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Hemorrhagic parapneumonic effusion in a 64 year-old patient as the first symptom of hemophilia B

Abstract

Hemophilia B is an inherited, X chromosome-linked disease. It is usually diagnosed in childhood, sometimes in adolescence. The commonest symptoms include spontaneous or post-traumatic bleeding into the joints and/or muscles, as well as mucosal bleeding. Respiratory symptoms are rarely reported.

We present the case of a 64 year-old man in whom bloody parapneumonic effusion (*hemothorax*) was the first symptom of hemophilia B. The reason for prolonged activated partial thromboplastin time (APTT) found on admission has not been elucidated. Since antibiotic therapy and pleural tube thoracostomy with intrapleural streptokinase were found to be ineffective, video-assisted thoracic surgery was performed with the right lung decortication. Post-operative treatment was complicated by massive pleural bleeding requiring two subsequent thoracotomies. Additional blood tests revealed factor IX deficiency and resulted in hemophilia B being diagnosed.

The presented case proves that hereditary bleeding disorders may be diagnosed even in late adulthood. Intrapleural bleeding related to pneumonia and pleural inflammation might be the first presenting symptom. Hemophilia should be considered as a potential cause of APTT prolongation, even in an elderly patient with atypical presentation. Explaining the reason for APTT prolongation before the surgical procedure could have allowed to avoid severe bleeding in the described patient.

Key words: spontaneous hemothorax, parapneumonic effusion, hemophilia B

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Introduction

Hemothorax is defined as the presence of blood in the pleural cavity. As in many cases blood mixes with pleural fluid, a criterion of the pleural fluid hematocrit $\geq 50\%$ of peripheral blood hematocrit was introduced in the diagnosis of this condition [1]. The most frequent cause of *hemothorax* is chest trauma, including iatrogenic manipulation (surgical or diagnostic procedures).

Spontaneous (non-traumatic) *hemothorax* results mainly from primary or secondary pleural malignancies. Other causes include a rupture of the thoracic vessels (e.g. aortic aneurysm or pulmonary arteriovenous fistula), or sub-diaphragmatic abdominal vessels (e.g. splenic artery aneurysm) [1], spontaneous *pneumothorax*, catamenial *hemothorax* or inflammatory diseases (tuberculosis, necrotizing pneumonia). In rare cases, bleeding into the pleural cavity may also result from anatomical

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anomalies [2], chickenpox pneumonia [3] and connective-tissue diseases [4].

Other conditions leading to non-traumatic *hemothorax* are inherited or acquired coagulation disorders (hemophilia, thrombocytopenia, anticoagulant therapy) [5]. However, in some patients, the cause of *hemothorax* remains unknown [6, 7].

We present the case of an adult man hospitalized due to bloody, parapneumonic pleural effusion classified as *hemothorax*, in whom, after detailed diagnostic work-up, a congenital deficiency of factor IX (hemophilia B) was recognized. This deficiency seemed to be the main cause of pneumonia-associated pleural bleeding and post-surgical hemorrhagic complications.

Case report

A 64 year-old man with right-sided pneumonia was admitted to our department with a ten day history of cough, pleuritic chest pain and elevated body temperature. On the fifth day of the symptoms' duration, ambulatory antibiotic therapy (amoxicillin clavulanate) had been administered without any effect. Radiological progression was observed (pleural effusion had appeared).

On admission, the patient was in a good condition. His vital signs were: body temperature of 37.8°C, respiratory rate of 18 breaths per min and a heart rate of 100 bpm. Physical examination revealed signs of right-sided pleural effusion and a systolic murmur over the aortic valve and apex. His past history included arterial hypertension, aortic valve disease (moderate valve insufficiency and mild stenosis), coronary artery disease complicated by a myocardial infarction three years ago, cardiac arrhythmia (paroxysmal atrial fibrillation and premature ventricular contractions), spine osteoarthritis and duodenal peptic ulcer disease. Four years earlier, the patient had undergone surgical treatment for hemorrhoids. There was no previous history of respiratory disease or chest trauma. The patient was an active smoker (25 pack-years), but denied alcohol abuse. He was treated with perindopril, sotalol and atorvastatin.

The chest radiograph performed on admission revealed a loculated pleural effusion in the antero-lateral region of the right pleural cavity with a lung consolidation above the fluid level (Figs. 1A, B). Laboratory investigations showed an elevated erythrocyte sedimentation rate (ESR, 125 mm/h) and C-reactive protein concentration (CRP 204 mg/l; normal value < 10 mg/l), WBC count of $10.42 \times 10^3/\mu\text{l}$ (neutrophils — 61.2%, lymphocytes — 24.2%, eosinophils — 1.8%, basophils — 0.4%, monocytes — 12.4%), normocytic anemia (hemoglobin concen-

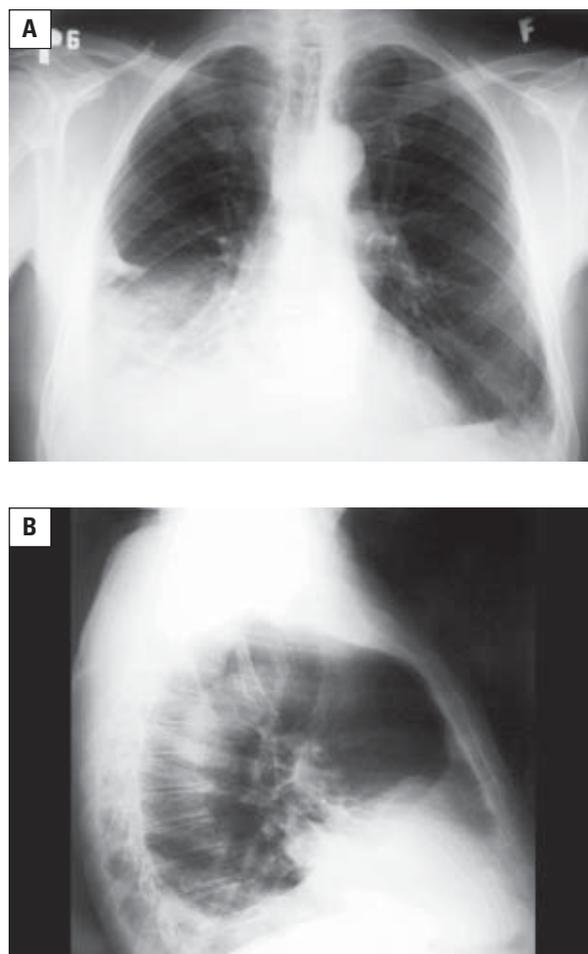


Figure 1. Chest X-ray on admission PA (A) and right lateral (B)

tration 11.10 g/dl), increased transaminase activity (AST 59 U/l, normal range 5–40 U/l; ALT 70 U/l, normal range 7–56 U/l), prolonged APTT 45.5 s, (normal range 26–38 s). Prothrombin time and platelet count were in the normal range. Arterial blood gas analysis revealed hypoxemia (PaO_2 68.0 mm Hg), hypocapnia (PaCO_2 33.8 mm Hg) and slight respiratory alkalosis (pH 7.46).

Antibiotic therapy was continued (amoxicillin clavulanate intravenously). Additionally a mucolytic agent was added and respiratory rehabilitation initiated. Moreover, acetylsalicylic acid (75 mg/day) was administered due to the history of coronary artery disease and myocardial infarct.

Ultrasonography (US) confirmed the presence of an encapsulated right-sided pleural effusion (65 × 60 mm) adhering to the chest wall between the right parasternal line and anterior axillary line. A thick layer of clots and thin septa within were revealed (Fig. 2). US-guided thoracentesis was performed and 40 ml of bloody fluid evacuated. Laboratory studies showed pleural fluid pH 7.4, lactate dehydrogenase (LDH) 940 U/l, glucose 74 mg/dl,



Figure 2. Pleural ultrasonography revealing loculated pleural effusion with thick layer of clots (large arrow) and thin septa (small arrow) within

with lymphocyte predominance (55%) and granulocytes 37%. Neither the total cell count nor the hematocrit of the fluid were assessed due to the presence of clots.

On the basis of the clinical manifestation, and additional examination results, right-sided pneumonia with parapneumonic effusion was diagnosed. A closed-tube drainage was initiated and an intrapleural fibrinolytic agent (streptokinase 250 000 U) was administered as standard treatment of loculated parapneumonic effusion. Circa 500 ml of bloody effusion (Ht 20%) was drained during the first 24 hours. However, on the second day the chest tube had to be removed due to its occlusion by fibrinous tissue.

Afterwards, epistaxis and tawny sputum were observed. Otolaryngological examination and bronchofiberoscopy failed to identify the source of bleeding. Subsequently, a decrease in the hemoglobin concentration (9.0 g/dl) was noted. The ultrasound appearance of the right pleural effusion did not change significantly. However, in the chest computed tomography the encapsulated pleural effusion was found not only adjacent to the chest wall, but also in the paramediastinal and sub-pulmonic regions and in the interlobar fissure (Fig. 3). The pleura was thickened (5 mm) and the heterogeneous fluid attenuation (39 to 73 HU) suggested the presence of blood. Resolving infiltrates in the middle lobe were noted. A second thoracentesis was performed and 20 ml of bloody effusion obtained for examination (fluid HGB level 13.6 g/dl, Ht 23.2%, RBC $3.08 \times 10^6/\mu\text{l}$). Subsequently, the patient had a transfusion of two units of packed red blood cells.

Over the following days, a deterioration in the patient's general condition (fever up to 38.8°C,

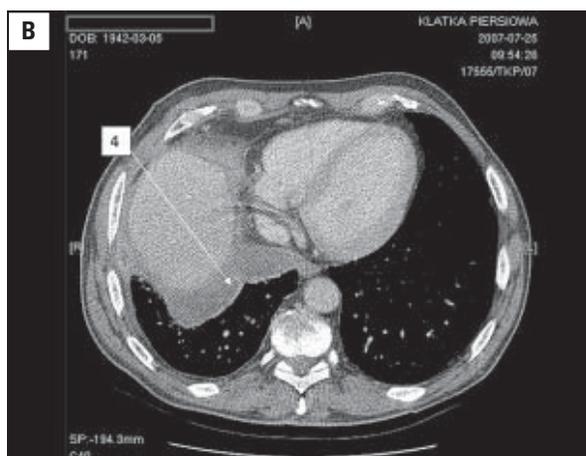
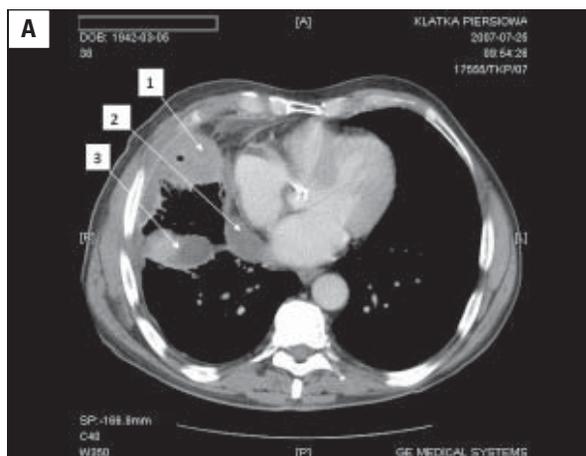


Figure 3. Chest CT scans (mediastinal window) showing encapsulated pleural effusion in different areas of the right pleural cavity: (1) adjacent to antero-lateral part of the chest wall, (2) paramediastinal, (3) in the interlobar fissure (A), and (4) subpulmonic (supradiaphragmatic) (B)

chills) and an increase of serum CRP concentration, were observed. In order to exclude a superinfection of the pleural effusion, another thoracentesis was performed. The pleural fluid did not have a purulent appearance, but the microbiological examination revealed the presence of *Staphylococcus aureus*. Since the previously applied tube thoracostomy was considered ineffective, the patient was scheduled for surgical treatment. However, referral to the Department of Surgery was delayed due to atrial fibrillation. Both pharmacological (amiodarone) and electrical cardioversion failed to restore the sinus rhythm. Therefore anticoagulation therapy (enoxaparin 80 mg/d) and bisoprolol for heart rate control was introduced.

In the Department of Surgery, video-assisted thoracoscopic surgery (VATS) was performed with right lung decortication and removal of the purulent and fibrous material. In the early post-opera-

tive period, bleeding to the right pleural cavity was observed, therefore a thoracotomy and re-thoracotomy within 36 hours after the first procedure was performed. No source of the recurrent bleeding was found. Packed red blood cells and fresh frozen plasma were transfused. The cause of bleeding remained undetermined. Its association with acetylsalicylic acid intake and treatment with enoxaparin seemed unlikely, as they were both withdrawn before the operation. Therefore, a detailed examination of the blood coagulation system in a search for coagulopathy was performed. The prothrombin time was normal, no deficiency of either fibrinogen or vitamin K dependent factors (II, VII, VIII, XI) was found. APTT was prolonged up to 44 sec. In the mixture of 1 volume patient plasma with 1 volume of control plasma, APPT was in the normal range. This result excluded the presence of an inhibitor and indicated a deficiency of a clotting factor in the intrinsic pathway of coagulation. Determined factor IX activity was 21% (normal range 50–150%). Therefore, mild hemophilia B was diagnosed.

Finally, the bleeding was stopped by factor IX intravenous administration. The patient was transferred to our department for further treatment.

During the next few days, the pleural drainage gradually decreased. Normal body temperature and a slow reduction of serum CRP concentration were observed. On the sixteenth day after the last surgical procedure, the chest tube was removed after a prophylactic factor IX infusion. In the chest radiograph and pleural ultrasonography a small encapsulated pleural effusion adjacent to the lateral chest wall was described. The patient was discharged and referred for further treatment to the Institute of Hematology and Transfusion Medicine. At a six-month follow-up no recurrence of bleeding was observed and a regression of the changes in the chest radiograph was noted.

Discussion

Hemophilia is a bleeding disorder inherited in a sex-linked recessive pattern. The two main types of the disease are caused by a deficiency of clotting factors synthesized in the liver: factors VIII (hemophilia A) and IX (hemophilia B). The genes for these factors are located on the X chromosome. Therefore hemophilia is transferred by females to male descendents. The prevalence of hemophilia in Poland is one case per 5600 males, and the ratio of hemophilia A to B is 6.2:1 [6]. The clinical manifestation of both entities is similar and depends on the level of the factor VIII, or IX, deficiency, respectively. In severe disease, the factor

(VIII or IX) activity is lower than 1%, in moderate 1–5%, and in mild 6–40%. The most typical symptom for severe hemophilia is spontaneous bleeding to joints and muscles. In moderate disease, spontaneous bleeding is less frequent and in mild hemophilia signs of coagulation disorders may be absent [9, 10]. Bleeding after dental extraction or tonsillectomy and bleeding associated with trauma or surgical procedures occur in both types of the disease [9–11]. Prolonged APTT is a typical laboratory finding. The quantitative assessment of the clotting factors' activity (first factor VIII, then IX) is mandatory.

Respiratory symptoms (e.g. hemoptysis) are rare [9]. Although hemophilia may be a cause of *hemothorax*, only a few such case reports can be found in the literature [12–15]. They describe cases related mainly to hemophilia A. Rasaretnam et al. presented a patient in whom the disease was diagnosed during *hemothorax* therapy [12], while Kay and Williams reported cases in which hemophilia A was recognized prior to the bleeding to the pleural cavity [13, 14]. Barrett [15] not only describes three cases of *hemothorax* in hemophilic patients, but also presents a review of the literature from the first half of the twentieth century. However, he does not mention the type of hemophilia involved. Case reports of *hemothorax* related to spontaneous *pneumothorax* also affected patients with hemophilia A [16]. To the best of our knowledge, hemophilia B-associated *hemothorax* was described only by Turiaf et al. [17].

In our reported case, bloody pleural effusion was obtained during the very first thoracentesis. However, the medical history was so suggestive for pleuropneumonia, that we assumed that the presence of blood in the pleural fluid was related to the thoracentesis itself. We also considered primary *hemothorax* with subsequent bacterial infection. However, no history of chest trauma and typical evolution of the clinical manifestation made that possibility unlikely. An association between intrapleural bleeding and streptokinase therapy seemed unlikely, since intrapleural fibrinolysis does not deteriorate blood coagulation. Moreover, intrapleural thrombolytic agents are used to improve the drainage of a recent *hemothorax* [18]. However, single cases of bleeding into the pleural cavity following intrapleural fibrinolysis were described [19, 20]. In our Department, therapy with thrombolytic agents has been applied for 15 years and no hemorrhage into pleural cavity has been observed (only a change in the drained fluid color was noted).

In our patient with mild hemophilia B, bleeding could have been influenced by anti-coagu-

lation therapy. Small doses of acetylsalicylic acid (ASA) exceptionally cause serious bleeding. However, the risk of coagulation disorders is increased in a hemophilic patient [21] or during therapy with another anti-platelet agent [22]. It has been documented that acetylsalicylic acid does not increase the risk of bleeding during fiberoptic bronchoscopy or transbronchial biopsy [23]. However, simultaneous treatment with ASA and clopidogrel is associated with an increased risk of bleeding complications [24].

The potential influence of enoxaparin should also be considered. The therapy was initiated to decrease the risk of thromboembolism induced by atrial fibrillation. This seemed to be the best treatment option, as low weight molecule heparins (LWMH) are easy to withdraw before surgery in order to reduce the probability of bleeding during the procedure and in the post-operative period. However, in a patient with an undiagnosed, inherited coagulation disorder, the use of ASA, which irreversibly inhibits platelets, together with LWMH, could have enhanced the bleeding. An intrapleural hemorrhage could have occurred after thoracoscopy in a patient with mild hemophilia, even without anticoagulant therapy.

Recurrent massive bleeding to the pleural cavity following VATS with no evident source identified in thoracotomy and re-thoracotomy imposed a detailed work-up of the blood coagulation system and resulted in hemophilia B diagnosis. In our opinion, the qualification for surgical treatment was proper. The presence of *Staphylococcus aureus* in a parapneumonic pleural fluid means a complicated effusion and local therapy is the treatment of choice [25, 26]. In case of an unsuccessful pleural drainage, surgical treatment is indicated. We may assume that if in the early stages of the disease, the two main facts (bloody effusion and prolonged APTT) had been associated together, the coagulation disorder could have been identified earlier and post-operative bleeding might have been avoided.

Initially, we did not focus on the prolonged APTT because of the negative history of coagulation disorders and the age of the patient. Previously reported cases of hemothorax in the course of hemophilia referred to patients aged under 30 [12, 16].

Mild hemophilia may be asymptomatic and remain unrecognized. However, even minor surgical procedures in these patients are associated with an increased risk of bleeding if the clotting factor is not administered prior to the procedure. In the Polish population the diagnosed incidence of severe hemophilia B is higher than in other Europe-

an countries (56.6 vs. 29–40%, respectively). This may be explained by the fact that mild and moderate hemophilia remains underdiagnosed in our country.

We suspect that in our patient with mild hemophilia B, the infection of the lung tissue and pleura resulted in a parapneumonic effusion and spontaneous bleeding. Data in the literature on that subject is scarce. ASA and LWMH therapy may have enhanced the process. Surgical procedures additionally increased the intrapleural bleeding.

Conclusion

Our case shows that a patient with a mild factor IX deficiency (hemophilia B) may reveal coagulation disorders in adulthood (even in advanced age) and respiratory symptoms may predominate in the clinical manifestation. Prolonged APTT requires explanation prior to surgical treatment because the outcome of the investigation may modify the therapeutic approach and help avoid hemorrhagic complications.

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