

Novel treatment (new drug/intervention; established drug/procedure in new situation)

A unique presentation of four thrombotic events at a time

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Summary

A 72-year-old man was referred to our hospital as a case of postcardiac arrest following a long distance air flight. Work-up in the emergency department revealed the presence of deep vein thrombosis (DVT), bilateral pulmonary embolism, inferior STEMI (ST elevation myocardial infarction) and ischaemic stroke. He received thrombolysis by recombinant tissue plasminogen activator (tPA) following which his haemodynamic status improved, but he developed haemorrhagic transformation of the stroke as a complication. The haemorrhagic lesion gradually resolved with conservative management, leaving behind a residual neurological deficit. His haemodynamic status was stable after the management. Although a diagnosis of right-to-left shunt lesion was highly suggestive in this condition, it could not be confirmed on the transthoracic echocardiogram. Our patient had a unique presentation of multiple thrombi in different organs that caused significant morbidity and haemodynamic instability. There are no well-established guidelines that discuss the acute management of such cases. This situation requires a careful assessment and management of the patient by a multidisciplinary team.

BACKGROUND

Such cases will be encountered more frequently with increasing ease of travel between different continents. This situation requires a careful assessment and management of the patient by a multidisciplinary team. There is very limited research done on this condition and no guidelines are available to guide physicians on this topic.

CASE PRESENTATION

A 72-year-old man landed transit in our city after he travelled a long-distance flight of 15 h duration. His medical history included ischaemic heart disease for which he had percutaneous coronary intervention conducted 5 years ago. While at the airport, he developed sudden onset of dyspnoea lasting for 20 min, after which he felt dizzy and collapsed. Cardiopulmonary resuscitation was done for 3 min but no shock was delivered and he was immediately shifted to our hospital. While transporting him, the paramedic staff noted that he was not moving the left side of his body. On arrival at the emergency department, the patient was unresponsive with a Glasgow Coma Scale (GCS) of 4/15. Examination revealed an obese man with blood pressure of 182/90 mm Hg, pulse of 95 beats/min, pulse oximetry of 94% on high flow oxygen. Cardiovascular and respiratory systems were unremarkable. The patient was intubated while he was being resuscitated in emergency department.

INVESTIGATIONS

His ECG showed sinus rhythm with ST elevation in inferior leads and ST depression from V2 to V6, I and aVL (figure 1).

The blood investigations showed haemoglobin 15 g/dl, white blood cells $18 \times 10^3/\mu\text{l}$, platelets $182 \times 10^3/\mu\text{l}$. Cardiac enzymes: creatine kinase was 77 U/l that rose to 737 U/l and Creatine Kinase myoglobin (CK-MB) was 17 U/l and then it became 109 U/l and troponin was 0.05 ng/ml then it rose to greater than 2 ng/ml. brain natriuretic peptide (Pro-BNP)

was 197 pg/ml, D-dimer was 6.09, random blood sugar was 188 mg/dl, procalcitonin 0.02 ng/ml, prothrombin time 15 s with international normalised ratio of 1.26, aPTT 29.9 s. Electrolytes and renal function tests were normal at the time of admission. Antidouble-stranded DNA antibodies and anti-nuclear factors were negative. Anticardiolipin antibodies (IgG and IgM), β -2-glycoprotein levels, phosphatidyl serine antibodies (IgG and IgM) were all negative. Thrombophilia screening which included assays for antithrombin III, protein C, protein S, activated protein C resistance (APCR) were all within the normal range for this patient.

Bedside echocardiography showed dilated right heart chambers with grade 2/4 tricuspid regurgitation and right ventricular systolic pressure (RVSP) of 40 mm Hg. The mid-basal septum and inferior segment was akinetic with an ejection fraction of 40%.

In view of the history of long travel and the clinical presentation the patient underwent CT pulmonary angiography which showed multiple filling defects in the peripheral branches of the left and the right main pulmonary arteries suggestive of bilateral pulmonary embolism (figure 2). Doppler ultrasound of the lower limbs confirmed the presence of deep vein thrombosis (DVT) in the left superficial femoral vein.

Brain CT scan that was done initially did not show any significant abnormality except age-related cortical involutional changes. Stroke was diagnosed clinically as he was noted not to be moving the left side of his body.

DIFFERENTIAL DIAGNOSIS

- ▶ Patent foramen ovale
- ▶ Ventricular septal defect
- ▶ Atrial septal defect
- ▶ Patent ductus arteriosus
- ▶ Arterio-venous malformation
- ▶ Thrombophilia
- ▶ Antiphospholipid syndrome

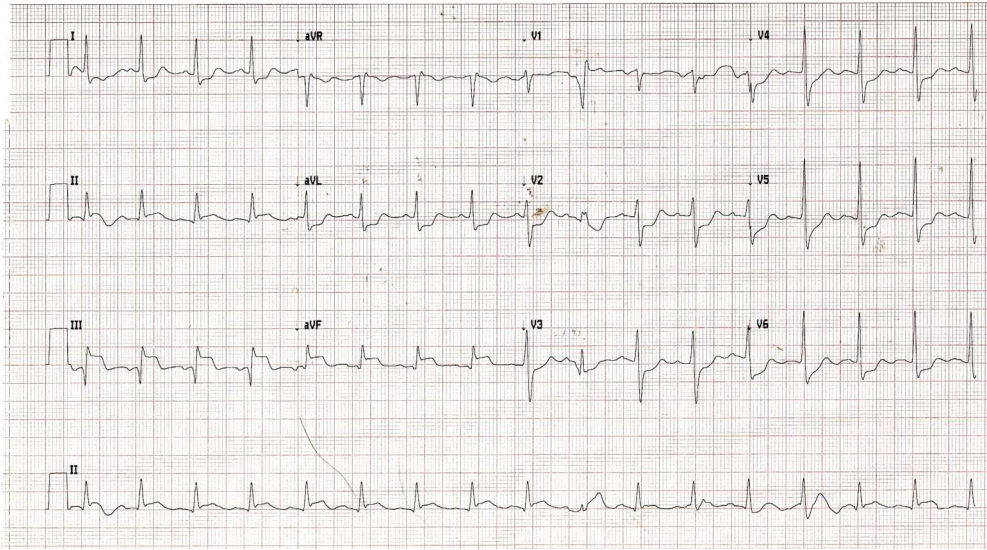


Figure 1 ECG at admission showing sinus rhythm with ST elevation in inferior leads.

TREATMENT

It was decided to administer thrombolytic therapy in view of his pulmonary embolism and inferior ST elevation myocardial infarction (STEMI). Taking into account the presence of left-sided hemiplegia and normal brain CT, possibility of early ischaemic stroke was considered. Since the patient had presented within 3 h of onset of symptom, this was within the window period for administration of thrombolysis for stroke cases. Recombinant tissue plasminogen activator (tPA) was given as per the protocol. Blood pressure at the time of thrombolytic was 122/83 mm Hg and pulse was 72 beats/min.

After giving tPA, the patient was shifted to Coronary Care Unit. He then developed a self-limiting episode of upper gastrointestinal bleeding, which caused an acute

drop in haemoglobin level. He was transfused 2 units packed red blood cells. However his haemodynamic parameters remained stable and he responded to conservative management with proton pump inhibitors. Low-molecular-weight heparin (LMWH) was started after 48 h. His GCS improved to 11/15. But he continued to require ventilatory support and was still unable to move the left side of his body. A follow-up brain CT after 5 days showed a large right hemispheric haemorrhagic infarction at the territory of the right middle cerebral, posterior cerebral and cerebellar arteries without any significant midline shift (figure 3). The neuromedical team was consulted and they advised to withhold all antiplatelet and anticoagulant



Figure 2 CT pulmonary angiogram showing bilateral pulmonary embolism.



Figure 3 Brain CT showing large right hemispheric hypodense area with patchy area of bleeding seen at the temporal lobe with associated mass effect but no significant midline shift.

medications, which could be restarted after 2 weeks if patient's condition remained stable. In the meantime his neurological status remained stable and he did not require any urgent neurosurgical intervention. Follow-up brain CT showed gradual resolution of the haemorrhagic infarction (figure 4). He was then gradually started on regular physiotherapy.

Angiography was not planned due to the patient's current condition. Transthoracic bubble contrast echocardiography was done but it did not show any shunt across interatrial septum, but the patient was unable to perform Valsalva manoeuvre due to poor respiratory effort. It was planned to do a transoesophageal echocardiography (TEE) as it is a more sensitive tool for identification of patent foramen ovale (PFO). However, the patient's relatives arranged for air ambulance in order to transfer him to his own home country for further medical care.

OUTCOME AND FOLLOW-UP

The patient was admitted in our hospital for over a month and was then transported to his own home country for further medical care. At discharge the patient was haemodynamically stable and able to maintain oxygen saturation in room air. Power in the left side was 2/5. His discharge medications included antihypertensives, pantoprazole, LMWH, clopidogrel and statin. He was advised to continue anticoagulation for 6 months and to undergo TEE and work-up for occult malignancy in his home country.

DISCUSSION

The patient had four thrombotic events—DVT, acute pulmonary embolism, inferior STEMI and stroke. In a scientific statement by American Heart Association in 2011, the indications for fibrinolysis in pulmonary embolism are

clearly outlined. They introduced a subcategory of acute pulmonary embolism without systemic hypotension, but with either right ventricular (RV) dysfunction or myocardial necrosis. They termed this as submassive pulmonary embolism and such patients with evidence of worsening respiratory insufficiency, severe RV dysfunction or major myocardial necrosis may be considered for fibrinolysis.¹ Since our patient had signs of respiratory failure, echocardiographic features of RV dysfunction (RV hypokinesia and right ventricular systolic pressure (RVSP) of 40 mm Hg) and elevated troponin which are evidence of increased severity of pulmonary embolism, he was considered for thrombolysis. Moreover, the beneficial effects of thrombolysis may also extend to the concurrently existing STEMI and ischaemic stroke, as he presented within the window period for both events.

Since the patient had both venous and arterial thrombosis at the same time, the possibility of paradoxical embolisation was considered. He had developed DVT due to prolonged period of immobilisation during the flight. The thrombus then dislodged from the leg veins and migrated to the pulmonary arteries where it caused a bilateral acute pulmonary embolism. This raised the right heart pressures which subsequently caused a right-to-left shunting of circulation through a probable intracardiac defect, causing a paradoxical embolism to the coronaries and right hemispheric circulation. The ischaemic stroke lesion then underwent haemorrhagic transformation as a complication of the thrombolytic therapy. Although angiography could not be done due to patient's condition, the classic ECG changes, pattern of elevation of cardiac enzymes and the echocardiography features are highly suggestive of STEMI.

Such a right-left shunt could be either caused by a cardiac or an extracardiac lesion. Such defects include PFO, atrial septal defect, ventricular septal defect, patent ductus arteriosus and pulmonary arterio-venous malformation. PFO is considered by far the most commonly observed cardiac shunt that is seen in over 25% of the population.² Paradoxical embolisation is considered an uncommon yet serious consequence of DVT. Paradoxical embolisation has also been known to occur as a complication of thrombolytic therapy in patients with massive pulmonary embolism who have a pre-existing right-to-left communication.^{3 4} There is now increasing interest in recognising cases of non-cerebral paradoxical embolism in patients with a shunt lesion. Such cases accounted for only 2.9% of the referrals to a specialised centre for the evaluation of PFO.⁵ Such diverse and relatively rarer presentations include acute limb ischaemia,^{4 6 7} renal infarction,^{8 9} ischaemia of the digestive tract¹⁰ and also myocardial infarction.^{11 12} Knobloch *et al*¹³ reported a similar case in a young man with myocardial infarction, popliteal artery occlusion and carotid thrombus. The patient was then retrospectively found to have pulmonary embolism and PFO, which led to the diagnosis of paradoxical embolism. Another case report by Ménager *et al*¹⁴ described a 64-year-old patient with myocardial infarction, pulmonary embolism and evidence of multiple cerebral infarcts. He was then found to have a thrombus in the right atrium with PFO. A recent interesting study by Wöhrle *et al*¹⁵ has shown the presence of subclinical myocardial infarctions that was demonstrated by cardiac MRI



Figure 4 Follow-up brain CT showing resolving haemorrhagic infarction.

in 10.8% of patients with PFO after a first cryptogenic cerebral ischaemic event.

Echocardiography with contrast, especially TEE is an important tool that is used in the work-up of patients with suspected intra-cardiac shunts.^{16 17} Such right-to-left shunting can appear transiently in normal individuals due to common daily activities like coughing or Valsalva manoeuvre.¹⁷ It may also occur due to cases of pathological elevation in the right heart pressures.

The management of such cases is controversial. A study by Furlan *et al*¹⁸ concluded that closure of a PFO with a device did not offer a greater benefit than medical therapy alone for the prevention of recurrent stroke or transient ischemic attack (TIA). However, a meta-analysis by Agarwal *et al*¹⁹ has estimated that the incidence of recurrent neurological events in patients with PFO who were managed by transcatheter closure was 0.8 events, as compared to 5 events/100 person-years in patients who underwent medical management.

Studies have shown that certain cardiovascular risk factors are also associated with venous thromboembolism.^{20 21} They include older age²² and obesity.^{23 24} Other possible diagnosis that was considered in this patient was antiphospholipid syndrome and thrombophilia; however, the results of blood tests did not favour the diagnosis.

Our patient had a unique presentation of thrombus in multiple sites that caused significant haemodynamic instability. There are no well-established guidelines which discuss the acute management of such cases.

Learning points

- ▶ Patients who present with concomitant multiple site thrombosis require careful assessment and management by a multidisciplinary team.
- ▶ Patients with acute pulmonary embolism or deep vein thrombosis who also present with symptoms or signs of arterial embolisation should be evaluated for a shunt lesion.
- ▶ A high index of suspicion is needed for paradoxical embolism in cases of unexplained arterial occlusion.
- ▶ Other possible diagnosis to consider in such cases include thrombophilia and antiphospholipid syndrome.

Competing interests None.

Patient consent Obtained.

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