

Table 1

Summary of reported literature for use of omalizumab in mast cell activation disorders

Study	Study subjects	Outcome	Duration of omalizumab (mo)	Omalizumab dose
Carter et al, 2007 ⁵	2 patients with SM and refractory anaphylaxis	no further episodes of anaphylaxis after starting omalizumab	24	300 mg SC every 4 wk
Douglass et al, 2010 ⁶	1 patient with SM and refractory anaphylaxis	no further episodes of anaphylaxis after starting omalizumab	14	150 mg SC every 2 wk for 1 mo, then every 4 wk
Kontou-Fili et al, 2010 ⁷	1 patient with ISM and recurrent anaphylaxis	no further episodes of anaphylaxis (unprovoked or due to hymenoptera stings)	30	300 mg SC every 4 wk
Bell et al, 2012 ⁸	1 patient with MCAS and recurrent anaphylaxis	rapid improvement with 1 episode of urticaria and shortness of breath after starting omalizumab	10	150 mg SC every 4 wk

Abbreviations: ISM, indolent systemic mastocytosis; MCAS, mast cell activation syndrome; SC, subcutaneously; SM, systemic mastocytosis.

showed spindled morphology and rare mast cells showed weak immunohistochemical staining with anti-CD25. Cytogenetic analysis showed the presence of Asp816Val *c-KIT* mutation, confirming the diagnosis of MMAS.

The patient was taking 20 mg/d of cetirizine at the time of presentation; and 150 mg of ranitidine twice daily, 10 mg/d of montelukast, and 200 mg of sodium cromoglycate 3 times daily were added at the initial visit. Ketotifen 4 mg twice daily was added (by up-titration) 2 months later after another systemic reaction requiring epinephrine. Desloratadine 5 mg/d was added 1 month later after another systemic reaction requiring epinephrine. Hydroxychloroquine 200 mg/d and a tapering course of prednisone were added 2 months later after 3 or 4 reactions requiring epinephrine treatment. Despite adherence to maximal medical therapy, the patient had 3 further systemic reactions over the next 4 months, all requiring treatment with epinephrine.

At this point, the patient had experienced more than 15 reactions, with most requiring epinephrine and emergency department treatment. After informed consent, omalizumab treatment was started at an empiric dose of 300 mg subcutaneously every 4 weeks (total IgE 68 IU/mL) and hydroxychloroquine was discontinued. Omalizumab has been continued for 11 months and has not been associated with adverse effects. Thus far, the patient has had 1 reaction requiring treatment with epinephrine and 2 milder reactions not requiring epinephrine. Ketotifen has been tapered to 3 mg 2 times daily and montelukast has been discontinued.

Omalizumab is a humanized murine monoclonal antibody that complexes with free IgE in serum, preventing IgE from binding to FcεR1 on mast cells and basophils and resulting in downregulation of FcεR1. There are 4 case reports of 5 patients on the use of omalizumab in the spectrum of mast cell activation disorders (Table 1).^{5–8} Although there are 2 previously reported cases of omalizumab therapy in patients with MMAS, these patients were not diagnosed according to the consensus World Health Organization criteria,³ which makes it difficult to interpret the outcomes.⁹ In idiopathic mast cell activation disorders, mast cell degranulation is not primarily driven by allergen specific IgE, so the mechanism by which omalizumab modulates mast cell activation is not clear. Baseline serum tryptase and urinary N-methylhistamine excretion have shown decreases with omalizumab therapy in some^{6,7} but not all cases.⁸ For this reason, it is believed that omalizumab may interfere with the release of mast cell mediators.^{9,10}

Monoclonal mast cell activation syndrome can be associated with recurrent, unprovoked anaphylaxis despite maximal treatment.

In this case, the addition of omalizumab to standard therapy was effective in markedly decreasing the frequency of life-threatening anaphylactic reactions, with no adverse effects to date. Additional study is required to determine the mechanism underlying this clinical observation. This is the third reported case of omalizumab use in MMAS and suggests that omalizumab may be an effective adjunct to therapy in patients with MMAS and life-threatening reactions refractory to maximal medical therapy.

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A case of transient acquired C1 inhibitor deficiency



C1 inhibitor is a serpin that regulates both complement and contact (kallikrein-kinin) system activation. Acquired C1 inhibitor

deficiency (ACID) is a rare condition that has been associated with a number of malignant tumors. Most ACID has been reported in B-cell lymphoproliferative disorders¹ and is usually associated with increased catabolism of C1 inhibitor.² Some of these patients

express anti-idiotypic antibodies directed at the monoclonal antibodies produced by these tumors.³ Consumption of complement is also associated with monoclonal IgM gammopathy.⁴

ACID has been associated with a number of autoimmune diseases, including lupus, Sjögren syndrome, and vasculitis.^{5–7} This is presumably a result of production of autoantibodies to C1 inhibitor, resulting in steric hindrance of binding to C1s.

ACID with immunodeficiency associated with lymphoproliferative and autoimmune features has recently been reported,⁸ although the mechanism of induction of ACID is unclear. Transient acquired C1 inhibitor deficiency is an entity that is less well recognized. This has been associated with human immunodeficiency virus in one patient⁹ and parvovirus B17 infections in another case series.¹⁰ In the latter case, this may be the result of the primary infection or a lupuslike syndrome induced by this virus.

Our patient is a 55-year-old white woman who in summer 2013 was treated for Lyme disease that was documented by a positive enzyme-linked immunosorbent assay result with multiple band IgM and IgG reactivity on Western blot. Doxycycline was prescribed.

In fall 2013, she was admitted with a seizure associated with marked transglutaminase elevation that was ascribed to alcohol-induced hepatitis and was discharged after 3 days. One month later she presented to her primary physician with massive angioedema of the right forearm. While undergoing Doppler ultrasonography of her arm, she became hypotensive and was admitted to the hospital. She had a history of nausea, diarrhea, and abdominal pain for 3 to 4 days preceding her hospital admission, which was thought to be due to viral gastroenteritis. She also had a recent history of an erythematous, patchy rash on her right flank. She had no previous history of angioedema or abdominal pain before this. She had been taking lisinopril and amlodipine besylate daily for hypertension for years. Physical examination findings were remarkable only for right forearm edema with induration of the skin noted up to the elbow. On skin examination she had multiple faint, erythematous, macular, nonblanching patchy lesions noted on the right side of her abdomen, right flank, and right side of the groin. She was noted to be mildly diffusely tender to palpation on abdominal examination, but her abdomen was soft, and no guarding or rebound was appreciated.

The results of imaging of the right upper extremity by Doppler ultrasonography and computed tomography of the chest and abdomen were negative, other than soft tissue swelling being present. Significant laboratory results are given in Table 1. She had a decreased C1 inhibitor level, C4 level, and activated partial thromboplastin time. Laboratory tests revealed the following: C-reactive protein, 2.29 mg/dL; elevated D-dimer level; elevated Lyme antibody titers, with both IgG and IgM reactivity on Western blot;

lipase, 790 U/L; alanine aminotransferase, 91 U/L; and aspartate aminotransferase, 68 U/L. She had a normal C3 level of 108 mg/dL and negative antinuclear antibody and antineutrophil cytoplasmic antibody results. The mild elevation of rheumatoid factor was not believed to be clinically significant.

The angioedema was believed to be due to the lisinopril, so lisinopril treatment was discontinued. She was prescribed aggressive intravenous fluids, methylprednisolone, piperacillin, diphenhydramine, and famotidine. Her symptoms improved, and she was discharged and referred for follow-up with the infectious disease specialist and allergist. During a 5-month period, no further angioedema episodes were documented. Subsequent laboratory tests indicated normal results on C1 inhibitor measurement, immunofixation, free κ/λ ratio, human immunodeficiency virus screen, and C4 and C1q measurement. Liver enzyme, D-dimer, and C-reactive protein levels had normalized. The parvovirus B19 IgG level was elevated at 6.68 g/L, with a negative IgM test result.

The pathogenesis of this syndrome is unknown. It is tempting to speculate that this may be related to a brisk IgM response to a pathogen, possibly *Borrelia burgdorferi* (in antigen excess), with associated complement fixation and consumption of C1 inhibitor. If this were the case, however, one might expect this to be a more common event. Treatment with an angiotensin receptor blocker in our patient may have contributed to this syndrome. Although we cannot exclude that the abnormal levels may be an in vitro artifact, we believe this is unlikely because the patient had marked activation of the coagulation pathway as evidenced by the increased D-dimer level and decreased activated partial thromboplastin time. This syndrome may be misdiagnosed as anaphylaxis and missed completely because of its transient nature. This report is intended to be provocative and to stimulate research on the mechanisms of transient ACID.

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Table 1
Initial and follow-up laboratory test results

Component	10/17/2013	11/22/2013	1/20/2014
Functional C1 inhibitor (reference range, >40%)	30	77	
C1 inhibitor (reference range, 21–39 mg/mL)			35
C4 (reference range, 10–40 mg/mL)	7	79	26
C1q (reference range, 5–8.6 mg/mL)		7.3	
D-dimer (reference range, <0.6 mg/L)	10.1	0.47	
aPTT (reference range, 24.4–32.1 s)	22.3		
<i>Borrelia burgdorferi</i> antibody (reference range, 0–1.20)	3.86		
<i>B. burgdorferi</i> Western blot positive	IgM, IgG		IgG
Rheumatoid factor (reference range, <14 IU/mL)			50

Abbreviation: aPTT, activated partial thromboplastin time.
Abnormal values are noted in bold.

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