

## Successful treatment of acetylsalicylic acid-induced chronic urticaria and angioedema with warfarin

Asetilsalisilik asit ile indüklenen kronik ürtiker ve anjiyoödemde warfarinle başarılı tedavi

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### ABSTRACT

The mainstay for off-label use of warfarin in chronic urticaria is the growing evidence for the involvement of coagulation cascade in the pathogenesis of the disease. We report a 63 year-old patient presented with acetylsalicylic acid-induced urticaria/angioedema due to treatment of retinal vein occlusion. His symptoms completely resolved with cessation of acetylsalicylic acid and start of daily warfarin therapy instead in order to prevent recurrence of thrombotic events. After four year follow up without any recurrence of urticarial symptoms or thrombotic events oral challenge with acetylsalicylic acid was performed and came out to be negative. Warfarin may be considered for treatment of acetylsalicylic acid-induced urticaria/angioedema in otherwise asymptomatic individuals with history of thrombotic events or prothrombotic risk factors needing long term anticoagulation and impact of warfarin treatment on acetylsalicylic acid hypersensitivity may be further investigated.

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### ÖZ

Kronik ürtikerde endikasyon dışı warfarin kullanımının başlıca dayanağı hastalığın patogeneğinde koagülasyon kaskadının önemli olduğuna dair kanıtların giderek artmasıdır. Retinal ven oklüzyonu tedavisine bağlı asetilsalisilik asitle indüklenen ürtiker/anjiyoödem ile başvuran 63 yaşındaki hasta sunulmaktadır. Hastanın semptomları asetilsalisilik asit tedavisinin kesilmesi ve trombotik olayların yinelenmesini önlemek amacıyla başlanan warfarin tedavisiyle tam olarak düzelmiştir. Dört yıllık takibi boyunca ürtikeryal semptomları tekrarlamayan ve yeni trombotik olay izlenmeyen hastaya asetilsalisilik asitle oral provokasyon testi yapılmış ve negatif bulunmuştur. Tromboz öyküsü ya da protrombotik risk faktörü nedeniyle uzun süreli antikoagülasyon ihtiyacı olan asetilsalisilik asitle indüklenen ürtiker/anjiyoödemli olgular için warfarin tedavisi bir seçenek olup warfarin tedavisinin asetilsalisilik asit duyarlılığı üzerine etkisinin araştırılması faydalı olabilir.

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**Key words:** Angioedema, acetylsalicylic acid, urticaria, warfarin

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## INTRODUCTION

There is a growing evidence for the involvement of coagulation cascade in the pathogenesis of chronic urticaria and new treatment modalities including oral anticoagulants are reported to be promising in the treatment of patients<sup>[1,2]</sup>. We report a case with acetylsalicylic acid-induced urticaria/angioedema unresponsive to antihistaminics. The symptoms of the patient resolved completely after cessation of acetylsalicylic acid intake together with the start of warfarin therapy.

## CASE REPORT

A 63-year-old man was referred to our allergy clinic with generalized pruritus, urticarial rash and swelling in the lips for the last three months. He had been on daily acetylsalicylic acid treatment for the last three months since when he had been diagnosed retinal vein occlusion in ophthalmology clinic upon sudden loss of vision. Urticarial plaques and angioedema first appeared within a few hours after he ingested first dose of acetylsalicylic acid three months ago. Since he had taken acetylsalicylic acid a few times in his mid-fifties in several occasions and did not experience any adverse reactions, he did not think that acetylsalicylic acid intake could be the reason for his existing complaints. So he self-medicated himself with levocetirizine for his urticarial rash and angioedema and did not discontinue acetylsalicylic acid. Upon his complaints he was referred from ophthalmology clinic with the initial diagnosis of acetylsalicylic acid hypersensitivity.

When he was admitted to the allergy clinic he had urticarial plaques and swollen lips. Physical examination was otherwise normal. His medical history revealed hyperlipidemia which was controlled only with dietary regula-

tion. He had smoked 45 pack-years and quit smoking two years ago. He had no previous history of atopy or urticaria. The laboratory examinations for chronic urticaria including complete blood count, erythrocyte sedimentation rate, thyroid function tests, total IgE, C4 and C1 inhibitor, protein C and S levels were within normal limits. Hepatitis B and C serologies, anti-nuclear antibody, lupus antibody and factor 5 leiden mutation were negative. Skin prick tests with aeroallergens and food came out negative.

Based on the patient's data he was diagnosed as acetylsalicylic acid-induced urticaria/angioedema. Because the history was typical for acetylsalicylic acid hypersensitivity reaction acetylsalicylic acid challenge was not planned. Acetylsalicylic acid medication was halted and the patient was put on daily warfarin therapy with a target international normalized ratio (INR) of 2-3 in order to prevent recurrence of thrombotic events. Complaints of the patient disappeared completely with this treatment alteration. Accordingly for maintenance of anticoagulation warfarin treatment was continued for the next four years in the follow-up. The patient had neither urticarial symptoms nor new thrombotic events during this period. Moreover, in the follow-up oral challenge with acetylsalicylic acid with cumulative dose of 705 mg was performed and came out to be negative in 2011 and the patient was put on daily acetylsalicylic acid treatment with withdrawal of warfarin.

## DISCUSSION

Warfarin is among the medications reported to have beneficial effect in chronic urticaria and angioedema unresponsive to antihistamines in the recent studies<sup>[1,2]</sup>. The mainstay for

off-label use of warfarin in chronic urticaria is the growing evidence for the involvement of coagulation cascade in the pathogenesis<sup>[1,2]</sup>. Previously elevated plasma levels of prothrombin fragment F1+2 were reported to be related to the severity of urticaria in addition to a marked increase in plasma markers of thrombin generation and fibrinolysis during severe exacerbations of the disease. According to these findings clinical trials are held to inhibit coagulation cascade as adjuvant treatment for chronic urticaria. It is reported that administration of intravenous/subcutaneous unfractionated heparin or oral anticoagulant drugs improve clinical symptoms<sup>[2]</sup>. Parslew et al. reported with a small but double-blind, placebo-controlled trial in which six of eight chronic urticaria patients responded to warfarin<sup>[3]</sup>. Tranexamic acid is also postulated to be effective in controlling symptoms in angioedema patients<sup>[2]</sup>.

The case presented is classified as non-steroidal anti-inflammatory drug-induced urticaria/angioedema in otherwise asymptomatic individuals<sup>[4]</sup>. He had remitting urticarial and angioedema attacks inspite of regular use of antihistamines. Since he had thrombotic events in the medical history, both to prevent recurrence of thrombotic events and to take the advantage of potential beneficial effect of oral anticoagulant therapy in urticaria, acetylsalicylic acid therapy was ceased and warfarin was started with a target INR of 2-3. The patient responded well with total disappearance of the symptoms

and no recurrence was observed for the next four years. In December 2011 oral acetylsalicylic acid challenge was performed and found negative.

In conclusion we think that this is an interesting case since acetylsalicylic acid challenge is negative after four year warfarin therapy although the initial clinical findings were compatible with acetylsalicylic acid-induced urticaria/angioedema. Accordingly warfarin may be considered for treatment of non-steroidal anti-inflammatory drug-induced urticaria/angioedema in otherwise asymptomatic individuals with history of thrombotic events or prothrombotic risk factors needing long term anticoagulation. Additionally impact of warfarin treatment on acetylsalicylic acid hypersensitivity may be further investigated with case series.

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