Serum levels of BAFF for assessing the disease activity of Takayasu arteritis

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ABSTRACT

Objective. *Takayasu arteritis (TA) is a chronic vasculitis that affects large elastic arteries. Monitoring of disease activity is crucial because the disease may progress despite treatment with glucocorticoids. Elevated levels of B cell activating factor belonging to TNF family (BAFF) have been observed in patients with autoimmune diseases. In this study, we investigated whether dysregulation of BAFF occurs in TA.*

Methods. *Serum levels of BAFF were measured in sera from 9 patients with TA including 6 patients with follow up after induction therapy.*

Results. *Circulating BAFF levels in TA patients were higher than in those in healthy subjects. The high levels of BAFF in active TA patients were decreased when the patients entered remission.*

Conclusions. *To our knowledge, this is the first study to show elevated levels of BAFF in active TA patients. These findings suggest that this cytokine contributes to vasculitis in TA and raise the possibility that monitoring of serum BAFF might aid clinicians in making adequate treatment adjustments in TA patients.*

Introduction

Takayasu arteritis (TA) is a chronic vasculitis that affects primarily large elastic arteries, such as the aorta and its main branches (1). The histological characteristics of TA include inflammatory cell infiltration and necrosis of the arterial vascular cells (2, 3). TA is thought to be an autoimmune disease, and both cellular as well as humoral immunity are likely involved in the pathogenesis, since T cell and B cell immune responses to certain autoantigens have been demonstrated in TA (4). Furthermore, elevated levels of IL-6 have been demonstrated in TA (5). BAFF and IL-6 play important roles in the survival, differentiation and isotype switching of B cells (6). Therefore, B cell abnormalities may contribute in part to the pathogenesis of TA. The diagnosis of TA is often made late in the disease course, when irreversible damage has already occurred. Symptomatic improvement usually occurs following high-dose corticosteroids and the erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) may be helpful in assessing disease activity and the response to treatment in TA (2). However, analysis of the acute phase reactants is an unreliable indicator, and normal acute phase reactants may mislead the physicians regarding disease activity (7). Additionally, in a review of patients with clinically inactive disease (based on the absence of systemic clinical features and normal ESR), new angiographic changes were detected in 60% suggesting ongoing vascular inflammation (8). Therefore further investigations are necessary to identify additional biomarkers that are reflective of the disease activity of TA. Recent studies have documented quantitative and qualitative alterations in cytokine production in systemic vasculitis (9). In the present study, we focused on BAFF and measured serum BAFF levels in 9 TA patients. We show that circulating levels of BAFF may be helpful in diagnosing TA and could be useful as a disease marker for TA.

Patients and methods

Patients

We investigated a consecutive series of 9 patients with TA (1 male and 8 females, aged 19 to 79 years) referred to the department of Rheumatology of Nagasaki medical center and Nagasaki University Hospital. All patients fulfilled more than 3 of the 1990 American College of Rheumatology criteria for classification of TA (10). None of

Table I. Clinical details of patients with Takayasu arteritis.

Patient	Age (gender)	C-reactive protein (mg/dl)	Vascular Features	Vascular Lesions	Systemic Features	Elevated ESR	Disease* Activity Score	Corticosteroid Therapy	Immuno-suppressive Therapy	Adittional treatments
1	19F	7.62	1	0	1	1	3	No (untreated)	No	Corticosteroid +MTX
2	65F	11.41	1	0	1	1	3	No (untreated)	No	Corticosteroid
3	33F	<0.30	0	1	0	0	1	Yes	No	(-)
4	23F	17.27	1	1	1	1	4	Yes	No	Infliximab
5	27F	4.52	1	1	0	1	3	Yes	MTX	Infliximab
6	25M	2.76	1	1	0	1	3	Yes	MTX, CYC	Infliximab
7	40F	1.65	1	1	0	1	3	Yes	MTX	(-)
8	56F	0.77	1	1	0	1	3	Yes	No	(-)
9	79F	1.78	1	0	1	1	3	No (untreated)	No	Corticosteroid

MTX: methotrexate; CYC: cyclophosphamide; Zero absent: 1, present.
*Disease activity scores were estimated according to the criteria of Kerr *et al*. (8).

them had cranial symptoms, a clinical picture of temporal arthritis or polymyalgia rheumatic. All patients were evaluated by the criteria for disease activity as reported by Kerr *et al*. (8): (1) presence of systemic features such as fever or musculoskeletal problems: (2) elevated ESR; (3) presence of features of vascular ischemia or inflammation; and (4) typical angiographic features.

Enzyme-linked immunosorbent assay for BAFF

The sera were frozen and stored at -20°C until the assays were performed. The concentrations of BAFF were measured with human BAFF/BlyS/TNFSF13B immunoassay kit (R&D Systems, Minneapolis, MN, USA) according to the manufacturer's instruction. The detection limit of serum BAFF is 60pg/ml.

Statistical analysis

Data were expressed as mean ± SD. Differences between groups were analysed by the Mann-Whitney U-test with StatView 5.0 software. A value of $p<0.05$ was considered statistically significant.

Results

We examined the correlation between TA disease activity and levels of BAFF in 9 TA patients (Table I). The TA patients exhibited significantly elevated levels of BAFF compared to controls (Fig. 1). Among the 9 TA patients, 6 were followed for the remainder of the

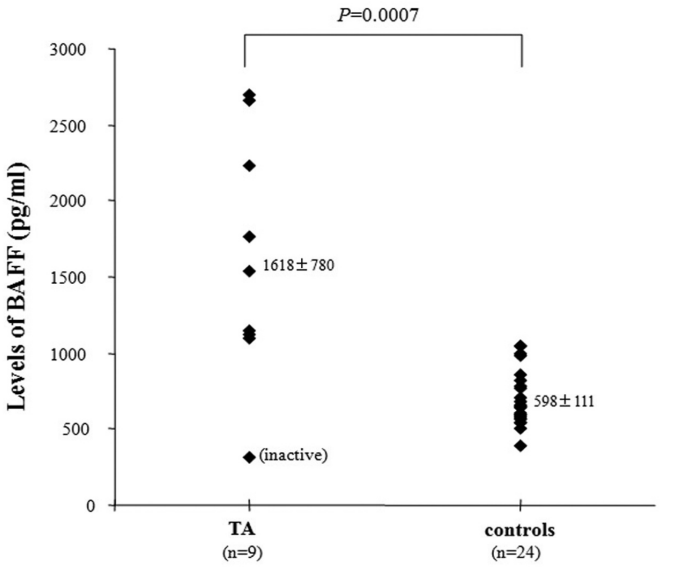

Fig. 1. Serum BAFF levels in patients with active and inactive TA patients and in controls. Each dot represents data of an individual subjects. Serum BAFF levels were significantly elevated in TA patients compared to controls.

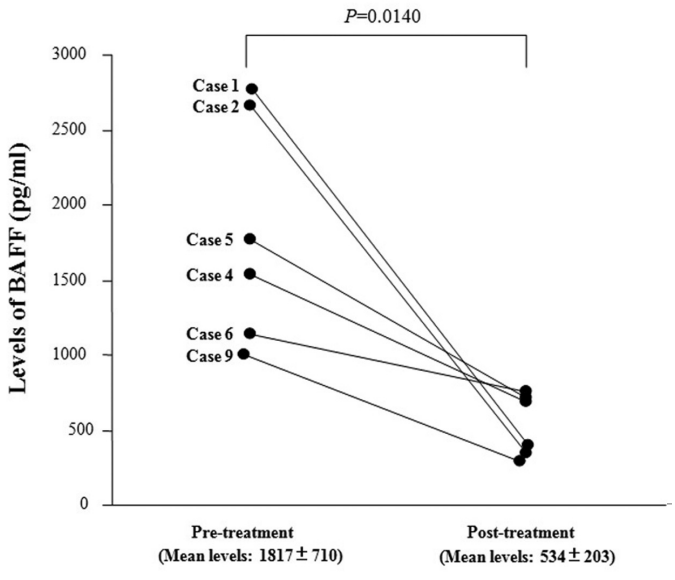

Fig. 2. Serum BAFF concentrations in 6 TA patients studied both during active phase and remitted phase.

study for a mean duration of 6.9±3.4 weeks. Among these 6 TA patients, 3 untreated patients were treated with corticosteroids (patients 1, 2, 9), and the remaining 3 patients were treated with infliximab (3mg/kg) in combination with corticosteroids or immunosuppressive agents (patient 4, 5, 6) after obtaining informed consent from the patients and the approval of the ethics committee of Nagasaki University Hospital. After the initial or any additional treatments, remission was achieved in these 6 patients and paired blood samples were obtained. Serum BAFF levels during remission, post-treatment, were significantly decreased compared with those obtained during the active stage before treatment (Fig. 2).

Discussion

Takayasu arteritis (TA), a rare large vessel vasculitis of unknown etiology, remains a difficult disease to manage and the delay in diagnosis can result in irreversible vascular damage (8). The disease may progress despite treatment with glucocorticoids (11). Therefore, once the diagnosis of TA is made, it is essential to determine the disease activity to select the appropriate therapeutic strategy. In the current study, we demonstrated that serum BAFF levels were elevated in patients with TA. Additionally, longitudinal analysis in 6 TA patients indicated that serum BAFF levels were elevated in the high disease activity stage and were reduced in response to the additional treatments, including TNF-blockers. It remains unclear which mechanisms and cell types contribute to the elevated BAFF levels in TA. BAFF is synthesised constitutively by myeloid cells and its production can be further induced by cytokines (6). It is possible that cytokines or inflammatory cells infiltrating into the aorta trigger the increased production of BAFF in TA. Recent work has shown that non-lymphoid cell types also produce BAFF (12). Neutrophils are known to contain BAFF and to release it upon exposure to inflammatory stimuli (13). Local production of BAFF by neutrophils or non-myeloid cells in inflammatory sites may also contribute to the increased circulating BAFF in TA, by forming a positive feedback loop between BAFF and inflammation. Although gender and the mean age at onset of the disease are discriminatory variables between TA and Behçet's disease (BD), both diseases exhibit large vessel vasculitis. More recently, Hamzaoui *et al*. demonstrated that serum BAFF levels were elevated in active BD patients and correlated with the disease activity of BD (14). Taken together, it is possible that BAFF-mediated inflammatory processes contribute to the development of this large vessel vasculitis. Further studies of a larger patient population and evaluating disease phenotype and activity are warranted to further interpret our hypothesis.

In TA patients who relapse while on corticosteroid monotherapy, a combination of corticosteroids and immunosuppressive drugs is most commonly used. No immunosuppressants that have been used for TA have been evaluated in randomised controlled trials. However, weekly oral methotrexate has been shown to be effective for corticosteroid-resistant TA (15). When discussing the role of combination immunosuppressive therapy in TA, it is also important to evaluate the TA disease activity. ESR may be an unreliable marker of disease activity. While angiography is considered the gold standard, its use should be limited due to its invasive nature. PET-CT is useful in detecting vascular wall inflammation or in the early diagnosis of TA (16). However, it may not provide information regarding advanced complications of TA, such as vascular wall thickening, stenoses, occlusion and aneurysms (16). Therefore, sensitive and specific markers of disease activity are needed to guide medical intervention. The use of biological agents that block the inflammatory cytokines has not been established in TA, since a pathogenic role of cytokines in TA has not been demonstrated. We show that active TA patients exhibit elevated BAFF levels. In particular, BAFF has been shown to be a therapeutic target in systemic lupus erythematosus (SLE) (17). Although the efficacy of B-cell-targeted therapy in TA is not yet known, it is possible that BAFF could be a disease-perpetuating factors and a new candidate therapeutic target in TA.

In conclusion, the most pressing issues in TA are how to measure disease activity and how to safely minimise the use and toxicity of corticosteroids or immunosuppressants. The present study suggests that monitoring of circulating levels of BAFF could be helpful as a marker in diagnosing TA and as an indicator of disease activity. BAFF monitoring might also help provide adequate evaluation of therapeutic decision-making in TA patients.

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