

The first case of methemoglobinemia associated with omalizumab



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Clinical Implications

- Omalizumab, the mAb targeting IgE, is a highly effective management option for refractory chronic spontaneous urticaria. We describe the first case of omalizumab-associated methemoglobinemia. Clinicians should be aware of this potentially fatal condition and its management.

TO THE EDITOR:

Omalizumab is a recombinant, humanized mAb that targets IgE, reducing its binding capacity to mast cells and basophils.¹ It is a management option for chronic spontaneous urticaria.² Methemoglobinemia is an uncommon but potentially fatal condition. We describe the first reported case of omalizumab-associated methemoglobinemia.

A 50-year-old woman with treatment-refractory chronic spontaneous urticaria presented for an omalizumab graded challenge.

Our patient had suffered from symptomatic urticaria for 3 years despite daily cetirizine 40 mg, ranitidine 300 mg, montelukast 10 mg, dapsone 50 mg, and systemic steroid bursts. She was otherwise healthy and taking no other medications, with no significant family history. Glucose-6-phosphate dehydrogenase levels were normal before starting dapsone.

She had previously received omalizumab 150 mg monthly for 9 months, while on the aforementioned medications, with an excellent response. However, omalizumab was discontinued once light-headedness developed after 2 consecutive doses. This occurred 8 hours after each dose and had resolved before she sought medical review (12 hours duration). Consequently, the omalizumab was discontinued. Her urticaria eventually recurred and a poor quality of life prompted an omalizumab graded challenge, scheduled over 3 days (day 1, 50 mg; day 2, 100 mg; day 3, 150 mg).

The initial dose was well tolerated with no adverse effects. Approximately 8 hours following the second dose our patient developed light-headedness and an associated headache.

Upon presentation for dose 3 (never administered) she had peripheral and central cyanosis in association with tachycardia (heart rate, 130 beats/min). Hypoxia (SpO₂ 85%-89% on fractional inspired oxygen [FiO₂] 21%) failed to correct with supplemental oxygen (FiO₂ 60%). Methemoglobinemia was confirmed on arterial blood gas, with a normal pH (7.41), sufficient oxygenation (204 mm Hg) and critically elevated methemoglobin of 27% (normal, 0%-2%).

Methylene blue was administered intravenously as an antidote. A clinical and biochemical recovery was observed (methemoglobin dropped to 3%). Dapsone was deemed the culprit in

view of its well-documented association,³ and an absence of other known causative agents, and discontinued.

Over the following 3 months, without treatment with dapsone or omalizumab our patient remained well and methaemoglobin levels normal.

Her urticaria returned, necessitating systemic corticosteroids. She was reluctant to trial treatment with alternative immunosuppressive agents; instead, she requested a rechallenge with omalizumab given its previous efficacy.

In the absence of dapsone, 150 mg omalizumab was administered. Our patient developed a headache and palpitations within hours. Examination identified cyanosis, tachycardia, and hypoxia (SpO₂ 85%) despite supplemental oxygen. Six hours after omalizumab, her methemoglobin level was 38%. Methylene blue provided a rapid symptomatic improvement correlating with a reduction in levels (16%). Seven hours later, worsening hypoxia accompanied a rebound elevation of methemoglobin (25%). Repeat methemoglobin saw a further increment to 28%. Methylene blue was readministered, this time with symptomatic and biochemical improvement (5%).

However, her tachycardia and hypoxia did not resolve. Recurrence of headache, dizziness, and dyspnea prompted recognition of another rebound in levels (18%) and these remained elevated (15%-18%). By day 3, the patient's symptoms and hypoxia worsened (SpO₂ 83%) correlating with levels of 19%. A third dose of methylene blue precipitated a conclusive fall to 5%, without evidence of hemolysis. Clinical stability and well-being was determined by day 6. Evaluation 2 days postdischarge found our patient asymptomatic with normalized methemoglobin levels (1%).

The patient has remained well with normal methemoglobin levels 9 months later.

Following the 2017 EAACI/GA2LEN/EDF/WAO chronic urticaria guidelines, omalizumab is recommended as add on therapy.⁴ Relatively safe, the most common side effects are headaches and injection-site reactions.⁵ Anaphylaxis is the most common serious adverse reaction.⁶

Methemoglobinemia characterized by functional anemia and tissue hypoxia can be toxic, with proportional symptomatology. It develops when ferric ions in hemoglobin are irreversibly oxidized into the ferrous state, thereby decreasing the oxygen-carrying capacity of hemoglobin. Healthy individuals develop a small amount of methemoglobin but equilibrium is maintained by reducing enzymes, including cytochrome B5 reductase. The presumed mechanism of medication-induced acquired methemoglobinemia relates to significant oxidative stress. Heterozygous cytochrome B5 reductase deficiency is a known predisposing risk for some cases of methemoglobinemia. Our patient elected not to undergo this testing.

Patients suffering methemoglobinemia will typically have pulse oximetry values that do not correct with increased FiO₂.⁷ Levels above 15% to 30% may cause fatigue, headache, dyspnea, and tachycardia, whereas death may occur above 70%.⁸

This case provides strong temporal evidence that omalizumab may cause acquired methemoglobinemia.

Although the initial episode of methemoglobinemia was attributed to dapsone, it could not be implicated with the second.

The prolonged course and rebound following the antidote with episode 2 suggests that the offending agent possessed a longer half-life, in keeping with omalizumab (26 days, vs 28 hours for dapsone).

It is unlikely that any of the excipients in omalizumab contributed to methemoglobinemia because they are all considered inert. No additional medications were administered around the time of omalizumab.

Methylene blue (1-2 mg/kg) is considered the primary emergency treatment for symptomatic methemoglobinemia, or if levels exceed 20%.⁹ Clinicians should be aware that methylene blue may be ineffective in patients with glucose-6-phosphate dehydrogenase deficiency.

To our knowledge, this is the first reported case of methemoglobinemia associated with omalizumab, or any mAb. The adverse drug reaction has been reported to the Australian pharmaceutical regulatory agency (Therapeutic Goods Administration) and Novartis Pharmaceuticals.

When prescribing omalizumab clinicians should be aware of this potentially life-threatening condition.

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