RESEARCH ARTICLE

D-Dimer Defects in Histopathologically Proven Urticarial Vasculitis

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ABSTRACT

Background: Urticarial vasculitis (UV) is an uncommon form of chronic urticaria characterized by urticarial lesions that persist more than 24 hours. Differentiating UV from chronic spontaneous urticaria remains difficult due to overlapping clinical pictures. Recent studies suggest that activation of the coagulation cascade, reflected by elevated serum D-dimer levels, may contribute to disease pathogenesis and morbidity.

Aim: To assess serum levels of D-dimer in urticarial vasculitis patients and evaluate their association with histopathological findings.

Methods: A retrospective case control study was conducted in Mosul, Iraq, between June 2022 and January 2025. Fifty patients clinically diagnosed with urticarial vasculitis were included. Serum D-dimer levels were measured using quantitative ELISA during disease exacerbations. All patients underwent skin biopsy with histopathological examination. Demographic, clinical, laboratory, and pathological data were analyzed. A control group of 50 dermatology patients without vasculitis was included for comparison.

Results: The mean age recorded for the patients was 36.4 ± 9.1 years with female predominance (1.8:1). Elevated D-dimer levels were detected in 80% of UV patients and were significantly higher than controls. Histopathology confirmed leukocytoclastic vasculitis in all cases, with fibrinoid necrosis observed in 88% of biopsies. Elevated D-dimer concentrations showed a significant association with increased histopathological severity, particularly fibrinoid necrosis and endothelial swelling. A positive correlation was found between D-dimer levels and clinical disease activity.

Conclusions: Urticarial vasculitis is associated with significant activation of the coagulation system. Serum D-dimer appears to be a useful predictive marker for disease activity and histopathological severity, supporting its role as an adjunct diagnostic and prognostic indicator alongside skin biopsy evaluation.

Keywords: Coagulation, D-Dimer, Histopathology, Urticarial Vasculitis.

INTRODUCTION

Chronic urticaria (CU) is a prolonged skin inflammatory condition marked by an episodic urticarial eruption, with or without angioedema, that continues beyond a six-week duration [1]. A substantial proportion of cases fall under chronic spontaneous urticaria (CSU), where no identifiable precipitating factors are detected, leading to repeated episodes of short-lived, pruritic wheals [2-5]. However, an independent subset within the clinical and histopathological spectrum presents with urticarial lesions that last more than 24 hours and are often associated with pain or burning rather than pruritus. This condition is known as urticarial vasculitis (UV), a rare type of leukocytoclastic vasculitis which affects small dermal blood vessels in dermis essentially [6- 9]. It is difficult to diagnose and treat Urticarial vasculitis because it mimics clinically CSU. However, its underlying pathology is differed, in which immune activation and vascular wall inflammation is found [6- 9]. In clinical practice, UV lesions leave residual post-inflammatory hyperpigmentation or purpura, a feature that aids in distinguishing UV from non-vasculitis forms of CU [8, 9]. Moreover, UV may manifest purely as an isolated cutaneous disease or in conjunction with systemic autoimmune disorders, especially systemic lupus erythematosus, reflecting the heterogeneous nature of the disease [6-8]. Recently, coagulation cascade activation may occur together with immune dysregulation in pathogenesis of UV. Elevated serum D-dimer levels, indicative of enhanced fibrinolysis and thrombin generation, have been reported in patients with CU and UV and have been correlated with disease severity and activity [10-12]. Together, these findings indicate that disturbances in the coagulation system may

participate in promoting vasculitis and subsequent tissue injury in urticarial vasculitis. Consequently, D-dimer may serve not only as a biomarker of disease activity but also as a potential target for novel therapeutic strategies [10.12].

MATERIALS, PATIENTS AND METHODS

Study design

A retrospective case control study was performed at the dermatology and pathology departments of Ibn-Sina Teaching Hospital, in Iraq/Mosul, from June 2022 to January 2025. The investigation encompassed patients admitted with chronic urticaria persisting for a duration exceeding six months.

Patient population

Fifty patients were clinically diagnosed with urticarial vasculitis based on the presence of urticarial lesions exceeding 24 hours, accompanied by pain or burning and residual pigmentation or purpura. Clinical diagnosis was supported by the presence of systemic symptoms where applicable, and 50 randomly selected patients admitted to dermatological department for other skin diseases without clinical features suggestive of vasculitis (control group).

Laboratory Assessment

For all 50 clinically diagnosed UV patients, serum levels of D-dimer were assessed at the time of disease exacerbations to assess coagulation pathway activation. Blood samples were collected and analyzed using quantitative ELISA techniques according to standardized protocols.

Biopsy and Histopathology assessment: All 50 UV patients underwent skin biopsy for active lesions (4-mm punch biopsies). Samples were fixed in 10% formalin and processed for routine hematoxylin and eosin stain preparation. Data concerning immune complex deposition were collected from previously documented reports available in the pathology archives, which had been done using fluorescein isothiocyanate (FITC)-conjugated antibodies against human immunoglobulins (IgG, IgM, IgA) and complement component C3, and were included for correlation analysis.

Statistical analysis

Statistical procedures were carried out via SPSS Statistics (version 29). Descriptive statistics summarized patient demographics, clinical features, D-dimer levels, and histopathological results. parameters were represented as mean with or without standard deviation or median. Variables across study groups were examined through t-tests, Mann–Whitney U tests, Chi-square or Fisher's exact tests accordingly. Association between levels of serum D-dimer and histopathological extent or clinical burden was assessed using Pearson or Spearman correlation coefficients. A p-value considered statistically significant when it was less than 0.05.

Ethical Approval

The research framework was approved by the Review Board of the College of Medicine, University of Mosul (Ref. No. UOM/COM/MREC/24-25/APR26, dated April 9, 2025). Patient information was maintained confidentially throughout the study by anonymizing all data.

RESULTS

Patient Demographics and Clinical Features: Fifty patients were clinically diagnosed with urticarial vasculitis (UV) based on lesion characteristics persisting beyond 24 hours, associated pain or burning, and residual pigmentation. The mean age of UV patients was 36.4 ± 9.1 years, with a female predominance (32 females, 18 males; female-to-male ratio 1.8:1). The average duration of disease was 14.2 ± 7.3 months. Systemic symptoms such as arthralgia, low-grade fever, and malaise were reported in 14 (28%) of UV patients. Residual pigmentation or purpura following lesion resolution was observed in 28 (56%) patients.

D-dimer Levels and Coagulation Status: Serum levels of D-dimer were measured in all UV patients and 50 control group. The mean D-dimer level in UV patients was significantly elevated at 1.85 ± 1.12 mg/L compared to 0.45 ± 0.27 mg/L in controls ($p < 0.001$). Elevated levels of D-dimer (>0.5 mg/L) were detected in 40 (80%) of UV patients, while only 7 (14%) controls showed elevated levels. (Table 1).

Histopathological Findings: Skin biopsies from all 50 UV patients confirmed leukocytoclastic vasculitis, The remaining histopathological changes are distributed in different proportions as shown in Fig. 1.

Table 1
D-dimer Levels in UV Patients vs. Controls

Group	Number of cases	Mean D-dimer (mg/L ± SD)	Elevated D-dimer (>0.5 mg/L), n (%)
Urticarial Vasculitis	50	1.85 ± 1.12	40 (80%)
Control	50	0.45 ± 0.27	7 (14%)
p -value	<0.001	<0.001	

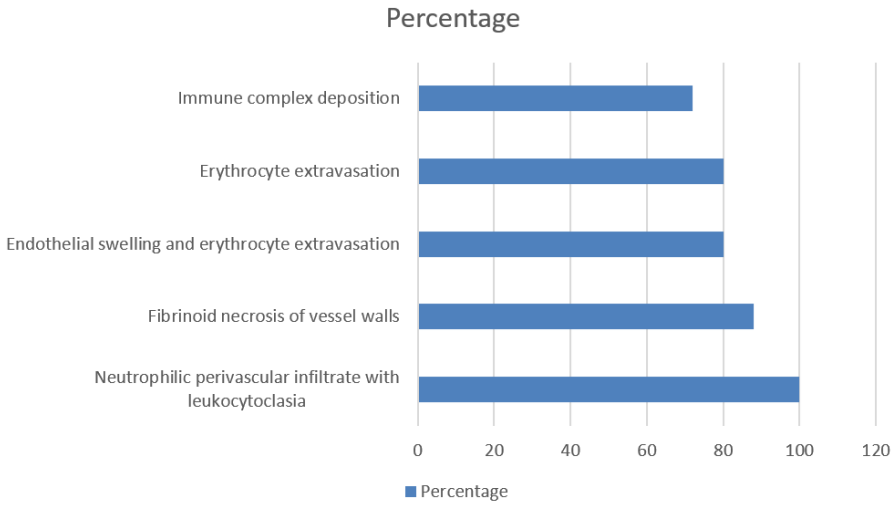

Fig. 1. Histopathological Features in UV Patients

Table 2
Association of Elevated D-dimer with Histopathological Severity

Histopathological Feature	High D-dimer (N=40)	Normal D-dimer (N=10)	P-value
Fibrinoid necrosis	40 (100%)	4 (40%)	0.003*
Endothelial swelling	36 (90%)	4 (40%)	0.02*
Immune complex	32 (80%)	4 (40%)	0.08

* Significant Statistically at $p < 0.05$

Association Between levels of D-dimer and Histopathology: Patients with high levels of D-dimer exhibited a significantly higher frequency of fibrinoid necrosis and endothelial swelling compared to patients with normal levels of D-dimer. (Table 2)

Clinical Correlations: High D-dimer associated positively with systemic symptoms and lesion severity scores ($r = 0.64$, $p < 0.001$). Patients presenting with systemic involvement had higher mean D-dimer levels (2.12 ± 1.03 mg/L) compared to those without systemic symptoms (1.55 ± 1.10 mg/L), though this difference is non- significant statistically ($p = 0.09$).

DISCUSSION

This research offered an important perspective of urticarial vasculitis (UV) regarding coagulation, and histopathological profile [13]. High levels of D-dimer in 80% of UV patients, together with histopathological features of leukocytoclastic vasculitis, demonstrates the role of coagulation stimulation in the UV pathogenesis [14]. Other studies conducted demonstrated elevated D-dimer levels in approximately 72% of patients with urticarial vasculitis and related inflammatory dermatoses [10]. A more recent study conducted showed increased markers of coagulation activation in nearly 70% of chronic urticaria patients, supporting the association between inflammation and coagulation pathways [11]. These results support previous studies regarding the association between chronic urticaria, vasculitis, and coagulation promotion [15]. Researchers also investigated coagulation markers in inflammatory disorders and found elevated D-dimer levels in a considerable proportion of cases, indicating a consistent activation of the coagulation cascade [15]. Female patients' predominance (64%) in the current study, along with the mean age of 36.4 ± 9.1 years, is consistent with previous findings [16, 17]. A retrospective study conducted demonstrated female predominance in approximately 60–68% of patients with a similar age distribution [16]. Likewise, another study conducted reported comparable epidemiological characteristics, with female predominance approaching 65% and a mean age within the third and fourth decades of life[17]. Accurate clinical distinction between UV and CSU remains a complex issue; however, the persistence of lesions beyond 24 hours, associated pain or burning sensation, and the presence of residual pigmentation or purpura in 56% of patients in this study proved UV diagnosis as shown by others [16]. Other studies also

demonstrated residual pigmentation in approximately 50–60% of UV cases, reinforcing its diagnostic significance [16].

The gold standard of UV diagnosis is biopsy, which demonstrated 100% sensitivity for leukocytoclastic vasculitis in the present study [18]. Similar findings were reported in other studies, where leukocytoclastic vasculitis was identified in nearly all confirmed cases [18]. The frequent detection of fibrinoid necrosis, immune complex deposition, complement activation and neutrophil infiltration corroborating additional support to immune mediated vascular injury as a part of pathogenesis [19, 20]. Furthermore, researchers highlighted the interaction between complement activation and coagulation pathways in inflammatory vascular conditions [20].

A marked increase in D-dimer concentration in most UV cases supports the involvement of coagulation and fibrinolytic system activation in disease pathogenesis, highlighting D-dimer as a valuable marker of disease activity and severity in addition to classical inflammatory markers such as ESR and CRP. Similar findings were reported in other studies [11].

CONCLUSIONS

In conclusion, this research illustrates the fundamental role of coagulation abnormalities and immune mediated vasculitis in understanding UV pathogenesis. The combination of D-dimer assessment and histopathological diagnosis establishes a reliable way for diagnosis and severity evaluation of UV. These findings encourage multidisciplinary approaches combining histopathology, dermatology and hematology to improve management of UV patients.

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Conflicts of Interest

The author affirms that there are no conflicts of interest and certifies that no financial, personal, or professional affiliations have influenced the content of this manuscript.

Author Contributions

All components of the study, including design, data collection, analysis, manuscript writing, and final approval, were rested solely with the author.

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