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LETTER TO THE EDITORS

A case of anaphylaxis to alemtuzumab

Charles J. S. Nye[1] · Annette Wagner[2] · Onajite Kousin-Ezewu[3] · Joanne L. Jones[3] · Alasdair J. Coles[3]

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Dear Sirs,

Alemtuzumab (Lemtrada) is a humanised monoclonal antibody targeting CD52 found on lymphocytes and monocytes, and is a highly effective treatment of relapsing–remitting multiple sclerosis [1–3]. At baseline five consecutive daily doses of 12 mg IV are given, with no further treatment until 12 months later, when patients receive three consecutive doses of 12 mg IV.

Over 90% of patients receiving alemtuzumab experience infusion-associated reactions. Work in the 1990s showed that these could be reduced or ameliorated by pretreatment with corticosteroids [4] and that the underlying mechanism was a programmed release of cytokines from natural killer cells, triggered by Fc cross-linking [5]. When severe, these reactions may include a rash, fever, hypotension and bronchospasm and so mimic anaphylaxis; they are, therefore, termed "anaphylactoid". This phenomenon has led to confusion in the current literature as to whether patients may develop genuine anaphylaxis to alemtuzumab.

A 22-year old female, with relapsing remitting multiple sclerosis, and no history of atopy, had previously received her first cycle of alemtuzumab without complication. This was in combination with placebo, in the context of a clinical trial (CAMTHY; EudraCT number: 2011-005606-30) designed to test whether palifermin (recombinant human keratinocyte growth factor), would promote thymic reconstitution. As is common, she had developed Grave's disease 6 months post-alemtuzumab and was being treated with carbimazole (40 mg OD) and thyroxine (75 µg OD).

One year later, she received the first dose of the second cycle of alemtuzumab, again combined with placebo. As is standard she received 1 g of methylprednisolone and oral anti-histamine immediately prior to treatment. Forty minutes into the infusion (1/6th of the dose) she developed generalized urticaria, facial swelling, tongue swelling, stridor, hypotension and wheeze. The infusion was stopped and her symptoms quickly resolved, without the need for further medications.

Her serum IgE was elevated at 314 kµ/l, rising to 374 kµ/l the following day (upper limit of normal 170 kµ/l) and her serum tryptase, taken during her symptoms, was elevated at 22 (upper limit of normal 14). Her baseline tryptase, recorded 10 days after the event and 1 year later was 3 ruling out mastocytosis, and supporting the conclusion that this was true anaphylaxis. Eighteen months later, she had allergy testing. A skin prick test of alemtuzumab 10 mg/ml was positive at 4 mm and an intradermal test (1:100) of alemtuzumab was positive with a 12 mm wheal and a flare greater than 300 mm (see Fig. 1).

The patient switched to fingolimod and has done well.

This is the first case of true anaphylaxis to alemtuzumab, confirmed by skin prick, intradermal testing and the confirmed rise in serum tryptase. Another case in the literature is likely to represent anaphylaxis [6] but did not have formal allergy testing. However, other reported cases are more likely represent severe anaphylactoid cytokine-induced infusion reactions. A typical example of the confusion is the case of "anaphylaxis" following use of alemtuzumab in B-cell CLL; as this occurred with the first dose of alemtuzumab it is very unlikely to be true anaphylaxis [7]. Features of anaphylaxis that would not be expected in a cytokine-release syndrome are stridor and facial and tongue swelling, as seen in our case. Our case report also shows the benefit of formal allergy testing to confirm true IgE mediated anaphylaxis versus the unavoidable adverse effects due to the physiological action of the drug.

In this case, her symptoms resolved on stopping the aletuzumab infusion. Presumably, premedication with high dose corticosteroids prevented worse manifestations of her

✉ Charles J. S. Nye
charles.nye@nhs.net

[1] University of Cambridge, Cambridge, UK

[2] Department of Allergy and Immunology, Cambridge University Hospitals NHS Foundation Trust, Cambridge, UK

[3] Department of Clinical Neurosciences, Cambridge University Hospitals NHS Foundation Trust, Cambridge, UK

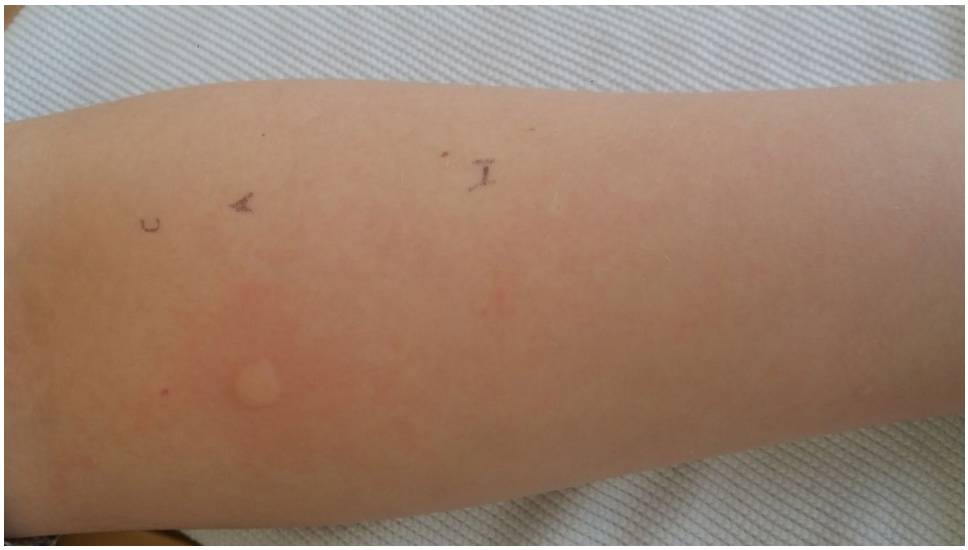

Fig. 1 Result of the skin prick testing showing the positive wheal and flare reaction to alemtuzumab and negative control

allergy. Nonetheless, further exposure to normal concentrations of the drug would be dangerous, so we elected to switch her to an alternative treatment. Another strategy might have been to attempt to induce desensitisation to alemtuzumab.

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Compliance with ethical standards

Conflicts of interest Both AC and JJ have received honoraria and travel costs for attending scientific advisory boards.

Ethical standards All human studies have been approved by the appropriate ethics committee and have been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments. The patient in this case study gave her informed consent for the report to be written.

References

1. Cohen JA, Coles AJ, Arnold DL, Confavreux C, Fox EJ, Hartung H-P et al (2012) Alemtuzumab versus interferon beta 1a as first-line treatment for patients with relapsing–remitting multiple sclerosis: a randomised controlled phase 3 trial. Lancet 380(9856):1819–1828
2. Coles AJ, CAMMS223 Trial Investigators Compston DAS, Selmaj KW, Lake SL, Moran S et al (2008) Alemtuzumab vs. interferon beta-1a in early multiple sclerosis. N Engl J Med 359(17):1786–1801
3. Coles AJ, Twyman CL, Arnold DL, Cohen JA, Confavreux C, Fox EJ et al (2012) Alemtuzumab for patients with relapsing multiple sclerosis after disease-modifying therapy: a randomised controlled phase 3 trial. Lancet 380(9856):1829–1839
4. Coles AJ, Wing MG, Molyneux P, Paolillo A, Davie CM, Hale G et al (1999) Monoclonal antibody treatment exposes three mechanisms underlying the clinical course of multiple sclerosis. Ann Neurol 46(3):296–304
5. Wing MG, Moreau T, Greenwood J, Smith RM, Hale G, Isaacs J et al. Mechanism of first-dose cytokine-release syndrome by CAMPATH 1-H: involvement of CD16 (FcgammaRIII) and CD11a/CD18 (LFA-1) on NK cells. J Clin Invest. 1996 98(12):2819–2826
6. Caon C, Namey M, Meyer C, Mayer L, Oyuela P, Margolin DH et al (2015) Prevention and management of infusion-associated reactions in the comparison of alemtuzumab and rebif® efficacy in multiple sclerosis (CARE-MS) program. Int J MS Care 17(4):191–198
7. Moreton P, Kennedy B, Lucas G, Leach M, Rassam SMB, Haynes A et al (2005) Eradication of minimal residual disease in B-cell chronic lymphocytic leukemia after alemtuzumab therapy is associated with prolonged survival. J Clin Oncol 23(13):2971–2979