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Case report

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HEMOSIDEROSIS IN A PATIENT WITH Hb YOKOHAMA β 31 (B13) Leu—Pro HEMOGLOBINOPATHY

SUMMARY

In this paper a case of 19 year old patient with severe transfusion dependent hemolytic anemia due to Hb Yokohama β 31(B 13) Leu-Pro, hemoglobinopathy is presented. The first symptoms of anemia were detected when he was only 7 months old. Splenectomy due to misdiagnosis was performed when he was 2 years old. Seven years later the correct diagnosis was made, using the high performance liquid chromatographic analysis. De novo mutation was confirmed by the sequencing of amplified DNA.

Chelation therapy was given infrequently and occasionally until he came to our institution. At the initial presentation he had fully developed respiratory insufficiency with heath failure and evidence of lung and liver hemosiderosis, chronic hemolytic anemia and protein-energy malnutrition. Intensive continuous intravenous chelation therapy, folic acid and B complex vitamins supplementation as well as oxygenation and cardiac supportive therapy were given. Intensive chelation therapy was unable to stop the progression of multi organ dysfunction and lethal outcome was inevitable.

Authors also discuss management protocols in a setting of extensive complications of iron overload in hemoglobinophatias.

Key words: **Hemoglobinophaty, iron overload, Yokohama hemoglobine**

INTRODUCTION

Unstable hemoglobines are occasionally encountered as "de novo" mutations. Not many patients with unstable hemoglobin follow an aggressive clinical course. Such a case is presented in this paper, with lung, hearth and liver hemochromatosis as late complications. Multi-organ dysfunction due to hemochromatosis in conjunction with hemolytic crisis and hemoglobin instability led to an unfavorable clinical outcome.

CASE REPORT

A 19-year-old male with severe transfusion dependent hemolytic anemia due to hemoglobinopathy with Hb Yokohama beta 31 (B13) Leu-Pro was treated at our institution. The first symptoms of anemia were detected when he was only 7 months old. Splenectomy was performed when he was 2 years old, due to misdiagnosis. A correct diagnosis was made seven years later, using the high performance liquid chromatographic analysis and this "*de novo*" mutation was confirmed with sequencing of the amplified DNA (1). During the next nine years he was treated with chelation therapy infrequently until he came to our institution.

He was admitted at our clinic in August 2000 with nausea, dyspnea, pallor and jaundice. He had 26 respiration/min with normal breath sounds. Cardiac auscultation revealed tachycardia and holosystolic murmur over the precordium with maxi-

mum at the apex. He had enormously enlarged liver (reaching umbilicus).

At the initial presentation he had fully developed respiratory failure and chronic cor pumonale, secondary to pulmonary hemochromatosis.

Laboratory evidence of hemolysis, liver disorder and protein-energy malnutrition were found. Extreme trombocytosis (850 x 10^9/L), leukocytosis (WBC 19,2 x 10^9/L) hematocrite 42 – 44% and pathological blood smear were the result of hemoglobinophaty and splenectomy (figure 1).

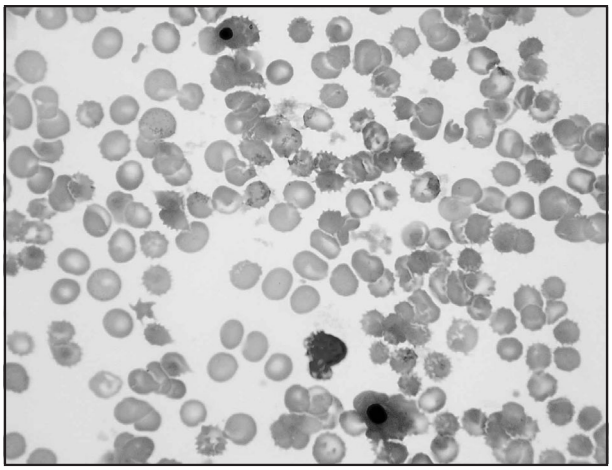

Figure 1. Anisocytosis, poikilocytosis, basophilic stippling were found on the blood film. As a result of splenectomy a large proportion of acydophilic erythroblasts as well as cells with Heinz bodies could be seen

Biochemical parameters revealed hyperbilirubinemia, both unconjugated and conjugated, as well as an elevation of uric acid and lactic dehidrogenase (LDH): Bilirubine conjugated 37.0 mmol/L, unconjugated 195.0 mmol/L, Fibrinogen 0.9 g/L, Glycaemia 5.0, Total proteins 76.9 g/L, AST, ALT in the normal range, Cholesterol 1.35 mmol/l, Triglycerides 0.52 mmol/l, uric acid 655.6 μmol/l, ALP 77.9 U/L, CPK 43.3 U/L, LDH was extremely elevated.

The ECG shows right axis deviation, with high p waves in D2 and V1-V3, and signs of right ventricular hypertrophy (high R in V1, deep S in V5 - V6). Enlargement of the heart was recorded on the chest radiogram (figure 2).

Intensive chelation therapy, supplementation of folic acid and B-complex vitamins as well as oxygenation and administration of methylxantines and digitalis were started. His status improved and he was released from the hospital with recommendation to continue the chelation and vitamin supplementation therapy.

In less than a month he was admitted for the last time with signs and symptoms of multi-organ dysfunction. Biochemical parameters displayed intensive elevation of aminotransferase enzymes as well as LDH, creatine-phosphokinase and intensive protein

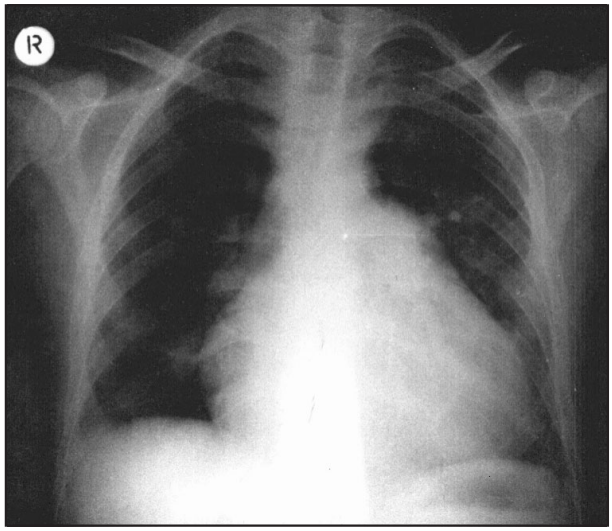

Figure 2. Enlargement of the heart with striking widening of the pulmonary artery and right ventricle shadows

and energy malnutrition: AST 452IU/L, ALT 1422.2 IU/L, Hol 1.46, Trigl 1.14, Uric acid 407.6 μmol/L, CPK1 2748.0 IU/L, LDH 2417.0 IU/L.

Blood gases parameters showed serious increase of arterial-venous shunt as well as deprivation of blood oxygen saturation: pH 7.47, $PaCO_2$ 23.6 mmHg, PaO_2 43mmHg, HCO_3 16.6 mmol/L, TCO_2 18.1 mmol/L, BEb –3.7 mmol/L, BEeff – 6.5 mmol/l, SBC 21.6 mmol/l, SaO_2 81.6% (figure 3).

Intensive chelation therapy and other supportive measures were unable to stop the progression of multi-organ dysfunction and the lethal outcome was inevitable.

DISCUSSION

Yokohama hemoglobin belongs to a group of unstable forms of hemoglobin. There are no data about its oxygen affinity, hydrofobicity and other features that could influence its physiological function in patients. It is obvious that such an unstable protein could limit oxygen delivery to tissues and in that way enhances the severity of respiratory failure resulting from ongoing pulmonary hemochromatosis. Measuring of arterio-venous shunt is therefore important in the assessment of severity of this combined failure. Our patient's blood gases results slightly improved after administration of oxygen therapy (saturation changed from 87.9–89.9%), emphasizing the negative impact of hemoglobinophaty on respiration.

Vigorous desferrioxamine therapy with standard dosage of 50 mg/kg/day could not stop the progression of cardiac and respiratory failure and higher dosage regimen could not be administered due to patient's noncompliance. The fact that desferrioxamine had to be administered chronically by

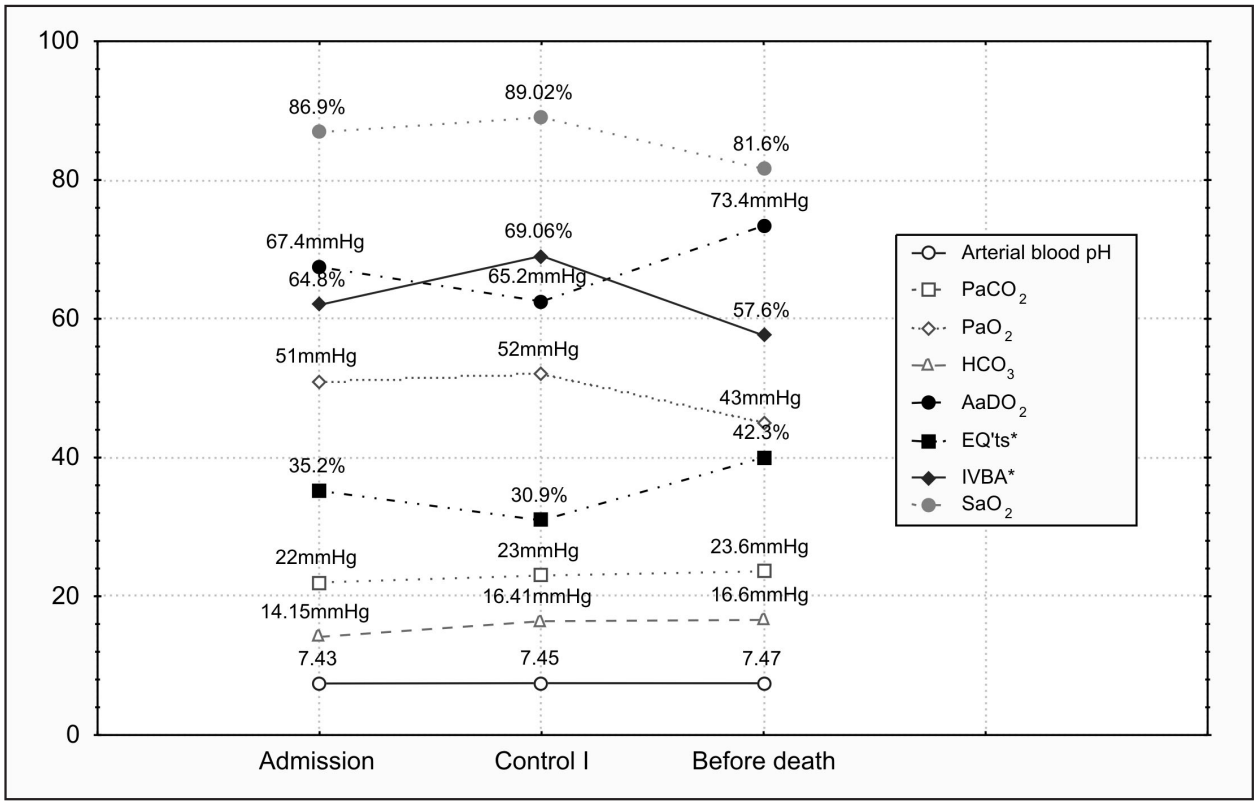

Figure 3. Blood gases and arterial-venous shunt values
Abbreviations: $PaCO_2$ – Arterial partial pressure of carbon dioxide; PaO_2 – Arterial partial pressure of oxygen; HCO_3 – plasma bicarbonate concentration; SaO_2 – oxyhemoglobine saturation; $AaDO_2$ alveolar-arterial oxygen difference; EQ' ts – estimated total R-L shunt; IVBA – index of venous blood arterialisation Parameters marked with * were calculated according to procedure described by Milićevic et al. (12)*

subcutaneous continuous 18 hour infusion through a battery-operated portable pump, severely strained the patients' compliance. Franchini et al. assessed the long-term efficacy of twice-daily subcutaneous bolus injections of desferrioxamine by analyzing ferritinemia in 27 transfusion-dependent adult patients with oncohematologic disorders and mild to moderate iron overload (2). After a 20-months follow-up, subcutaneous bolus injection of desferrioxamine was found to be well tolerated, and as safe and effective as subcutaneous continuous infusion in controlling iron burden. However, a very recent update of this study (3) has given rise to some concerns on the long-term tolerability of the method. In fact, three out of the eight patients still evaluable after a median follow-up of 76 months did not tolerate the volume of the bolus injections (10 ml every injection) and preferred to continue chelation therapy with the standard subcutaneous continuous infusion with a portable pump. Moreover, there are no studies evaluating the long-term efficacy and safety of this method in patients with higher iron overload who require larger doses of desferrioxamine, such as thalassemic patients.

Management of the multy-organ dysfunction with very high dosage regimen with 6–12 grams of desferrioxamine /daily in 12 hours infusion, proved to be successful in thalassemic patients after at least one year of treatment (4). Evaluation of cost-effectiveness of such an aggressive, toxic and costly regimens is also required, and desferrioxamine dose adjustment is mandatory (5). Clinical experience and literature data continuously urge for developing of potential alternatives to desferrioxamine in order to solve numerous problems concerning its adverse effects and its way of administration. Deferiprone (Ferriprox, Apotex Inc., Toronto, Canada) is the only orally active iron chelator currently available for clinical use. A meta-analysis of the main deferiprone clinical trials between 1989 and 1999 concluded that this drug, at a dose of at least 75 mg/kg/day, is clinically effective in inducing a negative iron balance and reducing the body iron burden in most patients with marked iron overload (6). The side effects of deferiprone therapy include arthropathy, abnormalities of liver function, gastrointestinal disturbances, mild neutropenia and agranulocytosis. In 1998, Olivieri et al. reported that hepatic fibrosis progressed in five out of 14 evaluable patients with thalassemia on long-term deferiprone treatment, (7) but their results were confuted by further studies (8). However, further studies are required to evaluate the impact of deferiprone on cardiac and liver disease.

Animal studies have shown that the novel tridentate oral iron chelator ICL670A is four to five times more effective than parenteral desferrioxamine in promoting the excretion, which is predominantly via the fecal route, of chelatable iron from hepatocellular iron stores. The first study in humans was conducted in Italy in 25 transfusion-dependent thalassemic patients receiving single oral doses of ICL670A ranging from 2.5 to 80 mg/kg. (9) A short-term evaluation of this phase I trial showed that the incidence of adverse events was low, even in the group of patients treated with the highest doses of this drug (80 mg/kg). On the basis of a pharmacokinetic study, the authors confirmed the predominant fecal iron excretion induced by ICL670A observed in previous preclinical studies, and identified that the daily effective dose in humans able to induce a negative iron balance lies between 10 and 30 mg/kg. A double-blind, placebo-controlled, dose-escalation trial conducted by Nisbet-Brown et al. evaluated the efficacy and tolerability of ICL670A in 24 transfusion-dependent thalassemic patients. The authors found that this drug at a dose of 20 mg/kg once a day can induce a net negative fecal iron balance with a good tolerability (four patients developed skin rashes associated in one case with raised transaminase levels) (10).

The results of the first trials on ICL670A are very encouraging. Its ability to mobilize and promote excretion of tissue iron and its good safety profile, as emerged from the first preclinical and clinical studies, make this drug the most attractive new iron-chelating therapy. Long-term studies of its safety and efficacy will establish whether this drug may have a role in clinical practice.

The presented clinical course of a young patient with unfavorable outcome significantly differs from the history and clinical presentation of other young Japanese females suffering from a milder form of the disease and with partially compensated hemolytic anemia (11).

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HEMOSIDEROZA KOD PACIJENTA SA HEMOGLOBINOPATIJOM Hb YOKOHAMA β 31 (B13) Leu—Pro

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SAŽETAK

Prikazan je slučaj 19 godina starog bolesnika sa teškom transfuziono zavisnom hemolitičkom anemijom sa hemoglobinopatijom Hb Yokohama β 31(B 13) Leu-Pro. Prvi simptomi bolesti otkriveni su u sedmom mesecu života koji su rezultovali splenektomijom u drugoj godini. Sedam godina nakon operacije, metodom tečne hromatografije se ova hemoglobinopatija dokazuje uz definitivnu potvrdu mutacije analiziranjem sekvencije amplificirane DNK.

Terapija helacionim sredstvima je davana retko i povremeno do dolaska u našu instituciju. Pri prvom pregledu uočene su: manifestna globalna respiratorna insuficijencija sa srčanom insuficijencijom i znacima hemosideroze jetre i pluća, hronična hemolitička anemija i malnutricija. Intenzivnom kontinuiranom terapijom helirajućim preparatima, folnom kiselinom, B vitaminima uz oksigenu i kardiološku potporu, progresija multiorganske disfunkcije je zadržana par meseci, nakon čega dolazi do pogoršanja i letalnog ishoda.

U radu se razmatraju terapijski postupci kod razvijenih komplikacija usled teškog opterećenja gvožđem u hemoglobinopatijama.

***Ključne reči*: hemoglobinopatija, hemosideroza, Yokohama hemoglobin**