

CORRESPONDENCE

Chronic idiopathic urticaria successfully treated by anticoagulant drugs

Chronic Idiopathic Urticaria (CIU) is a debilitating disease. Despite an extensive workup, the cause is often not identified. Intrinsic and extrinsic coagulation activation has been recently proposed as a plausible cause of recurrent CIU [1]. The authors performed a double blind, placebo-controlled trial with acenocoumarol in the same patient. In our case, we focused mainly on prothrombin fragment 1+2 (F1+2), thrombin-antithrombin complex (TAT) and D-dimer.

We report the case of a 59-year-old woman suffering from CIU since 2004. Medical history revealed bilateral breast cancer (2000, 2003) and several miscarriages. The patient underwent surgery and adjuvant radio-chemotherapy. Personal history revealed diabetes type I. After treatment with the selective COX-2-inhibitor rofecoxib (Vioxx®), severe symptomatic urticaria appeared. The distribution of the lesions included trunk and arms. Laboratory exams showed leucocytosis (15.1 G/L; n: 4-10 G/L) and thrombocytosis (414 G/L; n: 150-350 G/L). Infectious agents were excluded through routine laboratory and radiological exams. Numerous systemic antihistamines remained inefficient (*figure 1A*). Cyclosporin A, systemic steroids, dapsone and chloroquine have been used previously without any improvement.

Later, the patient developed a deep vein thrombosis of the right limb. She was started on low molecular weight heparin (nadroparin, Fraxiparin® 0.8 mL q12) 2×/day at therapeutic doses. A few hours later, CIU disappeared. The change to acenocoumarol (Sintrom®) happened without any relapse. All other treatments for CIU were stopped. We suspected antiphospholipid antibodies syndrome but lupus anticoagulant and anticardiolipin antibodies remained negative. 9 months anticoagulation was considered to be sufficient and the treatment was stopped. CIU relapsed

few days later after a one year disease-free period. We performed, with the informed consent of the patient, a double-blind, placebo controlled trial with acenocoumarol 2 mg daily versus placebo for 1 week each. We recorded the International Normalized Ratio (INR) during the first and second week of treatment. We noticed a global relief of the symptoms during the first week, corresponding to the anticoagulant effect of acenocoumarol (*figure 1B*). At beginning of the second week, CIU relapsed, concomitant to the placebo treatment (*figure 1B*). The initial blood sample showed increased levels of F1+2, TAT and D-dimer (*figure 1C*). After one week treatment with acenocoumarol, plasma levels stayed elevated but at a lower level (*figure 1C*). Then, an open test with nadroparin to the same dose as mentioned above was performed. CIU symptoms disappeared the next day.

Our observation suggests an involvement of coagulation activation in CIU. Intrinsic and extrinsic coagulation pathways are thought to be implicated (*figure 1D*). Coagulation activation markers (F1+2, TAT and D-dimer levels) are known to be elevated in CIU, suggesting a physiopathological link to coagulation activation [1]. This put under new light emerging drug options [2]. Thrombin might function as a modulator of inflammation and tissue repair through Proteinase-Activated Receptors (PARs) signaling on skin mast cells, thereby promoting histamine release. But thrombin increases vascular permeability through direct effect on endothelial cells, which cannot be blocked by antihistamines [3]. Furthermore, involvement of the pro-inflammatory effect of eosinophils in CIU [4] has to be considered. Elevated D-dimers are associated with disease severity and antihistamines remain often inefficient [1]. Finally, the association of the outbreak of CIU with rofecoxib seems unusual, because of its potential benefit in CIU management [5].

Based on these data and our case, it is worth measuring markers of coagulation activation. When not contraindicated (active bleeding, history of stroke), anticoagulant drugs should be prescribed in patients with CIU in order to prevent relapse. In case of prescribing antivitamin K

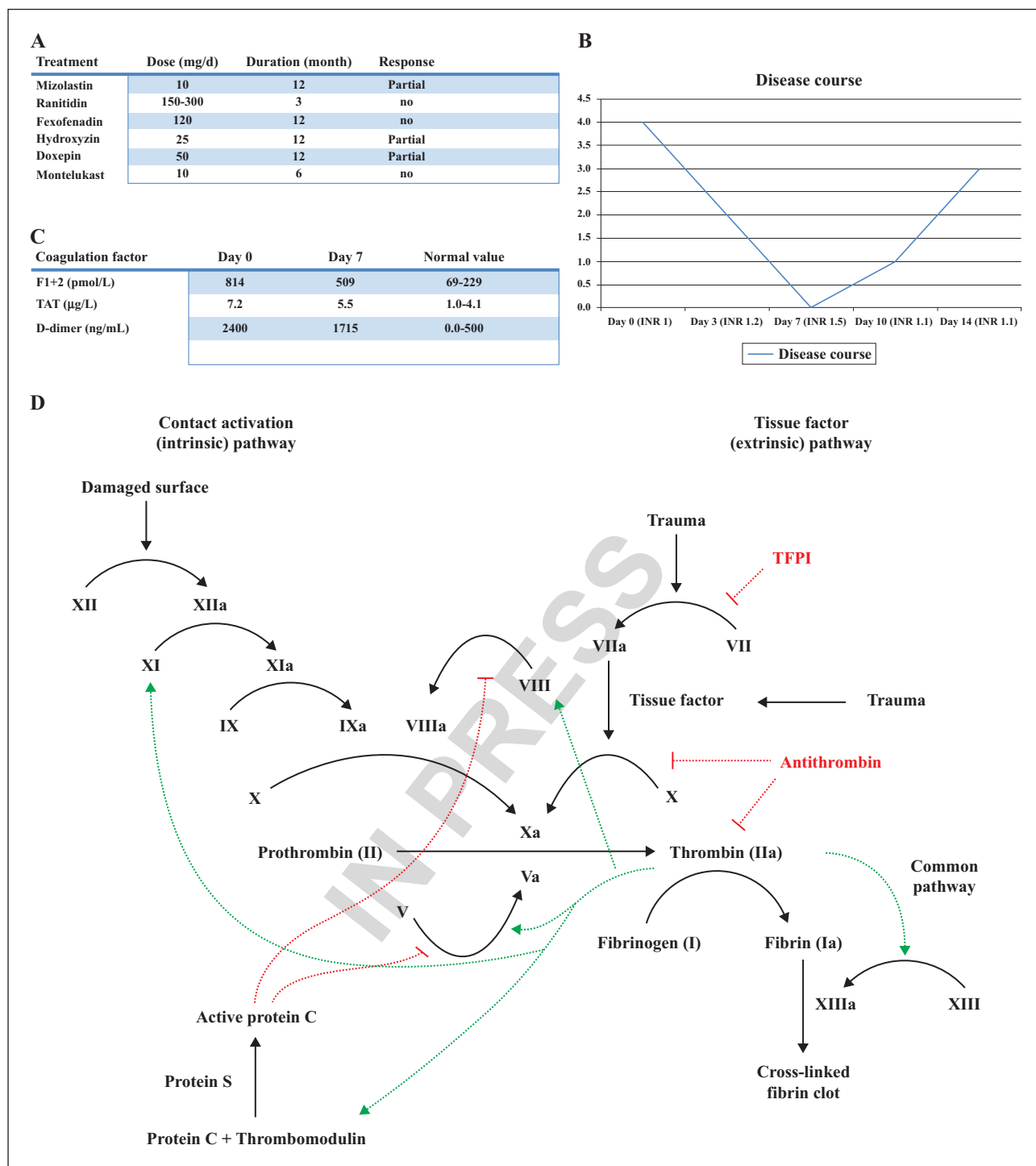


Figure 1. A) Chronology and dose of the various systemic antihistamines and antipruritic treatments used before anticoagulation. B) Clinical course during the 2 week trial with acenocoumarol (Sintrom®) and placebo. X: Measured values of International Normalized Ratio (INR) during the 2 weeks. Y: Disease intensity (1-5 scale). C) Levels of coagulation parameters (F1+2, TAT, D-dimer) at day 0 and day 7 of treatment with acenocoumarol (Sintrom®). D) Intrinsic and extrinsic blood coagulation cascade with F1+2 and TAT.

antagonists, INR values of 1.5 are sufficient. Recently, the use of the anti IgE antibody omalizumab (Xolair®) has been proposed with good results [6]. ■

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