

Angioedema 2 months after Administration of Rivaroxaban (Xarelto)

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Abstract

Angioedema is a local, non-inflammatory, self-limiting oedema that is circumscribed, and is caused by increased vascular permeability and leakage of plasma into the deeper skin layers. Angioedema can occur with or without urticaria. It can be acute or chronic (more than six weeks in duration) as well as being allergic, hereditary or idiopathic in nature. The reaction is self-limited, usually lasting few days, but may occur repetitively with each exposure to the allergen which may cause a fatal reaction at some point. This is the main reason behind the removal of the valuable drug (rivaroxaban) like in our patient because the result of angioedema occurred 2 months after administration of the rivaroxaban.

Keywords: Angioedema; Rivaroxaban; Chronic

Abbreviations: DVT: Deep Vein Thrombosis; PE: Pulmonary Embolism; FDA: U.S. Food and Drug Administration

Introduction

Pulmonary embolism is a common disease, with an estimated annual incidence of 70 cases per 100,000 population [1-3]. The condition usually leads to hospitalisation and may be fatal. For many decades the standard therapy for most patients with pulmonary embolism has been the administration of heparin, overlapped and followed by a vitamin K antagonist (warfarin). Recently developed oral anticoagulants that are directed against factor Xa or thrombin overcome some limitations of standard therapy, including the need for injection and for regular dose adjustments on the basis of laboratory monitoring [4]. Rivaroxaban one the new oral anticoagulant (NOAC) first orally active direct factor Xa inhibitor.

Furthermore rivaroxaban is similarly effective in comparison with warfarin for treatment and prevention of DVT and PE but reduces the risk of serious bleeding complications this in addition to the advantages on warfarin that rivaroxaban is administered once or twice in fixed daily dose, has rapid onset of action, no interactions with food and few interactions with drugs [4].

Based on regularly updated reports from FDA and eHealthme of 88,499 people who have side effects when taking rivaroxaban, among them, 70 people (0.08%) have had Angioedema. Angioedema is found among people who take rivaroxaban, especially for people who are female, >60 old, who have been taking the drug for <1 month, who also take Aspirin, and have past medical history of Stroke. The risk of angioedema is reduced from 80% in the first month to 0% after 2 years of starting rivaroxaban with moderate severity of symptoms/signs in most cases such as rashes, urticaria, itching, hypersensitivity and rarely breathing difficulty [5,6].

Case Report

An 81-years-old female with a past medical history of hypertension and normal pressure hydrocephalus associated with unsteady gait and decreased mobility. She was admitted to the hospital because of recurrent falls and a urinary tract infection, she remained in the hospital after treatment waiting for long term care. 6 weeks after admission she developed sudden onset of shortness of breathing and chest pain, the D dimer was 14 and the saturation was 83% in room air, bilateral pulmonary embolism was detected by computed CT angiography (Figures 1 and 2). She was put on 20 mg rivaroxaban, a daily dose. Two months later after starting rivaroxaban the patient developed an angioedema which appeared clearly as the marked swelling involving her lower lip and part

of the tongue as well as mild redness in the face around the cheeks. The Patient further claims lack of itching, and there was no visible sign of a rash. There were no symptoms of airway obstruction, and she remained hemodynamically stable.

The Angioedema was treated with a short course of IV hydrocortisone and antihistamine agents (H1 and H2 receptor antagonists). Neither Endotracheal intubation, tracheostomy nor epinephrine were required. As part of the management of angioedema all her previous medications were stopped including rivaroxaban which was replaced with Tinzaparin for a short period and the patient was observed for resolution of the angioedema [1,2]. Few days after the treatment of angioedema the symptoms resolved completely with the swelling in the lower lip and tongue disappearing. Shortly after resolving of the symptoms we restarted the patient's previous medications gradually with the exception of rivaroxaban because it was suspected that it had been the cause for the angioedema as it was used most recently. The previous medications were re-introduced one by one with caution and close monitoring for the recurrence of any symptoms. Angioedema was not present, and the patient remained asymptomatic.

Furthermore re-introduction of her previous medications (Calcichew-D3 Forte Chewable Tablets 500 mg/400 IU, pantoprazole 40 mg, Alendronate and cholecalciferol 70 mg/5000 IU) which she had been on for 5 years with no problem were not the cause of the symptoms/signs of angioedema, this in addition to Coversyl Plus 5 mg/1.25 mg which she had used safely for more than 10 years and discontinued only 3 months prior to the occurrence of the disease due to low blood pressure also had no part in the causing of the angioedema. The patient is not allergic to any medications or food throughout her life and there is no family history of allergies. Since the patient was in the hospital we are sure that there were no unusual food ingestions or recent changes in her environment.

Discussion

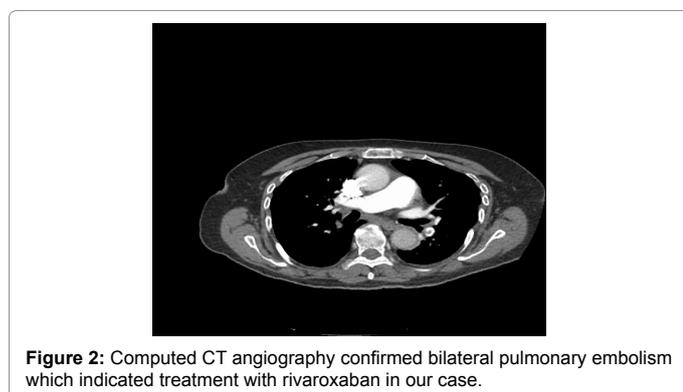
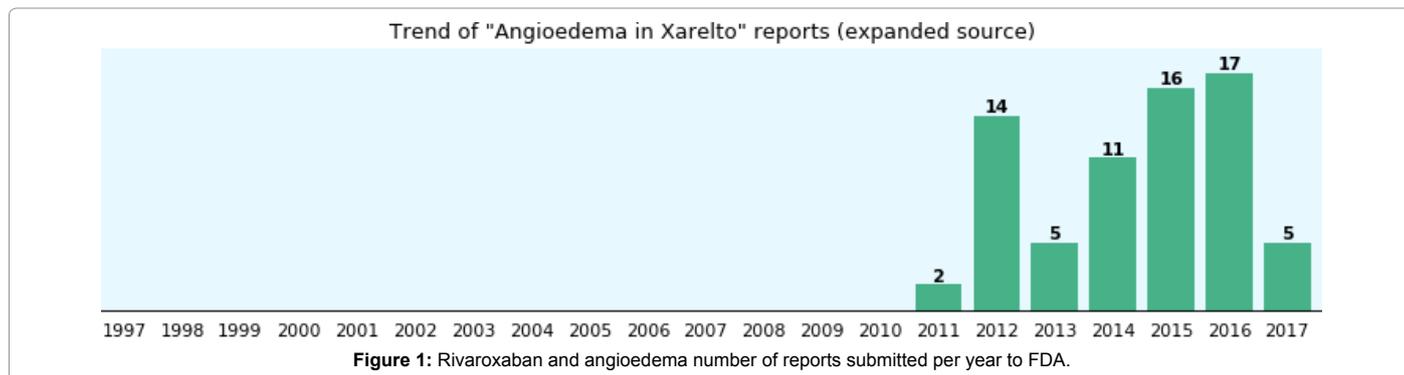
Hereditary angioedema was disregarded after tests including C1

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esterase inhibitor level (C1-INH), complement C4 level and CH50 produced normal results. The Immunoglobulin E (IgE) was tested and resulted with a normal level which in this case indicates acute reaction due to drug-related angioedema rather than an autoimmune-related chronic reaction particularly in the absence of any associated urticaria in this case. Autoimmune and rheumatological disorders were excluded by extensive autoimmune screening and workup. The patient was diagnosed with angioedema due to the new oral anticoagulant introduced, namely rivaroxaban. After rivaroxaban was discontinued the patient started taking warfarin instead. The patient was observed carefully for the reoccurrence of the angioedema and fortunately it did not reoccur.

Conclusion

It is well known that all anticoagulants, including rivaroxaban can cause bleeding that can be serious and rarely may lead to death. The Side effect angioedema is extremely rare especially after the first month of starting treatment. However, in this case angioedema due to rivaroxaban occurred after 2 months as a moderate reaction. One needs

to be mindful of the possibility of such a rare reaction occurring at any time during the treatment and may have fatal consequences.

Angioedema can be induced by drugs and many other causes. It has several pathophysiological mechanisms because it can be allergic or non-allergic [7]. If the patient started a new drug as in our case and developed swellings (typically include the face, tongue and lips) as well as an absence of urticaria and allergic history with normal workup of hereditary angioedema and fading away of the symptoms after stopping the suspected drug, Then special attention should be directed to the potential relation of angioedema with drugs [8].

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