

Beta-Thalassemia Minor Is Associated with IgA Nephropathy

Jung Hyun Kang, M.D.¹, Bo Rha Park, M.D.¹, Kyung Soo Kim, M.D.¹, Do Yeun Kim, M.D.², Hee Jin Huh, M.D.³, Seok Lae Chae, M.D.³, and Sung Joon Shin, M.D.¹

Divisions of Nephrology¹, and Hematology and Medical Oncology², Department of Internal Medicine; Department of Laboratory Medicine³, Dongguk University Ilsan Medical Center, Dongguk University College of Medicine, Goyang, Korea

Thalassemia refers to a group of hereditary diseases caused by a defect in alpha or beta globin synthesis [1]. This impaired synthesis leads to a reduced supply of globin chains and results in the malformation of hemoglobin, which gives rise to microcytic hypochromic anemia. However, since synthesis of the unaffected globin occurs at a normal rate, the alpha or beta subunits accumulate disproportionately. Consequently, inclusions lead to the destruction of erythroblasts in the bone marrow, and hemolytic anemia results as the surviving cells are cleared in the spleen [1, 2]. Thalassemia is most prevalent in the Mediterranean region, in countries such as Greece, Turkey, and Italy, in addition to Southeast Asia and North Africa. Although its occurrence is currently rare in Korea, it is expected to increase as a result of the surge in migration from Southeast Asia to Korea, experienced since the 1990s.

Microscopic hematuria is frequently observed in thalassemia patients, and is considered to be the result of tubular damage induced by iron deposition, hypercalciuria, hyperuricosuria, and deferoxamine. However, the existence and extent of tubular damage have not been thoroughly evaluated by renal biopsy. On the other hand, glomerulonephritis has not been considered to be a main cause of microscopic hematuria in thalassemia.

Here, we report a 70-yr-old Korean man who was diagnosed with beta-thalassemia minor that was associated with IgA nephropathy and complicated by microscopic hematuria and the

progression of renal failure. The patient had been diagnosed with anemia 10 yr earlier; follow-up had not included any further diagnostic studies or specific treatment. Hematologic tests revealed microcytic hypochromic anemia: Hb, 9.9 g/dL; hematocrit, 31.4%; mean corpuscular volume, 58.3 fL; mean corpuscular Hb, 18.4 pg; mean corpuscular Hb concentration, 31.5 g/dL. Peripheral blood smear showed anisocytosis, poikilocytosis (target cells), and basophilic stippling. Bone marrow examination revealed normocellular marrow with erythroid hyperplasia but no ringed sideroblasts (Fig. 1). Hb electrophoresis showed a normal pattern: 98.3% Hb A and 1.7% Hb A₂. Since the morphologic abnormalities detected in the peripheral blood smear and the bone marrow examination were associated with impaired Hb synthesis, thalassemia was suspected. We confirmed the absence of interracial marriages in his family history based on pedigree analysis. Consequently, the globin genes were analyzed, and all exons and introns of the Hb beta (HBB) gene, which is the causal gene of beta-thalassemia located on chromosome 11p15.5, were sequenced. Subsequently, a heterozygous substitution mutation was discovered in the ATG initiation codon, which changed it to AGG. Therefore, a final diagnosis of beta-thalassemia minor was confirmed. The patient did not have any history of transfusion or deferoxamine use.

During follow-up, the patient showed persistent microscopic hematuria with new-onset overt proteinuria and progression of

Received: July 18, 2012

Revision received: November 15, 2012

Accepted: January 14, 2013

Corresponding author: Sung Joon Shin

Division of Nephrology, Department of Internal Medicine, Dongguk University Ilsan Medical Center, Dongguk University College of Medicine, 27 Dongguk-ro, Ilsandong-gu, Goyang 410-773, Korea

Tel: +82-31-961-7145, Fax: +82-31-961-7141, E-mail: shine@duih.org

© The Korean Society for Laboratory Medicine.

This is an Open Access article distributed under the terms of the Creative Commons Attribution Non-Commercial License (<http://creativecommons.org/licenses/by-nc/3.0>) which permits unrestricted non-commercial use, distribution, and reproduction in any medium, provided the original work is properly cited.

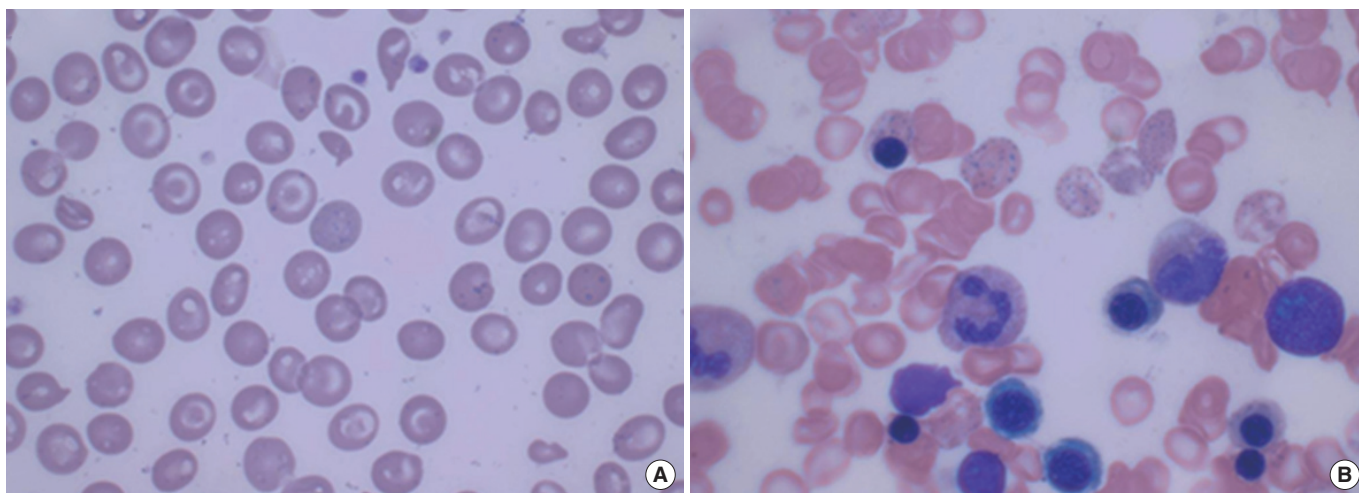


Fig. 1. (A) Peripheral blood smear showing microcytic hypochromic red cells with frequent targeting and basophilic stippling. (B) Bone marrow aspirate showing erythroid hyperplasia and basophilic stippling in erythroid cells (Wright stain, $\times 1,000$).

azotemia. Urinalysis showed proteinuria (2+) and blood (3+). More than 90% of the red blood corpuscles were dysmorphic. Serum IgA levels were elevated to 673 mg/dL; serum levels of other immunoglobulins (IgM, 90.0 mg/dL; IgG, 1,313.0 mg/dL), were normal. Rheumatoid factor and antistreptolysin O titer were also within the reference ranges. Levels of the complement proteins C3 (96.0 mg/dL) and C4 (26.0 mg/dL) were in the reference ranges as well; CH50 activity was slightly elevated to 57 U/mL. No viral markers were detected, including hepatitis B surface antigen, anti-hepatitis surface antigen antibodies, and human immunodeficiency virus markers. Tests for cryoglobulins and anti-neutrophil cytoplasmic antibodies were all negative. On the other hand, the fluorescent anti-nuclear antibody test was positive, with a dense fine speckled pattern; the anti-dsDNA antibody test was negative. Kidney ultrasonography showed a chronic renal parenchymal disease. Therefore, a renal biopsy was conducted, and 2 renal cortex cores with 35 glomeruli were obtained. Global sclerosis was detected in 26 of these glomeruli, and fibrocellular crescents were found in 2 glomeruli. Immunofluorescent analysis revealed prominent mesangial staining for IgA. Electron microscopy revealed no significant abnormalities. The patient was diagnosed with IgA nephropathy, based on the renal biopsy results.

It has been suggested that microscopic hematuria in thalassemia patients is caused by renal tubular abnormalities. Moreover, the severity of tubular dysfunction was found to be correlated with the degree of anemia. Other identified factors that could also contribute to renal tubular damage are: shortened red cell lifespan, rapid iron turnover, multiple blood transfusions, deferoxamine toxicity, iron overload, and tissue deposition of ex-

cessive iron [3-6]. Several studies have described renal tubular dysfunction in patients with thalassemia. For instance, Cetin et al. [7] reported that 6 of 41 patients with beta-thalassemia minor suffered from renal tubular dysfunction, including hypercalciuria, decreased tubular phosphorus reabsorption, renal magnesium and uric acid wasting, and tubular proteinuria. In addition, only anemic patients (46.3%) showed an increase in urinary zinc excretion and fractional excretion of sodium and uric acid. However, despite these results as well as the results from an animal study that identified focal proximal tubular necrosis as the morphological change in the renal cortex of anemic rats [8], these studies have not been confirmed by actual renal biopsies in thalassemia patients.

On the other hand, glomerulonephritis has not been considered to play a critical role in microscopic hematuria associated with thalassemia. Only 1 published study has confirmed IgA nephropathy by renal biopsy, in a Malaysian beta-thalassemia patient with microscopic hematuria [9]. In humans and other primates, the elimination process of immune complexes in the liver or spleen, which is important to their removal from circulation, requires their binding to erythrocytes through complement receptors [10]. Importantly, erythrocyte complement receptors exhibit genetic polymorphisms. Moreover, a high expression level of erythrocyte complement receptors enhances the formation of rosettes, which is associated with severe malaria such as cerebral malaria. Interestingly, populations in malaria-endemic regions exhibit very low complement receptor 1 expression levels [11], which can be advantageous from an evolutionary point of view. However, the low expression of erythrocyte complement receptors compromises immune complex clearance. IgA ne-

phropathy is an immune complex-mediated disease characterized by impairment of phagocytic function and the presence of abnormal IgA immune complexes in circulation and in the glomerular mesangium. In thalassemia patients, compromised elimination of the circulatory immune complex could lead to IgA nephropathy.

The recent rise in the number of multi-cultural families, due to the increase in migration and the growing number of international marriages, increases the possibility of encountering thalassemia during clinical practice in Korea [12]. In addition to renal tubular abnormalities, IgA nephropathy should be potentially considered as one of the main causes of microscopic hematuria, which is a complication frequently encountered in thalassemia patients.

Authors' Disclosures of Potential Conflicts of Interest

No potential conflicts of interest relevant to this article were reported.

REFERENCES

1. Forget BG. Thalassemia syndromes. In: Hoffman R, Benz EJ Jr, Shattil SJ, et al. eds. Hematology: Basic principles and practice. 3rd ed. New York: Churchill Livingstone, 2000:485.
2. Olivieri NF. The β -thalassemias. *N Engl J Med* 1999;341:99-109.
3. Cianciulli P, Sollecito D, Sorrentino F, Forte L, Gilardi E, Massa A, et al. Early detection of nephrotoxic effects in thalassemic patients receiving deferoxamine therapy. *Kidney Int* 1994;46:467-70.
4. Koliakos G, Papachristou F, Koussi A, Perifanis V, Tsatra I, Souliou E, et al. Urine biochemical markers of early renal dysfunction are associated with iron overload in β -thalassemia. *Clin Lab Haematol* 2003;25:105-9.
5. Koren G, Bentur Y, Strong D, Harvey E, Klein J, Baumal R, et al. Acute changes in renal function associated with deferoxamine therapy. *Am J Dis Child* 1989;143:1077-80.
6. Aldudak B, Karabay Bayazit A, Noyan A, Ozel A, Anarat A, Sasmaz I, et al. Renal function in pediatric patients with β -thalassemia major. *Pediatr Nephrol* 2000;15:109-12.
7. Cetin T, Oktenli C, Ozgurtas T, Yenicesu M, Sanisoglu SY, Oguz Y, et al. Renal tubular dysfunction in β -thalassemia minor. *Am J Kidney Dis* 2003;42:1164-8.
8. Kaissling B, Spiess S, Rinne B, Le Hir M. Effects of anemia on morphology of rat renal cortex. *Am J Physiol* 1993;264:F608-17.
9. Harada T, Ozono Y, Miyazaki M, Yamaguchi K, Kanamoto Y, Hara K, et al. Association of IgA nephropathy and β -thalassemia. *Clin Nephrol* 1994;41:181-2.
10. Hebert LA and Cosio G. The erythrocyte-immune complex-glomerulonephritis connection in man. *Kidney Int* 1987;31:877-85.
11. Sinha S, Jha GN, Anand P, Qidwai T, Pati SS, Mohanty S, et al. CR1 levels and gene polymorphisms exhibit differential association with falciparum malaria in regions of varying disease endemicity. *Hum Immunol* 2009;70:244-50.
12. Lee JJ and Ahn JS. Recently increasing hematologic diseases in Korea. *Korean J Med* 2010;78:557-63.