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Community-acquired pneumonia complications in a patient with hereditary glucose-6-phosphate dehydrogenase deficiency

Powikłania zewnątrzszpitalnego zapalenia płuc u chorego z wrodzonym niedoborem dehydrogenazy glukozo-6-fosforanowej krwinek czerwonych

Streszczenie

Wrodzony niedobór dehydrogenazy glukozo-6-fosforanowej (G6PD) może prowadzić do ciężkich powikłań w przypadku zakażenia dolnych dróg oddechowych.

Przedstawiamy przypadek 68-letniego mężczyzny z wrodzonym niedoborem G6PD, u którego obserwowano ciężkie powikłania pozaszpitalnego zapalenia płuc. Niedobór G6PD u chorego rozpoznano w dzieciństwie, od wielu lat chory pozostawał bez objawów choroby. W opisywanym okresie w przebiegu zapalenia płuc obserwowano ropniaka opłucnej, przełom hemolityczny, ciężką niedokrwistość i niewydolność nerek wymagającą leczenia hemodializami. W celu wyleczenia ropnych powikłań wykonano u chorego wideopleuroskopię i drenaż opłucnej.

Pozaszpitalne zapalenie płuc może prowadzić do powikłań hemolitycznych u chorych z niedoborem G6PD. Ciężkie ropne powikłania zapalenia płuc u tych chorych mogą być związane z upośledzeniem funkcji granulocytów.

Słowa kluczowe: niedobór G6PD, zapalenie płuc, powikłania zapalenia płuc

Pneumonol. Alergol. Pol. 2007; 75: 283–288

Abstract

Severe complications of lower respiratory tract infection in a patient with hereditary glucose-6-phosphate dehydrogenase (G-6-PD) deficiency may occur.

The case of a 68-year-old man with hereditary glucose-6-phosphate dehydrogenase (G6PD) deficiency who developed severe haemolysis after community-acquired pneumonia is presented. G6PD deficiency in our patient was diagnosed during childhood. We observed complications of community-acquired pneumonia: empyema, haemolytic crisis and renal failure. Videopleuroscopy and pleural drainage were successfully performed.

Community-acquired streptococcal pneumonia may also lead to haemolysis in G6PD deficient patients. Acute haemolysis, severe anaemia and renal insufficiency secondary to haemoglobinuria can be observed. Severe purulent complications of pneumonia in G6PD deficient patients may suggest granulocyte function impairment.

Key words: G6PD deficiency, pneumonia, pneumonia complications

Pneumonol. Alergol. Pol. 2007; 75: 283–288

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Praca wpłynęła do Redakcji: 21.06.2007 r.

ISSN 0867–7077

Introduction

Respiratory medicine specialists sometimes observe unexpected consequences of relatively frequent respiratory diseases. Such consequences may be due to external factors influencing respiratory disease (for example environmental and work conditions) or internal genetic factors (malformations, genetic disorders).

We describe the case of severe complications of a lower respiratory tract infection in a patient with hereditary glucose-6-phosphate dehydrogenase (G-6-PD) deficiency.

G-6-PD deficiency is metabolic defect of erythrocytes. When a G-6-PD deficient patient makes contact with a provoking factor, a cascade of erythrocyte disintegration and symptomatic haemolysis may occur. Different clinical forms of haemolysis can be seen - from mild hyperbilirubinaemia to severe haemolytic crisis.

Case report

We describe the case of a 68-year-old man with hereditary glucose-6-phosphate dehydrogenase (G-6-PD) deficiency. The G-6-PD deficiency was diagnosed in early childhood, after an episode of mild prolonged jaundice. For many years the disease did not manifest. The avoidance of haemolysis risk factors such as food and medication was enough to preserve the patient's good health. He did not visit a haematologist and did not keep medical records of his disorder. At the time of presentation, the patient was retired. His history was significant for ~60 pack-years of smoking, although he quit 20 years ago. He reported paroxysmal atrial fibrillation, arterial hypertension and benign arterial stenosis. In the past, he underwent surgery for haemorrhoids. Due to benign prostate hyperplasia, the patient was under urologist care. Prostate-Specific Antigen was normal.

There was no family history of G6PD deficiency in the parents or siblings of the described patient, but his daughter and daughter's son were diagnosed with G6PD deficiency. The second patient's child, his son, did not show signs of G6PD deficiency.

The medical problems started suddenly when the body temperature of the described patient rose suddenly and reached 38.5°C. The family doctor stated a diagnosis of a flu-like infection and advised symptomatic treatment. After 3 days, due to lack of improvement, azitromicin was prescribed. Gradually the status of the patient deteriorated. The patient started to present diarrhoea, dehydration and severe weakness. Due to signs of dehydration, weakness and profuse sweating, the patient was referred to the local hospital where was treated for one day. In the hospital, the patient presented with signs of right lobe pneumonia (body temperature 39°C, abnormalities in chest X-ray) and acute haemolysis (increased serum bilirubine, decreased concentration of haemoglobin), acute renal failure with anuria, hyperkalaemia and atrial fibrillation with a ventricular rate of 170 beats/min. Acute renal failure was secondary to acute haemolysis, haemoglobinuria and hypovolaemia.

The patient was immediately transferred to the nephrology department where he underwent several days of haemodialysis. Due to signs of severe anaemia and haemolysis, the patient was supplemented with many units of erythrocyte mass and plasma. There were no laboratory signs of autoimmune haemolysis (Coombs test was normal). Treatment with high doses of corticosteroids was considered but not implemented because of a persistent large inflammatory mass in the right lobe. During treatment in the nephrology department, the normal sinus heart rhythm returned. Control chest X-ray performed several days after the onset of the diseases did not show any improvement. CT scans were performed showing exudate in the right pleura, inflammatory parenchymal changes and unilateral right hilar enlargement. After partial improvement of renal function (creatinine 3.0 mg/dl), the patient was transferred to the Institute of Tuberculosis and Lung Diseases in Warsaw for consecutive diagnostics of persistent respiratory symptoms. At the Institute, the patient presented with quite a good clinical state with respiratory frequency of 20 breaths/min, peak expiratory flow of 340 l/sec, transcutaneous oxygenation $SpO_2(-O_2)$ = 94% and blood pressure of 170/110.

Chest examination revealed alveolar ventilation and crackles in the lower part the right lung. Heart rate was 102 beats/min and regular.

The abdomen was normal, soft and non-tender, with hepatomegaly of 3 cm. There were no signs of exudates, hernia or abnormal peritoneal signs. The laboratory findings were: total leukocyte count 7.22 with 72% neutrophils, red blood count 3.18×10^{12}/l, haemoglobin 9.8 g/dl, platelet count of 368×10^{9}/l. Blood urea nitrogen was 67 mg/dl, creatinine 2.3 mg/dl, bilirubine 1.9 mg/dl, total protein 6.1 mg/dl and aspartate aminotransferase 43 mg/dl (normal 2–38). High concentrations of C-reactive protein: 147 mg/l (normal < 5 mg/l), D-dimer 4191 mg/l were observed. Urine specific gravity: 1.005, urine leukocyte 3–5 and erythrocyte 6–8. An arterial blood gas obtained on room air

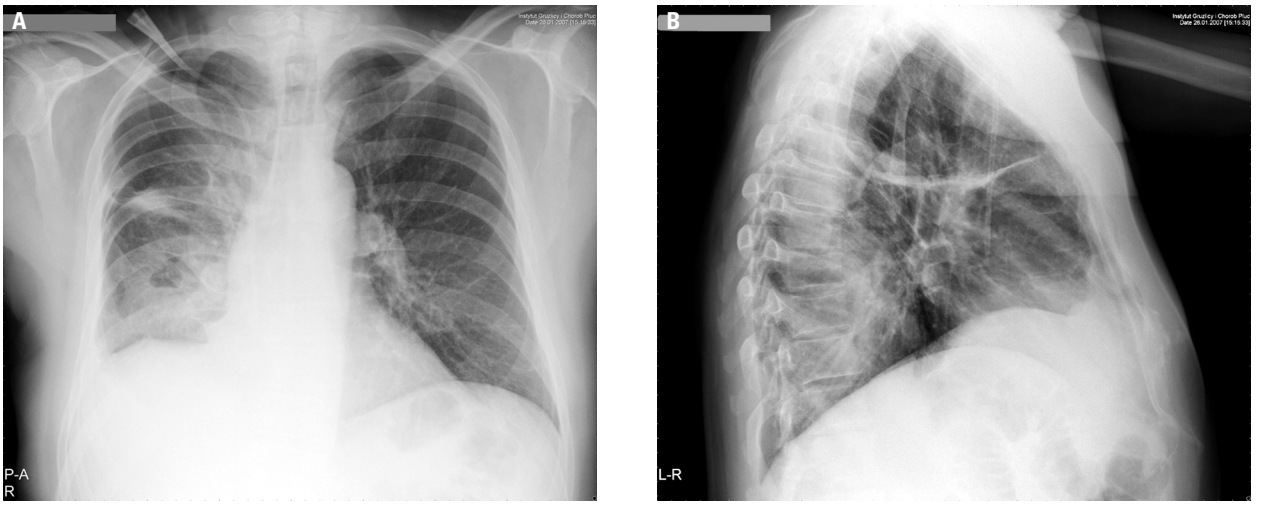

Figure 1A, B. Chest radiograph. In the lower and middle field of right lung parenchymal changes, partial lower lobe atelectasis and exudate in the right pleura

Rycina 1A, B. Zdjęcie rentgenowskie klatki piersiowej. W dolnym i środkowym polu prawego płuca zmiany śródmiąższowe, częściowa niedodma dolnego płuca oraz wysięk w prawej jamie opłucnowej

revealed oxygen tension (PaO_2) of 73 mm Hg and carbon dioxide tension ($PaCO_2$) of 31 mm Hg, pH 7.54.

A posterior-anterior chest radiograph was taken showing parenchymal densities in the lower-central field of the right lung, sings of atelectasis and a small amount of exudate in the right pleura (Fig. 1A, B).

Ultrasound scan of the pleura was performed. The presence of capsulated liquid at the level of the fifth intercostal space was seen. The amount of liquid was about 10 cm. A suspicion of pleural empyema was noted. The pleural puncture confirmed purulent origin of liquid. Other findings of pleural liquid: glucose concentration 3.0 mg/dl, protein 3.9 mg/dl, total cholesterol 90 mg/dl and lactate dehydrogenase 31740 U/l. Cytology examination of the pleural liquid showed high cytosis 24 cells $\times 10^9$ with 100% neutrophils.

As a treatment option, pleural drainage was chosen. At the same time, microbiologic diagnostics was provided. Bacterial and fungal cultures of pleural liquid were negative but cultures of sputum led to isolation of Citrobacter freundii, resistant to coamoxiciline and I and II generation of cephalosporin. A continuation of antibiotic (Tienam) started before admission to the Institute was decided. All decisions concerning drug administration were carefully considered for the reason that there was still a high risk of severe haemolysis.

Bronchoscopy with autofluorescence did not show any abnormalities. Normal fluorescence of the bronchial tree was seen. The following ultrasound scans of pleurae demonstrated a limited efficacy of drainage. Computed tomography obtained after a few days of drainage showed liquid space near the back side of the thorax (3 × 9 cm) and partial resolution of inflammatory changes in the right lung (Fig. 2A, B).

Because the risk of recurrence of severe haemolysis secondary to ongoing inflammatory status was still significant, a need for pleuroscopy revision of the pleura was discussed. The consultant haematologist was asked for an opinion. The haematologist supported the idea of pleural revision. According to the consulting haematologist, severe haemolysis was the consequence of community-acquired pneumonia and empyema of the pleurae. The acute renal insufficiency was the result of haemolytic haemoglobinuria. In addition, according to the haematologist, at the time of consultancy, there were no signs of apparent actual haemolysis. Increased reticulocyte count combined with normocytic anaemia was significant for erythroblast renewal. The haematologist advised continuation of wide spectrum antibiotic therapy and revision of inflammatory site. As a therapeutic option in case of patient deterioration, he proposed corticosteroids.

We prepared 3 units of erythrocyte mass for foreseeable haemolysis during surgery.

The patient underwent videopleuroscopy revision of the right pleural space. Histopathology examination of pleural biopsy showed *pleuritis fibroso-fibrinosa partim purulenta*. Neither fungi nor mycobacteria were found in the specimen. During and after surgery the patient's status was stable;

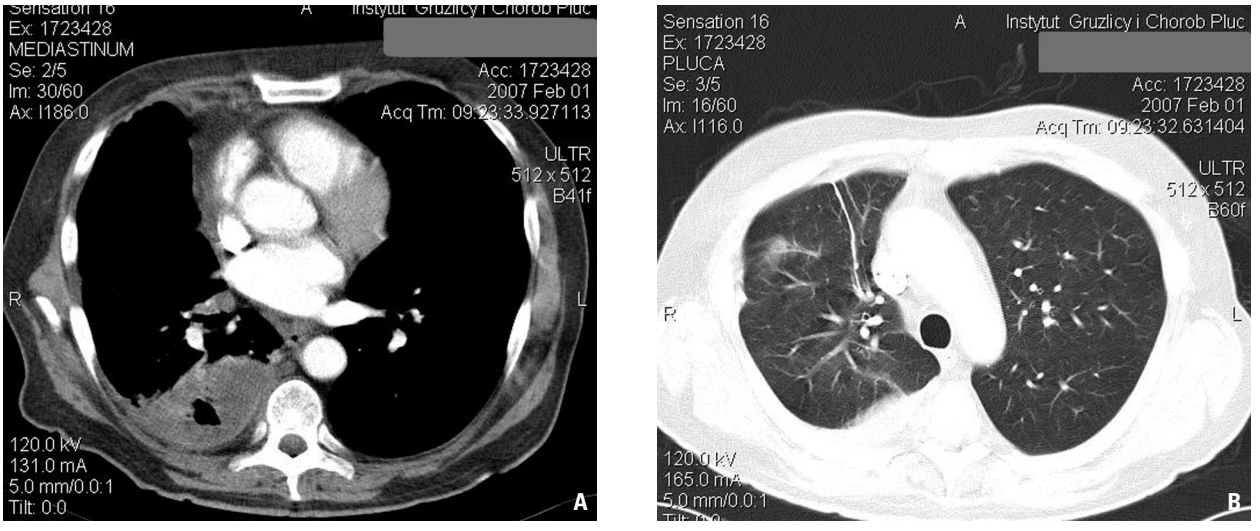

Figure 2A, B. Thoracic computed tomography. Exudate in the right pleura, probably empyema with air bubbles after pleural punctures. In the right lung postinflammatory parenchymal changes

Rycina 2A, B. Tomografia komputerowa klatki piersiowej. Wysięk w prawej jamie opłucnowej, prawdopodobnie ropniak z obecnością pęcherzyków powietrza po nakłuciu opłucnej. W prawym płucu pozapalne zmiany śródmiąższowe

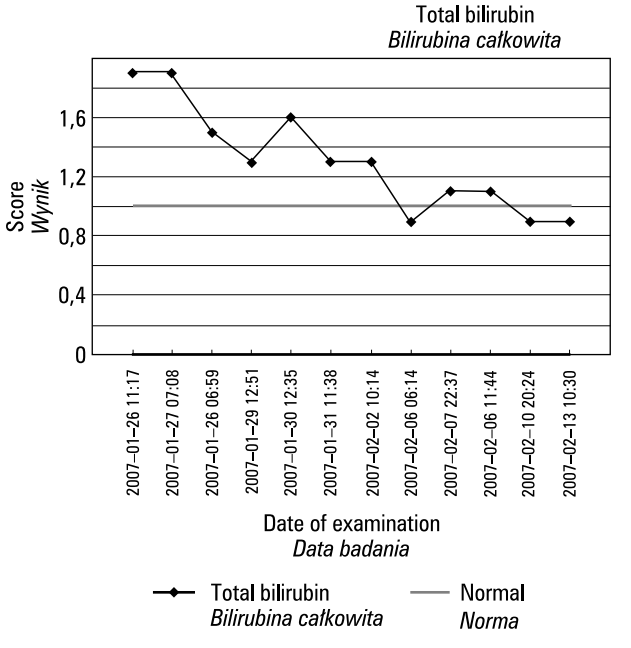

Figure 3. Total serum bilirubin in patient [mg/dl]

Rycina 3. Całkowita bilirubina w surowicy pacjenta [mg/dl]

we did not observe significant haemolysis. On the contrary, the patient's general status and blood indices improved (Fig. 3). The rapid normalization of C-reactive protein concentration was observed (but not to a normal level). It was noticeable that C-reactive protein concentration was a better parameter of patient inflammatory status than total white cell count or percentage of granulocytes (Fig. 4). After hospital discharge, follow-up at the outpatients clinic of the Institute of Tuberculosis and Lung Diseases was planned.

Discussion

G6PD deficiency is the most common erythrocyte enzyme deficiency, with a prevalence of 1/100 000 persons [1]. Symptoms of G6PD deficiency, like haemolysis and jaundice after ingestion of fava beans or inhalation of fava flower pollen, have been observed for centuries. This form of disorder is called *favism*. Acute haemolysis and hyperbilirubinaemia occurs after 5–24 hours of exposure to the stressor, especially among inhabitants of Mediterranean regions for example Italy or Greece. The prevalence of the disease is correlated with a warm climate because G6PD deficiency has a protective role against malarial infection. Glucose-6--phosphate dehydrogenase plays a role in the pentose phosphate pathway, protecting cells from oxidative damage of its components. When deficiency of G6PD is significant, precipitation of haemoglobin in the cytoplasm may occur. Such a mechanism leads to acute haemolysis, severe anaemia and renal insufficiency secondary to haemoglobinuria. The inheritance of G6PD deficiency is sex--linked; women are passive carriers, and the disease symptoms in women are less intense than in men. The likelihood of haemolysis in men depends on enzyme activity. G6PD deficiency symptoms in

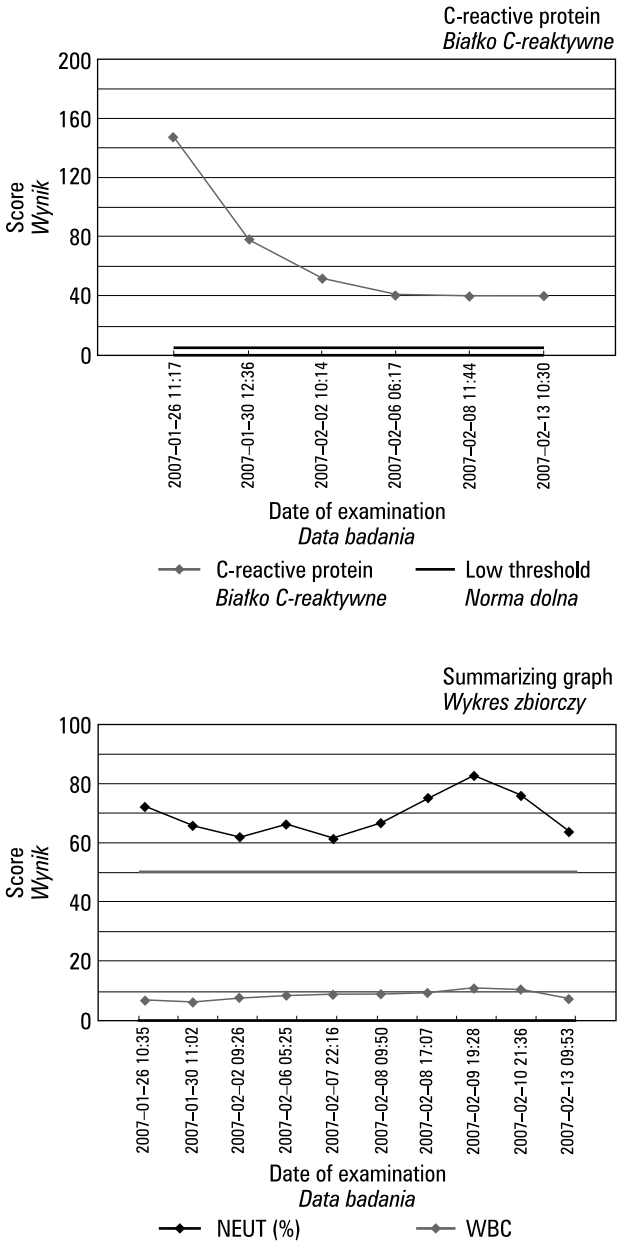

Figure 4. C-reactive protein (mg/l), total white cell count (N × 10^9/L) and neutrophil percentage (%) in patients blood

Rycina 4. Białko C-reaktywne (mg/l) — całkowita liczba białych krwinek (N × 10^9/l) i odsetek neutrofili (%) we krwi pacjenta

men may vary from weak asymptomatic haemolysis to acute haemolytic crisis (as in our patient). In clinical practice, it is of great importance for G6PD deficient patients to avoid exposure to oxidative drugs (antimalarial, sulfonamide, dapsone, nitrofurantoin, vitamin C and non-steroidal anti-inflammatory drugs).

In our patient, community-acquired pneumonia was diagnosed, but microbial etiology was unclear. Cultured sputum showed Citrobacter freundii, but the following cultures (bronchial aspirates) were negative. The patient was treated with antibiotics at the time of collection of microbiological materials, which influenced the microbiological investigations.

A case similar to that of our patient was described by Yang et al. [2]. They discussed the case of 35-year-old man with G6PD deficiency, who developed acute haemolysis and purulent complications after Acinetobacter baumannii pneumonia.

Typical community-acquired streptococcal pneumonia may also lead to haemolysis in G6PD deficient patients. Kasper proposed that the mechanism of Pneumococcal damage of erythrocytes in G6PD deficient patients is dependent on complement activation and subsequent binding of the bacterial immune complexes to the red blood cell complement receptors [3].

Tugwell and William's analysis of 27 cases of lobar pneumonia associated with jaundice showed that the majority of patients with hyperbilirubinaemia demonstrated G6PD deficiency [4].

Patients with erythrocyte G6PD deficiency may also express enzyme deficiency in leucocytes and in other tissue cells. Decreased activity of leukocyte G6PD below 5% of that predicted leads to severe infections due to loss of phagocytosis ability. The clinical picture in such a case may mimic chronic granulomatous disease [5]. Individuals with moderately decreased activity of G6PD in leukocytes (20––25% of normal, for example Mediterranean variant) do not show decreased resistance to infections [6].

Activity of leukocyte G6PD in our patient, according to investigations performed 25 years before the described period, was 24% of that predicted [7]. DNA study showed cytosine-thymine replacement in the 563rd position of the G6PD gene, which took effect in the serine-phenylalanine change in the 188th position of the polypeptide chain. The result was similar to the Mediterranean variant [8]. The presented data of early enzymatic and genetic studies of our patient entitle his leukocyte G6PD deficiency to be classified as moderate. However, observations of severe purulent complications of pneumonia in our patient may suggest granulocyte function impairment as well.

In conclusion, all clinicians need to consider G6PD deficiency when facing difficult or complicated pneumonia.

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