



Letter

Detection of IgE binding component to infliximab in a patient with infliximab-induced anaphylaxis

Infliximab is an inhibitor of tumor necrosis factor α (TNF- α) widely prescribed to patients with various chronic inflammatory diseases. Common adverse reactions to infliximab include upper respiratory tract infections, headache, and nausea. Immediate hypersensitivity reactions are less frequent and generally mild.¹ However, we encountered a case of anaphylaxis after administration of infliximab (Remicade; Janssen Biotech, Inc, Horsham, Pennsylvania) for the treatment of ankylosing spondylitis (AS).

A 28-year-old man visited our allergy clinic with a history of anaphylaxis to infliximab. He was diagnosed as having AS 11 years ago and treated with infliximab (400 mg) every 8 weeks for 44 months. His AS symptoms were well controlled after treatment with infliximab, and no adverse reactions were noted until the 26th injection of infliximab. However, he had a temperature of 38°C without other complications during the 27th and 28th administrations of infliximab even though acetaminophen and diphenhydramine were premedicated 90 minutes before infliximab administration. On the 29th course of treatment, he developed urticaria 30 minutes after starting the infusion of infliximab (50 mg) and subsequently experienced chest discomfort and dyspnea. On physical examination, wheezing was noted from both lung fields, and he was noticeably tachypneic. However, his blood pressure, heart rate, and oxygen saturation were normal. The symptoms disappeared after stopping infusion and initiating treatment with antihistamine and steroids. Laboratory studies indicated an elevated serum total IgE level of 688 kU/L compared with a previous sample of 178 kU/L collected 2 years ago. The patient's was diagnosed 12 years ago as having a history of bronchial asthma, allergic rhinitis, and food allergy to shrimp. After 5 years of allergen immunotherapy to house dust mites and weed pollens, his allergic diseases have been in remission without medication. A methacholine challenge test performed 2 months after the event produced a negative result. He had no history of a drug allergy.

We investigated immunologic studies to understand the pathogenic mechanism. A skin prick test (SPT) and intradermal test (IDT) with the infliximab solution (0.001, 0.01, 0.1, 1, and 10 mg/mL) produced negative results. To detect circulating serum specific IgE to infliximab, enzyme-linked immunosorbent assay (ELISA) was performed using anti-IgE antibody as a second antibody and infliximab as a solid phase in serum samples from the patient and negative controls, which resulted in a negative response; in addition, a basophil activation test (BAT) using the patient's basophils with serial additions of infliximab produced negative results. However, IgE immunoblot analysis using the patient's serum revealed a remarkable band of 149 kDa not observed in the 2 controls (Fig 1). As an alternative medication, adalimumab was

prescribed, and the patient's symptoms were controlled without any adverse reactions.

To the best of our knowledge, this is the first report to demonstrate the IgE-binding component of infliximab using an IgE immunoblot analysis in a patient with infliximab-induced anaphylaxis. Infliximab is a chimeric antibody with a molecular weight of 149.1 kDa that consists of a human constant region of IgG1 coupled to the variable regions of mouse anti-TNF- α and is approved for the treatment of a variety of inflammatory conditions, such as rheumatoid arthritis and AS.¹ The patient was treated with infliximab for AS for 44 months. During that time, the patient was sensitized, and a severe immediate reaction developed at the 29th infusion. The incidence of infusion-related reactions by infliximab is approximately 5%; however, severe hypersensitivity reaction (such as anaphylaxis) is rarely reported.^{1,2} The incidence of an acute systemic reaction that includes a hypersensitivity reaction is known to be higher in patients treated with infliximab than in those treated with other kinds of monoclonal antibody to TNF- α ,^{2,3} such as etanercept or adalimumab. Atopic status is not related to hypersensitivity reactions.⁴ Most severe hypersensitivity reactions develop by the 10th infusion^{4–7} and are associated with a distant reinfusion interval.⁸ In the present study, the patient had atopy and developed anaphylaxis at the 29th infusion.

Regarding the pathogenic mechanisms of monoclonal antibody infusion-related anaphylaxis, several mechanisms are suggested, such as IgE- and non-IgE-mediated hypersensitivity reactions and cytokine release syndrome.^{2,3,6} Previous studies have found that all patients with immediate hypersensitivity reactions to infliximab had negative responses on SPT to infliximab up to higher dose; however, a few cases had positive results on IDT and/or displayed anti-infliximab antibodies.^{5,6} This finding suggests that SPT with infliximab solution could not predict hypersensitivity reactions.^{5–7} In this study, we performed SPT, IDT, ELISA, and BAT, but none of them produced a positive result. However, we identified the IgE-binding component (149 kDa), which is equivalent to its molecular weight using IgE immunoblot analysis, and suggested that the patient's anaphylaxis symptoms may be mediated by a specific IgE antibody. The level of serum specific antibodies to infliximab decreased rapidly in patients with hypersensitivity reactions to infliximab,⁶ which is the reason ELISA and BAT produced negative results in this study because both tests were performed 2 months after the anaphylaxis reaction. Further studies are required to perform SPT, ELISA, and BAT with a different time schedule in a larger cohort of anaphylaxis patients.

The accelerated development of modern molecular biology techniques and medical needs has increased the use of biologic drugs; subsequently, severe hypersensitivity reactions to monoclonal antibodies (including infliximab) may increase. The exact pathogenic and

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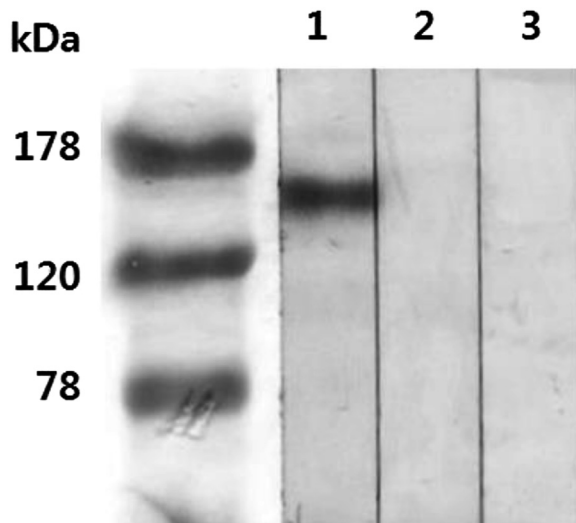


Figure 1. The result of IgE immunoblotting using serum samples from the patient (No. 1) and 2 controls (Nos. 2 and 3).

immunologic mechanisms remain unclear, and further studies are required to define the pathogenic mechanisms of potential risk factors and establish diagnostic tests to predict anaphylaxis.

In conclusion, we report a case of infliximab-induced anaphylaxis with the identification of an IgE-binding component where the IgE-mediated response was suggested as a pathogenic mechanism.

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