Cutaneous Vasculitis : A New Plasma Marker

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Abstract:

This study includes thirty-four patients with cutaneous vasculitis (CV). Clinical and microscopic examinations were done for all patients. Other investigations included ESR, CBC, blood sugar, liver and kidney function tests, urine and stool analysis. Hepatitis markers, anti DNA, ANCA, ACA and abdominal sonography were performed on selected cases. The aim of this study was to assess the role of the coagulatory system in the pathogenesis of C.V.

Plasma levels of tissue factor (TF) procoagulant and tissue factor pathway inhibitor TFPI (anticoagulant) were measured in the patients and were compared to their levels in ten healthy controls. The results were also correlated to disease duration (> or <2 weeks), clinical manifestation (palpable purpura only, versus palpable purpura with skin ulcers) and histopathological type of the disease. A highly significant increase ($P<0.01$) was found in TF level in patients as compared to controls. The TF level correlated with the disease duration and was higher in patients with disease duration >2 weeks than in patients with shorter disease duration ($p<0.05$). The TF level was found to be higher in patients with lymphocytic vasculitis than in patients with leucocytoclastic vasculitis and this may be presumably due to endothelial cell injury which is more apparent in the late cases and in lymphocytic type of CV, in addition to the hypofibrinolytic phase occurring in these late cases. The level of TFPI was found to be insignificantly lower in CV patients than controls possibly due to anticoagulant consumption.

The study highlights evidence of TF as a plasma marker in CV and brings into consideration the possible use of recombination TFPI in the treatment of resistant cases.

Introduction and Aim of Work:

Vasculitis is a clinicopathologic process characterized by inflammation and consequent damage to blood vessels [1]. Cutaneous vasculitis usually affects the postcapillary venules [2].

Cutaneous vasculitis is a heterogeneous group of disorders, which can be confirmed to the skin or may be part of an associated systemic disease. Primary and secondary forms of cutaneous vasculitis exist. Secondary vasculitis has been linked to several processes, including infections, drugs and allergic, rheumatologic and neoplastic diseases. Various etiological agents, as well as conditions that mimic skin vasculitis, usually present with similar features mainly palpable purpura. The skin biopsy usually shows leukocytoclastic vasculitis. Initially, the pathogenesis of cutaneous vasculitis is immune complex related, but in its later stages different pathogenic mechanisms may intensify the reaction and lymphocytes may predominate in the infiltrate [3].

In systemic vasculitis, increased levels of plasma endothelial cell derived proteins have been described and this implies endothelial activation or injury [4]. Also, cutaneous fibrinolytic activity namely tissue plasminogen activator which is one of endothelial cell-derived proteins is increased in the early phase and reduced in the late phase of leukocytoclastic vasculitis leading to intravacular and perivascular deposits of fibrin with subsequent tissue hypoxia and necrosis [5].

Also another tissue factor which is one of endothelial cell derived proteins that initiate blood coagulation and also von Willebrand factor are increased. The increase in tissue factor creates a local stimulus for firbin formation and thrombosis [6]. It is known that tissue factor pathway inhibitor as an anticoagulant play a primary role in regulating the procoagulant tissue factor.

This work aimed to measure tissue factor and tissue factor pathway inhibitor and find out the relationship of each factor with respect to the clinical and histological types of cutaneous vasculitis and to assess their role in the pathogenesis of cutaneous vasculitis.

Patients and Methods:

A group of 44-cases was the subject of this study [34 consecutive patients with cutaneous vasculitis and 10 controls]. The patients were evaluated at the inpatient wards in the Department of Dermatology, Kasr El-Eini Hospital, Faculty of Medicine, Cairo University. The study was performed over a period of 31 months (Nov. 1997 till May 2000).

All patients did not receive medication for their vasculitis for a least two months prior to their investigation.

Patients were subjected to the following investigations:

I) Clinical study

* Which included detailed history taking, general examination and complete dermatological examination to determine the type, pattern and distribution of lesions. The affection of mucous mem-

branes and the presence of other dermatological diseases were also noted.

II) Skin biopsy for histopathological examination

A 4 mm punch skin biopsy was taken from a fresh lesion of vasculitis in-patients to confirm the diagnosis. The biopsies were stained by hematoxylin and eosin and were examined under the light microscope.

III) Routine laboratory investigations, which include:

* CBC, ESR, Liver and kidney function tests, blood glucose
* Stool, urine analysis
* Antinuclear antibody tests

Additional investigations were performed in selected cases:

* These included: cryoglobulins, serum immunoglobulins, antistreptolysin 0 litre, antibodies to hepatitis B virus, hepatitis C virus, and abdominal sonography.

IV) Estimation of tissue factor (TF):

The TF ELISA kit is an enzyme-linked immunoassay for quantitative determination of human TF in plasma. The lower detection limit is approximately 10/pg/ml.

V) Estimation of total TFPI (tissue factor pathway inhibitor):

The total TFPI ELISA kit is an enzyme linked sandwich immunoassay for quantitation of TFPI in plasma. This ELISA detects both intact and truncated forms of TFPI as well as complexes with TF and factor VIIa (TF/VIIa/TFPI). Binary complexes with factor Xa (TFPI/Xa) and quaternary complexes with TF, factor VIIa and factor Xa (TF/TFPI/Xa) were also recognized by this ELISA, but with slightly lower sensitivity. The lower limit of detection for this assay is 0.360ng TFPI/ml sample.

Patients were divided into two groups according to the duration of the attack:

1- Early: disease duration is <2 weeks (group E)
2- Late : disease duration is >2 weeks (group L)

Also patients were divided into two groups according to the clinical picture:

1- Group (P): patients with palpable purpura without any ulceration or gangrenous skin.
2- Group (U): patients with skin ulcer (s) or gangrenous skin lesions with or without palpable purpura.

Also patients were divided into two groups according to the histopathological picture:

1- Group (A): patients with lymphocytic or granulomatous vassculitis
2- Group (B): patients with leukocytoclastic vasculitis.

VI) Statistical analysis:

The data were transferred to an IBM card using an IBM personal computer provided with the statistic program (Microstat V-2) to obtain:

1- Descriptive statistics:
   a) Mean, and
   b) Standard deviation (+ SD)
2- Analytic statistics:
   a) Student's test (to compare between two independent means)
   b) P-value (level of significant) where P>0.05 is non-significant (NS), P<0.05 is significant (S), and
   c) Correlation associations (r), the value of (r) #1 —> means perfect linear correlation, if (r) value is 0.3 – 0.5 means good correlation.

Results:

The sex distribution among the patients was equal (17 males and 17 females).

The age range was 17-62 years with mean of 36.7 + 13.1

The duration of present attack ranged from one day to 8-months with the mean duration of 33 days.

Lesions were bilateral in 32 (94.9%) cases and unilateral in 2

cases (5.9%). The lower limbs were affected in all except one case (97.1%).

Comparison between some positive and negative clinical manifestations (which include fever, arthralgia, arthritis and abdominal pain) in cases of cutaneous vasculitis was shown in Table (1).

Comparison between positive and negative history of drugs, infections preceding the attack and chronic disease in cases of cutaneous vasculitis was also shown in Table (1).

Histopathological types found in the patients were shown in Table (2).

Table (1): Frequency of some manifestations in patients with CV.

Clinical manifestation	Negative	Positive
Fever	22/34 (74.7%)	12/34 (35.3%)
Arthralgia	14/34 (41.2%)	20/34 (58.8%)
Arthritis	32/34 (94.1%)	2/34 (5.9%)
Abdominal pain	33/34 (97.1%)	1/34 (2.9%)
* Drug intake preceding the attack	26/348/34 (76.5%)	(23.5%)
** Infections preceding the attack	31/34 (91.2%)	3/34 (8.8%)
***Chronic diseases	24/34 (70.5%)	10/34 (29.5%)

* *Implicated drugs included: NSAID, insulin, oral contraceptive, oral hypoglycemics and muscle relaxants.*

** *Infections included: uninary tract infections, sinusitis and abscess*

*** *Chronic diseases included: DM, breast cancer, chronic lymphocytic leukemia.*

Results of laboratory investigations:

ESR was elevated in 16 patients (47%) and liver enzymes were elevated in 6 patients (17.6%).

CBC: anaemia was present in 2 patients (6%), one patient (3%) was neutropenic and an other patient (3%) had leukocytosis (CLL). The remaining 30 patients (88%) had a normal blood picture.

Urine analysis: RBCs were present in two cases (5.9%) and proteinuria in one case (3%).

Other laboratory investigations were shown in Table (3).

Results of ELISA test for estimation of serum TF and TFPI were shown in Tables (4-11)

Table (2): Histopathological types found in CV

Histopathological picture	Number	Frequency
Leukocytoclastic	26	76.5
Lymphocytic	7	20.5
Granulomatous	1	3.0
Total	34	100.0

Leukocytoclastic vasculitis was present in 76.5% of cases,while lymphocytic vasculitis in 20.5% of cases and granulomatous vasculitis in only 3% of cases.

Table (3): Frequency of some laboratory manifestations in pateints with CV.

	Negative	Positive	Total No. of Patients
* Occult blood in stools	32 94.1%	2 5.9%	34
* DM (increase blood sugar)	26 76.5%	8 23.5%	34
* ANA	22 88%	3 12%	25
* HCV	15 75%	3+ve Ab: (15%) 2+ve Ab & Ag: 10%)	20
* Cryoglobulins	6 60%	4 40%	10
* APA (antiphospholipid antibodies)	8 80%	2 %20	10

Table (4): Total test for TF levels (pg/ml) in patients and controls.

	Controls (n=10)	Cases (n=34)
Mean (pg/ml) Standard deviation	127.5 62.42	230.0 120.49
t – value	2.57	
p – value	<0.01	

From the previous table we observe the following:

* The patients showed higher TF production (mean=230.0 than controls (mean=127.5) and this elevation was statistically highly significant (p=value<0.01)
* The levels of TF in patients showed marked variation range (80-500) in comparison to control range (90-250).

Table (5): T-test for TFPI (ng/ml) in patients and controls

	Controls (n=10)	Cases (n=34)
Mean (pg/ml) Standard deviation	93.9 17.68	91.34 36.72
t – value	0.210	
p – value	NS	

From the previous table we observe the following:

* The patients showed slightly less TFPI (mean=91.34) than the control group (mean 93.9(, but this was not statistically significant.

Table (6): T-test for TF level (pg/ml) in paitents with early presentation <2weeks (E) vs patients with late presentation >2weeks (L) vs controls.

	Group E (n=9)	Group L (n=25)	Controls
Mean (pg/ml) Standard deviation	168.33 79.69	254.6 122.32	127.5 62.42

Group L patients showed higher TF levels (mean=254.6 pg/ml) than group E (mean=168.33), (t=2.389). This evaluation was statistically significant (p<0.2).

Group E patients showed higher TF levels (mean=168.33) than control (mean=127.5), (t=1.233). This elevation was statistically insignificant.

Group L patients showed higher TF levels (mean 127.5), (t=2.57). This elevation was statistically highly significant (p<0.01).

Table (7): T-test for TFPI (ng/ml) in group E vs group L vs controls.

	Group E (n=9)	Group L (n=25)	Controls
Mean (pg/ml) Standard deviation	84.44 29.22	93.84 39.25	93.9 17.68

Group L showed insignificantly higher TFPI (mean=93.84) than group E (mean 84.44), (t=0.748), p=NS).

Group E patients showed insignificantly lower TFPI levels (mean=84.44) than controls (mean=93.8), (t=0.838, p=NS).

Group L patients showed a similar TFPI levels (mean=93.83) to controls (mean=93.9), (t=0.006, p=NS).

Table (8): T-test for TF (pg/ml) in patients with palpable purpura without any ulceration or gangrenous skin lesions (group P) and patients with skin ulceration or gangrenous skin lesions with or without palpable purpura (group U) vs controls.

	Group E (n=9)	Group L (n=25)	Controls
Mean (pg/ml)	198.49	258.06	127.5
Standard deviation	119.83	117.21	62.42

Group U patients showed higher TF levels (mean=259.06) than group P (mean=193.49), (t=1.465). This elevation was insignificant.

Group P patients showed higher TF levels (mean=198.44) than controls (mean=127.5), (t=1.723). This elevation was insignificant.

Group U patients showed higher TF levels (mean=258.06) than controls (mean 127.5), (t=3.257). This elevation was highly significant (p<0.01).

Table (9): T-test TFPI (ng/ml) in group P vs group U vs controls.

	Group E (n=9)	Group L (n=25)	Controls
Mean (pg/ml)	90.25	92.33	93.9
Standard deviation	27.52	44.12	17.68

Group P patients showed insignificantly lower TFPI (mean=90.25) than controls (mean=93.9), (t=0.0411), p=NS).

Group U patients showed insignificantly lower TFPI (mean=92.33) than controls (mean=93.9), (t=0.132, p=NS).

Table (10): T-test for TF levels (pg/ml) in patients with lymphocytic or granulomatous vasculitis (group A) and patients with leukocytoclastic vasculitis (group B) vs controls.

	Group E (n=9)	Group L (n=25)	Controls
Mean (pg/ml)	352.5	194.42	127.5
Standard deviation	86.49	100.2	62.42

Group A patients showed higher TF levels (mean=325.5) than group B (mean=194.42), (t=4.34). This elevation is highly significant (p<0.001).

Group B showed statistically significant elevation of TF (mean=194.42) than control (mean=127.5), (t=2.394. p=<0.05).

Group A patients showed higher TF levels (mean=325.5) than controls (mean=127.5), (t=6.182). This elevation was highly significant (p<0.001).

Group P patients showed insignificant lower TFPI (mean=90.25) than group U (mean=92.33), (t=0.167, p=NS).

Table (11): (-test for TFPI level (ng/ml) in group A and group B patients vs controls.

	Group E (n=9)	Group L (n=25)	Controls
Mean (pg/ml)	84.88	93.35	93.9
Standard deviation	21.31	40.43	17.68

Group A patients showed insignificantly lower TFPI (mean=84.88) than group B patients (mean=93.35) (t=0.774, p=NS).

Group A patients showed insignificantly lower TFPI (mean=84.88) than the control group (mean=93.9) (t=0.961, p=NS).

Group B patients showed insignificantly similar TFPI (mean=93.35) to controls (mean=93.9) (t=0.056), p=NS).

Discussion:

Cutaneous vasculitis (CS) comprises a diverse group of disorders that combine segmental inflammation with necrosis of blood vessels. The vascular damage results from immunologic and or inflammatory mechanisms. Clinical syndromes are based on criteria that include the gross appearance and the histologic alterations of the vascular lesions, the blood vessels caliber of the affected specific organs, and the presence or absence of laboratory abnormalities [8].

Although all sizes of blood vessels may be involved in the skin, CV predominantly involves postcapillary venules. CV may occur in association with an underlying chronic disease, may be precipitated by infection or drugs, or may develop for unknown reasons. Initially, the pathogenesis of CV is immune, complex related,

but in its later stages different pathogenic mechanisms may intensify the reaction and lymphocytes may predominate in the infiltrate [1,2].

Fibrin deposition and vascular thrombosis are seen in cutaneous vasculitis syndromes, suggesting local endothelial cell activation. Endothelial cells are important regulators of procoagulant and anticoagulant intravascular processes. The procoagulant properties are formed by the production of TF and synthesis of VWF and factor V. The anticoagulant properties are formed by expression of heparin-like glycosaminoglycans (that can bind thrombin) and by release of coagulation factor inhibitors such as protein S and TFPI. In addition, vascular endothelial cells have firbinolytic properties. Firbinolytic proteins can assemble on endothelial cells, and they synthesize and release t-PA, (tissue plasminogen activator) which initiates fibrinolysis. Tissue-plasminogen activator is inhibited by PAI-1 (plasminogen activator inhibitor-1) which is released also from endothelial cells [6].

Abnormal firbinolysis has been demonstrated in patients in which a massive release of t-PA is present. In late lesions, a state of hypofibrinolysis exists which is associated with reduction of t-PA and increased levels of PAI (7,8). The reduction of fibrinolytic activity leads to intravascular deposition of fibrin (with subsequent areas of necrosis). In addition to abnormal fibrinolysis, abnormalities in procoagulant and anticoagulant systems occur in CV. Levels of TF, VWF (procoagulants) and TM (thrombomodulin) (anticoagulant) were found to be increased in various forms of CV. TF has also previously been reported to be increased in the plasma of patients with disseminated intravascular coagulation (DIC), thrombotic thrombocytopenic purpura, diabetic microangiopathy and vasculitis with collagen diseases[8].

This study included a group of 34 patients; 17 males and 17 females; age 17-62 years (mean 36.7 +13.1) with cutaneous vasculitis diagnosed clinically and investigated histopathologically. All patients were subjected to routine investigations (CBC, ESR, Liver kidney function, urine and stool analysis, antinuclear antibodies test). Additional investigations were performed in selected cases. These included: anti-DNA antibody, ANCA, anticardiolipin antibodies, cryoglobulins, serum Ig, hepatitis B and C virus. Plasma levels of TF and TFPI serum tPA and PAI levels were estimated using ELISA in the 34 patients with cutaneous vasculitis and ten controls. The patients were subdivided according to duration into early (<2 weeks) and late (>2 weks) groups, and according to histopathologic picture into leukocytoclastic and lymphocytic groups, and also according to clinical picture into patients with palpable purpura only and patients with ulcer either only or with palpable purpura.

The aim of this work was to measure the levels of TF and TFPI in CV and to assess their relation to clinical type, duration of the lesion and histopathological examination to discuss their role in the pathogenesis of the disease.

In the present study, all patients except two had the lesions distributed bilaterally. The lesions were commonly found on the lower legs, in which an elevated hydrostatic pressure and tortuous vessels may provoke more distorted and turbulent blood flow pattern (9).

Results of the present study demonstrate that drug intake may be a precipitating cause for vasculitis in 23.5% of cases. Implicated drugs included nonsteroidal anti-inflammatory, insulin, aminosalicylic acid, oral contraceptives and oral hypoglycaemics.

History of infection preceding the attack was present in 8.8% of the patients. Infections included urinary tract infection, sinusitis and abscess.

History of systemic signs and symptoms such as fever, arthralgia, arthritis and abdominal pain were present in 35.5%, 58.8% and 2.9% of the cases respectively.

The histological picture was leukocytoclastic vasculitis in 76.5% of cases, while lymphocytic vasculitis and granulomatous vasculitis were detected only in 20.5% and 3% of cases, respectively.

In some cases the vasculitis was not affecting the skin only and systemic affection was detected by investigations. Haematuria was present in 5.9% of cases and proteinuria in 3% of cases. Therefore, urine analysis is mandatory because although haematuria and proteinuria may be minimal, ongoing renal vasculitis can lead to irreversible renal damage as steted by Dahl (10).

Diabetes mellitus was present in 23.5% of cases and the occuring vasculitis could be explained by the known thrombotic tendency in diabetics. Increase PAI-I was detected in insulin dependent diabetes mellitus which contributes, together with concomitant hypertriglyceridemia, to the vascular complications. Another factor precipitating the vasculitis attack in the studied patients may be the use of insulin or oral hypoglycaemic agents. Increase of TFPI activity in diabetes was previously detected and reflects vascular endothelial damage [11].

The liver enzymes were elevated in six cases. Four

of the cases had polyclonal cryglobulins and three of the four cases had HCV antibodies. A number of cases of mixed cryoglobulinaemia associated with HCV infection has been reported [12]. In most, anti-HCV Ab, HCV-RNA and rheumatoid factors, were detected. The pathogenesis of cutaneous vasculitis associated with cryoglobulinaemia and HCV infection is still unknown. It is possible that HCV anti-HCV Ab immune complex cryoprecipitate in vessels by some mechanisms thus activating complement and leading to vasculitis [13, 14].

The results of this study agree with the hypothesis put forward by Lotti et al., (1996)[15]. These authors hypothesized that circulating immune complexes interacting by means of their Fc receptors with venous endothelial cells may produce a massive release of endothelial t-PA (hyperfibrinolytic phase) with subsequent activation of the local fibrinolytic system. This influences the vasopermeability facilitating the passage of serum and immunocomplexes and affecting their deposition in tissues. All this activates the complement cascade, kinin and the prostaglandin synthesis. This initial hyperfibrinolytic phase, characterized clinically by urticarial wheals, is followed by late hypofibrinolytic phase that seems related to the reduction of the endothelial t-PA release and to high levels of inhibitors of plasminogen activation. The reduction of fibrinolytic activity leads to excessive intravascular deposition of fibrin (with consequent area and more injury to endothelial cells with more production of tissue factor). This leads to microvascular thrombosis and both amplification and continuation of tissue damage [15, 16].

This study highlights evidence of endothelial cell activation in cutaneous vasculitis using plasma markers. Results of the present study show that the level of tissue factor in patients with cutaneous vasculitis was significantly higher ($p<0.01$) than its level in the controls. This finding was also detected by Jurd et al. [16] and Koyama et al. [9]. TF is absent from the unperturbed endothelial cell surface, but is upregulated by cytokines such as IL-1 and TNF creating a local stimulus for fibrin formation and thrombosis.

Also C5a (which can be produced during immune complex mediated vasculitis) can induce tissue factor on endothelial cells and this activation may present one of many potential interrelationships between the inflammatory and coagulation schemes [17].

In this study also a significant elevation of TF was found in cases with late presentation (>2 weeks) ($p<0.01$) and cases with lymphocytic vasculitis (P0.001) than cases with early presentation (<2 weeks and leukocytoclastic vasculitis, respectively. This may be due to the type of infiltrating cells in these cases which is mainly mononuclear cells. Tissue factor can be induced in blood monocytes by a variety of cytokines [18] and this may be a cause for the increase of TF in these late and lymphocytic cases. Another explanation is the hypofibrinolysis (caused by increase of PAI-1 or consumption of t-PA) present in late phase in patients with CV[7, 8].

In addition, the result of this study showed a highly significant increase ($p<0.01$) in TF in patients presenting with ulcer as compared to controls. This might be explained by the increase in endothelial cell injury occuring in such cases that causes an increase in TF[19]. The increase in TF resulted in increase clot formation and occurrence of ulcer[20]. Also these four cases with ulcers might have been late or severe cases in which there was hypofibrinolysis. The reduction of fibrinolytic activity leads to intravascular deposition of fibrin. This leads to microvascular thrombosis and maintenance of tissue damage [3].

This categorizes TF as a plasma marker for cutaneous vasculitis that can be more specific than ESR especially that it denotes endothelial cell injury (the healthy endothelial cells do not synthesize TF under normal conditions).

The results of the present study show that the levels of TFPI were insignificantly lower in patients than the control group. This may possibly by attributed to consumption. This findings was also detected by Broz [21] and Sandset & Bendz [22]. However, Bajaj & Bajaj[23] found that the level of TFPI was variable and this may be related to the severity of endothelial damage. The elevated plasma TFPI levels may possibly be caused by mobilization of TFPI from the vessel wall and adherent monocytes. The low levels of TFPI in some patients may be also attributed to consumption.

Conclusion and Recommendation:

From the finding in this work one can recommend that the measurement of TF as a plasma marker is possibly more specific than the non-specific markers (C-reactive protein and ESR) to monitor vasculitic activity (being absent from unperturbed endothelial cells and specially that it denotes endothelial cell injury). Also the beneficial effect of anti-TF antibodies and recombinant TFPI (which have been found to be effective in animals models of several diseases complicated by TF-

induced coagulation) as a line of treatment is recommended to be assessed especially in cases not responding to different lines of treatment.

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