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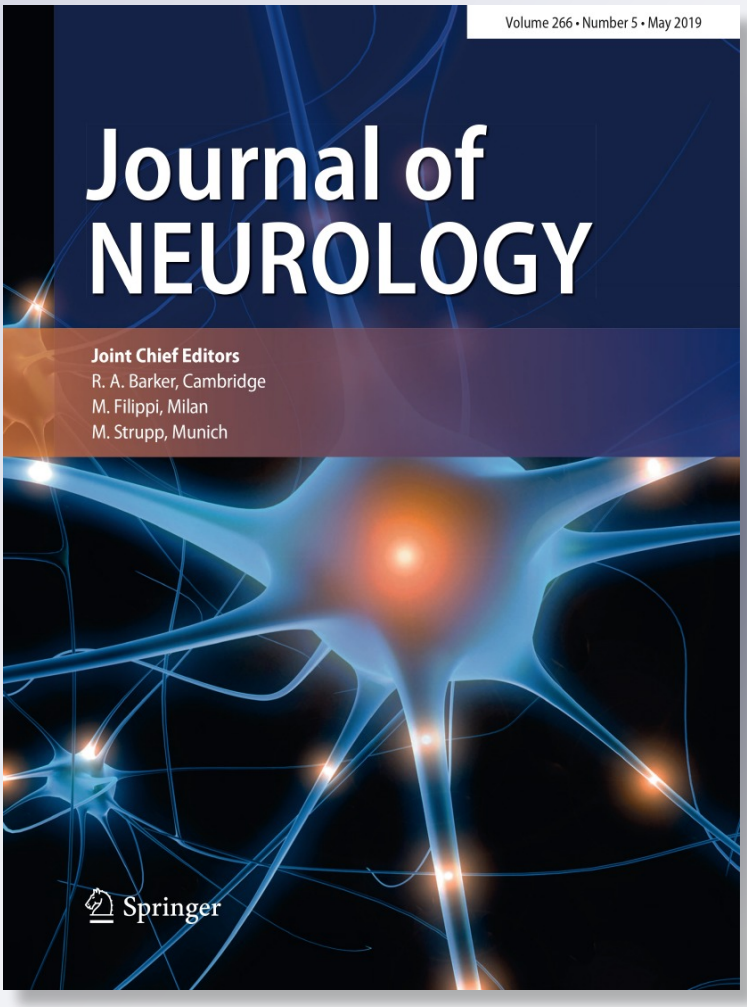

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LETTER TO THE EDITORS

Two cases of diabetes mellitus type 1 after alemtuzumab treatment for multiple sclerosis: another probable secondary autoimmune disease

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Dear Sirs,

Alemtuzumab (ATZ) is an established highly effective treatment in relapsing-remitting multiple sclerosis (RRMS) [1–3]. Secondary autoimmune disorders in MS patients treated with alemtuzumab have been reported in a frequency of about 40% for thyroid disorders, 3% for thrombocytopenic purpura (ITP) and below 0.3% for glomerulonephritis [4]. So far, one case of diabetes type 1 (T1D) as a possible secondary autoimmune disease following alemtuzumab treatment has been published [5].

We report on two patients who had an acute increase in their blood glucose level several months after the second course of alemtuzumab. In both cases, a diagnosis of T1D was made. In addition, thyroid disorders occurred in both cases over the course of time.

Case #1

A 37-year-old male patient had the first symptoms of RRMS at the age of 19. He had no history of autoimmune disorders, but his mother has MS reaching immobility at the age of 50. During interferon therapy, he experienced about one relapse per year. The therapy was changed to natalizumab with stable disease for 9 years until the age of 35. The EDSS was stable at 2.0. A switch to ATZ due to a high PML risk (JCV index 3.8) was performed. Fourteen months after the second course of ATZ, acute symptoms like polyuria, polydipsia and a reduced general condition occurred. He had an elevation of blood glucose up to 540 mg/dl, and urine glucose > 500 mg/dl with ketonuria. Further laboratory test showed a highly increased level of specific diabetes autoantibodies such as GAD (glutamic acid decarboxylase antibody) with 754 mU/ml (norm < 70 mU/ml). Tests for further antibodies against IA-2 (protein tyrosine phosphatase- antibodies), IAA (anti-insulin), ZnT8 (zink transporter 8-antibodies), ICA (islet cell antibodies) and insulin (IAA) were negative. At the same time, without symptoms of thyroid dysfunction, TSH was elevated at 15.6 µU/ml [norm 0.35–3.50 (µU/ml)] for the first time, in addition to increased thyroid autoantibodies with anti-TPO > 950 IU/ml (norm < 35 IU/ml) and anti-thyreoglobulin (TAK) 877 IU/ml (norm < 3,9 IU/ml). Free T3 and T4 were still normal. Thyroid sonography showed a hypoechoic, inhomogeneous internal reflex pattern as a typical finding of autoimmune thyroiditis. With the onset of insulin therapy, rapid normalization of blood glucose levels and general condition occurred. In addition, L-thyroxine therapy with 75 µg was started.

Case #2

This 25-year-old female had her first symptoms of RRMS at the age of 10 and was diagnosed when she was 13 years old. She had epilepsy from the age of 14, but no history of other autoimmune diseases. Interferon-beta 1a s.c was initiated after diagnosis and was changed to glatiramer acetate because of the side effects 1 year later. She stopped treatment after another year because of problems with the injections and remained stable and untreated for 8 years. At the age of 23, she experienced new symptoms; her cerebral MRI

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revealed several new lesions and treatment with ATZ was initiated.

Ten months after the first treatment cycle with ATZ, she developed autoimmune thyroiditis with TSH 260 µU/ml, free T4 < 6.0 pmol/l, anti-TPO 241 IU/ml and thyroid receptor antibodies (TRAS) 25 IU/l. She did not report symptoms and her laboratory values were stable under treatment with L-thyroxine.

Ten months after the second treatment cycle with ATZ, her general condition rapidly worsened with polydipsia, tachycardia and shortness of breath. Upon admission, her blood glucose was 12.9 mmol/l and the urine was positive for ketones. Anti-GAD 1.40 and P-IA2 antibodies > 3.00 were consistent with autoimmune diabetes. Her condition improved rapidly after treatment with insulin was initiated and blood glucose levels normalized. She has had no new symptoms or new MRI lesions after alemtuzumab was initiated.

Here we report two cases with acute onset of symptoms consistent with T1D following several months after the second course of ATZ. In both cases, well-defined autoantibodies were detected confirming the diagnosis of T1D. A secondary autoimmune genesis is therefore most likely. The assumption is supported by the fact, that both cases also have developed autoimmune thyroiditis.

A first comparable case of autoimmune diabetes was already communicated in 2014 and documented in detail [5]. Epidemiologic studies have shown a higher prevalence of T1D in MS patients compared to the general population, but the large majority of the patients had T1D diagnosed before the onset of MS [6–8].

Our first case developed thyroiditis at the same time as T1D, whereas the second case was diagnosed with thyroiditis after the first cycle and 1 year prior to T1D, a possible association was not clear. All three cases imply that after treatment with ATZ, there should be clinical vigilance regarding the development of T1D. Other rare secondary autoimmune diseases have been described in association with ATZ treatment. Beside the well-known thyroid disorders, thrombocytopenic purpura (ITP) and glomerulonephritis cases of vitiligo, hemophilia A and even Lambert–Eaton myasthenic syndrome (LEMS) have been reported recently [9–11]. In some cases, T-cell-mediated autoimmunity in addition to an autoantibody-mediated pathogenesis has also been assumed to be present. All described cases demonstrate the need for strong alertness to detect treatable secondary autoimmune disorders following therapy with ATZ.

Compliance with ethical standards

Conflicts of interest Stephan Richter has received honoraria for advisory board councils and travel expenses for attending meetings from Biogen, Celgene, Genzyme, Merck, Novartis and Roche. Bert Wagner has received honoraria for advisory board councils and travel expenses for attending meetings from Biogen, Genzyme, Merck, Novartis and Roche. Elisabeth G. Celius has received honoraria for advisory boards and/or speaker honoraria from Biogen, Merck, Roche, Novartis, Genzyme and Teva, and unrestricted research grants from Novartis and Genzyme.

Ethical standards This article does not contain any studies with human participants or animals performed by any of the authors.

References

1. Cohen JA, Coles AJ, Arnold DL, Confavreux C, Fox EJ, Hartung HP, Havrdova E, Selmaj KW, Weiner HL, Fisher E, Brinar VV, Giovannoni G, Stojanovic M, Ertik BI, Lake SL, Margolin DH, Panzara MA, Compston DA (2012) Investigators C-MI. Alemtuzumab versus interferon beta 1a as first-line treatment for patients with relapsing-remitting multiple sclerosis: a randomized controlled phase 3 trial. Lancet 380:1819–1828
2. Coles AJ, Twyman CL, Arnold DL, Cohen JA, Confavreux C, Fox EJ, Hartung HP, Havrdova E, Selmaj KW, Weiner HL, Miller T, Fisher E, Sandbrink R, Lake SL, Margolin DH, Oyuela P, Panzara MA, Compston DA (2012) Investigators C-MI. Alemtuzumab for patients with relapsing multiple sclerosis after disease-modifying therapy: a randomised controlled phase 3 trial. Lancet 380:1829–1839
3. Havrdova E, Horakova D, Kovarova I (2015) Alemtuzumab in the treatment of multiple sclerosis: key clinical trial results and considerations for use. Ther Adv Neurol Disord 8:31–45
4. Coles AJ, Cohen JA, Fox EJ, Giovannoni G, Hartung HP, Havrdova E, Schippling S, Selmaj KW, Traboulsee A, Compston DAS, Margolin DH, Thangavelu K, Chirieac MC, Jody D, Xenopoulos P, Hogan RJ, Panzara MA, Arnold DL (2017) Alemtuzumab CARE-MS II 5-year follow-up: Efficacy and safety findings. Neurology 89:1117–1126
5. Malmeström C, Andersson BA, Lycke J (2014) First reported case of diabetes mellitus type 1 as a possible secondary autoimmune disease following alemtuzumab treatment in MS. J Neurol 261:2016–2018
6. Wertman E, Zilber N, Abramsky O (1992) An association between multiple sclerosis and type I diabetes mellitus. J Neurol 239:43–45
7. Marrosu MG, Cocco E, Lai M, Spinicci G, Pischedda MP, Contu P (2002) Patients with multiple sclerosis and risk of type 1 diabetes mellitus in Sardinia, Italy: a cohort study. Lancet 359:1461–1465
8. Hussein WI, Reddy SS (2006) Prevalence of diabetes in patients with multiple sclerosis. Diabetes Care 29:1984–1985
9. Ruck T, Pfeuffer S, Schulte-Mecklenbeck A, Gross CC, Lindner M, Metze D, Ehrchen J, Sondermann W, Pul R, Kleinschnitz C, Wiendl H, Meuth MD, Klotz SG (2018) L. Vitiligo after alemtuzumab treatment, Secondary autoimmunity is not all about B cells. Neurology 91:e2233–e2237
10. Della Valle P, Coluccia A, Martinelli V, Comi G, D´Angelo A, Moiola L (2018) Acquired haemophilia a as a secondary autoimmune disease after alemtuzumab treatment in multiple sclerosis: a case report. Mult Scler Relat Disord 27:403–405
11. Hoffman BM, Zeid NA, Alam U, Caress JB (2019) Lambert-Eaton myasthenic syndrome associated with alemtuzumab administration. Mult Scler Relat Disord 27:131–132