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# Platelet Activation as a Possible Indicator of Disease Activity in Chronic Urticaria: Link with Blood Coagulation and Mast Cell Degranulation

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## Abstract

**Background:** Much attention has been paid to activation of the blood coagulation cascade during urticaria attacks. Elevated levels of plasma D-dimer and prothrombin fragment 1+2 have been reported. The final product of the coagulation cascade, thrombin, may induce mast cell degranulation, complement fragmentation, or platelet-activating factor expression. However, the involvement of platelets in urticaria is poorly understood.

**Methods:** We examined the relationship between disease activity and plasma levels of platelet factor IV, β-thromboglobulin, D-dimer, and prothrombinfragment (Fr) 1+2 in 23 patients with chronic urticaria.

**Results:** We observed elevated plasma levels of platelet factor IV (13/23) and β-thromboglobulin (15/23) in patients with chronic urticaria that returned to normal after anti-histamine therapy. Platelet re-activation was observed in recurrent urticaria. Some cases showed clinical response to anti-platelet therapy or *Helicobacter pylori* decolonization in combination with anti-histamine treatment.

**Conclusions:** Platelet activation is a possible indicator of disease activity in chronic urticaria. Platelet-derived factors with or without blood coagulation products might induce mast cell degranulation in chronic urticaria.

**Keywords:** Urticaria; Platelet factor IV; β-Thromboglobulin; Coagulation factors; Anti-platelet therapy

## Introduction

Chronic urticaria is one of the most common skin diseases encountered in daily practice. Physicians must occasionally select appropriate medications for refractory patients who have long histories of anti-histamine-resistant urticaria, oral allergy syndrome, or aspirin intolerance due to complex pathologic mechanisms, impaired daily quality of life, or life-threatening attacks [1,2]. Recent reports suggest involvement of blood coagulation factors in the induction of urticaria in addition to well-known pathologic mechanisms, such as IgE-mediated allergic reactions [1-6]. These include activation of tissue factors, degranulation of mast cells by thrombin, or elevated plasma D-dimer during the active phase of urticaria [4-7]. The results presented here suggest that platelet-derived factors play roles in chronic urticaria related to infection, drug treatment, or mental stress with activation of tissue factors in the microcirculation of the cutaneous environment. Thus, platelet activation may be a novel disease marker and promising target of anti-platelet therapy in refractory urticaria.

## Patients and Methods

The study included 23 patients (11 men and 12 women) with chronic urticaria, which was defined by persistent disease for more than one month. The average age of patients was 45.69 years (range: 16-76 years of age). All subjects gave informed consent.The study was approved by the Osaka University ethics committee and conducted in accordance with the Declaration of Helsinki. To minimize platelet activation during sample collection, blood was drawn from antecubital veins through 20-gauge needles and mixed with one-tenth the volume of acid citrate dextrose. All laboratory values, including PF4, β-thromboglobulin, D-dimer, and prothrombinFr1+2were measured at the clinical laboratory of Osaka University Medical Hospital. Laboratory tests were performed every other month, and evaluation was based on the patient's diary or self-evaluation.

## Statistical Analysis

Data are expressed as medians ± standard deviation, and comparisons between groups were performed with the Mann-Whitney U-test. Correlation coefficients were obtained by Spearman tests. *P* values lower than 0.05 were considered to be significant.

## Results

The first case in this study was a 57-year old male with a history of chronic urticaria for more than 3 years at another university hospital clinic. He had been treated with oral betamethasone, warfarin, and anti-histamines for 3 years with unfavorable clinical effects. He was positive for *Helicobacter pylori* IgG. Therefore, *H. pylori* decolonization was initiated. We also started anti-platelet therapy for tapering warfarin.

The numbers of urticarial attacks were reduced within several months of starting this regimen. Surprisingly, the platelet-derived factors platelet factor IV and β-thromboglobulin were initially present at elevated levels but returned to normal once the urticarial attack subsided according to the patient's record (Figure 1). Thus, we measured platelet-derived factors in patients with chronic urticariaas possible indicators of disease activity. Elevated plasma levels of platelet factor IV (13/23) and β-thromboglobulin (15/23) were observed in patients with chronic urticaria. Plasma levels of FDP (11/17) and Fr 1+2 (9/12) were also elevated (Figure 2 and Table 1). These platelet-derived factors and coagulation cascade products returned to normal

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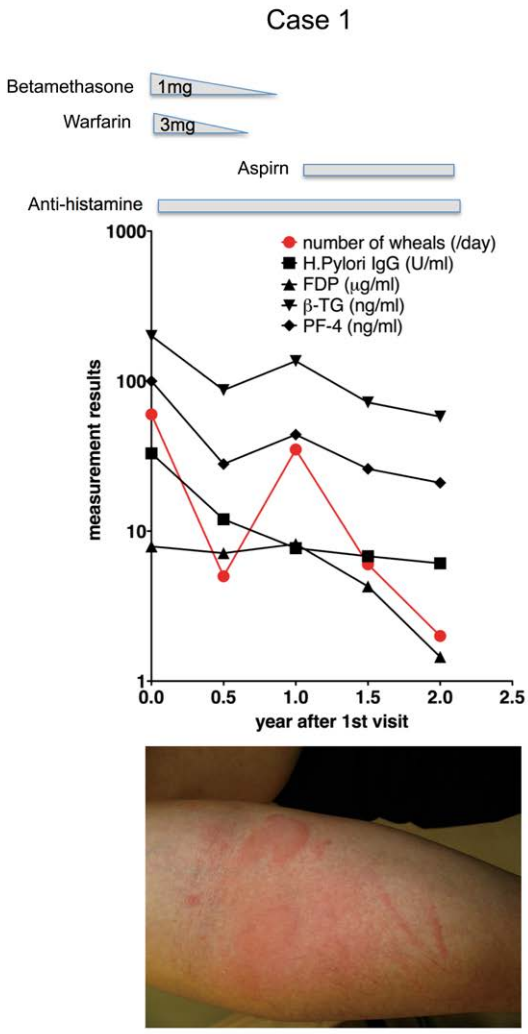


**Figure 1:** Clinical course of a patient with chronic urticaria: According to the patient's record, the platelet-derived factors platelet factor IV (PF-4) and β-thromboglobulin (β-TG) were elevated initially but returned to normal levels after the urticaria attack subsided.

after anti-histamine therapy when the urticarial attack subsided (Figure 3). In our study, a statistically significant parallel correlation was observed between PF-4 and β-thromboglobulin (Figure 4). Some cases showed clinical responses to anti-platelet therapy or *Helicobacter pylori* decolonization in combination with anti-histamine treatment. Relapsed platelet activation was observed with recurrence of urticaria in some cases.

## Discussion

Asero et al. recently reported that elevated blood coagulation factors, such as prothrombin fragment 1+2 or D-dimer, are elevated in patients with chronic urticaria [3]. Thrombin, which is generated through the coagulation cascade, is a candidate for mast cell degranulation. Mast cell degranulation induces a wheal-flare reaction similar to C5a, major basic protein, or well-known pathologic mechanisms, such as IgE-mediated allergic reactions (Figure 5) [1-3]. Tissue factor, which can be induced by signals, such as chemicals, microbes, or stress, is thought to activate the coagulation cascade during the active phase of urticaria [8,9].

However, the involvement of platelet activation in urticaria has been sparsely reported except for in a topic dermatitis by Kasperska-Zajac et al. [10]. Recently, Katoh et al. reported that platelet activation results in P-select in induction followed by inflammatory cell recruitment to the skin in a late-phase reaction of atopic dermatitis [11,12]. As reported previously, strong expression levels of iNOS and CD23 are observed in urticarial skin lesions [13]. TNFα and IL3 are also strongly expressed in various types of urticarial skin lesions in the absence of sparse inflammatory cell infiltration [14]. These results suggest that platelet-derived factors regulate expression of cytokines in urticaria.

In the present study, similar platelet activation was observed in patients with urticaria. However, the relationship between platelet activation and disease severity has not been clarified. The scratching behavior of mice with atopic dermatitis is suppressed by serotonin inhibitors, suggesting that platelets might be activated in atopic dermatitis [15]. Serotonin is possibly derived by platelets and is involved in the elicitation phase of murine contact dermatitis [16]. In mice, serotonin is derived from platelet and mast cells. In contrast, human mast cells do not generate serotonin, which suggests that platelet activation is important for allergic inflammation. Rajappa et al. recently reported that platelet oxidative stress plays some role in induction of

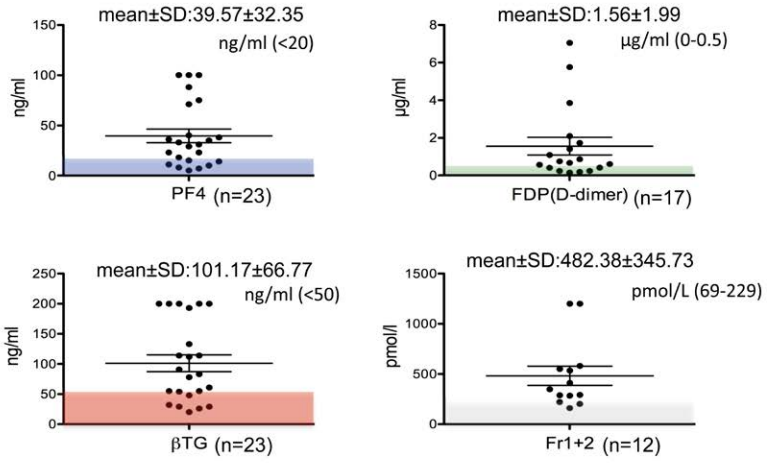


**Figure 2:** Plasma levels of platelet-derived factors and coagulation cascade products. Elevated plasma levels of platelet factor IV (PF4, 13/23) and βTG (15/23) were observed in patients with chronic urticaria. Plasma levels of FDP (11/17) and Fr 1+2 (9/12) were also elevated.

| No | Age | gender | β-TG (ng/ml)<50 | PF4(ng/ml)<20 | FDP(D-Dir), μg/m1)<0.5 | Fri +2(pmol/L)69-229 | IgE<173 | RAST | TARC<450 | CRP<0.04 | Course | *H. Pylori* IgG/ Decolonization |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | 43 | M | 200 | 100 | 7.9 | 160 | ND | ND | | | 9 M | +/ND |
| 2 | 37 | F | 200 | 100 | 0.86 | | 21 | DP | 216 | | 6 M | |
| 3 | 57 | M | 200 | 100 | 7.05 | | ND | ND | | | 2Y | +/+ |
| 4 | 71 | M | 37 | 13 | | | 2750 | JCP | | <0.04 | 2-3M | |
| 5 | 62 | M | 48 | 11 | 5.76 | 550 | 421 | | | 0.41 | 2 M | +/+ |
| 6 | 76 | M | 32 | 15 | | | 438 | JCP | | 0.34 | 4 M | +/+ |
| 7 | 53 | M | 20 | 7 | 0.24 | | 190 | | | 0.08 | ND | |
| 8 | 27 | F | 133 | 40 | 0.75 | 348 | 387 | JCP | 561 | 0.12 | 2 M | |
| 9 | 43 | F | 91 | 33 | 0.41 | | 15.3 | | 627 | | ND | |
| 10 | 71 | F | 83 | 31 | 1.41 | 534 | 793 | JCP | 135 | | 20Y | + /ND |
| 11 | 16 | M | 55 | 23 | | 1200 | 150 | | 140 | | ND | |
| 12 | 67 | F | 50 | 18 | 1.73 | 315 | 45.3 | JCP | 192 | 0.07 | 1 M | |
| 13 | 43 | F | 114 | 36 | 0.18 | | 154 | | | | ND | |
| 14 | 21 | F | 36 | 10 | | | 251 | DP | 182 | | ND | |
| 15 | 37 | F | 26 | 5 | 0.6 | | 2140 | | 1522 | 0.29 | 2-3M | |
| 16 | 16 | F | 29 | 8 | 0.4 | | 113 | | | 0.04 | 2-3Y | |
| 17 | 63 | M | 29 | 10 | | | 362 | JCP | | 0.34 | 2 Y | +/ND |
| 18 | 42 | FF | 54 | 14 | 0.56 | 288 | 1140 | Several | 1003 | 0.97 | 3M | +/ND |
| 19 | 70 | | 58 | 21 1.29 | 245 | 30.4 | JCP | 397 | | 6 M | | |
| 20 | 39 | F | 114 | 35 | 1.09 | 292 | 427 | JCP, DP | 196 | 0.04 | 6 M | - |
| 21 | 63 | M | 61 | 18 | | 202 | 23.8 | (-) | 293 | 0.04 | 4W | +/ND |
| 22 | 17 | M | 78 | 29 | 0.14 | 221 | 42.2 | 6 Pollens | 438 | 0.05 | 2W | |
| 23 | 17 | M | 55 | 23 | 2.1 | 1200< | 150 | JCP | 140 | | 4 M | |

JCP: Japanese Cedar pollen

**Table 1:** Patients' characteristics.

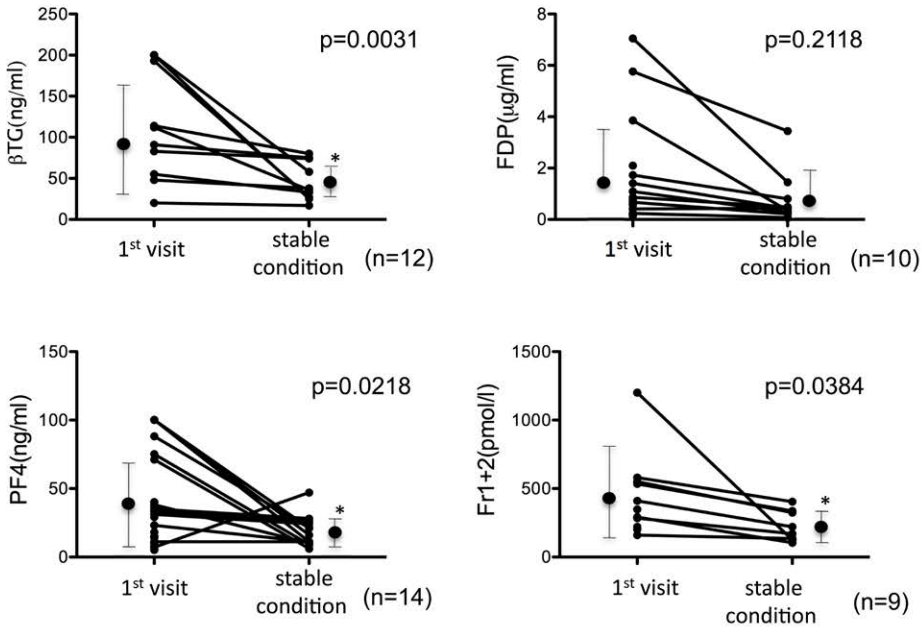


**Figure 3:** Plasma levels of platelet-derived factors before and after treatment. Platelet-derived factors and coagulation cascade products returned to normal after anti-histamine therapy when the urticaria attack subsided. Laboratory tests were performed every other month. Evaluation was based on the patient's diary or self-evaluation.

chronic spontaneous urticaria with elevated malondialdehyde and decreased superoxide dismutase or glutathione peroxidase [17]. Apart from delayed-type allergic skin diseases, Asero et al. reported the very interesting observation that activation of blood coagulation occurs in urticaria. Furthermore, thrombin, a final product of the coagulation cascade, induces mast cell degranulation [3]. They also reported that tissue factors are strongly expressed in skin lesions of chronic urticaria [4]. Mast cell-derived mediators, especially histamine, were believed to play a central role in the pathogenesis of urticaria until recently. However, their reports suggest that plasmin, another final product of the activated coagulation cascade, activates mast cells, resulting in histamine release and urticarial reaction. To support their observation,

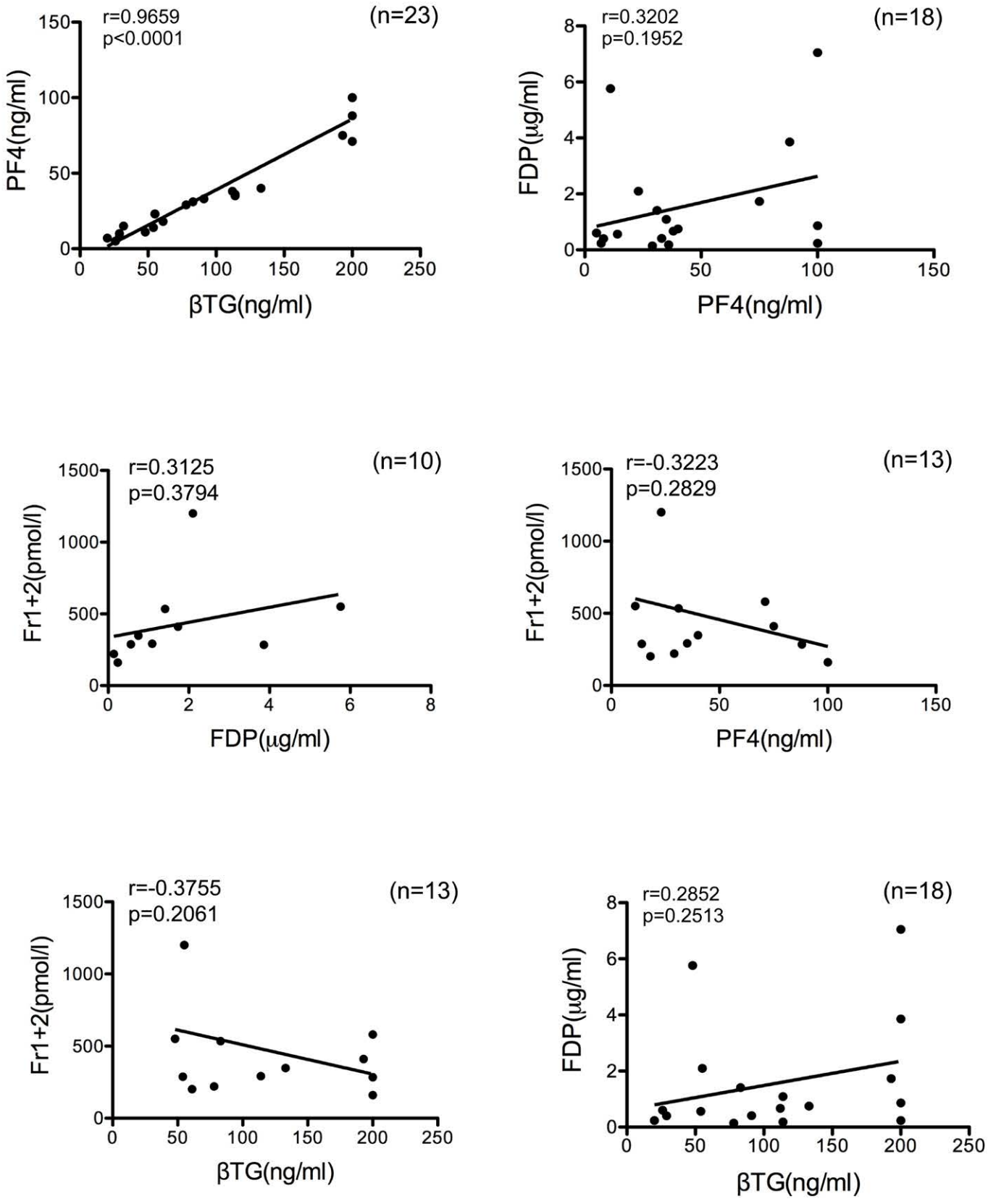


**Figure 4:** Correlation of platelet-derived factors and coagulation cascade products: Significant parallel correlation between PF4 and β-thromboglobulin was observed.

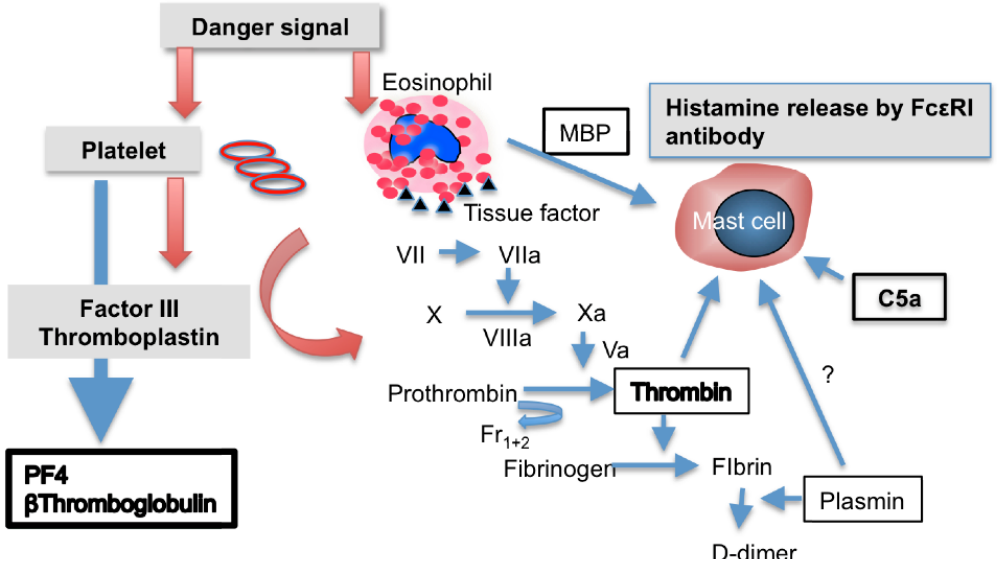


**Figure 5:** Platelet activation and accelerated coagulation cascade. Thrombin is generated through the coagulation cascade and is a candidate for mast cell degranulation. Mast cell degranulation induces a wheal-flare reaction similar to C5a, major basic protein (MBP), or well-known pathologic mechanisms, such as IgE-mediated allergic reactions.

Takahagi et al. reported that the anticoagulant warfarin shows clinical benefit in controlling refractory urticaria [5]. We observed that plasma levels of platelet-derived β-ThromboGlobulin (βTG) or platelet factor IV were elevated in urticaria. These data suggest that platelet activation is important for inducing the urticarial reaction. Interestingly, elevated levels of βTG or platelet factor IV returned to normal levels after anti-histamine therapy (Figure 3) but increased again when urticaria recurred. Therefore, these platelet-derived factors might be promising candidates as disease markers in urticaria. Further studies are required to confirm these results. These data support possible anti-platelet trialsin chronic refractory urticaria in addition to anti-coagulant therapy, as proposed by Asero [18,19].

Platelet activation could be induced or increased by scratching and is not the cause for scratching. Animal experimentation showed, on the one hand, that scratching was induced by platelet activating factor [20]. On the other hand, however, treatment with PAF receptor antagonist did not affect scratching behavior [21] that might be attributable to inter-species differences e.g. in serotonin secretion. Therefore, anti-platelet therapy for refractory urticaria with high plasma level of platelet derived factors should be explored and evaluated in the future work.

The role of *H. pylori* eradication in chronic urticaria is not clear at present although several controversial results were reported [22]. In our series of the study, only the patients with gastric complaint were analyzed for H *pylrori.* The clinical effect of *H. pylori* eradication was obscure in this study.

## Conflict of Interest

**Ichiro KATAYAMA**: Speaker at sponsored seminar by Sanofi, Kyowa hakko-Kirin, and Maruho.

**Hiroyuki MUROTA**: Speaker at sponsored seminar by Kyowa hakko-Kirin, Sanofi, Tanabe Mitsubishi, and Maruho.

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