

Case Report/Case Series

D-Dimer Levels as a Marker of Cutaneous Disease Activity

Case Reports of Cutaneous Polyarteritis Nodosa and Atypical Recurrent Urticaria

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IMPORTANCE Biochemical markers of disease allow clinicians to monitor disease severity, progression, and response to treatment. C-reactive protein and erythrocyte sedimentation rate are commonly used biochemical markers of inflammatory disease. We present 2 cases that indicate that D-dimer levels may be useful as a potential biochemical marker of disease activity in certain cutaneous inflammatory conditions.

OBSERVATIONS We report 2 cases in which clinical disease activity correlates with D-dimer levels. The first case is a woman in her 50s with a diagnosis of cutaneous polyarteritis nodosa. The second case is a man in his 20s with recurrent urticaria. In both patients, plasma D-dimer levels increased with clinical evidence of disease activity and decreased with treatment and resolution of the disease flare. Interestingly, serum C-reactive protein levels did not correlate with disease activity and were found to be normal during clinically active disease.

CONCLUSIONS AND RELEVANCE We show the potential value of D-dimer measurements as a marker of vasculocentric and/or vasculopathic inflammation and suggest that vascular endothelial damage may be ongoing in certain cutaneous inflammatory conditions.

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Autoimmune and inflammatory diseases present with a wide variety of clinical manifestations. Often the cutaneous signs and symptoms do not accurately reflect the degree of immune activation and tissue damage. Adjunct tests, such as those for serum C-reactive protein (CRP) level and erythrocyte sedimentation rate, can help clinicians assess the degree of inflammation and tailor management.¹ During the active phases of certain inflammatory diseases, leukocyte-mediated damage of the blood vessels can occur, resulting in vasculitis.² Damage to blood vessels can also lead to activation of the coagulation cascade, thrombus formation, and D-dimer release into the bloodstream.² It follows that D-dimer levels might be a useful marker to track inflammation and blood vessel damage.

D-dimers are small protein fragments generated by fibrinolysis of a thrombus or blood clot. D-dimer assays are often used in the diagnosis of deep venous thrombosis or pulmonary embolus and have been used to predict the likelihood of recurrent venous thromboembolism. Previous reports have indicated that there is an increased risk of venous thromboembolic events in patients with vasculitis.^{3,4} Furthermore, D-dimer levels have been shown to be elevated in patients with vasculitis such as Henoch-Schönlein purpura, Kawasaki disease, and eosinophilic granulomatosis with polyangiitis (Churg-Strauss syndrome).^{3,5,6} The wider application of

D-dimer levels as a marker of inflammation has been suggested by work in nonvasculitic conditions such as bullous pemphigoid and chronic urticaria.^{7,8}

Here for the first time, to our knowledge, we demonstrate disease activity correlated with D-dimer levels in a patient with cutaneous polyarteritis nodosa (PAN) and another with recurrent atypical urticaria. We suggest that measuring D-dimer levels in a variety of inflammatory conditions might be of clinical use in assaying disease activity, assessing response to treatment, and in potentially stratifying patient risk of venous thromboembolic events.

Report of Cases

We present 2 cases of cutaneous inflammation showing a correlation of disease activity with D-dimer levels.

Case 1

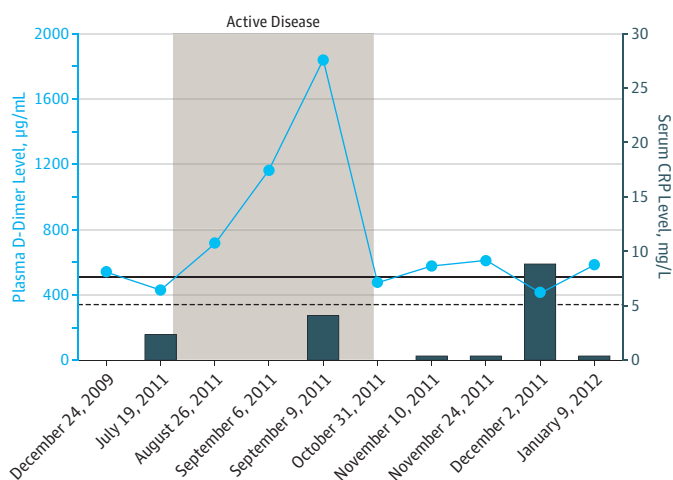
The first case is of a woman in her 50s who presented to dermatology clinic with a history of livedoid erythema (Figure 1A) and recurrent leg ulcers (Figure 1B). The patient first developed skin problems 6 years prior after hiking when she noticed blue skin discoloration on her legs. This discoloration extended to her buttocks, thighs, and arms during a period of

Figure 1. Cutaneous Polyarteritis Nodosa Disease Activity



Clinical images of patient 1 showing livedo pattern on thighs (A) and ulcerations on legs during active disease phase (B). After treatment, clinical images show healed ulcers (C and D).

Figure 2. Cutaneous Polyarteritis Nodosa Disease Activity Correlated With D-Dimer and C-Reactive Protein (CRP) Levels

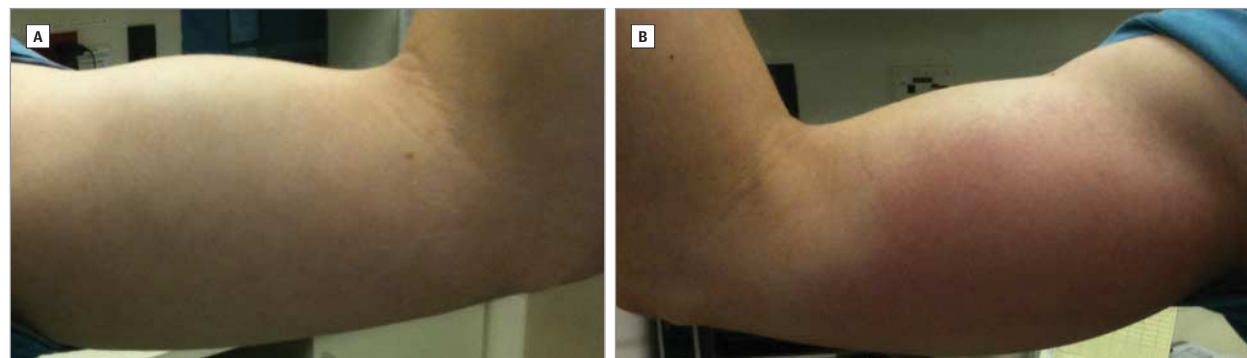


Chronologic D-dimer levels (circles) and serum CRP levels (bars) associated with disease activity in patient 1 as determined by clinical assessment. Reference value for plasma D-dimer level ($<500 \mu\text{g/mL}$ [to convert to micromoles per liter, multiply by 5.476]) is indicated by the solid horizontal line, and reference value for serum CRP level ($<5.0 \text{ mg/L}$ [to convert to nanomoles per liter, multiply by 9.524]), by the dashed horizontal line.

approximately 2 years. Four years before presentation, she developed a foot drop and associated numbness. She next developed superficial ulcers of the legs that resolved with use of systemic and topical nifedipine and appropriate dressings. One year before presentation, the fourth and fifth toes of the right

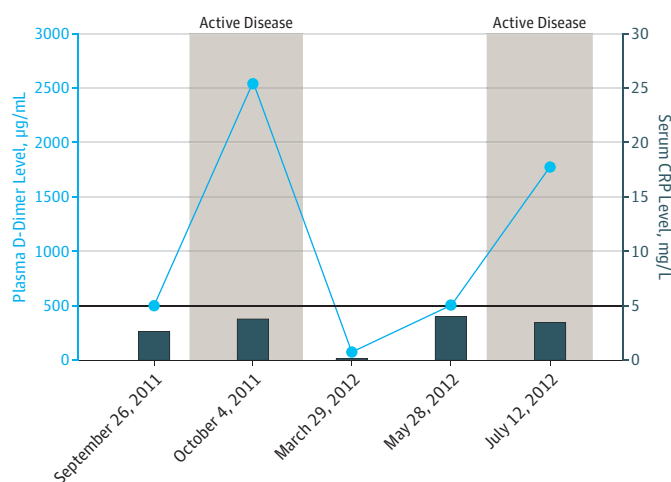
foot became ischemic and this resolved with dalteparin sodium anticoagulation therapy. The patient was observed by thrombosis clinic staff with a presumptive diagnosis of livedoid vasculopathy and D-dimer levels were checked from 2009 onward (Figure 2). When no active disease was present, her

Figure 3. Recurrent Atypical Urticaria Disease Activity



Clinical images of patient 2 showing normal-appearing left arm (A) and swelling and erythema on right arm (B).

Figure 4. Recurrent Atypical Urticaria Disease Activity Correlated With D-Dimer and C-Reactive Protein (CRP) Levels



Chronologic plasma D-dimer levels (circles) and serum CRP levels (bars) associated with disease activity in patient 2 as determined by clinical assessment. Reference values for plasma D-dimer level (<500 µg/mL [to convert to micromoles per liter, multiply by 5.476]) and serum CRP level (<5.0 mg/L [to convert to nanomoles per liter, multiply by 9.524]) are indicated by the solid horizontal line.

baseline plasma D-dimer levels were in the range of 400 to 600 µg/mL (reference value, <500 µg/mL [to convert to micromoles per liter, multiply by 5.476]). At presentation, the patient had experienced a 2-month flare of her condition with the development of numerous ulcers of the legs and a marked rise in D-dimer levels to a maximum of 1839 µg/mL. A biopsy performed during this flare showed vasculitis involving deep dermal vessels. Other investigations including liver function, renal function, hepatitis serologic analysis, cryoglobulins, antineutrophil cytoplasmic antibodies, and antiphospholipid antibodies had negative results. Given the lack of systemic manifestations (kidney, heart, liver) usually seen in systemic PAN, a diagnosis of cutaneous PAN was made on the basis of the clinical presentation and biopsy result.⁹ The flare of the cutaneous PAN subsided with intravenous IgG and systemic steroid therapy and her D-dimer levels returned to her normal range. She was subsequently treated with azathioprine and has not had any further flares of her disease (Figure 1C and 1D).

Case 2

The second case involves a man in his 20s who presented to the emergency department with right foot erythema and

swelling that was initially thought to be a deep venous thrombosis. His plasma D-dimer level was more than 4000 µg/mL, but there was no radiological evidence of thrombosis. On further review, a history of recurrent periodic episodes of swellings with associated erythema dating back 2 to 3 years was obtained. His lesions would affect various parts of the body including the torso, extremities, and genitals and lasted for hours to days (Figure 3). The patient was subsequently investigated by internal medicine staff for angioedema. Laboratory tests including those for levels of immune complexes, antinuclear antibodies, functional C1 inhibitor, C3, and C4 all had results within normal ranges. The D-dimer test was repeated a few weeks after the initial presentation when the erythema and swelling had resolved, and the level was found to be 501 µg/mL. Over the course of the next year, the patient had 2 more episodes of swelling with erythema, accompanied by elevations in D-dimer levels (with values of 2545 and 1771 µg/mL), and he had normal D-dimer levels during quiescent intervals (Figure 4). Interestingly, the serum CRP levels changed little during the flares of his disease. The patient is now being observed by the dermatology service with a working diagnosis of

atypical recurrent urticaria based on clinical evidence of episodes of sustained swelling that are unresponsive to antihistamines.⁸ Skin biopsy revealed pathologically normal skin, without the neutrophilic infiltrates noted in urticarial vasculitis or neutrophilic urticaria. Treatment with dapsone and colchicine has abolished further swelling episodes during 1 year of follow-up.

Discussion

C-reactive protein is a well-established biochemical marker of inflammation. Previous studies have suggested a link between inflammation, elevation of serum CRP levels, vascular damage, and elevation in plasma D-dimer levels.^{10,11} Herein we present 2 patients who had negative results on a CRP test and positive results on a D-dimer test during active disease, indicating that markers of acute inflammation may be less sensitive than markers of activation of coagulation. Medication use may play a role in these differences. Particularly, many of the patients included in the study of Nikpour et al¹² were receiving anti-inflammatory medications that have been shown to suppress CRP levels. This would provide an additional reason to use D-dimer levels as a biochemical marker of disease activity because they are less likely to be directly affected by immunosuppressive medications and as such more directly reflect vascular inflammation-mediated activation of the coagulation cascade and fibrinolysis.

Although CRP is the more widely used biochemical marker of inflammation, there have been a few case reports and case series that correlate D-dimer levels with disease activity and risk of venous thromboembolic events. Perhaps the most studied is the association between systemic lupus erythematosus and the incidence of thrombosis. Arterial and venous thromboembolism has a prevalence of 10% in patients with systemic lupus erythematosus and is believed to be related to hypercoagulability, premature atherosclerosis, and increased incidence of vasculitis.¹¹ Vasculitis seems to be a common pathophysiologic link between the other

reports of inflammatory conditions and elevated D-dimer levels.^{10,13} These reports include Henoch-Schönlein purpura, Kawasaki disease, eosinophilic granulomatosis with polyangiitis (Churg-Strauss syndrome), and Behçet syndrome.^{5,6,13,14} In addition, several groups have shown that the coagulation cascade is activated in patients with chronic urticaria and atypical urticaria and that D-dimer levels were elevated in these patients and associated with disease severity.^{8,15} One study examined the activation of the coagulation cascade in patients with bullous pemphigoid and found a correlation between disease activity and increased D-dimer levels.⁷ When patients with bullous pemphigoid were treated and clinical manifestations of their disease subsided, their D-dimer levels decreased to normal.⁷ These findings from a wide variety of inflammatory conditions support the findings of this study and the use of D-dimer as a potential biochemical marker of disease activity.

Conclusions

We report, to our knowledge, the first documented case of cutaneous PAN that shows a direct correlation between disease activity and D-dimer levels. Furthermore, we confirm the previously reported association between recurrent atypical urticaria and elevated D-dimer levels. In both cases, CRP levels did not correlate with clinical disease activity. We propose that D-dimer measurements may play a role as a biochemical marker of inflammatory skin disease activity. Elevated D-dimer levels in patients with vasculocentric and/or vasculopathic inflammation suggest that vascular endothelial damage may be occurring and that these patients may be at higher risk of venous thromboembolic events. Whether elevated D-dimer levels in patients with inflammatory skin disease identify patients with increased risk of thromboembolism remains to be determined. Clinicians should be aware of the potential utility of D-dimer levels to evaluate disease severity, track patient response to treatment, and assess the need for anticoagulation therapy.

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Study concept and design: Kirchhof, Dutz.

Acquisition of data: All authors.

Analysis and interpretation of data: Kirchhof, Dutz.

Drafting of the manuscript: Kirchhof.

Critical revision of the manuscript for important intellectual content: All authors.

Administrative, technical, and material support: Kirchhof, Dutz.

Study supervision: Dutz.

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