

Case report

Case of paradoxical adverse response to mepolizumab with mepolizumab-induced alopecia in severe eosinophilic asthma

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SUMMARY

Recent years have seen an increase in use of mepolizumab and other biological therapies for the treatment of severe eosinophilic asthma. A few cases of paradoxical responses to mepolizumab therapy have now been reported and are hypothesised as being a response to immune complex formation. We present a case of mepolizumab-induced alopecia in a patient with paradoxical adverse response to mepolizumab given for severe eosinophilic asthma. We postulate this could be secondary to autoimmune mechanisms and that it could help herald poor response to treatment, thereby facilitating early identification of patients having paradoxical responses.

BACKGROUND

Severe asthma is characterised by uncontrolled symptoms and exacerbations despite treatment with optimised inhaled and oral pharmacotherapy.¹ It represents a heterogeneous phenotype and clinical course, likely related to differences in pathophysiology.² Introduction of biological therapy has improved outcomes in the allergic and eosinophilic subsets of severe asthma and transformed the quality of life of most patients. Specifically in the case of eosinophilic asthma anti-interleukin (IL)-5 therapy such as mepolizumab can significantly decrease exacerbation rates (defined as requiring a course of high-dose systemic corticosteroids) when compared with standard therapy.³ Side effects are rare but can include headache, fatigue, arthralgia and myalgia, as well as hypersensitivity reactions.⁴ We present a case of a patient with severe eosinophilic asthma who experienced paradoxical deterioration in her asthma control on mepolizumab together with myalgia and alopecia. Paradoxical responses to mepolizumab have previously been hypothesised as being secondary to autoimmune reactions to antibody–cytokine immune complexes,^{5 6} but these limited reports have not previously described alopecia as a feature of these paradoxical responses.

CASE PRESENTATION

A 32-year-old female patient of North African origin was referred to the severe asthma service with a history of poorly controlled asthma ever since the birth of her son 2 years prior. Her symptoms manifested with shortness of breath, wheeze, chest tightness and nocturnal cough.

Her activities of daily living were limited due to breathlessness needing frequent inhaled salbutamol despite a combined budesonide 400 µg/formoterol 12 µg dry powder inhaler, one puff twice daily preventer therapy. A previous trial of montelukast had given no improvement to her symptoms. She had a background of intolerance to non-steroidal anti-inflammatories, allergic rhinitis and chronic rhinosinusitis with nasal polyposis, for which she was on a mometasone nasal spray. She was a never smoker and her body mass index was 23.7 kg/m².

Her baseline blood tests revealed a raised eosinophil cell count of $0.7 \times 10^9/L$ and a total IgE of 158 kU/L. Anti-neutrophil cytoplasmic antibodies (ANCA), antinuclear antibodies (ANA) and *Aspergillus fumigatus* IgG and IgE were negative. Cross-sectional imaging of her chest showed no evidence of bronchiectasis or pulmonary infiltrates. Lung function tests demonstrated a reduced forced expiratory volume in 1 s (FEV₁) of 1.69 L (58% predicted), forced vital capacity (FVC) of 2.65 L (79% predicted), FEV₁/FVC 0.6 with normal gas transfer. Spirometry post inhaled short acting bronchodilator showed an FEV₁ of 2.54 L, indicating significant bronchodilator reversibility.

She underwent multidisciplinary systematic assessment. Ear, Nose and Throat (ENT) review confirmed chronic rhinosinusitis with nasal polypsis and no vocal cord dysfunction. She scored 31/64 on the Nijmegen Questionnaire but no breathing pattern disorder was identified on physiotherapy assessment. Inhaler technique was reviewed and optimised by our asthma nurses.

After initial assessment, her inhaled corticosteroid–long-acting beta-agonist (ICS–LABA) combination inhaler was switched to a fluticasone 250 µg/formoterol 10 µg pressurised metered dose inhaler, 2 puffs twice daily via spacer, and inhaled tiotropium was added onto her therapy regimen, as well as omeprazole for gastro-oesophageal reflux symptoms. Additionally, she underwent nasal polypectomy. She continued to have frequent exacerbations including a short hospital admission when she was commenced on a weaning course of prednisolone with partial improvement in asthma control. At 20 mg/day prednisolone her eosinophil cell count remained elevated at $0.3 \times 10^9/L$ and her exhaled nitric oxide (FeNO) was 39 parts per billion (ppb), so she continued on this maintenance dose of prednisolone pending biologic therapy.



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Findings that shed new light on the possible pathogenesis of a disease or an adverse effect

Over the next 3 months while her breathing improved, it did not return to baseline. Her eosinophil cell count did become suppressed although it rose to $0.2 \times 10^9/L$ during a viral exacerbation of her asthma. High-performance liquid chromatography (HPLC)-Cortisol and serum prednisolone levels confirmed adherence to maintenance oral prednisolone. Following the licensing of mepolizumab, she was discussed at our regional multidisciplinary team meeting where the decision was made to start her on mepolizumab anti-IL-5 therapy.

After her first dose mepolizumab she started to experience troublesome headaches and myalgia, with occasional urticaria, but not of themselves of enough severity to stop mepolizumab treatment.

Four months into treatment with mepolizumab in addition to her maintenance dose of prednisolone 20 mg/day, her blood eosinophil count remained detectable at $0.1 \times 10^9/L$, FeNO was 54 ppb and she had not yet noticed any great improvement in her symptoms with an Asthma Control Questionnaire (ACQ-6) score of 3.8 compared with 4.5 pre-mepolizumab. She had also had a further exacerbation requiring a short-course of higher dose oral prednisolone. She also reported hair loss from her head, a side effect not previously known to be related to mepolizumab.

She continued on mepolizumab for a further 2 months; however, she had a further severe exacerbation and her maintenance oral prednisolone dose increased to 40 mg/day to control symptoms sufficiently for her to continue her daily activities. Her FEV₁ declined to 1.23 L (43% predicted). The decision was therefore taken to stop mepolizumab and switch biologic therapy. Dermatology review found no evidence of scarring to the scalp and a diagnosis of likely reversible alopecia secondary to biologic therapy was made. Repeat ANCA and ANAs were negative.

TREATMENT

She was rediscussed at our multidisciplinary meeting and a decision was made to switch to reslizumab given evidence this alternative anti-IL-5 biologic may be effective in patients not responding to mepolizumab.⁷ Within 1 month of initiation, an improvement in her clinical asthma symptoms was observed with less cough and less wheeze. This allowed successful weaning of her maintenance prednisolone and was reflected in a reduced ACQ-6 score from 3.83 to 1.83 despite reduced prednisolone. There was partial improvement in the hair loss with some hair re-growth. By 4 months her prednisolone had reduced to 5 mg/day with continuing improved asthma control.

OUTCOME AND FOLLOW-UP

Although her asthma improved on reslizumab therapy, the patient experienced a persistent severe sore throat. This is a recognised uncommon side effect on reslizumab.⁸ Due to the severity of the sore throat, she then opted to stop biological therapy until she could qualify for treatment with benralizumab. She remained off biological therapy and on a maintenance oral dose of prednisolone that rose to 20 mg/day over the following 10 months. During this period she had four exacerbations, all requiring high dose corticosteroids and hospital admissions. Multidisciplinary team decision was taken to commence benralizumab therapy as soon as nationally available.

On commencing treatment with benralizumab, her asthma control again improved although she has had occasional further exacerbations. Her prednisolone dose has weaned to 4 mg/day and further weaning has primarily been limited by

steroid-induced adrenal suppression. She has continued on benralizumab and continued to have some hair loss.

DISCUSSION

The National Institute for Health and Care Excellence (NICE) guidelines in UK recommend mepolizumab for treating severe refractory eosinophilic asthma where patients have a minimum eosinophil count of 300 cells/ μL ($0.3 \times 10^9/L$) with four or more exacerbations requiring oral corticosteroids in the last 12 months or maintenance steroids for the previous 6 months despite optimised standard therapy.⁹ Anti-IL-5 therapies such as mepolizumab halve the rate of exacerbations in this type of asthma.³ Indeed, halving of oral corticosteroid use or a clinically significant reduction in maintenance oral corticosteroids use is how an adequate response to mepolizumab is defined.⁹

However, paradoxical worsening of asthma symptoms and lung function with mepolizumab therapy has recently been reported.⁵ It is hypothesised to be due to local autoimmune reactions with anti-IL-5 antibodies forming immune complexes with IL-5 cytokines, which in turn lead to further excessive airway inflammation.⁶ This would account for deteriorating clinical asthma symptoms despite suppressed peripheral eosinophil counts. A similar mechanism may account for the development of alopecia in certain patients with paradoxical reactions to mepolizumab, as alopecia can undoubtedly be a manifestation of an autoimmune response. Whether through immune complex deposition or other autoimmune mechanisms unmasked by the suppression of eosinophils, alopecia and paradoxical responses to mepolizumab may be part of the same pathophysiology.

To the best of our knowledge, this is the first reported case of mepolizumab-associated alopecia. Since then we have had a further two cases of asthmatic patients who experienced alopecia in conjunction with a paradoxical response to mepolizumab. Interestingly, all three of these patients were from a similar North African ethnic background although the significance of this is uncertain. Worsening of urticaria was also seen in these patients. Furthermore, all three had partial improvement of their alopecia and in their asthma control on switching to benralizumab. Use of a genetic sequencing approach could potentially identify novel genetic associations with both beneficial and adverse responses to mepolizumab but would require larger numbers of patients.¹⁰

The likely immune complex mechanism was only considered in retrospect after discussion of the last of these cases at our multidisciplinary team meeting by which time all three cases had been switched to alternative biologics. Serum samples were unfortunately not available to retrospectively assay for immune complexes or for anti-mepolizumab antibodies. If future cases occur we would strongly suggest the development of alopecia in patients on mepolizumab should now prompt

Learning points

- ▶ Biologic therapy is a common treatment option for severe asthma.
- ▶ Paradoxical reactions to mepolizumab have been reported and may be related to autoimmune immune-complex reactions.
- ▶ Mepolizumab-induced alopecia may be an autoimmune-mediated phenomenon, which in turn may herald poor response to treatment and the need to switch to alternative therapy.

such testing, and in particular for presence or not of serum immune complexes.

Dupilumab as an alternative biologic for asthma, which targets IL-4/IL-13 signalling, was not available in the UK at the time of these cases but would have been an alternative biologic to which to switch. Indeed, dupilumab may be a better option in future patients with paradoxical responses to mepolizumab given its different molecular target and that it is an IgG4 subclass antibody in contrast to the IgG1 subclass of mepolizumab.¹¹

Alopecia may be a symptom heralding a paradoxical response to mepolizumab due to potential autoimmune mechanisms and may help clinicians consider an earlier switch to alternative biological therapy.

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