TRAUMATIC HEMOLYTIC ANEMIAS: CASE REPORT AND REVIEW OF THE LITERATURE

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SUMMARY – Two patients with intravascular hemolysis are presented. One patient had traumatic hemolytic anemia after mechanical heart valve reimplantation, and the diagnosis was made rapidly and easily. In the other patient, the diagnosis was not so easy complex and time-consuming. This patient had both traumatic hemolytic anemia caused by orthopedic prosthesis, and neutropenia. Fragmentation was caused by interaction of red blood cells with altered intravascular surfaces or by direct physical trauma to the cells due to excessive shear forces in the circulation. The following findings are seen in intravascular hemolysis: decreased hemoglobin, increased reticulocytes and lactic dehydrogenase, decreased serum haptoglobin, and presence of shizocytes in peripheral blood smear. Patients are considered to have intravascular hemolysis when lactic dehydrogenase is >460, along with the presence of two established criteria. If not causal, therapy is supportive.

Key words: *Anemia, hemolytic – etiology; Heart valve prosthesis, complications; Orthopedics, complications; Prosthesis, complications; Neutropenia, complications; Case reports*

Introduction

Mild anemia is frequently found in individuals exposed to strenuous and sustained physical activity. The first clue to the pathogenesis of this anemia was provided in 1881 by R. Fleischer, an army physician, who studied a young Prussian soldier complaining of passing dark urine following strenuous field marches[1]. In 1964, Davidson provided a logical explanation for this phenomenon. He proposed that red cells were destroyed in the soles of the feet during running, and the runners were encouraged to change the stride and especially to wear soft linings in their shoes, whereafter hemoglobinuria disappeared[2]. The individuals involved in strenuous and sustained physical activity are frequently found to be mildly anemic[3]. The cause of this anemia is complex but appears to involve traumatic hemolysis with hemoglobinuria, iron loss in urine and sweat, dilution of the red cell mass by an increase in plasma volume, and possibly adaptation to the right-shifted oxygen dissociation curve[4]. Disturbances in the formed blood cells due to intravascular trauma are shown in Table 1.

We report on our two patients with hemolytic anemias, to refresh the concept of hemolysis in the differential diagnosis of anemias.

Case Reports

Case No. 1

A 53-year-old man, who had often suffered sore throat in childhood, was first told to have heart murmur at the age of 29. At the age of 34, he was hospitalized at a cardiology ward of our Department, when the diagnosis of major aortic valve dysfunction (stenosis and regurgitation) was established. An operation was proposed and he had a Björk-Shiley valve implanted in the same year. In the next year, systolic-diastolic murmur was detected by a cardiologist, and the patient underwent frequent controls. At the age of 47, a second operation was performed, because his end-diastolic diameter of the left ventricle was

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*Table 1. Blood cell disturbances due to intravascular trauma**

Etiology	Fragments	Hemolysis	Thrombocytopenia
March hemoglobinuria	0	+	0
Cardiogenic	+ to ++++	+/- to ++++	0
Blood vessel diseases[a]	+++	+	+
TTP	++++	++++	++++
HUS	++++	++++	++++
Carcinoma	++++	++++	++++
Disseminated intravascular coagulation	++	+/-	++++

[a]malignant hypertension, eclampsia, renal transplant rejection, hemangioma, immunologic diseases (scleroderma)
*The table has been adapted from Harrison's Principles of Internal Medicine, 11th Edition, 1987

75 mm and aortic regurgitation 3+. A Carbomedics valve A-23 was implanted. Then, significant postoperative anemia developed. Ultrasonography of the heart showed minor dilatation of the left ventricle, end-diastolic diameter was 60 mm, and systolic gradient through the aortic valve was 5.3-6.6 kPa. Evaluation of this anemia was done at our Department of Hematology, where he was hospitalized. Ultrasonography showed no biliary tract calculi. Control ultrasonography of the heart, performed late in 1998, showed similar findings as after the second operation. Laboratory findings obtained in 1993 and on the last control in 1998 are shown in Table 2.

Table 2.Case No. 1: laboratory findings obtained in 1993 and on the last control in 1998

Laboratory parameter	1993	1998
Erythrocytes ($x10^{12}$/L)	3.01	3.57
Hemoglobin (g/L)	91	83
MCV (fL)	87.1	69.2
MCH (pg)	30.2	23.2
MCHC (g/L)	347	336
Leukocytes ($x10^9$/L)	5.3	4.4
Platelets ($x10^9$/L)	407	138
Reticulocytes (‰)	97	38
Bilirubin (mmol/L)	32.4	31.0
LDH (U/L)	3580	2440

Case No. 2

A 38-year-old man had initially visited a hematologist at the age of 29 for mild anemia. Laboratory findings were as follows: L $5.9x10^9$/L (immature 1%, segmented 15%, Ly 81%; Eo 1%; Mo 2%); E $4.1x10^{12}$/L; Hb 128 g/L; MCV 90.5 fL; MCH 30.7 pg; MCHC 339 g/L; Plt $188x10^9$/L; ESR 2; ferritin 128 (normal); Rtc 15‰; bilirubin 15.0 mmol/L; LDH 237 U/L; total protein 74.5 g/L (albumin 59.9%, alfa 1 2.7%, alfa 2 5.7%, beta 10.6%, gamma 22.1%). Haptoglobin and free hemoglobin were normal. The patient's history revealed he had lost both lower legs accidentally in childhood. Therefore he had orthopedic prostheses implanted. Then, other tests were performed. Micro IF antibodies for platelets and leukocytes were positive; IgG 3440 (normal 760-3260); IgM 3630 (normal 400-1620); hepatitis markers were negative; osmotic resistance was normal. Peripheral blood smear and bone marrow aspirate showed partly macroblastic and rich erythropoiesis and immature lymphocytes. Biliary tract ultrasonography showed no biliary calculi. Hemoccult done on three occasions was negative, and transferrin was normal. In 1993, the patient had low leukocyte count ($2.8x10^9$/L) for the first time, and he felt tired. In 1997, his haptoglobin was low, 420 (normal 790-2850), also for the first time. The patient had regular controls, and the last one, performed in 1998, yielded the following laboratory findings: E $3.22x10^{12}$/L; Hb 103 g/L; MCV 93.6 fL; MCH 32.0 pg; MCHC 324 g/L; Plt $151x10^9$/L; ESR 18; Rtc 19‰; L $3.4x10^9$/L (Gr 24%, Ly 72%, Mo 4%); LDH 492 U/L; bilirubin 25.6 mmol/L; the patient felt well.

Discussion

In case No. 1, the diagnosis was quickly and easily reached after transfusion incompatibility had been ruled

out, because hemolytic anemia developed during the immediate postoperative course. In case No. 2, however, the diagnosis was neither quick nor easy to reach. We believe that his hemolytic anemia was caused by orthopedic prostheses that were functionally better but seemed to have induced intravascular hemolysis. These orthopedic prostheses are unique for each individual patient. In aqueous suspension, the red cell membrane can withstand shear producing stress of up to 1.5 kPa[5]. In patients with valvular hemolysis, it is mild and rarely causes overt hemolytic anemia, except for those with severe aortic or subaortic stenosis generating a pressure gradient across the valve of 6.3 kPa or more[6]. All prosthetic cardiac valves have an orifice size smaller than the natural valve, and after implantation this orifice is further reduced by tissue ingrowth and endothealization[7]. According to the literature, about 50% of patients with mechanical heart valve have intravascular hemolysis, mostly mild, however, clinically significant intravascular hemolysis develops with thrombosis of the valve, perivalvular leak, or fracture of the valve. Currently, hemolytic anemia is considered a minor complication in reviews of large series of patients after implantation of the mechanical heart valve[8]. Since the first description of march hemoglobinuria, many additional cases of hemoglobinuria following long-distance running have been reported[9]. Even with well-designed padded insoles, there is still some traumatic disruption of red cells by pressure on the soles during running and walking[10]. Similar traumatic red cell destruction with hemoglobinuria has been reported after beating the head against the wall[11], hand-strengthening exercises in a subject practicing karate[12], and in those playing conga drums[13]. We found no reports connecting orthopedic prosthesis and intravascular hemolysis. Unfortunately, there are many patients with lower-leg orthopedic prostheses in Croatia, who sustained severe lower leg injuries during the war in Croatia. In our case No. 2, his anemia was in part considered functional pseudoanemia, although his plasma volume was not determined. The gain in plasma volume always exceeds the gain in red cell mass[14]. A reasonable comment is that we never found hemoglobinuria, however, it is not obligatory for the diagnosis. Tests for paroxysmal nocturnal hemoglobinuria (succrose lysis test) and paroxysmal cold hemoglobinuria (Donath-Landsteiner test) should be performed if any question arises. In case No. 2, neutropenia, possibly autoimmune, was also present, however, it has been proven difficult to unequivocally distinguish cases of autoimmune neutropenia from cases of chronic idiopathic neutropenia[15]. Patients diagnosed as having autoimmune neutropenia usually have selective neutropenia and one or more positive tests for antineutrophil antibodies. Patients are considered to have intravascular hemolysis when lactic dehydrogenase is >460, along with the presence of two established criteria[16]. Therapy for intravascular hemolysis consists of vitamins (B12 and folic acid), supplementation of iron according to ferritin level, erythropoietin and transfusion of washed red cells. A transfusion of washed red cells was necessary in our patient No. 1, however, on administering transfusion therapy one should always measure serum ferritin level to avoid hemosiderosis.

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Sažetak

TRAUMATSKE HEMOLITIČNE ANEMIJE: DVA PRIKAZA SLUČAJA I PREGLED LITERATURE

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Prikazana su dvojica bolesnika s intravaskularnom hemolizom, od kojih je jedan imao hemolitičnu anemiju nakon ponovljene ugradnje mehaničkog srčanog zalistka i u kojega je dijagnoza bila brza i jednostavna. U drugoga je bolesnika postavljanje dijagnoze zahtijevalo dosta vremena i truda. Ovaj je bolesnik imao mehaničku hemolitičnu anemiju uzrokovanu ortopedskim protezama, ali i neutropeniju. Fragmentacija je bila izazvana interakcijom eritrocita s promijenjenom površinom žile ili izravnom fizikalnom traumom stanica u krvotoku. Kod intravaskularne hemolize prisutni su sljedeći nalazi: sniženi hemoglobin, povišeni retikulociti i laktat dehidrogenaza, sniženi haptoglobin u serumu, te prisutnost shizocita u razmazu periferne krvi. Smatra se da bolesnici imaju intravaskularnu hemolizu kada je laktat dehidrogenaza viša od 460, uz prisutnost dvaju utvrđenih kriterija. Ako nije etiološka, terapija je potporna.

Ključne riječi: *Anemija, hemolitična – etiologija; Protetski srčani zalistak, komplikacije; Ortopedija, komplikacije; Proteza, komplikacije; Neutropenija, komplikacije; Prikazi slučajeva*