



Case Report

Pulmonary embolism with migrating thrombus through patent foramen ovale: A case for a mixed pharmacological and percutaneous management



Gloria Santangelo (MD)^{a,*}, Alfonso Ielasi (MD)^b, Francesco Pattarino (MD)^a, Antonio Tommaso Saino (MD)^a, Pasquale Antonio Scopelliti (MD)^a, Maurizio Tespili (MD)^b

^a Cardiology Division, Azienda Socio Sanitaria Territoriale Bergamo Est, Bolognini Hospital, Seriate (BG), Italy

^b Interventional Cardiology Unit, S. Ambrogio Cardio-Thoracic Center, Milan, Italy

ARTICLE INFO

Article history:

Received 7 May 2018

Received in revised form 20 August 2018

Accepted 26 August 2018

Keywords:

Paradoxical embolism

Patent foramen ovale

Pulmonary thromboembolism

Free-floating thrombus

Echocardiography

New oral anticoagulants

ABSTRACT

A 61-year-old man, admitted to our hospital for bilateral pulmonary embolism, complicated by right renal ischemia and multiple splenic infarcts due to a mobile thrombus entrapped in a patent foramen ovale, has been successfully treated with apixaban 5 mg twice daily followed by transcatheter patent foramen ovale closure.

<Learning objective: Apixaban could be a therapeutic alternative to thrombolysis and surgery in patients with warfarin-resistant thrombus straddling in the patent foramen ovale (PFO). Furthermore, apixaban could be a simple and useful option to manage patients undergoing transcatheter PFO closure. Finally, in the evaluation and treatment of PFO, it is necessary to remember that it is associated not only with cryptogenic stroke but also with non-cerebral, paradoxical systemic embolic events such as myocardial infarction renal, infarct, and limb ischemia.>

© 2018 Japanese College of Cardiology. Published by Elsevier Ltd. All rights reserved.

Introduction

Mobile thrombus entrapped in a patent foramen ovale (TSFO) is a complication of severe thromboembolic disease and PFO with the possibility of thrombus migration to left cardiac cavities secondary to pulmonary hypertension [1]. These patients are usually treated with anticoagulants, thrombolytic agents, or surgical thrombectomy, depending on thrombus morphology and the risk of thrombus dislodgment [2]. Some authors affirm the need to consider PFO closure in patients with pulmonary and paradoxical embolism in particular when right heart pressures are elevated [3].

Case report

A 61-year-old man, with a history of chest basal cell carcinoma five years previously, was hospitalized for bilateral pulmonary embolism (PE) (Fig. 1, Panel A). Transthoracic echocardiography

(TTE) revealed dilated right heart cavities and pulmonary hypertension (systolic pulmonary arterial pressure – PAPs – 108 mmHg- Fig. 1, Panel B). Hypercoagulable state testing and malignancy screening were normal. Ultrasound scan of lower limbs and abdomen was negative. Treatment with low molecular heparin 1.0 mg/kg every 12 h was started. The day after, due to back pain, the patient underwent abdominal computed tomography (CT) scan, which showed right renal ischemia, treated by emergent nephrectomy, and multiple splenic infarcts (Fig. 2, Panel A). At TTE and transesophageal echocardiography, a TSFO was diagnosed (Fig. 2; Panel B and C). After the nephrectomy, unfractionated heparin 18 IU/kg/daily was started and 48 h later, it was associated with warfarin. Despite 7 days of proper anticoagulation, the thrombus persisted. Due to the recent nephrectomy, the surgical removal of the left atrial thrombus was not performed. In consideration of the clinical conditions, apixaban 5 mg twice daily was prescribed, without loading dose since the international normalized ratio value was already in range for 7 days. Before direct oral anticoagulant (DOAC) administration, creatinine clearance was 50 ml/min (creatinine 1.55 mg/dl, weight 70 kg). The thrombus disappeared 48 h after the first apixaban administration (Fig. 3, Panel A). In order to exclude silent embolic lesions, after the disappearance of the thrombus, we performed abdominal

* Corresponding author at: Cardiology Division, Azienda Socio Sanitaria Territoriale Bergamo Est, Bolognini Hospital, Via Paderno 21, 24068 Seriate (BG), Italy.

E-mail address: gloriasantangelo@hotmail.it (G. Santangelo).

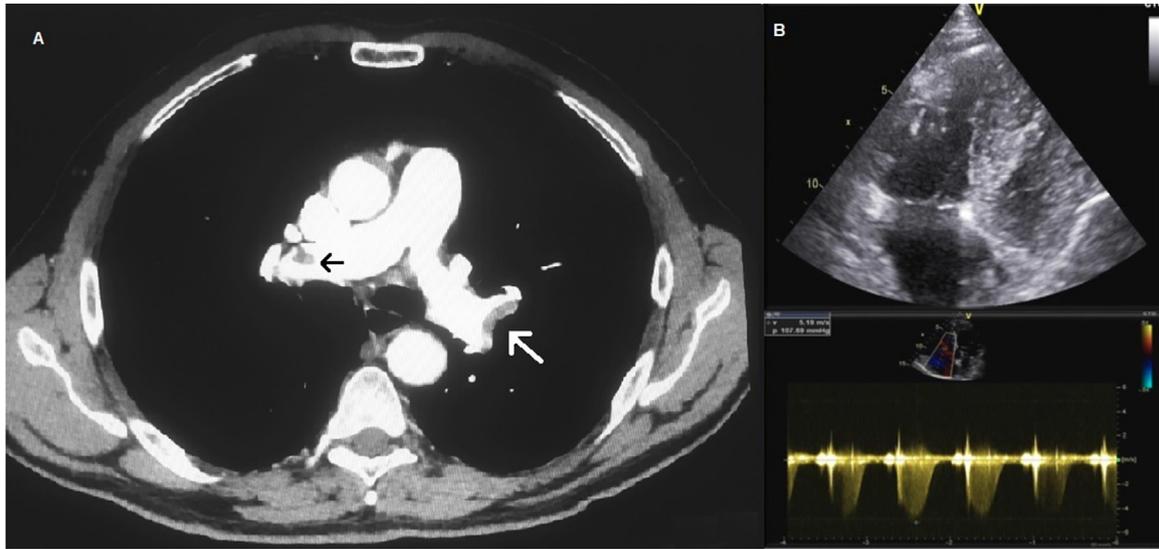


Fig. 1. (A) Thoracic computed tomography shows bilateral pulmonary embolism (arrow). (B) Transthoracic echocardiography revealed dilated right heart cavities and pulmonary hypertension (systolic pulmonary arterial pressure 108 mmHg).



Fig. 2. (A) Right renal ischemia and multiple splenic infarcts showed by abdominal computed tomography scan (asterisks). (B) Transthoracic echocardiography revealed thrombus entrapped in a patent foramen ovale (arrow). (C) Mobile thrombus entrapped in a patent foramen ovale diagnosed with transesophageal echocardiography (arrow).

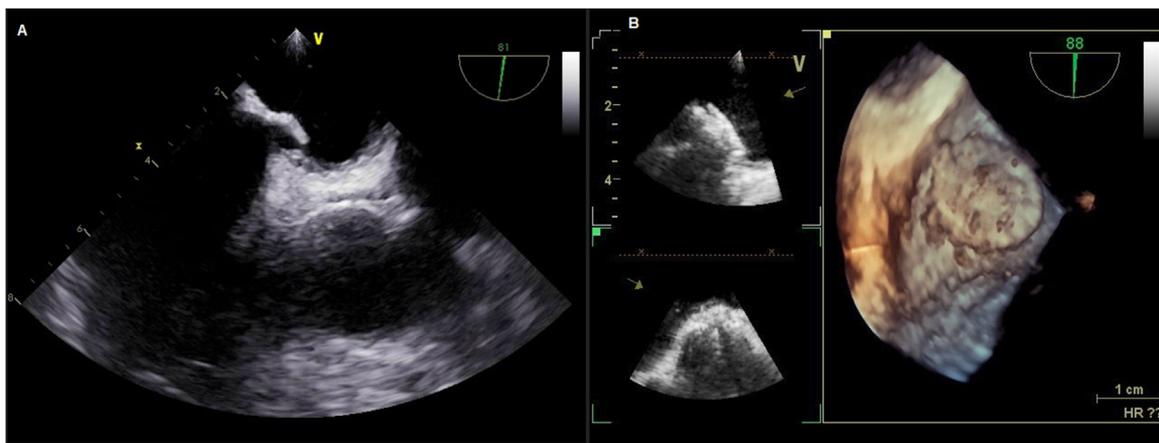


Fig. 3. (A) Thrombus entrapped in a patent foramen ovale disappeared 48 h after the first apixaban administration evaluated by transesophageal echocardiography. (B) Three-dimensional transesophageal echocardiography shows occluder device and patent foramen ovale.

and cerebral CT which resulted negative for ischemic embolism. There were no clinical signs of coronary or limbs embolization. We repeated a CT scan that showed marked reduction of pulmonary embolism. A new CT, performed 25 days after DOAC administration, demonstrated complete resolution of pulmonary embolism.

The D-dimer value normalized 10 days after thrombus disappearance.

With the aim to prevent other manifestations of paradoxical embolism such as stroke (the most common PFO-associated event), it was decided to perform a percutaneous closure of the PFO with Cardia Ultrasept (Cardia Inc., Eagan, MN, USA) 20 mm due to elevated PAPs reported at echocardiography (60 mmHg) (Fig. 3, Panel B, Video 1) and due to anatomical characteristic (atrial septal aneurysm; large left-to-right shunt; PFO size about 4 mm with a tunnel length of ≥ 1 cm). Apixaban administration was continued as a single anti-thrombotic therapy without any complication or residual shunt at 6-month follow-up. Six months after PFO closure, PAPs was 35 mmHg.

Discussion

A thrombus in transit through a PFO with impending paradoxical embolism is an extremely rare event. This condition is associated not only with cryptogenic stroke but also with myocardial infarction, limbs and mesenteric ischemia. Due to its transient nature, it is not possible to identify the thrombus and most of the cases have been reported at autopsy [4]. The best treatment for a PE with a thrombus straddled across PFO is unclear. The therapeutic options are cardiac surgery, thrombolysis, or anticoagulation with heparin or a combination of all these treatments [2].

Thrombolysis or anticoagulation appears hazardous and the risk of paradoxical embolism encourages most authors to be more aggressive in their treatment strategy. However, anticoagulant treatment appears to be an acceptable therapeutic alternative to surgery in patients with comorbidities (age, stroke, cancer) and/or highly mobile thrombus [2]. Thrombolysis is linked to the highest mortality, which could be explained by the severity of the patient's initial presentation. Furthermore, if the thrombus breaks spontaneously or as result of thrombolysis or manipulation, massive pulmonary and systemic thromboembolism can occur [5]. Surgical treatment appears justified in the prevention of paradoxical embolism and must be done immediately if it is the preferred treatment strategy [2].

Chitose et al. described a case of PE and contextual thrombus derived from the inter-atrial septum in the left atrium. The authors demonstrated thrombus reduction in the pulmonary artery and disappearance of the thrombus in the left atrium, refractory to two weeks of edoxaban therapy 30 mg daily, after 13 days of treatment with rivaroxaban 30 mg [6].

DOACs have the potential not only to contribute to the prevention of de novo thrombi, but also to enable the resolution of established thrombi. Recent reports have demonstrated that direct factor Xa inhibitors such as apixaban possess the ability to inhibit thrombin generation and platelet aggregation derived through the tissue factor pathway to a more effectively greater extent than direct thrombin inhibitors [7].

Because an indication of DOAC was expanded to treatment of venous thromboembolism and a prior experience [8], we decided to administer apixaban successfully.

Apixaban is a rapidly absorbed DOAC that inhibits the direct factor Xa, while it has a lower half-life and percentages of renal excretion compared to other DOACs. A fixed-dose regimen of apixaban alone (at a dose of 10 mg twice daily for 7 days, followed by 5 mg twice daily for 6 months) is non-inferior to conventional therapy for the treatment of acute venous thromboembolism and was associated with significantly less bleeding, so provided a

simple, effective, and safe regimen for the initial and long-term treatment of this sub-set of patients [9].

Probably, administration twice a day in a context of correct coagulation already, has determined blood concentrations of the apixaban such as to be effective as thrombolytic.

Furthermore it is necessary to consider PFO closure in patients with PE and paradoxical embolism in particular when right heart pressures are elevated. Today, PFO closure is a standardized and safe intervention in dedicated catheterization laboratories. Indications for PFO closure remain a source of debate and individualized solutions have to be sought [3].

Data on post-interventional medication show that between three regimens of anticoagulation used (aspirin alone, dual antiplatelet therapy with aspirin plus clopidogrel, and warfarin alone) there were no significant differences regarding thrombus formation [10].

This is the first study to affirm that apixaban could be a useful drug to resolve mobile thrombus entrapped in a PFO, in patients with PE, in a short time and without major complications. Furthermore, to our knowledge, this is the first study where a DOAC is used successfully as a single anti-thrombotic therapy after percutaneous PFO closure. Further, larger data are needed to confirm our anecdotal finding.

Acknowledgment

None.

Conflict of interest

The authors declare that there is no conflict of interest.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at <https://doi.org/10.1016/j.jccase.2018.08.007>.

References

- [1] Torbicki A, Galie N, Covezzoli A, Rossi E, De Rosa M, Goldhaber SZ. Right heart thrombi in pulmonary embolism: results from the International Cooperative Pulmonary Embolism Registry. *J Am Coll Cardiol* 2003;41:2245–51.
- [2] Fauveau E, Cohen A, Bonnet N, Gacem K, Lardoux H. Surgical or medical treatment for thrombus straddling the patent foramen ovale: impending paradoxical embolism? Report of four clinical cases and literature review. *Arch Cardiovasc Dis* 2008;101:637–44.
- [3] Rigatelli G, Dell'Avvocata F, Giordan M, Braggion G, Aggio S, Chinaglia M, et al. Embolic implications of combined risk factors in patients with patent foramen ovale (the CARPE criteria): consideration for primary prevention closure? *J Interv Cardiol* 2009;22:398–403.
- [4] Baydoun H, Barakat I, Hatem E, Chalhoub M, Mroueh A. Thrombus in transit through patent foramen ovale. *Case Rep Cardiol* 2013;2013:395879.
- [5] Konstantinov IE, Saxena P, Blacham R, Barrett T, Finn C, Newman MAJ. Thrombus straddling an atrial septal defect: surgical prevention of massive pulmonary and systemic embolization. *Tex Heart Inst J* 2008;35:475–6.
- [6] Chitose T, Yamashita T, Miura M, Matsuyama K. Complete response to rivaroxaban in a case of invaginated thrombus thought to have extended through a patent foramen ovale with an accompanying pulmonary embolism. *J Cardiol Cases* 2016;14:65–8.
- [7] Wan H, Yang Y, Zhu J, Wu S, Zhou Z, Huang B, et al. An in-vitro evaluation of direct thrombin inhibitor and factor Xa inhibitor on tissue factor-induced thrombin generation and platelet aggregation: a comparison of dabigatran and rivaroxaban. *Blood Coagul Fibrinolysis* 2016;27:882–5.
- [8] Santangelo G, Ielasi A, Scopelliti PA, Pattarino F, Tespili M. Apixaban-induced resolution of a massive left atrial and appendage thrombosis in a very elderly patient. *J Atr Fibrillation* 2016;9:1509.
- [9] Rachidi S, Aldin ES, Greenberg C, Sachs B, Streiff M, Zeidan AM. The use of novel oral anticoagulants for thromboprophylaxis after elective major orthopedic surgery. *Expert Rev Hematol* 2013;6:677–95.
- [10] Krumsdorf U, Ostermayer S, Billinger K, Trepels T, Zadan E, Hortvath K, Sievert H. Incidence and clinical course of thrombus formation on atrial septal defect and patent [sic] foramen ovale closure devices in 1000 consecutive patients. *J Am Coll Cardiol* 2004;43:302–9.