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Diffuse alveolar haemorrhage complicated by pulmonary embolism — problems with treatment

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Abstract

Diffuse alveolar haemorrhage (DAH) refers to a clinical syndrome resulting from injury of the alveolar capillaries, arterioles and venules leading to red blood cel accumulation in the distal air spaces. The conditions associated with DAH and underlying disease determine the prognosis and the treatment regimen. The coexistence of DAH with venous thromboembolism (VTE) is a seroius problem for clinicians and poses a challenge in the therapeutic management.

We describe a young patient who developed massive DAH in the course of anti-glomerular basement membrane (anti-GBM) disease (formerly called Goodpasture's syndrome) complicated by pulmonary embolism (PE).

Key words: alveolar hemorrhage, pulmonary embolism, treatment

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Introduction

Diffuse alveolar haemorrhage (DAH) is a potentially life-threatening manifestation requiring aggressive treatment [1]. Most commonly, it occurrs in the course of systemic vasculitis. In turn, venous thromboembolism (VTE) is a frequent complication of systemic vasculitis that poses a challenge in the therapeutic management when it occurs in patients with active haemorrhage [2].

We describe the young patient who developed massive DAH in the course of anti-glomerular basement membrane (anti-GBM) disease (formerly called Goodpasture's syndrome) complicated by pulmonary embolism (PE).

Case report

A 21-year-old woman who had a history of smoking was referred to a regional hospital because of severe anaemia and pulmonary infiltrates in chest-X ray (Fig. 1). She complained of weakness and fatigue, but she did not have cough, dyspnoea nor haemoptysis. For 2 years she used hormonal contraception. Upon admission, the patient's haemoglobin was 5.8 g/dl. Basing on the endoscopic examination of the gastrointestinal tract, bleeding was excluded. Serum tumour markers (Ca125, CEA-carcinoembryonic antigen, AFP-alpha fetoprotein, hCG-human chorionic gonadotropin) were absent. Bone marrow biopsy showed no pathology. Chest computed tomography (CT) scans revealed centrilobular nodules

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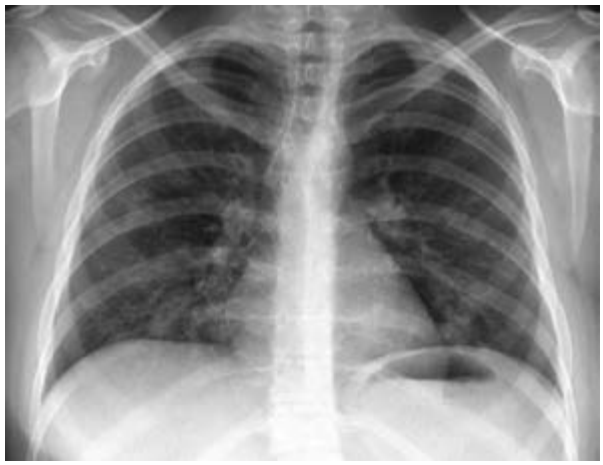

Figure 1. Posteroanterior chest X-ray shows bilateral ill-defined parahilar and lower-lobe opacities

Table 1. Wells scale (adapted from [3])

Clinical feature	Score
Active cancer (ongoing treatment ~~ongoing~~ or within previous 6 months or palliative)	1
Paralysis, paresis, or recent plaster immobilisation of the lower extremities	1
Recently bedridden for more than 3 days or major surgery within 4 weeks	1
Localised tenderness along the distribution of the deep venous system	1
Entire leg swollen	1
Calf swelling by more than 3 cm when compared with the asymptomatic leg (measured 10 cm below tibial tuberosity)	1
Pitting oedema (greater in the symptomatic leg)	1
Collateral superficial veins (non-varicose)	1
Alternative diagnosis as likely or greater than that of deep-vein thrombosis	–2

in both lungs forming the areas of ground-glass attenuation (Fig. 2A). After blood transfusion, the concentration of haemoglobin increased to 8.5 g/dl, but 1 week later, haemoptysis occurred with re -decrease in haemoglobin. The patient received antibiotics and underwent blood transfusion again and was transferred to our Department for further diagnosis (The National Research Institute of Tuberculosis and Lung Diseases in Warsaw).

Upon admission, the woman complained of small haemoptysis, but she was in good general condition. Respiratory rate was normal, but heart rate accelerated to 100/min. Blood pressure was 120/80 mm Hg. No changes of hearing over the lung were found. The lower limbs were normal, without oedema or swelling, without varicose vein. The number of points on the Wells scale (Table 1) was < 0, which indicated a low probability of DVT (deep venous thrombosis) [3]. The haemoglobin concentration was 11 g/dl and MCV (mean corpuscular volume), ferritin and TIBC (total iron binding capacity) were normal, but reticulocyte count was mildly elevated. The levels of liver enzymes, fibrinogen and coagulation parameters were within normal limits, but d-dimer and C-reactive protein were raised. Serum creatinine and calculated glomerular filtration rate (GFR) were normal, the urine sediment was active (microscopic erythrocyturia). The patient had no respiratory failure, the oxygen tension in blood was 79 mm Hg, with hypocapnia and respiratory alkalosis. The carbon monoxide diffusing capacity (DLCO) was reduced to a mild level. Because the patient used hormonal contraception for 2 years, angio-CT was performed despite the low probability of DVT in the clinical evaluation. Chest CT scans showed extensive progression of ground glass attenuation areas and bilateral pulmonary embolism with lung infarct in lingula (Fig. 2B, C). Deep venous thromboembolism in duplex sonography was excluded. On bronchoscopy, diffuse bleeding was detectable, which together with

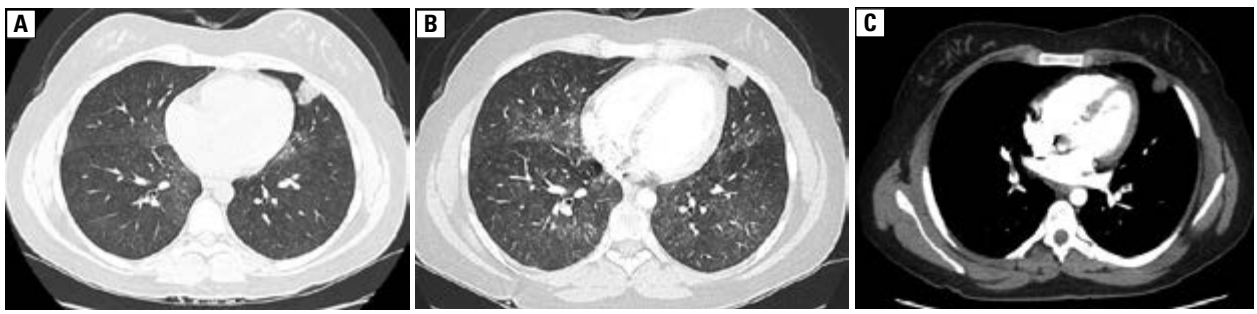

Figure 2 A, B — CT scans at the level of lower lobes. In comparison to the previous exam from two weeks there is progression of bilateral ill-defined parahilar and lower-lobe opacities. Moreover, CT scans show infarction of lingula; **C** — axial CT pulmonary aniogiogram shows intraluminal filling defect within the right lower lobe pulmonary artery and segmental arteries of the left lower lobe

the clinical symptoms, anaemia and chest CT image corresponded to diffuse alveolar haemorrhage. Immunological laboratory tests showed high positive titres for anti-glomerular basement membrane antibodies (anti-GBM = 146 U/ml, enzyme-linked immunosorbent assay, ELISA) in serum. Finally, anti-GBM disease with concomitant pulmonary embolism was diagnosed. Indications for the treatment of each of the diagnosed diseases were contradictory and mutually exclusive. For the best care, the patient was transferred to the Intensive Care Unit. Treatment was started with a 3-day course of intravenous methylprednisolone (500 mg/day), and then oral prednisone with cyclophosphamide was implemented. During the second pulse of steroids, anticoagulation with unfractionated heparin (UH) was added. The tolerance of treatment was good and there were no complications, so UH was turned into a low-molecular-weight heparin (LMWH). As a result of treatment, a quick clinical, immunological and radiological improvement was obtained (Fig. 3A, 3B). The control urine analysis showed no blood, and renal function was still maintained (calculated GFR was 89 ml/min).

Discussion

DAH refers to a clinical syndrome resulting from injury of the alveolar capillaries, arterioles and venules leading to red blood cell accumulation in the distal air spaces. Usually, it is defined by the clinical triad of haemoptysis, anaemia and hypoxaemia, but the final diagnosis requires confirmation by bronchoscopy in which serial bronchoalveolar lavage samples reveal persistent haemorrhagic fluid [1]. The most common causes of DAH are antineutrophil cytoplasm antibody (ANCA) associated vasculitis (AAV) and anti-GBM disease [4].

The incidence of anti-GBM disease is estimated to be 1 case per milion per year. The age distribution is bimodal, 20–30 years and 60–70 years. The prevalence of the disease is higher in men in the younger age group and women in the older age subgroup [5, 6]. Clinical manifestation is usually characterised by the combination of glomerulonephritis and DAH accompanied by anti-GBM in serum and/or tissue. Serologic assay for IgG anti-GBM antibodies are highly sensitive (> 95%) and specific (> 97%) for the disease, but not in all patients it is positive. Szczykowska *et al.* [7] described a 59-year-old patient with classic clinical presentation of anti-GBM disease with supporting histologic and radiologic evidence but with ambiguous serological evidence [7].

The aetiology of anti-GBM disease is not completely understood. The recent literature shows that an initial insult to the pulmonary vasculature is required for exposure of the alveolar capillaries to the anti-GBM antibodies, and predisposing factors for such exposure include the following: association with HLA-DR15, exposure to organic solvents or hydrocarbons, smoking, infection, cocaine inhalation, exposure to metal dusts and lymphocyte-depletion therapy [6, 8–10]. Our patient was a young 21-year-old woman with no medical history. She had no evident exposure to environmental predisposing factors, but she smoked cigarettes, which could have an impact on the occurrence of the disease.

VTE is a frequent complication of systemic vasculitis, but its presence in anti-GBM disease is very rare. The occurrence of VTE should be treated with anticoagulants, but on the other side — anticoagulation may increase pulmonary bleeding. De Souza *et al.* [11] presented their experience of dealing with AAV patients

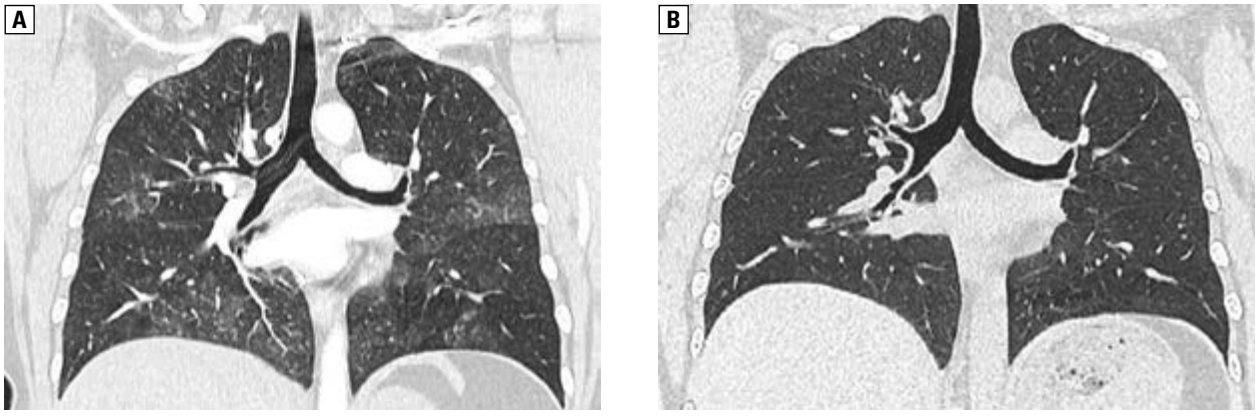

Figure 3 A, B. CT scans (axial reformations) show complete regression of ground-glass opacities after six months

Table 2. Risk factors for venous thromboembolism (adapted from [12])

Strong risk factors (odds ratio > 10)	Moderate risk factors (odds ratio 2–9)	Weak risk factors (odds ratio < 2)
1) trauma or fractures	1) non-oncological surgery	1) age
2) major orthopaedic surgery	2) oral contraceptives and hormone replacement therapy	2) bed rest (> 3 days)
3) oncological surgery	3) pregnancy and puerperium	3) prolonged travel
	4) hypercoagulability	4) metabolic syndrome
	5) previous venous thromboembolism	5) air pollution

presenting with this combination of VTE and concurrent DAH. The authors showed that in their cohort of 35 patients with DAH secondary to vasculitis, 20% of the subjects had concurrent VTE. Among patients with DAH, 57% of cases were diagnosed with AAV, 29% with anti-GBM disease and 14% with anti-synthetase syndrome. VTE was diagnosed by a combination of CT angiography in 6 patients and duplex sonography in 5 subjects. Six of these patients were treated with an anticoagulant, mostly in the form of LMWH with insertion of vena cava filtres in half of them. This approach was successful in 5 cases, without worsening of DAH, but provoked the new onset of haemorrhage in the six patients 2 weeks after anticoagulation treatment had been initiated. One patient received a vena cava filter but no systemic anticoagulant. Three of 6 anticoagulated patients also underwent plasmapheresis. What is important, no patient died and only the patient who did not receive anticoagulation treatment developed a further PE following treatment [11].

Our patient applied hormonal contraception, which was a moderate risk factor for VTE (Table 2). Oral contraceptives modify the plasma levels of several coagulation factors (Table 3), but these changes are often modest and the concentrations of coagulation factors usually remain within the normal range [12]. The impact of transfusions cannot be excluded as a risk factor for VTE, too. Kumar *et al.* [13] presented a relationship between the red blood transfusion and an increased risk of VTE in neurological patients (with subarachnoid haemorrhage). A dose-dependent association exists between the number of units transfused and thrombosis, the age of blood does not appear to play a role. Our patient was transfused twice, which could have a clinical relevance. It is interesting that the number of points on the Wells scale was < 0, which indicated a low probability of DVT, and the ultrasonography was negative. Only the angio-CT revealed pulmonary embolism, but hypocapnia was a suggesting factor for the disease. Our patient was treated with immunosuppression and anticoagulation first in the form of

Table 3. Haemostating changes during oral contraceptive use (adapted from [12])

Haemostating parameter	Change during oral contraceptive use
Procoagulant factors	
fibrynogen, V, VII, VIII, IX, X, XII	increase
XI	no change or increase
Von Willebrand factor	no change
Anticoagulant proteins	
antithrombin	decrease
protein C	no change or increase
protein S	decrease
resistance to activated protein C (ratio)	decrease
Markers of thrombin formation	
F1+2[1], TAT[2] complexes, fibrinopeptide A	increase
d-dimer	increase
Fibrinolytic factors	
TAFI[3], PA1 and 2[4]	increase
t-PA[5]	decrease

[1]prothrombin fragment 1+2; [2] thrombin-antithrombin complex; [3]thrombin activatable fibrinolysis inhibitor; [4]plasminogen activator inhibitor type 1 and 2; [5]tissue plasminogen activator

UH in order to better control treatment. Initially, she was monitored in the ICU, but no complications of the treatment were observed. The patient did not have DVT, and filter implantation was not neccesary. Due to the preserved renal function and good clinical and immunological response to immunosuppressive therapy, plasmapheresis has not been applied.

The prognosis in the anti-GBM disease is serious and it can lead to death. In the series of 122 French patients, three predictive factors of death within the first 12 months were identified: being aged > 60 years, a low number of plasmapheresis sessions and the requirement for an alternative immunosuppressive agent because of refractory or relapsing anti-GBM disease [14]. New data indicate that preexisting chronic interstitial pneumonia is an independent factor of a poor prognosis in anti-GBM disease. Tashiro *et al.* [15] reported a case of anti-GBM disease complicated by preexisting chronic interstitial pneumonia

and positive myeloperoxidase anti-neutrophil cytoplasmic antibody (pANCA). They reviewed six similar cases described in the literatue, and concluded that anti-GBM disease with preexisting interstitial pneumonia and pANCA is related to a poor prognosis. In the case of our patient, there were no unfavourable factors, therefore the prognosis was good.

This case emphasises the need for awareness of the possibility of VTE in patients with active DAH, especially, when risk factors are involved. It presents a rare case of the coexistence of anti-GBM disease and PE. It shows that a good clinical condition and the normal oxygen tension in the blood do not exclude the coexistence of these two severe diseases. In our patient, decreased $PaC0_2$ was the alarming sign suggesting VTE. It is possible, that the combination of VTE and DAH is more common than we imagine, as not all patients with DAH are routinely assessed with regard to PE or DVT. The clinical decision regarding the timing of anticoagulation is therefore important as clearly both immunosuppression and anticoagulation are a vital step in achieving favourable outcomes.

Conflict of interest

The authors declare no conflict of interest.

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