Membranoproliferative glomerulonephritis in β-thalassemia intermedia; a case report

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ARTICLE INFO

Article type: Case Report

Article history:
Received: 17 January 2021
Accepted: 14 June 2021
Published online: 2 July 2021

Keywords: Case report Anemia Thalassemia intermedia Renal complication Glomerulonephritis

ABSTRACT

Introduction: β-thalassemia intermedia reduces the body’s ability to produce adult hemoglobin and causes anemia. In contrast to β-thalassemia major, β-thalassemia intermedia patients do not require lifelong transfusion and are often independent of blood transfusion until young age. Moreover, chronic hypoxia and iron overload may cause tubular and glomerular dysfunction in patients with thalassemia.

Case Presentation: We report a 21-year-old female with β-thalassemia intermedia (β-TI) presenting with generalized edema and proteinuria and showed membranoproliferative glomerulonephritis (MPGN) after renal biopsy.

Conclusion: The possibility of occurrence of MPGN in patients with thalassemia should be considered. To our knowledge, it is the first case of thalassemia that was reported with MPGN and, more investigation is required to assess the association of thalassemia and MPGN.

Implication for health policy/practice/research/medical education: We report a 21-year-old female with β-thalassemia intermedia presented with generalized edema and proteinuria, which renal biopsy showed membranoproliferative glomerulonephritis.

Please cite this paper as: Shafiee M, Zomorodian SA, Owji SM, Roozbeh Shahroodi J, Torabi Jahromi M. Membranoproliferative glomerulonephritis in β-thalassemia intermedia; a case report. J Nephropathol. 2022;11(2):e17186. DOI: 10.34172/jnp.2022.17186.

Introduction

Beta-thalassemia refers to autosomal recessive hemolytic anemia that has been categorized as minor, major, and intermedia based on their alpha-globin or beta-globin imbalance, the severity of anemia, and clinical presentation (1). In the middle, lies β-thalassemia intermedia (β-TI) which describes patients with moderate manifestations (2). β-thalassemia has a prevalence of 80-90 million carriers worldwide and incidence of symptomatic patients is estimated at 1 in 100,000 per year worldwide (3). Thalassemia is more prevalent in the Mediterranean area, in regions like Greece, Turkey, Italy, Southeast Asia, North Africa and Iran which is called the thalassemia belt and has a high thalassemia carrier rate (4,5). The clinical manifestations are due to ineffective erythropoiesis, chronic anemia, medullary expansion, extra-medullary hematopoiesis, and iron overload (2,6). Iron overload develops from increased iron absorption in patients with non-transfusion dependent thalassemia, mediated with downregulation of hepcidin by the increased production of erythroferrone in the absence of blood transfusion during the early stages of the disease (7-9). However, thalassemia patients have multisystem involvement such as skeletal deformities, silent brain infarctions, pulmonary hypertension, leg ulcers, endocrine disorders, and thromboembolic event (10), knowledge on renal complications in β-thalassemia is still limited. Chronic anemia, hypoxia, iron overload, and iron chelator may cause tubular and glomerular cell dysfunction (11). Recently, few studies have investigated

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proteinuria, aminoaciduria, decreased urine osmolarity, and increased secretion of proximal tubule injury markers, like N-acetyl-β-D-glucosaminidase in patients with β-thalassemia (12,13). Additionally, several studies confirmed IgA nephropathy in patients with thalassemia by renal biopsy (14-19). The present study describes the first case of membranoproliferative glomerulonephritis (MPGN) in a case of β-thalassemia.

Case Presentation

A 21-year-old female with the chief complaint of proteinuria and generalized edema was admitted to our center. She was diagnosed with anemia in childhood but no further evaluations have been performed and also did not have a significant past medical and drug history. Physical exam revealed bilateral lower extremity and periorbital edema with the positive sign of hepatosplenomegaly.

The hematologic test revealed microcytic hypochromic anemia. Hemoglobin was 5.1 g/dL, hematocrit was 16%, mean corpuscular volume was 72.2 fL, mean corpuscular hemoglobin was 22.1 pg, and mean corpuscular hemoglobin concentration was 30.2 g/dL. Peripheral blood smear showed severe anisocytosis, poikilocytosis, target cells, and elliptocytosis. Hemoglobin electrophoresis showed HbA: 10%, Hb A2: 4.8% and Hb F was 85%. All of these hematologic findings and the fact that the patient hasn’t needed blood transfusion yet; was in favor of β-thalassemia intermedia. Although the patient did not have a positive history of transfusion or iron chelator use, blood transfusion has been started in this admission due to a low level of hemoglobin. Urine analysis revealed proteinuria (2+) and blood (3+). Additionally, 24-hrs urine analysis was significant for 3.836 g protein content with volume 2.8 liters and creatinine 1.736 g. Additionally, estimated glomerular filtration rate was 124 mL/min/1.73 m² that was calculated through EPI equation with serum creatinine; 0.7 mg/dL and BUN: 20 mg/dL. Another serum test was significant for albumin 2 g/dL and protein 4.8 g/dL. Levels of C4 complement protein were in the normal levels as well as CH50 activity but C3 complement protein was 79 mg/dL a little less than the normal level (90 mg/dL). No viral markers were detected including hepatitis B surface antigen, anti-hepatitis C antibodies, and human immunodeficiency virus markers. Test results for anti-double-stranded DNA antibody, anti-neutrophil cytoplasmic antibodies and anti-nuclear antibody came back negative and test for cryoglobulinemia was negative as well. Serum and urine protein electrophoresis and immunoglobulin electrophoresis were negative for monoclonal gammopathies. Ultrasonography showed normal size and echogenicity of kidneys. Echocardiography revealed mild left ventricle hypertrophy with good systolic function and ejection fraction was 60%. Therefore, due to nephrotic range of proteinuria and significant generalized edema without cardiac origin, a renal biopsy was conducted.

Percutaneous renal biopsy recovered a tissue specimen with 10 glomeruli that four of which were globally sclerotic (4/10). All of the remaining non-sclerotic glomeruli exhibit lobular accentuation, moderate to severe endocapillary hypercellularity (Figure 1A) with capillary wall thickening, and focal mesangial interposition (focal double layering) in periodic acid–Schiff (PAS) and silver stains (Figure 1B and 1C). In addition, sub-endothelial and sub-epithelial depositions and increased mesangial matrix were seen. The interstitium demonstrated mild patchy mononuclear inflammatory cells infiltration and mild interstitial fibrosis (Figure 1D). Vascular changes were within normal limits with no evidence of vasculitis.

Electron microscopic study showed nine glomeruli that most of them revealed diffuse basement membrane thickening as well as mesangial cell proliferation and mesangial matrix expansion. The interstitium was edematous with mild mononuclear cell infiltration.

There were multiple electron-dense depositions in the sub-endothelial area of the basement membrane, sub-epithelial, and mesangial area (Figure 2). Diagnosis based on light and electron microscopy findings was compatible with MPGN. The patient underwent lupus diagnostic tests several times during the four years that she was followed up. However, no clinical or laboratory signs for confirming lupus erythematosus disease was found except for a slightly lower C3 level. Finally, she progressed to end-stage kidney disease.
Discussion

Despite the fact of progressing β-thalassemia patients’ care that leads to better survival, this achievement has permitted previously undiagnosed complications to reveal; including some renal dysfunctions. Clinical studies have revealed tubular dysfunction and glomerular abnormalities as common complications in patients with thalassemia that chronic anemia, iron overload and iron chelators are underlying causes. Patients with β-TI are often transfusion independent, however, they can also develop iron overload due to ineffective erythropoiesis that leads to increased intestinal iron absorption (7). Chronic anemia increases renal plasma flow and glomerular filtration rate secondary to reduction in systemic vascular tonicuity that leads to hyperdynamic circulation (20). Glomerular hyperfiltration finally results in damage to the glomerular capillary wall with subsequent epithelial and endothelial cell injury (21). Hypoxia increases the metabolic demand of tubular cells leads to the development of tubulointerstitial damage and finally glomerulosclerosis and fibrosis (22,23). Additionally, iron overload causes tubulointerstitial damage and glomerulosclerosis which leads to glomerular filtration rate decrease. Other factors that contribute to decreasing renal function in these patients include transfusion-related viral hepatitis or HIV infections, which may eventually lead to glomerulonephritis (23). To the best of our knowledge, the association between β-thalassemia and MPGN has not been reported. However, the association of thalassemia and IgA nephropathy has been reported in few studies (14-18).

In this case, we report a β-thalassemia intermedia patient with MPGN accompanied by generalized edema in which the presentation of edema and diagnosis of glomerulonephritis was concurrent with the onset of demand to blood transfusion. It is not possible to distinguish between idiopathic MPGN and secondary to hemoglobinopathy. The association of sickle cell disease and glomerulopathy is well understood. The activation of mesangial cells with fragmented RBC leads to the synthesis of matrix protein and glomerular basement membrane reduplication Another hypothesis in sickle cell glomerulopathy is immune complex-mediated, in which antibody against tubular epithelial antigens releases after tubular damage secondary to hypoxia and hemodynamic alteration leading to glomerular deposition of an immune complex (24). The same mechanisms can explain the relation between thalassemia and glomerular injury, but more investigations are needed to explore this association. Moreover, Ni et al have highlighted that impaired elimination of circulating immune complexes may lead to IgA nephropathy in a patient with thalassemia (13). Decreased complement activity in thalassemia patients has been also reported in various studies (19).

Hepatosplenomegaly along with anemia are the markers of ineffective extramedullary erythropoiesis that trigger excessive gastrointestinal iron absorption (7). Iron overload is associated with tubular cell injury that may cause the expression of tubular antigens that possibly leads to activation of the immune system that eventually results in glomerulopathy. However, this hypothesis needs more study.

Conclusion

We report a case of β-thalassemia intermedia with generalized edema and proteinuria. Renal biopsy disclosed MPGN. This study is the first one representing MPGN as a novel renal association for thalassemia. The association of thalassemia and glomerular disease is not clear and most studies showed tubular damage in this group. More research is required to investigate the true mechanisms, incidence and consequences of kidney damages in patients with thalassemia. Studies including patients with transfusion independent β-thalassemia intermedia are also essential due to lack of data in this group.

Authors’ contribution

MS was responsible for designing and interpretation of data and writing manuscript. SAZ contributed to interpretation of data and writing manuscript. SMO performed pathological interpretation of the renal tissue and contributed to writing manuscript. JR contributed to managing the patient and assessing the data. MTJ contributed to managing the patient. The authors read

Figure 2. (A) Electron micrograph of normal kidney glomerular basement membrane without any deposition. (B, C, D) Electron micrograph of MPGN that shows multiple electron dense depositions in sub-endothelial, mesangial and sub-epithelial area of the basement membrane of glomerular capillary wall. (uranium acetate, lead citrate, A ×14400, B × 8400, C ×6400, D ×10800).
and approved the final manuscript.

Conflicts of interest
The authors declare that they have no competing interests.

Ethical issues
Ethical issues (including plagiarism, data fabrication, double publication) have been completely observed by the authors. The patient received all information regarding this case report. Written informed consent was obtained from the patient.

Funding/Support
There was no funding.

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