Increased concentration of platelet-derived chemokines in serum of patients with delayed pressure urticaria

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ABSTRACT. ***Background.*** **Delayed pressure urticaria (DPU) is a distinct form of urticaria, characterized by marked dermal swelling, deep inflammatory infiltrate and systemic symptoms. Little is known about inflammatory mediators involved in this disease.** ***Objective.*** **To investigate secretion of platelet-specific chemokines, platelet factor 4 (PF-4) and beta-thromboglobulin (beta-TG) during the course of DPU.** ***Methods and material.*** **Plasma concentrations of PF-4 and beta-TG were measured in eight adult DPU patients and in 15, age- and sex-matched, healthy controls.** ***Results.*** **Plasma PF-4 and beta-TG concentration scores were significantly higher in the DPU group as compared with the control subjects.** ***Conclusion.*** **The present study, as well as an earlier contribution, suggest that distinct platelet activity may be identified in different types of urticaria. In contrast to chronic idiopathic urticaria, chronic urticaria with a positive response to autologous serum skin testing, and acute urticaria, delayed pressure urticaria may be associated with increased secretion of platelet chemokines, similar to that observed in cold urticaria.**

Keywords: delayed pressure urticaria, platelet activation, platelet factor 4, beta-thromboglobulin

Delayed pressure urticaria (DPU) is a distinct form of urticaria, the pathogenesis of which has not yet been well characterised. Among the urticarias, DPU shows some special features such as delayed cutaneous erythema and oedema, which occur four to six hours following application of sustained pressure, along with substantial subcutaneous swelling and deep dermal inflammatory infiltration. DPU is frequently associated with systemic symptoms of which concomitant chronic idiopathic urticaria is the most common [1, 2]. Moreover, histamine seems not to play an essential role in the development of this type of urticaria as antihistaminic drugs are generally ineffective [3]. It has been suggested that cytokines, including TNF-alpha, are involved in DPU pathology, possibly by inducing subthreshold inflammation [4]. This has been proved by tests pointing to the effectiveness of anti-TNF-alpha therapy in this disease [5]. Platelet-derived chemokines, such as platelet factor 4 (PF-4) and beta-thromboglobulin (beta-TG), exert a wide range of pro-inflammatory and immunomodulatory properties, including mast cells activation, leukocyte accumulation and activation at inflammatory sites [6, 7]. In addition, PF-4 that is released by platelet into the blood stream is capable of permeating blood vessel walls following endothelial cell injury [8]. PF-4 was also found in tissue mast cells granules [9].
Given the important role of platelet-derived chemokines in immune-inflammatory events, it is to know how important these molecules are in the processes occurring during the course of DPU. Therefore, plasma concentrations of PF-4 and beta-TG were evaluated in DPU patients.

PATIENTS AND METHODS

Eight patients (five males and three females; mean age 40.5 years) with DPU *(table 1)* were enrolled. They all showed large, painful hives. The patients had received no medication (corticosteroids and/or antihistamines) for at least 48 hours before the test. No other diseases were present. The control group comprised 15 healthy, age- and sex-matched subjects.

Blood sampling; beta-TG and PF-4 measurement

Blood was obtained in the morning (in the fasting state) into Diatube® H tubes (Becton Dickinson) to minimize *ex vivo* platelet activation [10], then immediately placed in an ice/water bath. The tubes were then centrifuged at 2 500 g for 30 minutes at 4°C, and the top third of the resultant plasma supernatants was collected and frozen at -20°C for evaluation. Plasma levels of beta-TG and PF-4 were measured by enzyme-linked immunosorbent assay (ELISA), using a commercial Asserachrom® kit (Diagnostica Stago, France).

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Table 1
Demographic and clinical characteristic of DPU patients

Patient number	Sex	Age (years)	Disease duration (months)	Concurrent chronic urticaria	General symptoms	ESR
1	M	45	48	+	+	30
2	M	40	24	+	+	20
3	M	50	132	+	-	10
4	M	38	11	+	-	5
5	M	43	8	+	-	8
6	F	25	5	-	-	15
7	F	47	62	-	-	18
8	F	37	12	-	-	10

M: male; F: female; erythrocyte sedimentation rate (ESR).

Table 2
PF-4 and beta-TG plasma concentrations in DPU patients and in healthy controls

Parameters analysed Unit	Healthy controls (n = 15) Median range	DPU patients (n = 8) Median range	Statistical analysis (p)
PF-4 (IU/mL)	5.0 1.2-7.4	9.95 6.8-14.2	0.001
Beta-TG (IU/mL)	21.5 10.0-29.0	30.75 19.0-48.0	0.01

n: number of subjects; DPU: delayed pressure urticaria.

Statistical analysis

Data were delivered as medians and ranges, and comparisons between the groups were performed using the Mann-Whitney's unpaired rank sum test. The correlation coefficient was obtained using the Spearman test. P values below 0.05 were considered significant.

RESULTS

Table 2 points to significant differences between patients with DPU and the control subjects for the indices of platelet activity examined. Plasma beta-TG and PF-4 concentration scores were significantly increased in the DPU group as compared to the control subjects. No differences in peripheral platelet counts for the two groups were noted (data not included). Moreover, no significant correlation was found between plasma concentrations of beta-TG and PF-4 and ESR in DPU patients.

DISCUSSION

Platelet infiltrates have been demonstrated in patients with cold urticaria [11]. It has been reported that platelet activation, measured by plasma levels of PF-4, may occur in patients suffering from cold urticaria [12] and cold urticaria accompanied by vasculitis [13].
We have reported previously that platelet activity measured as plasma levels of platelet-derived chemokines did not increase in patients suffering from chronic idiopathic urticaria [14], patients with chronic urticaria with a positive response to autologous serum skin testing [15] or acute urticaria [16].
To identify any possible differences in systemic platelet activity in patients with different types of urticaria, the present study investigated plasma concentrations of PF-4 and beta-TG in DPU patients.
We observed increased plasma levels of PF-4 and beta-TG in patients suffering from DPU, suggesting an enhanced release of the platelet mediators. On one hand, increased platelet activity might be a consequence of mediators released from mast cells and during the later stage associated with the inflammatory response. Is this, however, a case of an excessive secretion of platelet-specific mediators involved in the development of DPU lesions? At present, the pathophysiological significance of such findings is unknown and the increased platelet activity might only be an accompanying phenomenon appearing as the response of different systems to the progressing illness.
The present study, as well as some earlier contributions, suggest that distinct platelet activity may be identified in different types of urticaria. In contrast to chronic idiopathic urticaria, chronic urticaria with a positive response to autologous serum skin testing and acute urticaria, delayed pressure urticaria may be associated with increased secretion of platelet chemokines, similar to that observed in cold urticaria.
Platelet-derived chemokines should be the subject of further investigation, and studies should be extended to include a larger group of DPU patients.

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