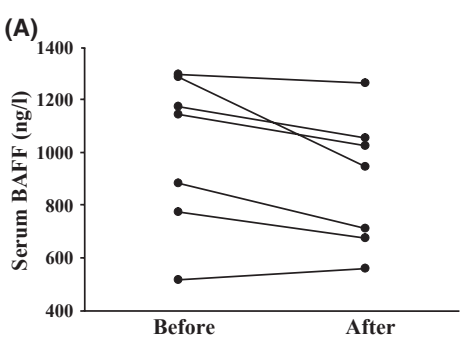
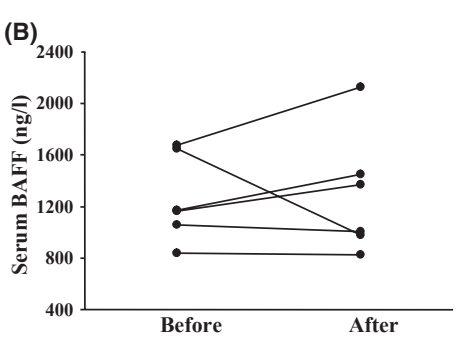
Alteration in serum B cell-activating factor levels in patients with idiopathic thrombocytopenic purpura after *Helicobacter pylori* eradication therapy

Idiopathic thrombocytopenic purpura (ITP) is an autoimmune disease characterized by the production of antiplatelet antibodies secreted by B cells resulting in enhanced destruction of platelets. B cell-activating factor (BAFF) and a proliferation-inducing ligand (APRIL), members of the tumour necrosis factor (TNF) family, are crucial survival factors for peripheral B cells (Mackay *et al*, 2007). Over-expression of BAFF leads to the development of autoimmune disorders in animal models, and high levels of BAFF and APRIL have been detected in the serum of patients with various autoimmune diseases including ITP (Emmerich *et al*, 2007) (Zhu *et al*, 2009a) (Gu *et al*, 2009). A recent study reported that eradication of *Helicobacter pylori* infection could increase the platelet count in some patients with ITP (Stasi *et al*, 2009). However, the precise mechanisms of platelet response remain obscure, and the effect of *H. pylori* eradication on B-cell immune responses in patients with ITP has not yet been elucidated. To investigate the possible relationship between *H. pylori* eradication and platelet and B-cell responses in patients with ITP, the serum levels of BAFF and APRIL were measured before and after *H. pylori* eradication therapy.

Fifteen adult Japanese patients with ITP and *H. pylori* infection were enrolled prospectively. This study was approved by the Institutional Review Board of our hospital; written informed consent was obtained from all participants. ^{13}C-urea breath tests (Otsuka, Tokyo, Japan) were used to diagnose *H. pylori* infection and assess eradication 8 weeks after treatment. The regimen for *H. pylori* eradication entailed twice daily administration of clarithromycin (400 mg), amoxicillin (1500 mg) and lansoprazole (60 mg) for 7 d. The serum BAFF and APRIL levels were measured using a specific enzyme-linked immune assay (R&D Systems, Minneapolis, MN, USA, and IBL International, Hamburg, Germany, respectively) according to the manufacturers' recommendations.



Age,sex	Platelet count Before	After	Response
48 F	36	134	CR
64 F	57	127	CR
70 F	17	211	CR
67 M	76	196	CR
46 F	27	276	CR
17 F	66	198	CR
61 M	33	80	PR



Age,sex	Platelet count Before	After	Response
54 M	18	13	NR
44 F	6	2	NR
37 F	103	106	NR
62 F	10	26	NR
52 F	45	44	NR
61 F	49	29	NR

Fig 1. Serum BAFF levels in platelet responders (A) and non-responders (B) after successful *H. pylori* eradication. The characteristics and outcome of each patient with ITP are shown. The platelet counts ($\times 10^9$/l) and serum BAFF levels before and 4 months after eradication are shown. CR, complete response; PR, partial response; NR, no response.

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H. pylori eradication was achieved in 13 (87%) of the 15 patients. Four months after the treatment, an increase in the platelet count was noted in seven successfully treated patients (platelet responders): six patients responded completely, showing an increase in the platelet count to more than 120×10^9/l; one showed a partial response with an increase to more than 20×10^9/l from the pre-treatment platelet count. The average serum BAFF level in these patients significantly decreased after the treatment (1001 ± 294 ng/l and 880 ± 250 ng/l before and after the treatment respectively; $P < 0{\cdot}05$ by Wilcoxon signed-rank test; Fig 1A). There was no significant correlation between altered platelet counts and serum BAFF levels in these patients. On the other hand, the average serum APRIL level did not alter after the therapy (3·96 ± 2·1 μg/l and 4·77 ± 2·9 μg/l before and after the treatment respectively; data not shown). Platelet recovery was not observed in the remaining six successfully treated patients (non-responders). These patients showed no significant change in their serum BAFF and APRIL levels after the treatment (BAFF: 1261 ± 334 ng/l and 1291 ± 476 ng/l before and after the treatment respectively; Fig 1B; APRIL: 5·41 ± 3·2 μg/l and 5·83 ± 2·3 μg/l before and after the treatment respectively; data not shown). Thus, the serum BAFF level significantly decreased only in the platelet responders. These findings suggest that BAFF but not APRIL may be involved in the pathogenesis of ITP associated with *H. pylori* infection.

Previous studies reported that serum BAFF levels were increased in patients with active ITP compared with those in healthy controls (Emmerich *et al*, 2007) (Zhu *et al*, 2009a). Prednisolone and high-dose dexamethasone therapy reportedly inhibits BAFF expression in patients with active ITP (Emmerich *et al*, 2007) (Zhu *et al*, 2009b). Clearly, such steroid treatment suppresses the expression of inflammatory cytokines and lymphocytes. As expected, BAFF expression was inhibited. Interestingly, our observation showed that *H. pylori* eradication modestly, but significantly, inhibited serum BAFF levels in the responding patients with ITP. Therefore, *H. pylori* infection might induce the B cell-mediated autoimmune pathogenesis of ITP. Although there is no established mechanism to explain how *H. pylori* could be implicated in the pathogenesis of immune-mediated platelet destruction, several hypotheses have been proposed regarding the platelet response to *H. pylori* eradication therapy, including molecular mimicry, platelet aggregation, and the Th1 phenotype favouring the onset and/or persistence of ITP (Stasi & Provan, 2008). As a member of the TNF superfamily, BAFF not only regulates B-cell immunity, including the survival and maturation of B cells, but also stimulates T cells by delivering co-stimulation to T-cell receptor-dependent signals. It is unclear whether increased levels of BAFF are the primary cause of autoimmunity or whether autoimmunity is the result of increased production of pro-inflammatory cytokines, such as type I interferons. To our knowledge, this is the first report regarding serum BAFF levels in patients with ITP treated for *H. pylori* infection. Our results suggest the involvement of *H. pylori* infection in the process of antiplatelet autoantibody production via BAFF production and/or stimulation. Further studies are required to clarify the exact mechanism by which *H. pylori* eradication affects serum BAFF levels in patients with ITP.

Conflicts of interest

All authors have no conflicts of interest to declare.

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