Abstract: The patients with hereditary spherocytosis (HS) mostly have mild degree of hemolytic anemia, mild jaundice and splenomegaly and usually respond well to splenectomy. In occasional instances, the diagnosis of HS may be overlooked and delayed for a very long time as in our case. She was a 26-year-old Thai patient who was simply diagnosed as severe thalassemia since childhood because of her typical thalassemic facies, severe microcytic hemolytic anemia, the prominent splenomegaly and her birthplace where various thalassemias and hemoglobinopathies were highly prevalent. She had been treated with regular blood transfusion every two or three months since then. The splenectomy and later cholecystectomy were performed at the age of 9 and 12 years old, respectively. The last blood test showed Hb 9.4 g%, Hct 25.3%, MCV 77.2 fL, MCHC 37.0, RDW 21.5%, hypochromia 1+, microspherocytosis 2+, ferritin 4,142-5,611 ng/mL. With repeated Hb electrophoresis, slightly increased percentage of Hb A2, 3.7-4.4 %, was the only one abnormality detected. Other blood tests included positive osmotic fragility test, negative direct anti-globulin test. The thalassemia genotype study revealed only alpha-thalassemia-2 (3.7 kb) trait, neither alpha thalassemia-1 nor beta thalassemia genotype was found, therefore the final diagnosis of severe HS with secondary hemosiderosis was established. The slightly increased percentage of Hb A2 overlapping that of beta thalassemia trait was presumably due to severe HS itself. Likewise, the so-called thalassemic facies in our case was supposedly from the active intramedullary erythropoiesis compensating to severe and chronic hemolysis since birth that could be documented in any case with either severe thalassemia or severe HS.

Hereditary spherocytosis misdiagnosed as severe thalassemia for more than two decades: A case report

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**Introduction**

Hereditary spherocytosis (HS) is a genetic disorder resulting in the defects of some proteins of the cell membrane of red blood cells (RBC), ankyrin, band -3, protein 4.2 or spectrin. This leads to loss of the membrane surface area, to form the spherocyte that will be trapped and destroyed in the spleen, causing hemolysis and splenomegaly. The main presentations consist of hemolytic anemia, mild jaundice and splenomegaly and the severity of anemia is extremely variable. Most cases have a well-compensated hemolytic anemia while the minority have severe anemia until RBC transfusion is needed.\(^1\)

The RBC in HS is characterized by lack of the central pallor and typical RBC indices consisting of decreased mean corpuscular volume (MCV) and increased mean corpuscular hemoglobin concentration (MCHC)\(^2\).
HS is common in the north European population but rather rare in oriental countries such as, Thailand, Japan, and Malaysia. Atypical cases of HS may be easily misdiagnosed especially in the patient with severe hemolytic anemia born in Nakhon Ratchasima, the area of the highest prevalence of thalassemia/ hemoglobinopathy. This report was aimed to study and discuss the case of severe HS whose proper diagnosis was overlooked and delayed for more than two decades.

**Case Report**

A 26-year old Thai married woman had been misdiagnosed as severe thalassemia since early childhood because of severe hemolytic anemia with hypochromia and microcytosis, and the typical thalassemic facies, frontal bossing, saddle nose and maxillary protrusion, prominent upper incisor. She was regularly transfused with the packed RB every 2 or 3 months since then. The splenectomy due to too frequent transfusion at the age of 9 years and the cholecystectomy because of gall stones cholecystitis with the were performed at the age of 12 years old.

Her weight was 45 kg, height was 1.65 m, and BMI was 16.5 kg/m². Besides the thalassemic facies, she had pallor, mild jaundice, generalized dark skin but no hepatomegaly. The last CBC: Hb 9.4 g%, Hct 25.3%, MCV 77.2 fL, MCH 28.6 pg, MCHC 37.0 g%, RDW 21.5%, WBC 19,200/mm³, platelet 781,000/mm³, hypochromia 1+, few anisocytosis 2+, microcytosis 2+, spherocytosis 2+.

Other tests: creatinine 0.5 mg%, albumin 3.7 g%, globulin 4.0 g%, direct bilirubin 0.9 mg%, total bilirubin 4.7 mg%, uric acid 3.7 mg%, erythropoietin 167 mIU/mL (normal 2.6-34.0), ESR 54 mm/hr, ferritin 4,142-5,611 ng/mL, serum iron 148 mcg% (normal 35-165), TIBC 321 mcg% (normal 259-388), FBS 100 mg%.

The repeated Hb electrophoresis using the high performance liquid chromatography (Bio-Rad) showed Hb A2A, Hb F 1.3-2.1%, Hb A2 3.7-4.4%, the thalassemia genotype study showed no common and rare beta-thalassemia, no alpha-thalassemia-1 (SEA and Thai deletions) but alpha-thalassemia-2 genes (3.7 kb deletion) detected.

Other hemolytic tests: negative direct antoglobulin test, positive osmotic fragility test, normal G-6-PD enzyme, negative Ham’s test, no urine hemosiderin. The flow cytometry showed no clone of paroxysmal nocturnal hemoglobinuria.

Her final diagnosis was severe HS, secondary hemosiderosis and alpha-thalassemia-2 trait. And she still has been receiving the blood transfusion every 2 or 3 months with deferiprone.

The pedigree could not be studied, her parents passed away in the traffic accident. She had no sibling and no offspring the birth control.
Discussion

Our case has been misdiagnosed as severe thalassemia for more than 2 decades because of the typical thalassemic or chipmunk facies in combination with microcytic hemolytic anemia. With familiarity, all cases with such microcytic hemolytic anemia found in Thailand are expected to have one of thalassemia and/or hemoglobinopathy although the Hb electrophoresis has never detected any severe form of thalassemia.

The misdiagnosis as severe thalassemia has been continued after the splenectomy because the Hb concentration is not dramatically improved that seems more consistent with the characteristic of severe beta thalassemia or beta-thalassemia / Hb E disease whereas it can be normalized in most patients with HS, except the patients who have the spectrin less than 30-74% or the severe form of HS that may respond only slightly to splenectomy.

Her final diagnosis of severe HS is definitely made after the full investigations of the hemolytic anemia show positive osmotic fragility test that has sensitivity ranging from 48 to 95% for the diagnosis, with the typical RBC indices; low MCV, high MCHC and high RDW although the new generation tests such as the eosin-52-maleimide-binding test, the acidified glycerol lysis test or pink test has not been performed yet.

The mean MCHC among cases with HS was 35.7 ± 1.3 g% while the RDW was 20.6 ± 4.5% and 70% of cases have MCHC more than 38 g%. The combination of MCHC >34.5 g% and RDW >14.5% have sensitivity 81% and specificity 98% for the diagnosis of HS. Some authors added MCV <80 fl upon the combination of MCHC > 38 g% and RDW > 15% for suggesting HS. The RBC indices in our case consisted of MCV 77.2 fl, MCHC 37.0 g% and RDW 21.5%. Not only they did not oppose but also support the diagnosis of HS.

The percentage of Hb A2 was slightly increased in our case for many times, 3.7-4.4%, almost overlapping the range of Hb A2 of beta thalassemia trait (BTT), 4.2-8.2%. Besides the misdiagnosis as a severe thalassemia, the slightly higher Hb A2 also misleads us to diagnose BTT with marked anemia from unknown etiologies until the beta thalassemia genotypes was proved to be absent. It seems to suggest that slightly increased Hb A2 may be directly due to HS itself. Likewise, the so-called typical thalassemic facies could be found in not only severe thalassemia but also in other congenital severe and long standing hemolytic anemia with the intra-medullary erythroid hyperplasia for compensation such as Gaucher’s disease. On the contrary, the thalassemia facies in cases with severe thalassemia may be prevented by the adequate transfusion.

Because BTT is highly prevalent, 1.7-6.0%, in Thailand, when the normal or mildly anemic patients with low MCV and slightly high Hb A2 level are encountered, the diagnosis of BTT is almost definitely concluded and HS will be easily overlooked. However the MCHC may be helpful to distinguish these two easily confusing entities because it is definitely different, 31.1±2.2 in BTT vs 35.7±1.3 g% in HS.

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Conclusion

A 26-year-old Thai woman was misdiagnosed as severe thalassemia for more than two decades because of transfusion-dependent microcytic hemo-lytic anemia with typical thalassemic facies. Based on the MCV 77.2 fl, MCHC 37.0 g%, RDW 21.5 %, positive osmotic fragility and only slightly increased Hb A2 concentration, the final diagnosis was corrected to be severe hereditary spherocytosis.

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