CASE REPORT

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Pulmonary embolism in patients after central nervous system haemorrhage — is it possible to optimise antithrombotic therapy?

Zatorowość płucna u chorych po krwawieniu do ośrodkowego układu nerwowego — czy optymalizacja leczenia przeciwkrzepliwego jest możliwa?

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Abstract

We here present descriptions of two patients who after bleeding to the central nervous system sustained pulmonary embolisms, and we discuss the therapeutic difficulties connected with the choice of safe antithrombotic treatment in acute pulmonary embolism.

Key words: haemorrhage, antithrombotic therapy, vascular malformation, pulmonary embolism

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Introduction

Symptoms of venous thromboembolism (VTE) include deep vein thrombosis and pulmonary embolism (PE). Pulmonary embolism is, after coronary artery disease and ischaemic stroke, the third most frequent cause of death due to cardiovascular causes. In the general population, its prevalence is estimated at 71–117 cases per 100,000 people [1, 2]. This disease is caused by a sudden closure or narrowing of the pulmonary artery or its branches by embolic material, which typically comes from deep veins of the lower extremities or the lesser pelvis. Less frequently, thrombi may come from veins in the upper part of the body or from right cardiac chambers [3, 4]. Factors which most strongly predispose towards PE, included in the Wells score and the modified Geneva score, are: a history of VTE, major surgery, immobilisation, thrombophilias, cancer and old age [4, 5].

Antithrombotic therapy is recommended for PE patients in order to prevent sudden death and recurrence of VTE. Currently, heparins and fondaparinux (5–10 mg once daily)

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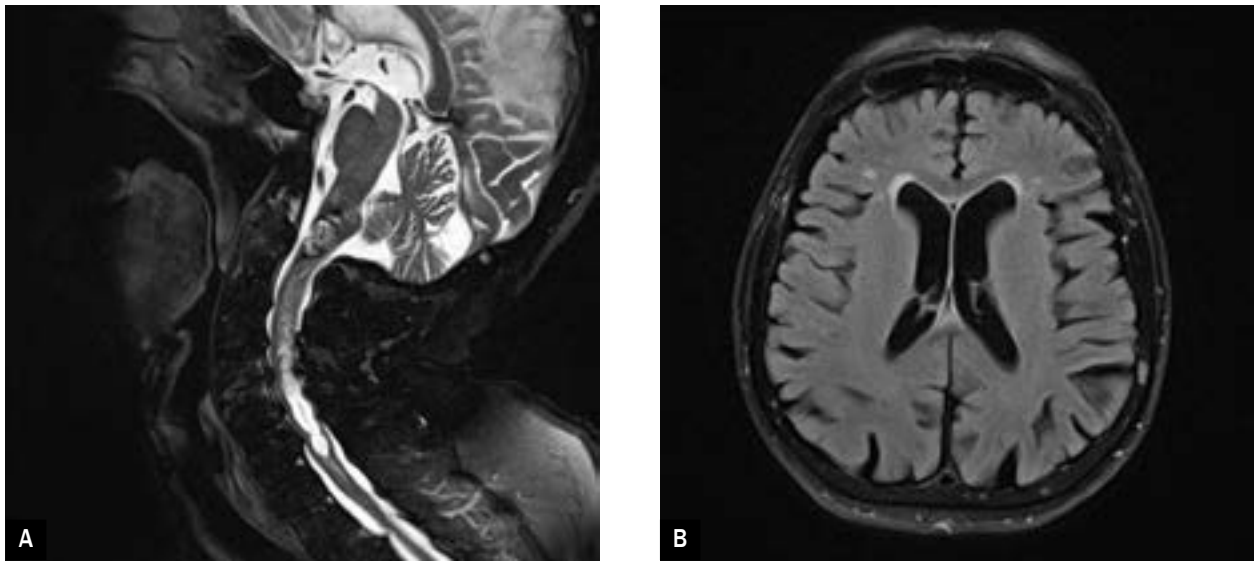

Figure 1. Patient 1. T2-weighted magnetic resonance images; head — left frontal area; cord — lesion between medulla oblongata and spinal cord at C2 vertebra level, with haemorrhage up to body of C7 vertebra

are registered in PE treatment, as well as vitamin K antagonists (therapeutic INR of 2.0–3.0 is the goal) (VKAs), apixaban, (10 mg twice daily), dabigatran (150 mg twice daily), edoxaban (60 mg once daily) and rivaroxaban (15 mg twice daily) in oral therapy [6].

Case reports

Patient 1.

An obese 80 year-old patient, with coronary syndrome, arterial hypertension, hypothyroidism and type 2 diabetes, was admitted to the clinic of cardiology due to PE. The patient was hospitalised in the neurology department due to weakness which had been progressing for a month, experienced especially strongly in the upper and lower extremities. Upon admission, the patient was diagnosed with flaccid quadriparesis. Magnetic resonance imaging (MRI) of the spine showed a 14 × 10 mm cavernous angioma with features of a haemorrhage at the level of the second cervical vertebra (C2), while below, within the cord, a 8.5 × 75 mm hyperintensive lesion, reaching all the way to the seventh cervical vertebra (C7), was imaged, which also corresponded to a haemorrhage (Figure 1). On the third day, the patient experienced sudden dyspnoea at rest. An electrocardiogram (ECG) revealed no features of acute myocardial ischaemia. Laboratory tests indicated an extremely high D-dimer concentration of 37,594 μg/L (normal concentration 0–500 μg/L) and correct levels of myocardial necrosis markers and B-type natriuretic peptide (BNP). The echocardiogram showed no features of right ventricular volume overload or left ventricular systolic dysfunction. Computed tomography angiography (CTA) of the chest revealed embolic material in arteries up to the upper and lower lobe of the left lung and all lobes of the right lung (Figure 2). No clinical features of venous thrombosis of the lower extremities were identified. After admission to cardiology department, the patient suffered from intermittent respiratory failure; dyspnoea and reduced saturation were observed, and passive oxygenation was employed. During the first days of PE, enoxaparin was administered at a therapeutic dose of 80 mg twice daily (1 mg/kg body weight, twice daily). In addition, MRI of the head indicated innumerable small foci of hypointensity corresponding to haemosiderin deposits caused by past small haemorrhages in both cerebral hemispheres, within the cerebellum and

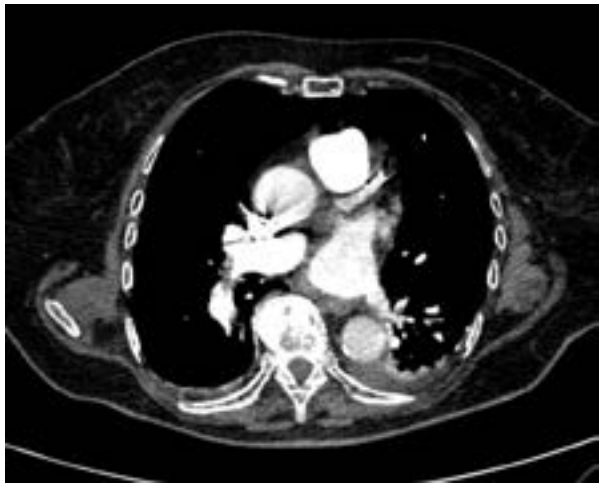

Figure 2. Patient 1. Computed tomography angiography of chest — embolic material in pulmonary arteries

in the midbrain and the brainstem. The patient underwent neurosurgery consultation due to numerous comorbidities suggesting an unfavourable course of the periprocedural period and extensive nature of the syringomyelic cavity. The patient was qualified for conservative treatment.

On the sixth day of hospitalisation, the patient was returned to the neurology clinic for further treatment. When the patient was discharged, after a week-long hospital stay and following neurosurgery and cardiology consultations, continued enoxaparin treatment was recommended, at a dose reduced to 40 mg twice daily due to a high risk of repeated central nervous system (CNS) haemorrhage. During observation over three months, the patient has remained stable; low-molecular-weight heparin (LMWH) is being administered.

Patient 2.

This 74 year-old patient with arterial hypertension was admitted to the cardiology department due to PE. On the fifth day of the stay at the clinic of neurology where the patient was hospitalised due to intracerebral haemorrhage (Figure 3), the patient was awoken by sudden dyspnoea. ECG revealed no features of acute myocardial ischaemia; sinus tachycardia and inverted T waves in precordial leads were observed. Myocardial necrosis marker and BNP levels were correct, while D-dimer concentration was, in fact, elevated, at 3,500 μg/L. Among irregularities which suggested right ventricular volume overload, the echocardiogram indicated only a shortened acceleration time (ACT) of flow through the pulmonary valve — 78 ms, with narrowing on the ascending limb. CTA of the chest revealed embolic material located

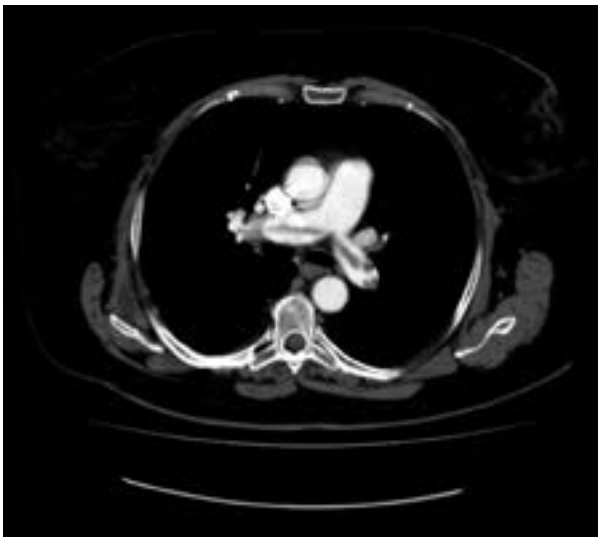

Figure 4. Patient 2. Computed tomography angiography of chest: a 'saddle' embolism

in the pulmonary trunk, at the point of bifurcation into the right and left pulmonary arteries (a so-called 'saddle' embolism) (Figure 4). The patient was administered LMWH at a dose of 60 mg twice daily (1 mg/kg body mass twice daily). A follow-up CT of the head revealed a malacic cavity caused by an intracerebral haematoma, but no features of an active haemorrhage (Figure 5). Dyspnoea subsided completely during hospitalisation, and symptoms of hemiparesis had been slightly weakening. The patient was discharged in a stable general condition, with sufficient cardiorespiratory function and a recommendation to take enoxaparin at a dose of 60 mg twice daily and undergo

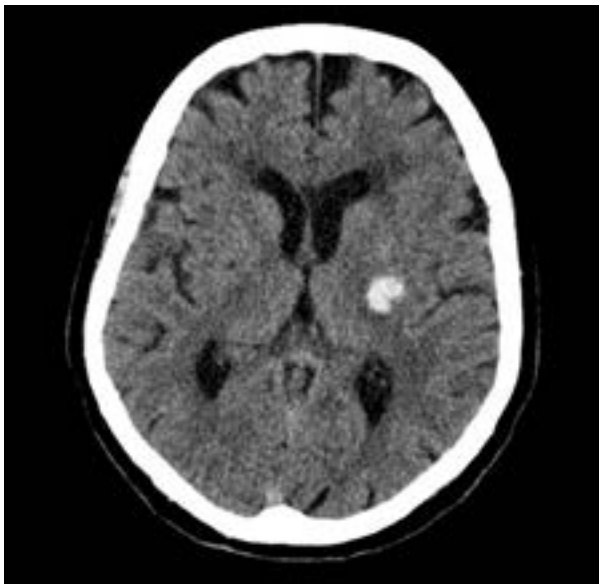

Figure 3. Computed tomography of head without contrast agent — intracerebral haematoma in deep structures on left

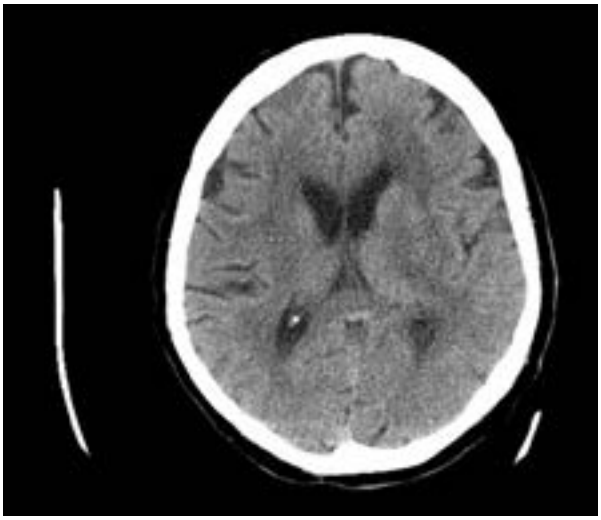

Figure 5. Computed tomography of head following diagnosis of pulmonary embolism — malacic cavity caused by intracerebral haemorrhage

a neurology consultation six weeks after discharge in order to consider whether an oral anticoagulant should be administered. Over a one-month observation, the patient has remained stable.

Discussion

Pulmonary embolism is a symptom of VTE and a condition which requires antithrombotic therapy [6]. Modern pharmacological treatment of PE already in the acute phase can begin with the administration of non-vitamin K antagonist oral anticoagulants (NOACs).

According to the latest guidelines of the European Society of Cardiology (ESC) concerning PE, for those patients from the low-risk group with PE for whom it is possible to administer oral coagulants, these drugs are preferred over VKAs. On the other hand, for patients from the low-risk group for whom treatment begins with parenteral therapy, LMWH and fondaparinux are preferred over unfractionated heparin (UFH) [6].

The subject patients were diagnosed with low-risk PE. The patients were similar in that for both the disease occurred after a CNS haemorrhage; consequently, their similarity extended to contraindications against standard treatment regimens for the acute phase of PE. Cerebral vascular malformations are a group of congenital and acquired abnormalities of cerebral vessels heterogeneous in structure and function. Due to the increasing availability of imaging tests, they are detected more and more frequently [7]. Cavernous angiomas found in Patient 1 are a rare form of CNS vascular malformations, occurring in 0.6% of the general population [8]. CNS haemorrhage of cavernous angiomas is the rarest symptom of these malformations; they typically manifest themselves through headaches or epileptic seizures, and the vast majority of affected people remain asymptomatic for their entire lives [9]. In the case of the subject patient, numerous haemorrhages, which manifested themselves fairly late, in the ninth decade of life, resulted in immobilisation, which probably predisposed towards PE. Patient 2 suffered an intracerebral haemorrhage probably due to improper management of arterial hypertension. Haemorrhagic stroke is a condition which constitutes an immediate threat to life. Between 30% and 50% of patients die within the first 30 days, wherein half of deaths happen within the first two days of occurrence [10].

Our two presented cases illustrate the difficulty concerning the administration of antithrombotic therapy in the acute phase of PE for patients with CNS haemorrhage. On the one hand, not administering antithrombotic drugs entails an increased risk of death in the course of PE (one of the patients was diagnosed with a 'saddle' embolism); on the other hand, administration of antithrombotic drugs adversely affects the size of haemorrhagic CNS foci [10]. Because there have been no large-scale, controlled clinical trials, the subject issue remains an unresolved multidisciplinary problem for both cardiologists and neurologists. There is also no literature which links the issue of haemorrhagic vascular malformations with PE. Assuming that PE in the presented patients was caused by an identified factor — immobilisation — then, in accordance with the current guidelines, antithrombotic therapy should be continued for at least three months [6]. A history of CNS haemorrhage was the strongest determinant behind the selection of antithrombotic treatment. Medicinal product characteristics for all NOACs list vascular malformations as a contraindication against their administration. Inclusion of VKAs for the subject patients was also impossible due to difficulty in predicting the effect of action, and contraindications against their use in the acute phase of CNS haemorrhage. LMWH, which is preferred over UFH, remained the safest treatment, as its administration entails a lower risk of severe haemorrhage and heparin-induced thrombocytopenia [11]. For subject patients, therapeutic doses of enoxaparin were administered during the initial days of PE; the dose for the patient with vascular malformations was reduced at discharge due to the high risk of repeated haemorrhage.

Summary

The optimisation of treatment in acute PE for patients after a CNS haemorrhage has been based on monitoring the parameters of cardiovascular function and neurological condition; neurological examinations and imaging tests were performed repeatedly, and the patient with vascular malformations also underwent neurosurgery consultation. In September this year, the ENRICH-AF (EdoxabaN foR IntraCranial Haemorrhage survivors with Atrial Fibrillation) study began; it is devoted to the issue of safety of antithrombotic therapy using edoxaban for patients with atrial fibrillation after an intracranial haemorrhage. We are hoping that it will contribute to a better understanding and selection of appropriate therapy for patients for whom antithrombotic therapy is simultaneously indicated and contraindicated.

Conflict of interest

BW-K: lecturer's fees for Boehringer Ingelheim, Bayer, Pfizer. IG: lecturer's fees for Boehringer Ingelheim, Bayer.

Streszczenie

Przedstawiono opisy 2 chorych, którzy po krwawieniu do ośrodkowego układu nerwowego doznali zatorowości płucnej, oraz trudności terapeutyczne związane z wyborem bezpiecznego leczenia przeciwkrzepliwego w ostrej zatorowości płucnej.

Słowa kluczowe: krwawienie, leczenie przeciwkrzepliwe, malformacja naczyniowa, zatorowość płucna

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