Autoimmune Angioneurotic Edema in a Patient with *Helicobacter pylori* Infection

Didier Mukeba, Kavitha Chandrikakumari, Jean-Baptiste Giot, Philippe Leonard, Christelle Meuris, Frederic Frippiat and Michel Moutschen

Department of Internal Medicine and Infectious Diseases, Centre Hospitalier Universitaire, Liege, Belgium

Keywords
Acquired autoimmune angioneurotic edema, *Helicobacter pylori*, autoimmune diseases, C1-esterase inhibitor.

Reprint requests to: Kavitha Chandrikakumari, Department of Internal Medicine and Infectious Diseases, Centre Hospitalier Universitaire, Liege, Belgium. E-mail: drchandrika@gmail.com

Abstract

Association of acquired autoimmune angioneurotic edema with other diseases is increasing. However, the precise mechanism by which antibodies to C1-esterase inhibitor (C1-INH) are produced, is not elucidated. We describe a patient with IgA antibodies against C1-INH without other autoimmune markers. Our patient had gastritis and *Helicobacter pylori* infection, proven by biopsy. This case suggests that *H. pylori* infection can act as triggering factor for acquired autoimmune angioneurotic edema.

Helicobacter pylori is known to cause gastroduodenal disorders. Emerging evidence implicates this bacteria in the development of autoimmune disorders such rheumatoid arthritis, Sjögrens syndrome, and idiopathic thrombocytopenic purpura. Although several mechanisms are elucidated, the precise process of initiating autoimmunity is not known. We describe a patient having autoimmune acquired angioneurotic edema in association with *H. pylori* infection.

In March 2004, a 52-year-old Caucasian man was admitted to our institution with severe abdominal pain and swelling involving the lips and eyelids. As per his wife's description he had temporary loss of consciousness and passed urine involuntarily. He did not have nausea, vomiting, or other systemic complaints. He had a history of myocardial infarction at the age of 37 years and was under regular follow up and treatment. He had several episodes of spontaneously resolving, mild swelling of eyelids, and lips since the age of 43 years. During these years he also had dyspepsia and aerophagia, for which he took symptomatic treatment. Physical examination showed angioedema of face, predominantly involving eyelids and lips. Diffuse abdominal tenderness and guarding was elicited. Other systemic examination appeared normal. His ECG and cardiac markers on blood examination were negative. To control his symptoms rapidly, methylprednisolone 375 mg was given intravenously. Abdominal CT scan showed gastric mucosal edema and mild ascites. Consequently, emergency exploratory laparoscopy was performed which revealed minimal ascites without any other abdominal pathology. Ascitic fluid cytology and culture were negative. Blood examination was normal; however, C1-esterase inhibitor activity was not measured. Favorable evolution of symptoms leads to his discharge the next day. Two weeks later, the patient re-presented with similar symptoms. Blood examination specifically for acquired angioedema revealed a low C4 levels (< 0.01 g/L; normal values: 0.10–0.41); decreased C1 esterase inhibitor activity (< 12.5%; normal values: 70–130), and CH50 activity (< 12.5%; normal values: 75–100). The patient was treated with 1500 U of C1-esterase inhibitor concentrate and fresh frozen plasma intravenously. Due to the aggravation of his dyspeptic symptoms, a gastroscopy was performed. The biopsy specimen showed infection with *H. pylori*, chronic duodenitis, and chronic gastritis with metaplasia involving the gastric antrum and fundus. Elevated serum IgA antibody against *H. pylori* was observed using the complement fixation test by Institute Virion which has a sensitivity and specificity 74.4% and 77.6%, respectively. Our patient was instituted with *H. pylori* eradication therapy comprising amoxycillin (1 g twice daily), clarithromycin (500 mg twice daily), and lansoprazole (30 mg twice daily) for 10 days.

For confirmation of the diagnosis of C1-INH deficiency, a sample was sent to Milan which showed IgA autoantibodies against C1-INH, with a normal concentration of the C1-INH protein. The patient was started on Danatrol 200 mg per day as prophylaxis. But he continued to have episodes of angioneurotic edema, following which the dose of Danatrol was increased to 200 mg three times per day. The dose of Danatrol was tapered over time and presently, our patient is doing well without further symptoms.

Discussion

Defective C1-INH function predisposes to episodes of self-limited, increased vascular permeability (angioedema) that is restricted to three specific sites, which include subcutaneous space, the gut, and the upper airway [1]. Acquired form of C1-INH deficiency was first identified and described by Caldwell et al. in 1972 and came to be known as acquired angioneurotic edema (AAE) [2]. Several authors have contributed to the description of AAE in the context of other disorders most commonly lymphoproliferative diseases (also cryoglobulinemia, adenocarcinoma, SLE, autoimmune hemolytic anemia, planar xanthomatosis, myelofibrosis, ovarian teratoma, recurrent panniculitis, and liver hydatidosis). Besides, this syndrome is recognizable in otherwise healthy subjects [3].

Autoimmune C1-INH deficiency was observed in the year 1986, in a patient without lymphoproliferation and whose serum contained autoantibody to C1-INH. Characteristic features of this syndrome included oligoclonal or monoclonal autoantibodies; low serum levels of C1q, C4, and C2; normal serum levels of C3; and normal or reduced serum levels of C1-INH protein, which is functionally inactive [4]. Therefore, two mechanisms of acquired defect of C1-INH are autoantibodies against this protein and an associated diseases causing increase catabolism [1]. Furthermore, it was observed that in autoimmune AAE, the autoantibody does not prevent the cleavage of C1-INH by the target proteases, but blocks its activity. The native C1-INH is depleted and the cleaved inactive form accumulates in plasma, resulting in higher levels of C1-INH antigen than C1-INH function [2].

In a study comprising 13 patients with nonhereditary angioedema, the relationship between presence of autoantibodies to C1-INH to the cleaved form of C1-INH and to paraproteins were evaluated. The authors suggested that autoantibodies destabilize the C1-INH-protease complex or enhance susceptibility of C1-INH to the cleavages by proteases which do not form stable complexes. It was demonstrated that circulating autoantibodies facilitate the accumulation of cleaved C1-INH in plasma and the contact system activation participates in this phenomenon [3]. Circulating autoantibodies were observed in all but one patient having chronic lymphocytic leukemia. Consequently, they mentioned the need to reconsider all patients so far described having AAE secondary to another disease may have autoantibodies induced AAE [3].

The etiology of AAE remains controversial and elusive. The triggering factor for the production of autoantibodies is not explained clearly. In this context, it was noticed that *H. pylori* infection acts as a triggering factor of attacks in patients with hereditary angioedema [5]. Moreover, several reports have suggested the association of *H. pylori* infection with various skin disorder which were previously considered as autoimmune disease [6,7].

In addition to gastroduodenal disorders, *H. pylori* is implicated in various autoimmune diseases such rheumatoid arthritis, Sjögrens syndrome, and idiopathic thrombocytopenic purpura. Although the precise mechanism by which *H. pylori* infection generates autoimmune disorders remains to be elucidated, the production of rheumatoid factors (RF) seems to be a key event in initiating autoimmunity. The authors demonstrated the active production of various B1-cell-associated autoreactive antibodies such as IgM-type RF, antisingle-stranded DNA (ssDNA) antibody, and antiphosphatidyl choline antibody as well as IgG3 in the culture supernatant of splenic B cells stimulated with purified *H. pylori* urease in vitro. B1 cells are thought to be the primary source of natural IgM antibodies, which are usually polyreactive and autoreactive against bacterial polysaccharide, lipids, and proteins as well as autoantigens such as ssDNA and IgG-like RFs. These self-antigens reactive antibodies may bind to their own components initiate an inflammatory response and contribute to the pathogenesis of various autoimmune disorders. Hence, normally the eradication of the organism should reduce the incidence of the disease [8].

Interestingly, besides the presence of antibodies against C1-INH, no autoimmune abnormalities namely antinuclear antibodies, RF, cryoglobulins, or antithyroid antibodies were noticed in our patient. We therefore suggest that *H. pylori* could be responsible for formation of anti-C1-INH antibodies and worsening angioedema. A case report from Germany on AAE (in the year 1999) suggested that excessive consumption of complement by antibodies directed against *H. pylori* is a potential cause of C1-INH deficiency [9]. With exception to this report, *H. pylori* as the probable cause of AAE was never considered before. Additionally, we postulate that autoantibodies directed against C1-INH could play a role in the attacks observed in the patients with the genetic form of the disease and with residual levels of protein and also in some cases of idiopathic urticaria where C1-INH function has never been investigated so far.

Conclusion

Accumulating evidence suggest the role of *H. pylori* in the evolvement of autoimmune diseases. Considering the higher incidence of infection with this bacteria and rarity of autoimmune diseases, genetic susceptibility should be considered as an important triggering factor.

Authors would like to thank Professor Marco Cicardi, University of Milan, Italy, for reviewing our article and providing his valuable suggestions.

References

1 Pappalardo E, Zingale LC, Terlizzi A, Zanichelli A, Folcioni A, Cicardi M. Mechanisms of C1-inhibitor deficiency. *Immunobiology* 2002;205:542–51.

2 Cicardi M, Bisiani G, Cugno M, Spath P, Agostoni A. Autoimmune C1 inhibitor deficiency: report of eight patients. *Am J Med* 1993;95:169–75.

3 Cicardi M, Beretta A, Colombo M, Gioffre D, Cugno M, Agostoni A. Relevance of lymphoproliferative disorders and of anti-C1 inhibitor autoantibodies in acquired angio-oedema. *Clin Exp Immunol* 1996;106:475–80.

4 Ponce IM, Caballero T, Reche M, et al. Polyclonal autoantibodies against C1 inhibitor in a case of acquired angioedema. *Ann Allergy Asthma Immunol* 2002;88:632–7.

5 Visy B, Fust G, Bygum A, et al. *Helicobacter pylori* infection as a triggering factor of attacks in patients with hereditary angioedema. *Helicobacter* 2007;12:251–7.

6 Wedi B, Kapp A. *Helicobacter pylori* infection and skin diseases. *J Physiol Pharmacol* 1999;50:753–76.

7 Wedi B, Kapp A. *Helicobacter pylori* infection in skin diseases: a critical appraisal. *Am J Clin Dermatol* 2002;3:273–82.

8 Yamanishi S, Iizumi T, Watanabe E, et al. Implications for induction of autoimmunity via activation of B-1 cells by *Helicobacter pylori* urease. *Infect Immun* 2006;74:248–56.

9 Farkas H, Gyeney L, Majthenyi P, Fust G, Varga L. Angioedema due to acquired C1-esterase inhibitor deficiency in a patient with *Helicobacter pylori* infection. *Z Gastroenterol* 1999;37:513–8.