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CASE REPORT

Fatal thromboembolism following physical restraint in a patient with schizophrenia

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Abstract Fatal thromboembolism during physical restraint in patients suffering from psychotic disorders is a very rare occurrence. In the case we present here, the criteria used in forensic pathology for the age determination of venous thrombi are applied to a case of pulmonary embolism in a patient suffering from schizophrenia who died after physical restraint. The possible association between conventional antipsychotic drugs and deep venous thrombosis, followed by pulmonary embolism, in a man with no predisposing risk factors, as well as the question concerning the appropriateness of medical care, are discussed.

Keywords Thromboembolism · Physical restraint · Death · Thrombus age · Schizophrenia · Forensic pathology

Introduction

The estimation of the timing of biological events has always been a controversial issue among forensic pathologists. New technologies have enhanced interest in this field [1–3]. As regards with thrombus age estimation, the use of conventional histopathological methods was proposed by Irninger in the 1960s [4] and by Leu [5] in the 1980s, while more recent studies have focused on immunohistochemical methods [6–8]. In the case we describe here, the criteria for the age determination of venous thrombi were applied to a case of fatal thromboembolism during physical restraint in a patient suffering from schizophrenia.

Physical restraint is considered a last resort treatment measure, sometimes used in psychiatric clinical practice to manage and treat patients with disruptive and/or violent behaviour who threaten themselves or others, thus posing a severe risk that cannot be controlled by means of other non-pharmacological or pharmacological approaches [9, 10]. In psychiatric clinical settings, a physically restrained patient is usually kept in bed with a waist belt or four-point restraint at the wrists and ankles, and thus, has a limited possibility of making free movements. A recent survey on the use of physical restraint in acute psychiatric hospitalisation showed that 11.1% of discharged patients had been restrained during hospitalisation [11]. Controversy surrounds the use of physical restraint in psychiatry since it may, it has been reported, result in severe adverse events, including sudden death [12–14].

A search in Medline databases, covering the period from 1966 to 2011 and conducted by cross-referencing deep venous thrombosis (DVT), pulmonary embolism (PE) and death against physical restraint, revealed only six case reports. Five of which described the presence of predisposing risk factors, such as hypertension, obesity, hyperlipidemia and heart infarction [11, 15–17], and only one was related to a young man in good health [11].

We report a case of sudden death due to thromboembolic disease in a patient with schizophrenia, on antipsychotic treatment, who had recently been physically restrained.

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The assessment of the age of the thrombus in this patient, who did not have any pre-existing risk factor, pointed to an association between the physical restraint and the venous thromboembolism (VTE). The question concerning the appropriateness of medical care is discussed. Another aim of the present case report is to increase awareness of a possible association between VTE/PE and physical restraint in patients undergoing treatment with antipsychotic drugs, which may raise doubts regarding the measures sometimes adopted in health care.

Case report

A 34-year-old male suffering from schizophrenia was admitted to the general hospital inpatient psychiatric treatment unit due to a recrudescence of acute persecutory delusions and severe agitation. The patient was in good general physical conditions and presented no obvious risk factors for thromboembolic events, with the exception of smoking (30 cigarettes/day), which is a very frequent risk factor in patients with psychosis.

He had no history of deep venous thrombosis or coagulopathies; moreover, he had not recently undergone surgery or been on any long-haul flight, nor did he have a family history of clotting disorders. No information was available regarding any previously performed haematological or coagulopathy screening. The routine physical examination and laboratory tests, including those for blood clotting, were normal if we exclude slightly increased of aspartate aminotransferase values. No signs of chronic obstructive pulmonary disease were present, nor did the patient display any evident physical trauma resulting from agitation. No investigations were carried out to search for possible genetic risk factors for thrombophilia since no pre-existing risk factors had emerged.

Upon admission to the emergency department, the patient received oral treatment with risperidone 4 mg, diazepam 6 mg and flurazepam 30 mg, which led to a slight improvement in the agitation. The patient was thus placed on treatment with haloperidol 5 mg t.i.d, chlorpromazine 100 mg t.i.d. and diazepam 10 mg t.i.d. As he continued to be extremely aggressive and verbally threatening despite this treatment, once in the psychiatric ward, the physicians decided to physically restrain him. The patient, who remained aggressive, was restrained for 6 days, being released for 45 min on day 2 and for 60 min on day 5. This procedure was applied according to the guidelines for physical restraint [18]. The patient was reassessed every 12 h; the padded bracelets used for restraint were wide enough to allow minimal movements of the limbs. During this period, the patient was apyretic and tachycardic and presented a mean arterial blood pressure of 140/80 mmHg. Peripheral blood oxygen saturation measurements, which were constantly conducted, fell within the normal range. The cardiovascular, respiratory, abdominal and neurological examinations were normal.

Upon his release after 6 days, he complained of dizziness while being escorted to the washroom and before collapsing. The patient was immediately transferred to the intensive care unit for further observation and treatment. PE was diagnosed, and the patient underwent fibrinolysis and treatment with heparin 25,000 U/h. A physical examination revealed unconsciousness, cyanosis, shortness of breath, a temperature of 39°C, a breathing rate of ~16 breaths/min and an oxygen saturation of 99%. Following the initial collapse, a gradual increase in fibrinogen (887 mg/dl on day 3, 1,054 mg/dl on day 4 and 1,140 mg/dl on day 5) and D-Dimer (497 ng/ml at day 3) concentrations was detected. He was pronounced dead after 5 days of coma.

Autopsy findings

An autopsy was requested to verify the appropriateness of medical care. No signs of physical trauma were observed upon external examination of the corpse. The examination revealed that this male patient (94 kg/183 cm; BMI= 28 kg/m^2) presented a concentric left ventricular hypertrophy with a wall thickness of 2 cm. Macroscopically, the right lung showed a bluish area, 5×5 cm in size, of increased consistency and clear margins (lung infarct). The remaining organs were unremarkable.

Upon examination, the vascular system revealed fragments of deep vein thrombosis in the right femoral–popliteal venous axis and fragments of thromboemboli in the right pulmonary artery (Figs. 1 and 2). Evidence of pulmonary infarction was observed in the right lung. No signs of arteriosclerosis were found. Specimens of the lung and of the thrombus from the right femoral–popliteal vein and from the right pulmonary artery were stained with haematoxylin

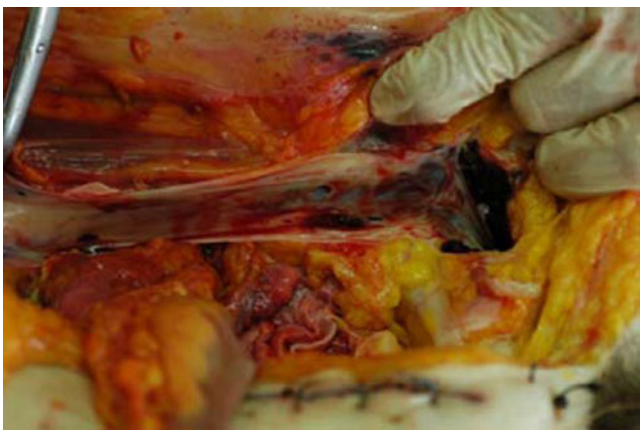

Fig. 1 Fragments of a deep vein thrombosis of the right femoral–popliteal venous axis

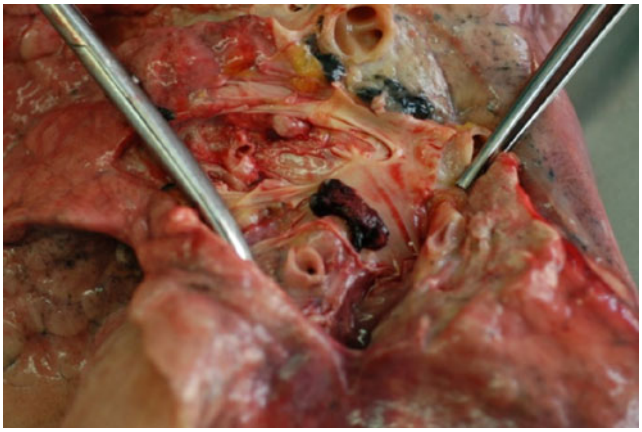

Fig. 2 Fragments of thromboemboli in the right pulmonary artery

and eosin, Masson for collagenous fibres, Weigert for elastic fibres, Perls for hemosiderin and PTAH for fibrin. Immunohistochemistry was performed using anti-fibrinogen polyclonal antibodies, anti-myeloperoxidase, CD3, CD20, CD45, CD68, CD31 and CD34 (results shown in Table 1).

Although criteria for the dating of infarcts and thrombi have been proposed in the literature, there are marked discrepancies between such criteria owing to the difficulties encountered by physicians when attempting to ascertain the precise time in which the thrombus originated. In the case we describe, however, the period of time in which the thrombus originated may be determined owing to the immobilisation of the patient. As the assessment of the histological age of thromboses and pulmonary embolisms is mandatory for medical liability purposes, we took into account some of the criteria proposed by Irninger [4], Leu [5], Fineschi et al. [6] and Nosaka et al. [7, 8].

Microscopic observations of the thrombosis samples, from both the right femoral–popliteal venous axis and the right pulmonary artery, revealed neutrophils (myeloperoxidase +); some of which were pyknotic and macrophages (CD68+), with a ratio of ~1.0, and fibrinous ribbon deposition with a layered growth (Zahn's lines), with normal blood platelets (CD31+), as well as agglomerates of well-preserved erythrocytes, which were concentrated above all in the centre, and were peripherally more loose (Figs. 3 and 4). No signs of capillary neoformation, hemosiderin-accumulating histiocytes or endothelium under the thrombus were observed.

According to Irniger's classification [4], the thrombosis and pulmonary embolisms had occurred 3–8 days previously [Phase II: Penetration of fibroblasts and endothelial budding. Free surface of thrombus may already be covered by endothelium. Onset of hyalinization, mainly central. Enclosed white blood cells pyknotic. Monocyte nuclei enlarged and bright. Through shrinking of thrombus, peripheral fissures and "sinuous" cavities can develop in which loosely aggregated erythrocytes are found. No signs of phase III (4th–20th day): first capillaries, fibroblasts, mesenchymal cells, hemosiderin-accumulating histiocytes, endothelium under thrombus or hyalinized thrombus split into separate large clumps], whereas Leu's classification indicated that they had occurred 4–8 days previously (stage II). The more recent classification proposed by Fineschi et al. [6] placed the timing of the thrombosis in phase I [i.e. 1^{st}–7^{th} day: flowing blood on an eroded endothelium, eliciting a platelet plug and fibrin deposition with a layered growth (Zahn's lines). No reaction between the endothelium and thrombus is visible. Erythrocytes are preserved and agglomerated. Initial white blood cell pyknosis. Monocyte cells with enlarged nuclei. Calcium is observed as precipitates with von Kossa stain. The thrombus at its initiation is firmly attached to a small portion of the vessel wall and is not easily removed, leaving fragments in situ. By contrast, the coagulum maintains the usual blood composition, i.e. prevailing red cells plus leukocytes and platelets and a fine fibrin network, is not attached to the endothelium and can easily be removed], thereby confirming the data yielded by Irninger's and Leu's classifications [4, 5]. Furthermore, according to recent studies conducted on mice by Nosaka et al. [7, 8], the neutrophil/macrophage ratio of ~1.0 indicates a thrombus age of 5 days or more.

The cause of death was reported as pulmonary thromboembolism, associated with pulmonary infarction, in a male

Table 1 Immunohistochemical staining used in the present investigation

Antigen	Clone	Pretreatment	Antigen distribution	Results
CD3	Rabbit (Dako)	Tris–HCl pH 9.9	Pan T lymphocytes	Negative
CD20	L26 (Dako)	EDTA pH 8	Pan B lymphocytes	Negative
CD45	UCHL1 +4kB5 (Dako)	EDTA pH 8	B lymphocytes, naive and memory T lymphocytes, monocytes	Negative
CD68	Kp1 (Dako)	EDTA pH 8	Myeloid cells and monocytes/macrophages	Positive
CD31	PGM1 (Dako)	EDTA pH 8	Vascular and lymphatic endothelium and platelets	Positive
CD34	QBend10 (Dako)	No treatment	Vascular endothelium and haemopoietic stem cells	Positive
Myeloperoxidase	Rabbit (Dako)	No treatment	Myeloid cells and neutrophiles	Positive
Fibrinogen	Rabbit (Dako)	EDTA pH 8	Fibrinogen	Positive

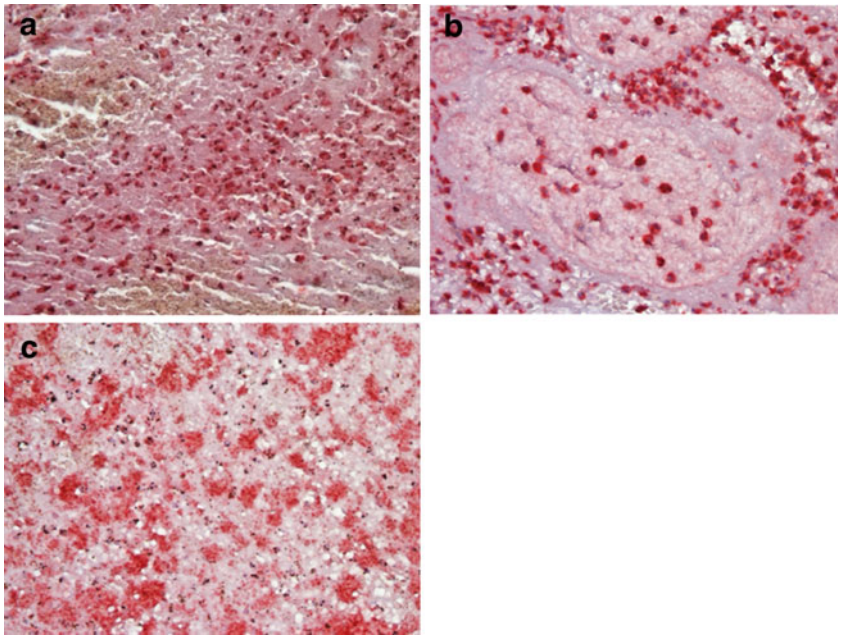

Fig. 3 Microscopic observations of the thrombosis samples from the right femoral–popliteal venous axis. **a** Agglomerates of neutrophils (myeloperoxidase +), some of which have pyknotic nuclei, surrounded by erythrocyte and fibrin. **b** Macrophages (CD68+), fibrinous ribbons and agglomerates of erythrocytes. The ratio between neutrophils and macrophages is ~1.0. **c** Normal blood platelets (CD31+), agglomerates of erythrocytes and fibrin

patient treated by means of physical restraint. No medical liability was found because of the rarity and unpredictability of such cases and because the guidelines for physical restraint do not explicitly state the need for heparin administration.

Discussion

Fatal thrombosis and physical restraint are rarely associated, and when they are, underlying predisposing risk factors are usually found. We describe a young man who died as a result of thromboembolism and had no pre-existing risk factors other than smoking, including the absence of arteriosclerosis at the autopsy and signs of heart failure that may have predisposed him to pulmonary infarction. Although it was not possible to assess the patient's specific or genetic risk for thromboembolism owing to the lack of evidence, application of the Wells Diagnostic Scoring System (WDSS) yielded a score of 3 points (immobilisation and tachycardia). The WDSS, which is the most widely used method to predict clinical probability for thromboembolic events and takes into account the patient's clinical history, the clinical findings and the possible alternative diagnoses, has a maximum score of 12.5 points. A score of 4 points corresponds to a likelihood of PE of only 8% [19].

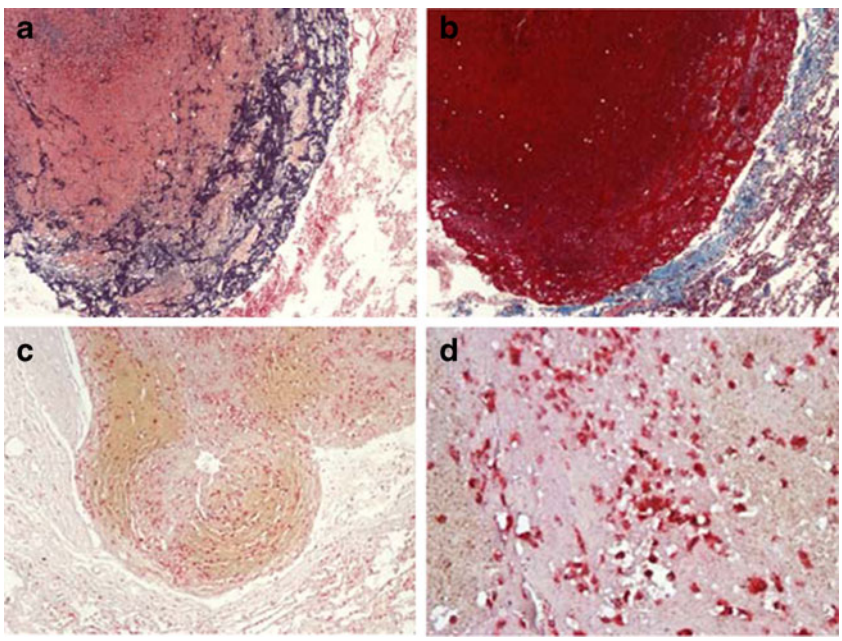

Fig. 4 Microscopic observations of the thrombosis samples, from the right pulmonary artery, coloured with PTAH for fibrin (**a**) and Masson for collagenous fibres (**b**), show no reaction between the endothelium and thrombus. The ratio between neutrophils (myeloperoxidase +) (**c**) and macrophages (CD68+) (**d**) is ~1.0

As the age estimation of the thrombus in the case we describe placed the age in the period of physical restraint (i.e. within 8 days), questions concerning medical care arose. VTE and PE may have been caused by the combined effects of immobilisation and medications. It is well known that physical restraint impairs the blood circulation. This may, in the presence of risk factors, cause DVT and, consequently, PE. Indeed, the sedative effects of antipsychotic drugs in a patient under physical restraint limits movement, thus creating predisposing conditions for venous thrombosis [20]. However, as histological age assessment has revealed that thrombosis may, even in the absence of other possible causes, develop very early during physical restraint, antipsychotic drugs must, in the case we describe, be considered as the likely cause of a thromboembolism that was associated with immobilization and, possibly, an undiagnosed thrombophilia.

Recent studies suggest that the use of antipsychotics is associated with a higher incidence of venous thrombosis in psychiatric patients [11]. A possible association between conventional antipsychotic drugs and VTE was first hypothesised in the 1950s following the introduction of phenothiazines [21]. In the years that immediately followed, a sevenfold increase in the risk of idiopathic VTE was detected in users of conventional antipsychotics <60 years of age and with no major risk factors [22].

More recently, an association between VTE and atypical antipsychotic agents, a newer class of drugs with different pharmacological, higher safety and better clinical profile, have been suspected among users of clozapine, a drug known to induce dyslipidaemia. This association is primarily supported by results of a large record linkage study that revealed a fivefold increase in lethal PE [23]. Three cases of VTE have recently been reported in elderly patients treated with olanzapine and in one young man with a psychotic disorder [24].

Although it has been suggested that amisulpiride may be a better therapeutic choice in patients in whom antipsychotics with a high affinity for the 5-HT_2 receptor have led to a previous episode of VTE [17], the choice of antipsychotics in the presence of VTE risk factors remains controversial. Lastly, one study, in which logistic regression analysis was performed on the autopsy records of 1,125 Japanese, found a possible association between risperidone and massive pulmonary thromboembolism [25].

Psychiatric patients taking conventional antipsychotic drugs under physical restraint, as well as those suffering from severe catatonia or neuroleptic malignant syndrome not restraint, appear to present an increased risk of developing DVT and PE, both of which are potentially life-threatening events [26–29]. According to the literature, the risk of VTE is highest during the first 3 months of treatment with atypical antipsychotics. Further studies are warranted to shed light on this association, and in particular, to determine the incidence rates and possible predisposing factors. This issue warrants particular attention since the prescription of atypical antipsychotic drugs is becoming increasingly widespread [17, 30].

In the case we report here, D-Dimer and fibrinogen concentrations were assessed only after PE had occurred, which points to a lack of awareness of the risk of VTE and PE in such patients. Self-limiting micro-pulmonary embolism of the small artery vessels may represent a much more frequent condition than overt pulmonary embolism, even in patients who undergo antipsychotic treatment and physical restraint. Since microembolism is often clinically silent, but may represent an early step in the pathogenesis of full pulmonary thromboembolism, we recommend regular coagulation pattern screening in all patients under physical restraint, even in order to avoid accusations of medical neglect. If these patterns are altered, treatment with low molecular weight heparin should be strongly recommended.

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