in a predominantly subepithelial location in idiopathic MN [17]. HBV-MN is typically confirmed by the presence of a renal HBV-Ag [18]. However, this may lead to false-negative results due to the following reasons: 1. levels of HBV or its antigens in glomeruli may have declined to undetectable levels at the time of renal biopsy [19]; 2. antibodies against HBV-Ag may be overproduced in the serum, saturating HBV-Ag binding sites in renal sections; and 3. the detection technique may be unavailable. Therefore, proof that HBV is the primary cause of renal disease can only be provided by improvement in renal disease with antiviral therapy alone and viral suppression. The patient was seropositive for HBV antigen, presented clinically with glomerulonephritis, excluding other secondary factors, and presented atypical MN by renal pathology. All laboratory indices and clinical manifestations were improved by anti-antiviral therapy alone, and the diagnosis of HBV-MN was made.

Conclusion

In conclusion, this is the first report of myeloid bodies found by renal biopsy of HBV-associated MN. The patient was successfully treated with anti-viral therapy alone, which sheds light on HBV-MN therapy. Myeloid bodies in renal biopsy specimens should be interpreted with caution.

Disclosure of conflict of interest

None.

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