CASE REPORT

Ocular myasthenic syndrome, adverse reaction to omalizumab? A case report

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Omalizumab is a biological therapy for severe allergic asthma. Omalizumab is a glycosylated humanized IgG1k monoclonal antibody that specifically binds to circulating immunoglobulin E (IgE). It has a biological half-life of 5 days. Omalizumab leads to a reduced response of the pro-inflammatory mediators and substantially reduces IgE activity, targeting allergen sensitization and allergic inflammation [1]. Several side effects have been described for the use of omalizumab. The most severe side effect is anaphylactic shock, occurring in one or two patients per 1000 [2]. In this case report, myasthenia gravis (MG) is proposed as a probable side effect of treatment with omalizumab. MG is the clinical manifestation of impaired neuromuscular transmission due to an autoimmune reaction against the acetylcholine receptor (AChR), or muscle-specific tyrosine kinase (MuSK), or possibly other rarer targets. Lipoprotein receptor-related protein 4 (LRP4)-specific antibody is described in some patients with double-seronegative MG [3]. MG caused by acquired immunological or genetic abnormalities has a progressive course. Prognosis for MG is generally fair as long as there is no disease progression to involve respiratory muscles. Of patients who initially present with ocular MG, 85% will develop systemic MG within 2 years of diagnosis.

Our patient is a 63-year-old, non-smoking male, receiving treatment for severe allergic asthma, which he has been suffering from since childhood. His medical history also notes maxillary sinus polypectomy and laparoscopic cholecystectomy. He once suffered exacerbation of his asthma after being given metamizole prior to surgery. The past 7 years he also acquired exceptional nasal symptoms and dyspnoea. After starting omalizumab in 2011, these symptoms improved. Additional medications were salbutamol and fluticasone. He had been on omalizumab 300 mg month$^{-1}$ for 5 years, when he first noticed diplopia. The ophthalmologist considered ocular myasthenia gravis and referred him to a neurologist. The physical neurological examination showed strabismus and left-sided ptosis. His symptoms disappeared after discontinuation of omalizumab.

Five months later his asthmatic symptoms had worsened and therefore monthly 600 mg omalizumab was initiated. Within 2 months the patient recognized the symptoms of diplopia and decided to stop omalizumab. He had no family or personal history of neurological diseases. At presentation, the physical neurological examination showed progressive strabismus and ptosis and fluctuating ocular muscle paresis, worsening by strain and focusing to the left corner of his eyes, suggestive of ocular myasthenic syndrome. Laboratory tests revealed no abnormal thyroid stimulating hormone and no detectable antibodies to AChR, MuSK and LRP4. IgG against omalizumab was not increased ($<12$ AE ml$^{-1}$). After discontinuation of omalizumab for 3 months, serum
Table 1
Cases from VigiBase® WHO-UMC [7, 8]a

<table>
<thead>
<tr>
<th>No.</th>
<th>Reported (year)</th>
<th>Sexe (M/F)</th>
<th>Age (years)</th>
<th>Dose omalizumab</th>
<th>Treatment duration</th>
<th>Comedication</th>
<th>Reactions</th>
<th>Latency</th>
<th>Action with drug</th>
<th>Outcome</th>
<th>Rechallenge</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2016</td>
<td>M</td>
<td>60–70</td>
<td>75 mg once monthly</td>
<td></td>
<td>Salbutamol; Beclometasone dipropionate/Formoterol fumarate; Desloratadine; Fluticasone</td>
<td>Ocular myasthenia</td>
<td>5 months</td>
<td>Discontinued</td>
<td>Recovering</td>
<td>Yes</td>
</tr>
<tr>
<td>2</td>
<td>2014</td>
<td>F</td>
<td></td>
<td></td>
<td></td>
<td>Cortisone</td>
<td>Fatigue; Hypoxia; Muscular weakness; Myasthenia gravis</td>
<td>Unknown</td>
<td>Unknown</td>
<td>Yes</td>
<td>Unknown</td>
</tr>
<tr>
<td>3</td>
<td>2009</td>
<td>F</td>
<td>150 mg twice a month</td>
<td></td>
<td>13 months</td>
<td>Salbutamol; Ipratropium; Diphenhydramine; Prednisone; Levothyroxine; Ranitidine</td>
<td>Ocular myasthenia</td>
<td>Dose not changed</td>
<td>Unknown</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>2009</td>
<td>F</td>
<td>375 mg twice a month</td>
<td>13 months</td>
<td>Myasthenia gravis</td>
<td>Fluticasone propionate/ Salmeterol xinafoate; Fexofenadine; Lansoprazole; Salbutamol; Ipratropium; Montelukast; Cetirizine</td>
<td>Myasthenia gravis</td>
<td>2.5 years</td>
<td>Discontinued</td>
<td>Not recovered</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>2009</td>
<td>M</td>
<td>375 mg twice a month</td>
<td>150 mg once monthly</td>
<td>13 months</td>
<td>Fluticasone; Fluticasone; Ranitidine; Montelukast; Topiramate</td>
<td>Myasthenia gravis</td>
<td>Dose not changed</td>
<td>Unknown</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>2008</td>
<td>F</td>
<td></td>
<td>150 mg once monthly</td>
<td></td>
<td>Levosalbutamol; Budesonide; Montelukast; Cetirizine</td>
<td>Dysarthria; Eyelid ptosis; Muscular weakness; Myasthenia gravis</td>
<td>1 year</td>
<td>Discontinued</td>
<td>Recovering</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>2008</td>
<td>F</td>
<td>375 mg twice a month</td>
<td>13 months</td>
<td>Myasthenia gravis</td>
<td>Fluticasone propionate/ Salmeterol xinafoate; Salbutamol; Montelukast; Lansoprazole; Allergens; Norethisterone acetate/ Ethinylestradiol; Prednisone; Fluticasone</td>
<td>Diaphragmatic disorder; Myasthenia gravis</td>
<td>Anaphylactic reaction; Anxiety; Seizure; Disorientation; Mental status changes; Myasthenia gravis; Restrictive pulmonary disease; Status asthmaticus; Vocal cord disorder</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>2005</td>
<td>F</td>
<td>40–50</td>
<td></td>
<td></td>
<td>Ipratropium bromide/Salbutamol sulfate; Diltiazem; Glipizide; Metformin; Prednisone; Guafenesin; Fluticasone; Omeprazole; Fluticasone; Terbutaline; Desloratadine; Levosalbutamol; Formoterol; Ipratropium</td>
<td>Anaphylactic reaction; Anxiety; Seizure; Disorientation; Mental status changes; Myasthenia gravis; Restrictive pulmonary disease; Status asthmaticus; Vocal cord disorder</td>
<td></td>
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</table>

aThe source of the information is the WHO Global Individual Case Safety Report database, VigiBase®. The information comes from a variety of sources, and the likelihood that the suspected adverse reaction is drug-related is not the same in all cases. The information does not represent the opinion of the World Health Organization.
omalizumab was 8.5 μg ml⁻¹, which suggests a normal clearance. MRI of the cerebrum demonstrated no intracranial pathology. Repeated neurological exam 4 months after cessation demonstrated full recovery.

To the best of our knowledge, no earlier studies reported this side effect of omalizumab. In the WHO VigiBase®, an international database of suspected adverse drug reactions, nine cases of MG as a suspected adverse drug reaction of omalizumab were identified. Of these reports, seven were considered generalized MG and two cases (including our case) ocular MG. For details see Table 1, with VigiBase® data. One hypothesis is that omalizumab mediates a secondary immune response or interaction with other immune cells. Another possible explanation is cross-reaction by recombinant monoclonal antibody with AChR. This might be triggered by an individual difference in sensitivity, for example by polymorphisms in genes active in the immune system. Yet another possible explanation could be immune effects induced by impurities present in the drug product. During the production of omaluzimab, leakage could be of protein A, which is known to have an immunogenic or mitogenic effect. Perhaps this mediates a secondary immune response and cross-reaction to the AChR [4]. Possibly there is a still unknown autoimmune mechanism in a similar pathogenesis as described in other drug-induced immunologic effects – for example, drug-induced lupus erythematosus, which induces immunologic effector mechanism, probably in a genetically predisposed individual [5]. Also penicillamine and interferon can cause MG development, but the mechanism is not completely understood. Ipilimumab and nivolumab in the treatment of small cell lung cancer are associated with MG [6].

In conclusion, this case report suggests a reversible side effect of omalizumab with clinical symptoms of ocular MG observed twice after treatment with omalizumab. The pathophysiology of this side effect and possible autoimmune mechanism is not yet clear and still has to be further elucidated.

Competing Interests

No potential conflict of interest exists with this research, and no study sponsor is involved. No honorarium, grant or other form of payment was given to anyone to produce this case report. The patient gave informed consent for this case report.

References