

D-dimer levels decline after immunosuppressive treatment rather than anticoagulant treatment in severe autoimmune chronic spontaneous urticaria

Abstract:

Chronic spontaneous urticaria (CSU) is a common dermatological condition presenting with wheals and/or angioedema for more than 6 weeks. The role of autoimmunity and inflammation in the pathogenesis of CSU have been studied, but the precise mechanism remains unknown. Association with coagulation cascade has been suggested based on the observations of increased coagulation indicators such as serum D-dimer levels. We report an omalizumab refractory case of severe CSU with high D-Dimer levels that declined only after disease remission with cyclosporine treatment but not with anticoagulation. Activation of coagulation cascade occurs secondary to the pro-inflammatory state in CSU patients and the correlation between D-dimer levels and disease activity may indicate the need for more studies to better understand the relationship of D-dimer levels and Omalizumab resistance. Clinicians should consider this relationship in CSU patients with significant D-dimer levels before considering treatment with anticoagulants.

Keywords: chronic urticaria, coagulation, cyclosporine, disease activity, D-dimer, treatment response

Impact statement: D-dimer levels decline after immunosuppressive treatment with cyclosporine rather than anticoagulant treatment in patients with severe autoimmune CSU.

Introduction:

Chronic spontaneous urticaria (CSU) is a condition characterized by the development of wheals and/or angioedema for longer than 6 weeks. Lesions can occur spontaneously or be induced by various stimuli and usually disappear in minutes to hours (1). It is a highly prevalent skin disorder with female predominance (2). It presents with a systemic inflammatory state and results from activation of mast cells with release of pro-inflammatory cytokines such as histamine and platelet-activating factors, leading to wheal formation (3). Although studies on the pathogenesis of CU have increased in recent years, the exact mechanism is still poorly understood. Until now, several studies have shown the effect of multiple mechanisms including autoimmunity, with some patients carrying IgE or IgG autoantibodies against a multitude of self-antigens, including those on mast cells and basophils (2), and some with recently discovered auto-reactive CD4+ T cells (4). The role of coagulation cascade has been recently proposed as part of the pathogenesis and the activation of the extrinsic pathway of clotting cascade has been found to be associated with disease severity in CSU (5). Additionally, there have been reports of increased levels of D-dimer in patients with CSU paralleling disease activity (6) and even anticoagulant treatment has been proposed as a potential treatment option in CSU (5). However there have been discussions whether this coagulation pathway activation is the cause or a result of the inflammation in CSU. Here, we report a case of CSU with extremely high D-dimer levels that declined with remission of disease with cyclosporine treatment but did not change despite anticoagulant treatment.

Case report:

A 45-year-old female patient has been on regular follow up for CSU and currently visited our institution for an ongoing urticaria attack for 5 months. She first noticed symptoms eight years ago, and attacks at that time had been under control with antihistamines and rare on-demand steroid treatments. Angioedema attacks occurred only in the first 6 weeks of symptom initiation and involved upper lips, cheeks, forehead, and periorbital area. No trigger has been reported for the initiation of CSU. The patient did not have any other systemic illnesses and was not on other systemic medications. She has been using various antihistamines without success and even though steroids provided temporary relief, they were ineffective in long term management of the lesions. Her current attack has continued for 5 months and there was no response to treatment with omalizumab 450 milligram/month. Biopsy was taken from the lesions, confirming the diagnosis

of CSU with a mixed inflammatory cell infiltrate and negative direct immunofluorescence staining. Autologous serum skin test (ASST) was intensely positive. Blood investigations of the patient showed an eosinophil percentage of 0.2% (reference range 0.5- 6.5%), basophil percentage of 0.1% (reference range 0.0-2.0) and an elevated CRP of 39 mg/L. Total IgE was 29 IU/ml (reference range < 100 IU/ml) and anti-thyroglobulin (anti-Tg) and anti-thyroid peroxidase (anti-TPO) IgG were negative at 13 IU/ml (reference range < 115 IU/mL) and 14 IU/ml (reference range < 35 IU/ml) respectively. Significantly elevated D-dimer levels of 5370 ug/L (reference range < 500 ug/L) were detected when she was on omalizumab treatment. D-dimer levels have been increasing since the attack has started and has reached a peak level of 5370 ug/L (reference range < 500 ug/L) (Figure 1). She was not on steroid treatment at that time. An internalist started subcutaneous enoxaparin injections 8000 IU (80 mg/0.8 ml) to the patient twice daily. However, D- dimer levels were still elevated even after using enoxaparin daily for two months and the patient had an urticaria activity score 7 (UAS7) of 36 after long term treatment with antihistamines, omalizumab and enoxaparin. After trying 450 mg/monthly omalizumab for 3 months with no meaningful response, treatment with cyclosporine 5 mg/kg was initiated. The patient responded very well to cyclosporine with apparent improvement visible even at the first week of treatment. With remission of the disease while on cyclosporine treatment after one month (UAS7 score:4) (Figure 1), D-dimer levels have decreased substantially to 390 ng/mL as well as CRP level to 3 mg/L (Figure 1)

Discussion:

Our case reflects an example of severe autoimmune urticaria with a positive ASST, eosinopenia, low total IgE and elevated CRP levels which favorably responded to immunosuppressive treatment but not to omalizumab treatment; probably representing the type IIb autoimmune type of CSU (7). We believe this case supports the idea of activation of coagulation cascade in CSU patients most probably developing secondary to the systemic pro-inflammatory state, rather than as a primary pathogenetic mechanism in CSU because 1) Two months of anticoagulant treatment did not yield either a clinical remission or decline in D-dimer levels 2) D-dimer levels dropped parallel to decrease in CRP levels and decrease in disease activity after immunosuppressive treatment (Figure 1). Although the enoxaparin dose may have been insufficient in lowering the D-dimer levels, based on the effective response to cyclosporine, we believe that the elevation of D-dimer was a

consequence of ongoing inflammation in CSU, rather than a coagulation process. The correlation of D-dimer with disease activity has been previously discussed (5) and elevated D-dimer as well as high CRP and high UAS-7 scores have been associated with antihistamine resistant CSU (9). Although elevated D-dimer levels has been associated with a favorable response to cyclosporine (3) and also a good response to omalizumab (8), in our case, high D-dimer was associated with omalizumab resistance which was also reported (10) Since the patient had quite low IgE levels compatible with type IIb autoimmune CSU, which has been accepted as a marker for poor response to omalizumab treatment (7), whether elevated D-dimer levels might be an indicator of type IIb autoimmune CSU needs to be further clarified in future studies. Elevated D-dimer levels in CSU patients, however, do not indicate an elevated risk of thromboembolic complications. Fujii et al demonstrated that CSU patients with high D-dimer levels had intense deposits of fibrinogen in dermis, along with normal laboratory parameters of other coagulation indicators, suggesting that the activation of coagulation cascade occurs outside of the vessels, not intravascularly, providing an explanation as to why CSU patients do not show an increased rate of thrombosis (11). As a conclusion, D-dimer may be found substantially elevated in severe autoimmune urticaria, but this does not necessarily prompt anti-coagulant treatment. Treating the patient properly to keep their symptoms under control leads to diminished D-dimer levels and lowers the proinflammatory state. Significantly elevated D-dimer levels and its relationship with type IIb autoimmune CSU and omalizumab resistance might be a subject for further studies which could aid recognizing poor response to omalizumab in advance to avoid patients' further devastation.

Conflict of interest

All authors declare that they have no conflicts of interest.

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Legends

Figure. 1 Progression of D-Dimer, CRP and UAS-7 Score levels

