Bilateral Parotidomegaly Following Anaphylaxis to Infliximab

To the Editor:

We present the case of a 56-year-old man who developed bilateral parotidomegaly after an infusion of infliximab that was complicated by anaphylaxis. He has a history of ileocolonic Crohn's disease for 26 years, with a number of past small bowel resections and a total colectomy resulting in an end ileostomy. He initially presented with abdominal pain and diarrhea, with inflammation of the neoterminal ileum shown on a computed tomography (CT) scan. He had a good response to a dose of 5 mg/kg infliximab given with intravenous hydrocortisone 100 mg and promethazine 12.5 mg as premedication.

On the second dose of infliximab given 2 weeks later as part of an induction regimen he developed acute lower back pain during the infusion and was given oral acetaminophen. Within minutes he developed a sensation of breathlessness, throat tightness, and flushing with pruritis. Wheeze was noted on auscultation. Blood pressure, heart rate, respiratory rate, and oxygen saturations were normal. There was no stridor, urticaria, or tongue or facial angioedema. The infusion was stopped and he was treated with further intravenous hydrocortisone and promethazine. He was not given adrenaline, and a serum tryptase was not requested. The patient's symptoms improved and he was discharged home several hours later.

Upon arriving home the patient noted the development of nonpainful bilateral swellings in the parotid areas. There were no associated sicca symptoms or fever. He did not notify his physician until reviewed 2 weeks later, at which stage he was noted to have bilateral parotid swellings measuring 4 × 8 cm, without associated lymphadenopathy. A CT scan of the neck and thorax confirmed these swellings and ruled out sialectasis or lymphadenopathy. Mumps IgG was positive and IgM negative, consistent with past infection. Antinuclear antibodies and antibodies to extractable nuclear antigens were also negative. The parotid swellings resolved spontaneously over a period of 6 weeks.

An immunologist reviewed the patient and considered the initial infusion reaction to be consistent with anaphylaxis. Acetaminophen allergy was ruled out by a graded oral challenge. Skin prick testing to neat infliximab was negative; however, this does not rule out an IgE-mediated reaction, as anaphylaxis to a metabolite of infliximab (broken down in the reticuloendothelial system) would not cause a local skin reaction. In addition, skin prick testing for infliximab has not been validated for anaphylaxis. As such, the patient was changed to subcutaneous adalimumab, a fully humanized antibody to tumor necrosis factor alpha, as opposed to infliximab, which is a chimeric murine/human antibody.[1] The adalimumab was well tolerated and resulted in clinical remission.

The diagnosis of anaphylaxis may be not straightforward, and this case illustrates the challenges with managing infusion reactions to monoclonal antibodies. Infusion reactions occur in 6%–19% of patients treated with infliximab,[2,3] and severe reactions occur in ≈1%.[3] The majority of reactions are felt to be related to activation of cells by Fc-IgG receptors, or activation of the complement system via immune complexes.[4] Nonetheless, anaphylaxis can occur secondary to infliximab administration. The World Allergy Organization defines anaphylaxis as "a severe, life-threatening generalized or systemic hypersensitivity reaction." This might be subclassified as *allergic* (e.g., mediated by IgE, IgG, or immune complexes) or *nonallergic*. Allergic anaphylaxis mediated by IgE antibodies is referred to as *IgE-mediated anaphylaxis*.[5] It is worth

Anaphylaxis is highly likely when any one of the following 3 criteria are fulfilled

1. Acute onset of an illness (minutes to several hours) with involvement of the skin, mucosal tissue, or both (e.g., generalized hives, pruritus or flushing, swollen lips / tongue / uvula) *and at least one of the following:*
   a. Respiratory compromise (e.g., dyspnea, wheeze / bronchospasm, stridor, reduced PEF, hypoxemia)
   b. Reduced BP or associated symptoms of end-organ dysfunction (e.g., hypotonia [collapse], syncope, incontinence)

2. Two or more of the following that occur rapidly after exposure *to a likely allergen for that patient* (minutes to several hours):
   a. Involvement of the skin-mucosal tissue (e.g., generalized hives, itch / flush, swollen lips / tongue / uvula)
   b. Respiratory compromise (e.g., dyspnea, wheeze / bronchospasm, stridor, reduced PEF, hypoxemia)
   c. Reduced BP or associated symptoms (e.g., hypotonia [collapse], syncope, incontinence)
   d. Persistent gastrointestinal symptoms (e.g., crampy abdominal pain, vomiting)

3. Reduced BP after exposure to *known allergen for that patient* (minutes to several hours):
   b. Adults: systolic BP of less than 90 mm Hg or greater than 30% decrease from that person's baseline

PEF, Peak expiratory flow; BP, blood pressure.

FIGURE 1. Clinical criteria for diagnosing anaphylaxis.[6]

DOI 10.1002/ibd.20801
Published online 9 December 2008 in Wiley InterScience (www.interscience.wiley.com).

noting that anaphylaxis does not have to be IgE-mediated. A recent symposium has attempted to create a consensus definition as to which symptoms qualify as anaphylaxis; their findings are summarized in Figure 1.[6]

The diagnosis of anaphylaxis is important, as fatalities can occur.[7] Anaphylaxis to infliximab is not ruled out by a negative skin prick test, or by a negative serum tryptase level, as the sensitivity of this test for anaphylaxis is low. Serum IgE levels to infliximab are experimental and as such not validated. Intramuscular adrenaline should be given if anaphylaxis is suspected, as it has been shown to reduce mortality secondary to anaphylaxis.[7] In this case, the bilateral parotidomegaly may have represented an unusual reaction to infliximab, or alternatively may have represented a viral illness that lowered the patient's threshold to developing anaphylaxis to infliximab, known as *summation anaphylaxis*.[8] Anaphylaxis should be considered in all severe infusion reactions, and involvement of a clinical immunologist or allergologist may be prudent. If desensitization is to be attempted, it should be in a center with appropriate expertise and supervision.

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