

CASE REPORT

Renal failure in thalassemia: Thinking outside the box

Ganesh Kasinathan 

Department of Hematology, Ampang Hospital, Jalan Mewah Utara, Pandan Mewah, Ampang, Malaysia

Correspondence

Ganesh Kasinathan, Department of Hematology, Ampang Hospital, Jalan Mewah Utara, Pandan Mewah, 68000 Ampang, Selangor, Malaysia.
Email: ganeshkasinathan11@hotmail.com

Funding information

Self-funding.

Abstract

Berger's disease should be considered an imperative cause of renal dysfunction in thalassemia. This case highlights the importance of early diagnosis, clinicopathological correlation and prompt therapy in Berger's disease.

KEYWORDS

Berger's disease, corticosteroids, nephrotic syndrome, renal failure, thalassemia

1 | INTRODUCTION

A 24-year-old splenectomized Hb E beta thalassemia female presented with anasarca and acute kidney injury. She has hemosiderosis in which she is on iron chelation therapy. The renal biopsy was consistent with Berger's disease-induced nephrotic syndrome. She was treated promptly with corticosteroids. Currently, she is in complete remission.

Thalassemia is a genetic disorder in which the production of one or more globin chain synthesis is reduced resulting in ineffective erythropoiesis. The highest incidence of thalassemia is seen in the Mediterranean region, Southeast Asia, and North Africa.¹ Hemoglobin E is the most common Hb variant of beta globin gene in Southeast Asia mainland bordering Thailand, Laos, and Cambodia, thus giving rise to the term "Hb E triangle."² Hb E is characterized by a point mutation in exon 1 at codon 26 (GAG to AAG) on chromosome 11, which results in the substitution of lysine for glutamic acid.³ The interaction of Hb E and beta thalassemia gives rise to Hb E beta thalassemia which is a very heterogeneous condition with clinical diverse phenotypes. Renal dysfunction is commonly seen in patients with thalassemia which are attributed to a variety of factors. A patient with Hb E beta thalassemia who presents with acute kidney injury attributed to Berger's disease is described below.

2 | CASE PRESENTATION

A 24-year-old female of Malay ethnicity presented to the thalassemia ward with progressive worsening of generalized body swelling, frothy urine, and exertional dyspnea for the past 2 months. She is known to have Hb E beta Thalassemia, in which, she has been transfusion-dependent monthly since the age of 3. She underwent splenectomy at the age of 10 due to increasing transfusion requirement associated with rising ferritin levels. She is on subcutaneous deferoxamine and oral deferiprone iron chelation therapy. She has a family history of Hb E beta thalassemia with no other significant past medical history. There is no history of parental consanguinity. She is a nonsmoker and a teetotaler and works as a cashier at a grocery.

Physical examination revealed a female with short stature, hyperpigmentation, prominent frontal bossing, depressed nasal bridge, and maxillary protrusion. Generalized anasarca was present. Her lungs revealed bibasilar crackles. She had hepatomegaly of 5 cm. Shifting dullness was present consistent with ascites. Other systems were unremarkable.

The complete blood count revealed hypochromic microcytic anemia with leukocytosis and thrombocytosis. She had severe hyperferritinemia of 8500 ng/mL. The other laboratory parameters are tabulated in Table 1. Peripheral blood film (Figure 1A) which was taken 3 weeks post-transfusion

TABLE 1 Tabulation of laboratory parameters

Laboratory parameters	Values (unit and normal range)
Hemoglobin	7.4 (11.5-16 g/L)
Total white cell count	25 ($4-10 \times 10^9/L$)
Platelet	750 ($150-400 \times 10^9/L$)
Urea	20 (1.8-7 mmol/L)
Creatinine	340 (40-100 $\mu\text{mol/L}$)
Albumin	19 (35-50 g/L)
Alanine aminotransferase	28 (0-40 U/L)
Serum triglyceride	7.4 ($<1.7 \text{ mmol/L}$)
Serum IgA	850 (70-400 mg/dL)
Hep Bs Ag	Not detected
Anti-Hep C	Not detected
Anti-HIV-1,2	Not detected
Antistreptolysin O-titer (ASOT)	Negative
Anti-nuclear antibody (ANA)	Negative
c-Antineutrophil cytoplasmic antibody (c-ANCA)	Negative
p-Antineutrophil cytoplasmic antibody (p-ANCA)	Negative

(as the patient was transfusion-dependent) portrayed features consistent with hemoglobinopathy associated with chronic hemolysis. Capillary electrophoresis showed the absence of Hb A, elevated Hb A2 of 5%, a high Hb F of 55%, and a Hb E of 40%. The DNA analysis of beta globin gene demonstrated substitution of lysine for glutamic acid on codon 26 of chromosome 11 and mutation in IVS 1-1 (G to T) which was consistent with Hb E beta thalassemia.

There was an acute decline in renal function to a creatinine of 340 $\mu\text{mol/L}$. Her renal function was previously normal. The urine analysis showed protein 4+ and blood 2+. Dysmorphic red blood cell casts were seen on urine microscopy. Her 24-hour urine protein analysis of 9.0 g was consistent with nephrotic syndrome.

An ultrasonogram showed hepatomegaly, normal sized kidneys with no evidence of obstructive uropathy. Magnetic resonance imaging (MRI) T2* of the cardiac and liver utilizing T2* axial liver and short axis heart sequences (Figures 1B and 2A,B) showed severe liver iron overload and normal cardiac iron load. FerriScan R2-MRI imaging technology was unavailable at our center for more accurate liver iron concentration analysis. A percutaneous liver biopsy was not performed due to the risk of bleeding which may be associated with the presence of probable concomitant extramedullary hematopoiesis in the liver.

At presentation, the acute kidney injury was thought to be attributed to the iron chelation therapy and iron overload. Despite a trial of discontinuation of the iron chelation drugs for more than a week, the nephrotic syndrome persisted with progressive decline in renal function.

A decision was made to perform a renal biopsy. Two cores of renal cortex containing up to 18 glomeruli were analyzed. They showed features of IgA nephropathy exhibiting focal endocapillary proliferation with active crescents in 2/18 glomeruli, global sclerosis in 8/18, segmental sclerosis in 3/18, and mesangial cell proliferation in the background. There was moderate to severe tubular atrophy and interstitial fibrosis associated with moderate lymphocytic infiltrates admixed with occasional eosinophils. Immunofluorescence revealed IgA (2+), IgM (1+), and C3 (1+) mainly in the mesangium.

On the basis of these findings, a diagnosis of IgA nephropathy-induced nephrotic syndrome was made.

She was pulsed with intravenous methylprednisolone 500 mg daily for 3 days followed by oral prednisolone 1 mg/kg daily for a month which was then tapered gradually based on response. Her proteinuria and renal function improved significantly. Currently, she is on 3-month follow-up at the thalassemia and nephrology clinics.

3 | DISCUSSION

This is a rare case of IgA nephropathy-induced nephrotic syndrome in a patient with Hb E beta thalassemia. There are numerous factors that could contribute to renal disease in a patient with thalassemia. Among them are iron overload, chronic anemia, hypoxia, acquired Fanconi syndrome, inappropriate use of iron chelation, nephrotoxic drugs, infectious agents, postsplenectomy, and nephrolithiasis. Glomerulonephritis is often not considered an important cause for renal dysfunction in patients with thalassemia as renal biopsies are frequently not performed, thus missing out on such an imperative diagnosis.

Ig A nephropathy which is also known as Berger's disease as seen in this patient is the most common glomerulonephritis globally.⁴ It is characterized by the presence of circulating and glomerular immune complexes consisting of galactose-deficient IgA1 and C3.⁵ These immune complexes contribute to glomerular inflammation and proliferation in the mesangium. Stimulation of the renin-angiotensin system further results in glomerulosclerosis and tubulointerstitial fibrosis.⁵ In nonthalassemic humans, these immune complexes bind to the erythrocyte complement receptors, thereby removing them from the circulation via the liver and spleen.⁶ The lower levels of erythrocyte complement receptors in patients with thalassemia compromise clearance of these immune complexes, thus leading to Ig A nephropathy.

Hemosiderosis in this patient could be attributed to various factors. Among them are regular packed red blood cell transfusion, rapid iron turnover, shortened erythrocyte life span, and intramedullary destruction of erythrocyte

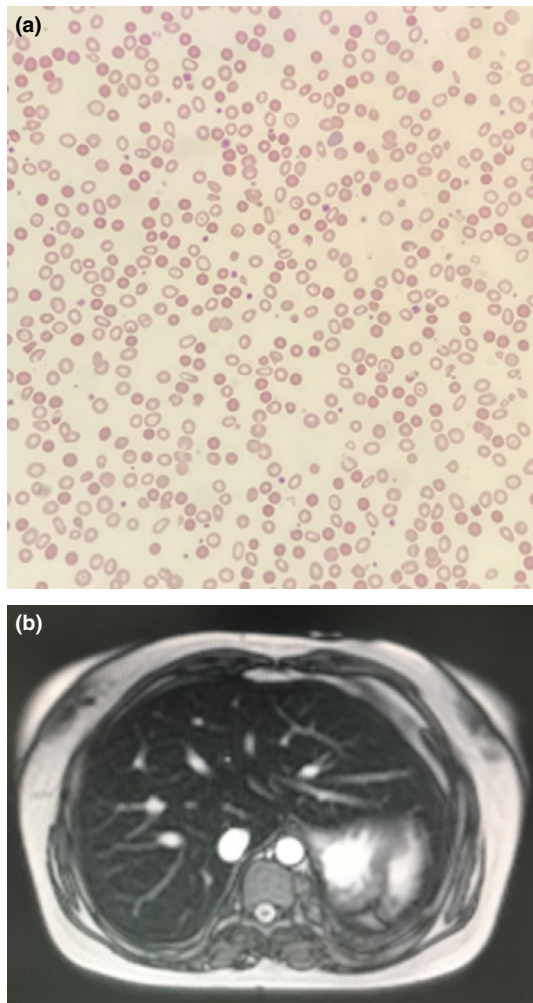


FIGURE 1 (A) Peripheral blood film (post-transfusion sample as this patient is transfusion-dependent) shows hypochromic microcytic red blood cells, anisopoikilocytosis, numerous target cells, and irregular contracted cells with features of chronic hemolysis. (B) MRI T2* of the liver shows liver iron quantification done with region of interest in the right lobe measuring 36.2 mg/g with corresponding T2* of 0.9 ms (severe liver iron overload)

precursors.⁷ Many similar studies have shown that excessive iron deposition results in the production of reactive oxygen species which aggravates renal cellular injury.⁷

A renal biopsy would be effective in providing information on iron deposition in the kidneys. However, it may not be feasible in many thalassemic patients due to the invasive nature of the procedure. A MRI T2* of the kidneys would be ideal to assess renal hemosiderosis. A study was conducted in Iran in which 83 patients with thalassemia major and 37 patients with thalassemia intermedia were enrolled, and all of them were on iron chelation.⁸ The study demonstrated moderate correlation between serum ferritin and kidney T2* relaxation.⁸

Iron chelation may contribute to renal impairment in patients with thalassemia. Most patients with thalassemia are on iron chelation. There have been reports suggesting that

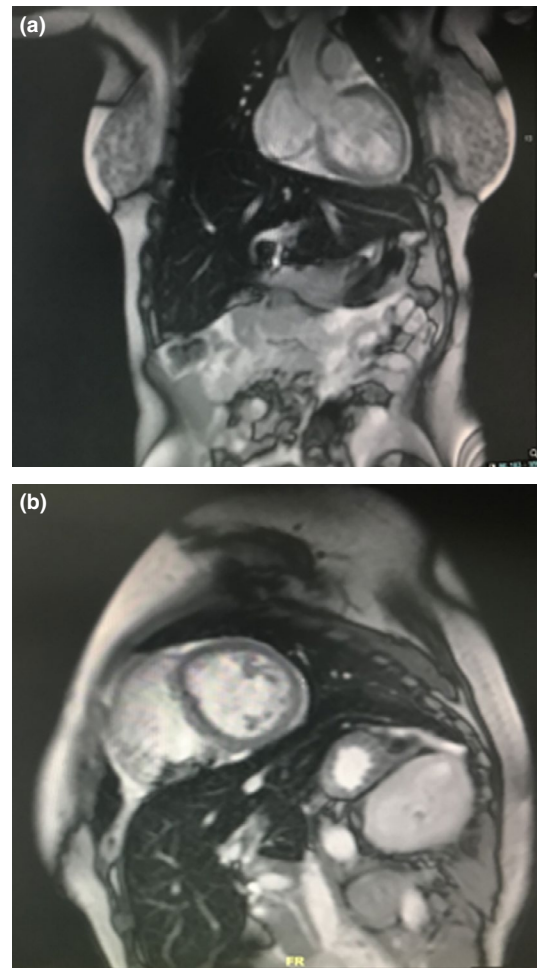


FIGURE 2 (A, B) MRI T2* of the cardiac shows cardiac iron quantification with the region of interest in the interventricular septum measuring 1.01 mg/g with the corresponding T2* of 22.5 ms (normal iron load of the heart)

overdosage of deferoxamine due to pump malfunction could result in renal failure. Renal biopsy often reveals proximal tubule damage which is often reversible in nature.⁹ Deferasirox may also result in fluctuations in serum creatinine and an increased incidence of Fanconi syndrome.¹⁰ Frequently, overchelation with deferasirox leads to dramatic depletion of ferritin and reduction in glomerular filtration rate. The dramatic depletion of iron results in damage to renal tubule mitochondria, increased production of adenosine triphosphate and arachidonic acid cascade imbalance, with all these contributing to loss of renal function.¹⁰ Deferiprone is associated with 1%-2% of agranulocytosis which could aggravate sepsis which might be an important cause for acute tubular necrosis.¹⁰

Chronic anemia is often associated with reactive oxygen species production and may induce tubulointerstitial hypoxia leading to glomerulosclerosis and renal fibrosis.¹¹ Reduced systemic vascular resistance and resulting hyperdynamic circulation lead to stretching of the capillary walls of the

glomeruli and endothelial injury further precipitating decline in renal function.¹¹

The patient in this case underwent splenectomy at the age of 10. Splenectomy is an independent risk factor for renal tubular abnormalities. Increased levels of N-Acetyl-beta-D-glucosaminidase (NAG), alpha-1 microglobulin, and hyperferritinemia are seen in splenectomized patients.¹²

The presence of nephrolithiasis in transfusion-dependent thalassemia might contribute to renal impairment. The prevalence of nephrolithiasis in transfusion-dependent thalassemia might reach 59% as shown in a study involving 27 subjects with beta thalassemia major by CT urography.¹³ Hypercalciuria, hyperuricosuria, and cystinuria are probable mechanisms in renal stone formers. The majority of renal calculi were struvite (33%) followed by calcium oxalate (31%) and cystine (22%).¹³ Many studies have demonstrated calcium and vitamin D intake in patients with thalassemia were not risk factors for nephrolithiasis.

Hence, there are many factors through various mechanisms which might contribute to acute renal injury in a particular patient with thalassemia as portrayed in this case. Some may predominate over the other. More longitudinal studies investigating the true incidence and mechanisms of renal dysfunction in thalassemia are required as data are lacking in this group of patients.

4 | CONCLUSION

Ig A nephropathy should be considered as one of the main causes of renal dysfunction in a patient with thalassemia. Disease progression and end-stage kidney disease can be prevented by reaching an early diagnosis and instituting prompt therapy. This case also highlights the importance of clinicopathological correlation in managing patients with thalassemia as these patients often have other concomitant systemic manifestations.

5 | DATA AVAILABILITY MATERIAL

Not applicable.

ACKNOWLEDGMENT

None.

CONFLICT OF INTEREST

The author declares there are no conflicting interests.

AUTHOR'S CONTRIBUTION

The author solely contributed toward the writing of this manuscript.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Not applicable.

CONSENT

Written informed consent was obtained from the patient for publication of this case report and any accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal.

ORCID

Ganesh Kasinathan  <https://orcid.org/0000-0002-7489-9261>

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How to cite this article: Kasinathan G. Renal failure in thalassemia: Thinking outside the box.

Clin Case Rep. 2020;8:811–814. <https://doi.org/10.1002/ccr3.2738>