

Pulmonary embolism after brain hemorrhage in a hypertensive patient: the therapeutic dilemma

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Published online: 30 May 2007
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Abstract Massive pulmonary embolism is a life-threatening condition to be treated with anticoagulants or even thrombolytic agents in selected cases. However, these drugs are controindications after a recent hemorrhagic episode. We report the case of a 46-year-old patient with uncontrolled systemic hypertension who was affected by severe spontaneous cerebral hemorrhage and left hemiparesis. After some days of rehabilitation care he developed sudden dyspnea, tachycardia and hypotension secondary to bilateral pulmonary embolism. Owing to controindications to the use of thrombolytic agents, anticoagulant therapy with high-dose intravenous unfractionated heparin followed by oral warfarin was begun, with a successful and uncomplicated outcome. The therapeutic approach to similar not uncommon cases is debated and some hypotheses are made about the aetiology of pulmonary embolism in these patients.

Keywords Anticoagulant therapy · Deep vein thrombosis · Intracerebral hemorrhage · Pulmonary embolism · Thromboembolic disease

Introduction

Acute pulmonary embolism (PE) is frequent in patients affected by brain ischemia and prolonged immobilization,

since in this population thromboembolic complications have been reported in 30–60% of cases [1]. In these cases, prophylaxis of deep-vein thrombosis and thromboembolic disease with low-dose low-molecular weight heparin (LMWH) or unfractionated heparin (UFH) appears to be safe and well tolerated [2]. Moreover, it is well known that therapy of a non-massive pulmonary embolism in medical patients with the same drugs is generally also feasible [3–4]. On the other hand the treatment of a massive and potentially life-threatening PE can request thrombolytic agents [1, 5] and dicumarol derivatives which however can have dangerous side-effects in patients with extensive brain damage, mainly if secondary to hemorrhage. We report the case of a patient with severe brain hemorrhage, massive bilateral pulmonary embolism and obvious controindications to thrombolysis. Standard therapy with prolonged UFH infusion followed by warfarin allowed a successful uneventful outcome.

Case report

A 46-year-old man with chronic systemic hypertension not controlled by regularly taken drugs was affected by a severe spontaneous hemorrhage in the right brain hemisphere and in proximity of the basal ganglia, and subsequent left hemiparesis. The patient had a history of hypertensive heart disease with concentric myocardial hypertrophy, but denied previous diagnosis of coronary artery disease or diabetes mellitus, nor was affected by bleeding diathesis. His drug therapy consisted of an association of amlodipine, ramipril, a potassium-sparing diuretic and transdermal clonidine. After a two-weeks hospitalization period in another stroke unit he was transferred to our Hospital for the rehabilitation care. The first

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brain computed tomography (CT) scan requested on admission to our Hospital showed a right capsulo-talamic intraparenchymal hematoma with maximal diameter of 2 cm, and peri-lesional edema involving the posterior arm of the right internal capsule, the right external capsule and fronto-parietal region, with a mass effect on the lateral ventricle. Some old lacunar infarcts were also diagnosed (Fig. 1). Two days after arrival he developed sudden chest pain, hypotension and tachycardia so that a chest CT was requested for the suspicion of an acute pulmonary embolism. Indeed the CT showed multiple bilateral massive filling defects in pulmonary arteries, mainly in both inferior lobes and in the right superior one (Fig. 2). Lung scintigraphy confirmed bilateral embolism. A contemporary lower limb compression ultrasonography was negative for deep-vein thrombosis. The patient was therefore transferred to our Cardiology unit. Owing to the recent severe brain hemorrhage, thrombolytic therapy with rt-PA was contraindicated, while conventional anticoagulant therapy with unfractionated heparin and warfarin was deemed at high-risk for the danger of rebleeding. However, considering the PE severity as depicted by both CT and lung scintigraphy, and the hemodynamic unstable conditions of the patient with tachypnoea, hypotension, tachycardia and hypoxia, unfractionated intravenous heparin was begun with a loading bolus of 5000 IU, followed by continuous infusion at an average dose of 1,000 IU/hr, constantly maintaining the aPTT at 2 times the baseline value. Contemporary administration of warfarin was begun with a target INR of 2 to 3. The patient and his relatives gave their consent to this therapy after having been widely informed about the potential risks of recurrent brain hemorrhage. After a ten-days uncomplicated period of careful watching in our unit the patient was doing completely well and the follow-up CT had improved, so allowing us to submit him to further



Fig. 1 CT scan of the brain (see text)

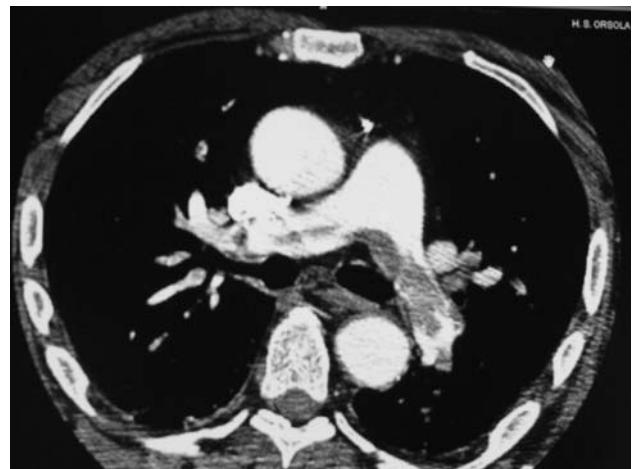


Fig. 2 CT scan of the chest (see text)

careful rehabilitation, maintaining oral anticoagulant therapy with a target INR interval of 2 to 3.

Discussion

The prevention and treatment of thromboembolic disease and acute PE in patients affected by an acute ischemic stroke represents a ticklish problem since the use of anticoagulants in these patients is associated with a modest but significantly increased risk of hemorrhagic transformation of brain ischemia: high heparin doses have potential benefit however counterbalanced by increased intracranial bleeding, so that they are warranted only for patients at high thrombotic risk [6–12]. However, it is generally admitted that the prophylaxis of thromboembolic events in patients with ischemic stroke can be accomplished with LMWH [2, 7, 13].

On the other hand, a logically more difficult problem that clinicians face is how to handle anticoagulation therapy in patients who have had a cerebral hemorrhage [14–15], which above all is a contraindication to thrombolysis with rt-PA [1]. A support for a wide range of treatments, but not a consensus, exists on how to treat patients with life-threatening thrombosis after cerebral hemorrhage [16]. The problem is not a minor one, since acute PE and other pulmonary complications have a high incidence in patients surviving intracerebral hemorrhage (ICH), carrying high mortality and morbidity rate so suggesting the importance of an aggressive treatment [1, 17]. At the same time, long-term high-intensity anticoagulant therapy itself carries an 8 to 11 fold increase of risk of ICH [18], while warfarin increases both the likelihood and the mortality of ICH particularly in patients with prior ICH, so that it is suggested that, for instance, patients

with lobar ICH and chronic atrial fibrillation should be withdrawn from anticoagulant therapy [19].

Anyway Bertram in patients with ICH and urgent need for anticoagulation receiving full-dose heparin did not observe rebleeding probably because brain tissue contains large quantities of thromboplastin which are released after brain damage, so activating the extrinsic clotting cascade. Furthermore, heparin could not be able to enter the site of cerebral hemorrhage, since small vessels are compressed within hematoma [18]. This could also help explain why UFH therapy was so well tolerated in the case presently reported by us.

As for alternative therapeutic options, surgical embolectomy in patients with ICH, acute PE and right heart failure was reported as successful [20–21], while insertion of an inferior vena cava filter in a patient with PE, deep vein thrombosis and primary ICH did not prevent from recurrent multiple pulmonary embolism and death [22].

In any case it is amazing that, notwithstanding a reported high incidence of acute PE in patients with brain damage and prolonged immobilization, no one specific paragraph is dedicated to this topic and to this therapeutic dilemma, neither in the official guidelines of the European Society of Cardiology on PE [1] nor in those on prevention of stroke and on complications of transient ischemic attacks [14].

Before drawing final conclusions about the present case we would still add some considerations about the possible aetiology of pulmonary thromboembolism in patients with brain damage and prolonged bed stay. Even though the absence of deep-vein thrombosis can be encountered in patients with acute pulmonary embolism, in this case we were amazed by the disproportion between the severity and bilateral extension of lung embolism, and the result of compression ultrasonography of the inferior limbs which was totally normal. We therefore wondered if bilateral pulmonary artery thrombosis could, at least in some cases, be a consequence of local clotting for reduced chest motility and respiratory excursions during prolonged bed stay. Indeed, this could be a causal mechanism not so different from that of prolonged stasis in the limb veins after post-traumatic leg immobilization, considering that pulmonary circulation occurs in low-pressure high-capacitance vessels similar to limb veins, and pulmonary arteries at rest have a very low baseline tone [23]. The same mechanisms that precipitate coagulation and thrombosis could act at different levels of the same vessel network. If this hypothesis should be confirmed, early respiratory rehabilitation could perhaps be a helpful preventive measure.

Another concurrent mechanism for thrombosis in stroke patients could be the stroke-induced sympathetic excess which may predispose to undesirable activation of the inflammatory and coagulation pathway in the vascular bed

[24]. Indeed rapid and dramatic improvement of symptoms was obtained with stellate ganglion block in some patients with massive PE and extremely severe clinical conditions [23].

The uncomplicated successful outcome of the case presently reported by us cannot be considered more than anecdotal and we cannot suggest routine use of anticoagulant therapy in patients with recent ICH and acute PE. However, the aim of the present report was also that of raising the problem of how to manage these difficult clinical situations, for which well defined guidelines still do not exist. Therefore we hope that further investigations and controlled trials will be conducted on populations of non uncommon cases of ICH and acute PE, with the aim of establishing definite guidelines for daily clinical practice.

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