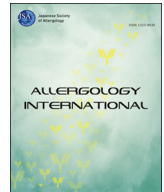




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Letter to the Editor

Critical role of platelets in the production of thymus and activation-regulated chemokine in children: A case series study

Dear Editor,

Thymus and activation-regulated chemokine (TARC), a member of the CC chemokine family, is a ligand for CC chemokine receptor 4 that is expressed Th2 lymphocytes. TARC plays important roles in Th2-type immune response by selectively recruiting CC chemokine receptor 4+ Th2-polarized memory/effector T cells into inflamed tissues. Atopic dermatitis (AD) is a chronic inflammatory skin disease characterized by pruritic eczema associated with predominant infiltration of Th2 cells in the lesional skin. A serum TARC level serves as a reliable biomarker of AD disease severity in clinical practice. It is reported that serum levels of TARC are significantly higher in infants and children than adults even in the absence of AD.^{1,2} TARC is produced by thymus, epidermal keratinocytes, endothelial cells, bronchial epithelial cells, dendritic cells (DCs), and platelets.³ TARC is also reported to be expressed in dermal vessels of the noninflamed skin.⁴ However, the source of serum TARC in AD remains controversial. We, first, found that a serum TARC level was undetectable in a boy with acute immune thrombocytopenia (ITP) despite the complication of AD (case 1), suggesting that a serum TARC level is dependent on platelet counts. We assessed AD severity using objective Scoring Atopic Dermatitis (O-SCORAD). The clinical course of case 1 is as follows: An 11-month-old boy was referred to our hospital because of AD that lasted for two months. Physical examination demonstrated intermingling pruritic erythematous papules, excoriations, and petechiae in the face, trunk, and extremities. The severity of his AD scored 30.8 by O-SCORAD and accordingly classified as moderate. Laboratory results were as follows: platelet count, $2 \times 10^9/L$; serum TARC, <100 pg/ml (normal range, <1367 pg/ml); IgE 54 IU/ml (normal range, <19.32 IU/ml). Specific IgE antibodies (normal range, <0.34 UA/ml) were positive for egg white (4.23 UA/ml), wheat (4.33 UA/ml), and ω 5-gliadin (2.35 UA/ml) by Immuno-Cap system. He was diagnosed with ITP based on the presence of platelet-associated IgG (31.8 ng/ 10^7 platelets; normal range; 0 – 27.5 ng/ 10^7 platelets) (Table 1) and an increased megakaryocyte count without malignant cells in his bone marrow. Platelet counts recovered following intravenous IgG treatment. His eczema responded well to topical glucocorticoid treatment. Four months later, platelet count and serum TARC level were $381 \times 10^9/L$ and 725 pg/ml, respectively. Then, he also underwent oral food challenge test for egg white and wheat and subsequently started to consume the safety doses of both foods. At the ages of 21, 27, and 32 months, serum TARC levels were 1226 pg/ml, 817 pg/ml,

and 797 pg/ml, respectively. He is now 38 months old and in good health with mild AD (O-SCORAD, 10.6). To confirm this observation, we analyzed serial serum TARC levels in patients with ITP.

Serum TARC levels were tested in six patients with ITP who were consecutively admitted to our hospital between February 2016 and January 2018. Serum TARC levels were measured by chemiluminescent enzyme immunoassay using HISCL TARC assay kit (Sysmex, Kobe, Japan) at BML. Complete blood counts and serum TARC levels were prospectively examined at the time of admission and/or ITP diagnosis and during drug-free remission of ITP in four patients. In the other two patients, sera obtained at diagnosis and remission of ITP were stored at -20 °C and later tested for TARC concentrations. This study was approved by the Ethics Committee of KKR Sapporo Medical Center (No. 30-2) under the written informed consent from the guardians of patients.

Profiles and clinical findings of the six patients are summarized in the Table 1. Serum TARC levels were undetectable at the time of diagnosis in all six ITP patients regardless of the presence of a complicating AD. When platelet counts were normal (i.e., before onset and/or after remission of ITP), serum TARC levels were detectable within or above age-matched upper normal limits.

In all cases, serum TARC levels correlated with platelet counts but not with eosinophil count or serum lactate dehydrogenase levels. Serum levels of TARC in AD are reported to reflect its overproduction in the skin lesions.⁵ On the other hand, a rapid decrease in serum TARC level (3308 pg/ml to <100 pg/ml) in only seven days in case 5 corresponded exactly with that of platelet counts ($212 \times 10^9/L$ to $10 \times 10^9/L$) (Table 1). A recent report has demonstrated that serum levels of TARC are low in a child with AD complicated by mild thrombocytopenia.⁶ Our results support this observation and strongly suggest a critical role of platelet in the production of TARC.

Platelets are abundant components of the blood and mediate immune responses by various mechanisms, e.g. recruitment of leukocytes via expression of P-selection, on activation.⁷ Patients with AD show elevated levels of β -thromboglobulin and platelet factor 4. Furthermore, these markers correlated with the severity of AD, indicating that platelets are activated in AD. As well, platelets from AD patients express higher TARC levels than control.⁸ TARC is also secreted by DCs, which is enhanced in the presence of stimulated platelets but not when platelets are unstimulated or depleted.⁹ In murine models of chronic hapten-induced dermatitis, which resembles AD in certain features, blood platelet depletion greatly reduced the degree of skin inflammation.¹⁰ These suggest that platelets play important roles in the pathology of AD. In this regard, the rapid response of eczema to topical glucocorticoid

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Table 1
Clinical profiles of six patients with ITP.

	Case 1		Case 2		Case 3			Case 4		Case 5			Case 6	
Age at onset	11 months		5 years		5 years			1 year		4 years			8 years	
Sex	Male		Male		Female			Male		Male			Male	
	ITP Dx	Remission (27 months later)	ITP Dx	Remission (3 months later)	3 years before ITP onset	ITP Dx	Remission (3 months later)	ITP Dx	Remission (3 months later)	7 days before ITP Dx	ITP Dx	Remission (2 months later)	ITP Dx	Remission (4 months later)
Platelets ($\times 10^9/L$)	2	342	4	192	139	15	148	3	395	212	10	288	6	296
TARC (pg/ml)	<100	982	<100	201	387	<100	251	<100	1015	3308	<100	365	<100	172
PA-IgG (ng/ 10^7 platelets)	31.8	ND	61.0	17.0	ND	20.3	<12.5	46.2	12.7	ND	42.0	13.2	33.8	<12.5
Eosinophils (μL)	416	450	0	56	0	180	ND	96	332	87	89	90	174	61
LDH (U/L)	305	265	566	273	189	197	ND	383	291	314	235	204	266	172
Skin rash	AD (moderate)	AD (mild)	no	no	no	no	no	no	no	transient erythema	no	no	no	no
Treatment	IVIG		GC for 2 months			GC for 1 month			IVIG followed by GC for 2 months			IVIG followed by GC for 2 weeks		GC for 3 months

ITP, immune thrombocytopenia; Dx, diagnosis; TARC, thymus and activation-regulated chemokine; PA-IgG, platelet-associated IgG; IVIG, intravenous IgG; GC, glucocorticoid; ND, not done; LDH, lactate dehydrogenase.

TARC normal range: 6–12 months, <1367 pg/ml; 1–2 years, <998 pg/ml; >2 years, <743 pg/ml; adults, <450 pg/ml.

PA-IgG normal range: 0–27.5 ng/ 10^7 platelets.

treatment in case 1 might have reflected a low level of TARC expression associated with thrombocytopenia.

There are several limitations in this study. First, we have included only a small number of children with ITP. Second, we did not evaluate the levels of serum TARC in adult patients. In addition, pathological roles of TARC in the development of AD are still unclear. Nevertheless, our results indicate that platelets are main cellular sources or potential inducers of TARC, and suggest a possible role of platelet in the pathology of AD.

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Conflict of interest

The authors have no conflict of interest to declare.

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References

1. Fujisawa T, Nagao M, Hiraguchi Y, Katsumata H, Nishimori H, Iguchi K, et al. Serum measurement of thymus and activation-regulated chemokine/CCL17

- in children with atopic dermatitis: elevated normal levels in infancy and age-specific analysis in atopic dermatitis. *Pediatr Allergy Immunol* 2009;**20**: 633–41.
2. Thijs J, Krastev T, Weidinger S, Buckens CF, de Bruin-Weller M, Bruijnzeel-Koomen C, et al. Biomarkers for atopic dermatitis: a systematic review and meta-analysis. *Curr Opin Allergy Clin Immunol* 2015;**15**:453–60.
3. Katoh N. Platelets as versatile regulators of cutaneous inflammation. *J Dermatol Sci* 2009;**53**:89–95.
4. Chong BF, Murphy JE, Kupper TS, Fuhlbrigge RC. E-selectin, thymus- and activation-regulated chemokine/CCL17, and intercellular adhesion molecule-1 are constitutively coexpressed in dermal microvessels: a foundation for a cutaneous immunosurveillance system. *J Immunol* 2004;**172**:1575–81.
5. Morita E, Takahashi H, Niihara H, Dekio I, Sumikawa Y, Murakami Y, et al. Stratum corneum TARC level is a new indicator of lesional skin inflammation in atopic dermatitis. *Allergy* 2010;**65**:1166–72.
6. Ozawa M, Sasahara Y, Aiba S. Case of atopic dermatitis concurrent with idiopathic thrombocytopenic purpura, whose serum thymus and activation-regulated chemokine level remained undetectable. *J Dermatol* 2018;**45**:606–8.
7. Semple JW, Italiano Jr JE, Freedman J. Platelets and the immune continuum. *Nat Rev Immunol* 2011;**11**:264–74.
8. Fujisawa T, Fujisawa R, Kato Y, Nakayama T, Morita A, Katsumata H, et al. Presence of high contents of thymus and activation-regulated chemokine in platelets and elevated plasma levels of thymus and activation-regulated chemokine and macrophage-derived chemokine in patients with atopic dermatitis. *J Allergy Clin Immunol* 2002;**110**:139–46.
9. Nakanishi T, Inaba M, Inagaki-Katashiba N, Tanaka A, Vien PT, Kibata K, et al. Platelet-derived RANK ligand enhances CCL17 secretion from dendritic cells mediated by thymic stromal lymphopoietin. *Platelets* 2015;**26**:425–31.
10. Tamagawa-Mineoka R, Katoh N, Ueda E, Takenaka H, Kita M, Kishimoto S. The role of platelets in leukocyte recruitment in chronic contact hypersensitivity induced by repeated elicitation. *Am J Pathol* 2007;**170**:2019–29.

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