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Review article

Intracardiac thrombi during warfarin anticoagulation – A case report and a brief literature review

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ABSTRACT

A 78-year-old woman with a history of ischaemic heart disease and permanent atrial fibrillation, on treatment with warfarin, was admitted to the Emergency Department because of paroxysmal nocturnal dyspnoea. Instrumental findings indicated an early phase of acute heart failure. The latest INR value was 3.64, and previous available INR values were all within the therapeutic range (2–3). A transthoracic 2D echocardiographic examination showed left ventricular dilatation and a severe reduction in systolic function. An echogenic pedunculated mass was observed in the left atrium, adherent to the interatrial septum. Twelve hours later, the patient reported the acute onset of pain in the left arm. A thromboembolic occlusion of the left humeral artery was documented, and this was acutely treated with Fogarty embolectomy. In the first hour after this intervention, a series of relapsing thromboembolic events led to the final amputation of the arm. Warfarin was discontinued and treatment with dabigatran 150 mg BID enacted, followed by the disappearance of the thrombotic mass and clinical resolution.

Contents

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Introduction and Background

Oral anticoagulant (OAC) therapy is key in the management of most patients with atrial fibrillation (AF) [1]. Antithrombotic therapy is recommended in non-valvular AF patients with one or more risk factors for thromboembolism, according to the CHA_2DS_2VASc score [1]. Current therapeutic options include OAC therapy with either a well-controlled vitamin K antagonist (VKA with an International Normalized Ratio (INR) 2–3) or one of the non-vitamin K antagonist oral anticoagulants (NOACs) [1]. For over 60 years, VKAs have been the only available agents for long-term anticoagulation, and warfarin has been the most widely used [2]. VKAs exert their anticoagulant effect by interfering with the synthesis of the vitamin K-dependent coagulation factors, inhibiting the vitamin K epoxide reductase complex subunit 1 (VKORC1) in the liver [2,3]. The effectiveness of VKA anticoagulation is strictly related both to the degree of anticoagulation achieved (assessed by the INR value) and the time in therapeutic range (TTR), as well as treatment duration.

Warfarin is metabolized in the liver by a group of enzymes encoded by the cytochrome P450 (CYP) 2C9 gene, largely responsible for its hepatic metabolism [3]. Such pharmacokinetic properties account for the long-standing observation that doses required to exert the anticoagulant effect are highly variable from patient to patient. The variety of enzymes involved and, at least in part, polymorphisms in the CYP2C9 and VKORC1 genes play a role in affecting the pharmacokinetics and pharmacodynamics of warfarin, with a resulting highly variable clinical response [4,5]. In addition, because CYP2C9 is involved in a large number of metabolic pathways, many foods and drugs can affect warfarin metabolism and half-life. All these characteristics explain the narrow therapeutic window of warfarin, with oscillations between the risk of thromboembolism in case of insufficient dosing and the risk of bleeding in case of excessive dosing. This has prompted the search for non-vitamin K antagonist oral anticoagulants (NOACs), with a more predictable anticoagulation profile [3]. NOACs have indeed recently emerged as an alternative for VKAs for thromboembolic prevention in patients with non-valvular AF, because of their more predictable effect, no need for routine monitoring, no food and fewer drug interactions, a shorter plasma half-life, and improved efficacy/safety ratio [6]. Among the NOACs, dabigatran is an oral direct, competitive thrombin inhibitor, ingested as a pro-drug (dabigatran etexilate), and then activated to dabigatran by intestinal and serum esterases [6]. Dabigatran is not metabolized by the CYP P450 enzymes or other oxidoreductases, is a substrate for P-glycoprotein, and is almost entirely excreted renally [7]. Dabigatran 150 mg twice daily (BID) was associated with lower rates of stroke or systemic embolism compared with warfarin in the RE-LY study; dabigatran 110 mg BID was associated with rates of stroke and systemic embolism similar to warfarin, but with lower rates of major bleeding [8].

Case presentation

A 78-year-old woman with a history of ischaemic heart disease was admitted to the Emergency Department of the Chieti University Hospital because of the sudden onset of shortness of breath during the night. Three years before, the patient had had an ST-elevation acute myocardial infarction (STEMI) without obstructive coronary disease documented at coronary angiography. Because of this, she had received dual antiplatelet therapy with aspirin 100 mg/day and clopidogrel 75 mg/day for 1 year. Because of the subsequent occurrence of permanent

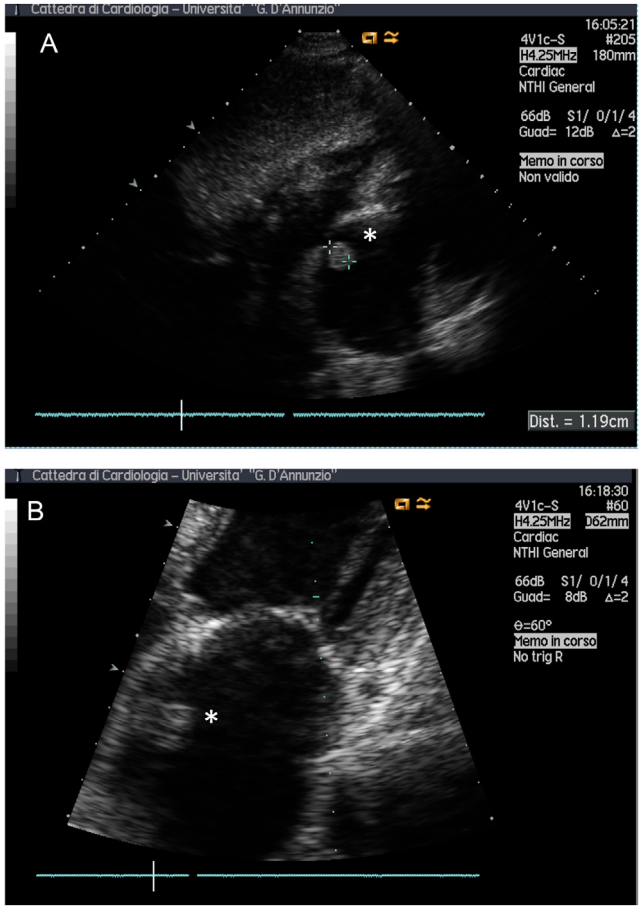

Fig. 1 – Transthoracic echocardiographic examination performed after the episode of heart failure at admission. An echogenic pedunculated, movable mass, with sharp margins, can be seen in the left atrium, adherent to the interatrial septum (*). (A) Subcostal 4-chamber view; (B) apical 4-chamber view.