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Rescue therapy with alemtuzumab in B cell/antibody-mediated multiple sclerosis

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Abstract: Alemtuzumab exerts its clinical efficacy by its specific pattern of depletion and repopulation of different immune cell subsets. Recently, single cases of multiple sclerosis patients who developed severe exacerbation after the first alemtuzumab application, accompanied by re-appearance of peripheral B cells, were reported. Here we present a case with underlying B cell-driven multiple sclerosis that impressively improves after alemtuzumab, although peripheral B cell repopulation took place. Our detailed clinical, histopathological, imaging and immunological data suggest that alemtuzumab can act as an effective rescue treatment in highly active B cell-driven and antibody/complement-mediated multiple sclerosis type II patients.

Keywords: alemtuzumab, B cell-mediated multiple sclerosis, multiple sclerosis exacerbation, rescue treatment in highly active multiple sclerosis

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Introduction

The monoclonal anti-CD52 antibody alemtuzumab mediates its efficacy by antibody and complement-dependent cytotoxicity and results in depletion of CD52-positive cells and an altered distribution of different peripheral T and B immune cell subtypes in multiple sclerosis patients.^{1,2} In post-marketing experience, single cases of severe clinical exacerbation with respective development of tumefactive lesions after alemtuzumab use were reported.^{3,4} In addition, alemtuzumab has failed in several cases of neuromyelitis optica.⁵ For these cases, the authors suggested a B cell-mediated process causing the clinical and MRI exacerbation, since the clinical exacerbation was paralleled by the re-appearance of B cells in the periphery. This is of special interest as B cells seem to play a significant role in multiple sclerosis pathogenesis. B cell-depleting therapies have been extensively and successfully tested in relapsing, remitting and primary progressive multiple sclerosis and have already been approved with ocrelizumab.

Case report

We report a patient with histopathologically proven antibody/complement mediated pattern

type II multiple sclerosis, in which alemtuzumab has been successfully applied as rescue therapy. After multiple sclerosis diagnosis in 2006, a 34-year-old female started interferon-beta treatment. Because of high disease activity she was escalated to natalizumab treatment in 2008. The JC virus antibody status was positive in December 2014, and thus therapy was changed to fingolimod in March 2015 because of the high risk of developing progressive multifocal leukoencephalopathy. One month later she suffered a severe relapse with headache, and an MRI presented a novel subset of large ring-enhancing lesions among otherwise typical multiple sclerosis lesions (Figure 1(a), first row). Additional evaluation of cerebrospinal fluid (CSF) was negative for JC virus DNA testing. A first brain biopsy was performed to exclude opportunistic infections and confirmed multiple sclerosis typical lesions with signs of active demyelination, allowing this case to be classified as multiple sclerosis pattern II (antibody/complement mediated). The patient was treated with steroids, and fingolimod was continued. After an additional relapse, fingolimod was stopped in September 2015 and the patient was treated with steroids again. Due to vaccination, alemtuzumab initiation was delayed.

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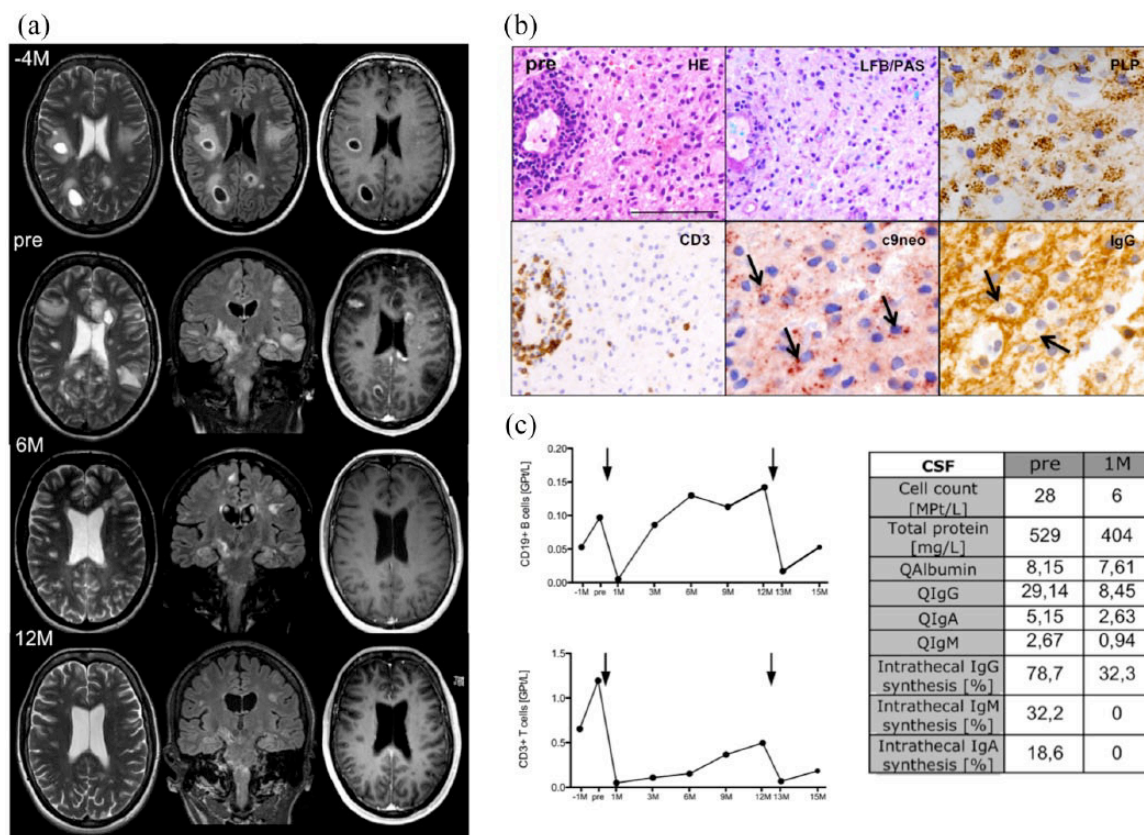


Figure 1. (a) MRI data. First row: initial MRI 4 months before alemtuzumab revealed inhomogeneous lesions pattern including large ring-enhancing lesions in juxtacortical white matter admixed with smaller lesions of infrequent nodular enhancement. Second row: MRI prior to alemtuzumab administration revealed new enhancing lesions and now extensive brainstem involvement. Third row: MRI 6 months after alemtuzumab treatment revealed reduction in lesion size as well as perifocal edema and gadolinium enhancement disappearance. Fourth row: 12 months after alemtuzumab, lesion consolidation was found. Formerly acute lesions revealed progressive T1 hypointensity.

(b) Biopsy was taken from the subcortical right middle frontal gyrus before alemtuzumab application (pre). Multiple sclerosis lesion with involvement of the humoral immune system (type II pattern): HE staining shows a macrophage-rich lesion with perivascular inflammation and a reactive gliosis. The lesion is demyelinated (LFB/PAS stain with missing blue myelin). Numerous macrophages with myelin degradation products in their cytoplasm are present, indicating an active demyelinating lesion (anti-proteolipid protein). Within the lesion, T cells are located in the perivascular space and within the parenchyma (anti-CD3). Activated complement components (anti-C9neo) and immunoglobulins (anti-immunoglobulin G) are present with macrophages, indicating a complement/immunoglobulin mediated demyelination (pattern II; arrows indicate complement and IgG-laden macrophages). Scale bar: 100 μ m for HE, LFB/PAS and anti-CD3. 50 μ m for anti-PLP, anti-c9neo and anti-IgG.

(c) Analysis of peripheral immune cell subtypes and CSF markers: peripheral blood immune cell subtypes including CD19+ B cells and CD3+ T cells were evaluated prior to and after alemtuzumab infusion. One month before alemtuzumab administration (-1M) lymphocyte counts were still decreased due to previous but interrupted fingolimod treatment and were normalized directly before alemtuzumab initiation (pre). CD19+ B cells were markedly decreased after the first alemtuzumab cycle but demonstrated an overshooting repopulation before the second alemtuzumab cycle (12M). Arrows indicate first and second alemtuzumab application. CSF was investigated directly before (pre) and one month (1M) after alemtuzumab. Intrathecal inflammation and damage of the blood-brain barrier were markedly decreased after alemtuzumab. Q, quotient. Reference values: CD19+ B cell in peripheral blood 0.175–0.575 GPt/L; CD3+ T cell in peripheral blood 1.5–4.0 GPt/L; CSF cell count <5 MPt/L; total protein 150–450 m/L; QAlbumin 6.5; intrathecal IgG, IgM or IgA synthesis 0%.

Subsequently, in October 2015 she suffered another severe relapse with hemiparesis and aphasia unresponsive to steroids, and plasmapheresis

necessitating intensive care with intubation. MRI revealed an increasing number of contrast-enhancing lesions in cerebral and spinal MRI

(Figure 1(a), second row). The MRI at this stage revealed numerous new acute inflammatory lesions of similar pattern as in the initial relapse. At this stage, multifocal lesions in the brainstem were detectable in the MRI. Inadequate response toward the intensive anti-inflammatory therapy led to another brain biopsy to rule out other differential pathologies than ongoing acute demyelination. This second biopsy confirmed the highly inflammatory, active demyelinating multiple sclerosis lesions with antibody/complement deposits (multiple sclerosis pattern II) (Figure 1(b)).

The first course of alemtuzumab was performed in the intensive care unit. Therapy was well tolerated. The clinical condition stabilized rapidly and the patient was extubated a few days after alemtuzumab treatment. After the second alemtuzumab cycle in October 2016 the patient had recovered, with an EDSS score of 3.5. MRI demonstrated lesion regression with resolved blood–brain barrier disruption, although peripheral B cells demonstrated an overshooting repopulation (Figure 1(a) third and fourth rows; Figure 1(c)).

Discussion

Characterizing the histopathology of early multiple sclerosis lesions, type II pattern multiple sclerosis has been described, involving antibodies and complement in lesion formation.^{6,7} This pattern is often associated with ring-enhancing MRI lesions as described in the published cases.^{3,4,8} Disease exacerbations in patients with antibody-mediated central nervous system demyelination such as multiple sclerosis pattern II or neuromyelitis optica spectrum disorders are known for mainly T cell directed multiple sclerosis therapies such as interferon-beta, natalizumab or fingolimod.^{6,9} The exact pathophysiological mechanisms for these observations are not yet clear, but might have also played a role in the three cases reported by Haghikia and colleagues and Barton and colleagues.^{3,4} Due to its mechanism of action, repopulation of distinct B cell subtypes is seen even 6 months after alemtuzumab application, whereas T cell subtype repopulation is delayed and decreased even after 12 months. Based on the different distribution of B and T cells after alemtuzumab, Barton and colleagues and Haghikia and colleagues supposed B cell-mediated severe clinical exacerbation. After initial depletion, they documented re-appearance of peripheral B cells and concluded relation to clinical disease activity and

development of tumefactive lesions in MRI, especially in B cell-driven multiple sclerosis subtypes. Here we present a case with underlying B cell-driven multiple sclerosis that impressively improves after alemtuzumab, although peripheral B cell repopulation took place. Although it cannot be excluded that disease exacerbation during alemtuzumab therapy may occur in single patients with a suggested underlying B cell-driven autoimmunity, our case proves that alemtuzumab may act as an effective rescue treatment in highly active antibody/complement-mediated multiple sclerosis type II patients.

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Conflict of interest statement

K. Akgün received personal compensation from Novartis, Biogen Idec, Sanofi Genzyme and Roche for consulting services. Imke Metz reports personal fees from BiogenIdec, Bayer Healthcare, Teva, Novartis, Genzyme and Roche, as well as grants from BiogenIdec, outside the submitted work. W. Brück has received honoraria for lectures by Bayer Vital, Biogen, Merck Serono, Teva, Genzyme, Roche and Novartis. He is a member of scientific advisory boards for Teva, Biogen, Novartis and Genzyme, and receives research support from Teva, Biogen, Genzyme and Novartis. H. Kitzler has received travel grants, speaker's honoraria, financial research support, consultancy fees from Bayer, Biogen Idec, Novartis and Teva. He served on advisory boards for Novartis and Biogen Idec. He received a research grant from Novartis. T. Ziemssen received personal compensation from Biogen Idec, Bayer, Novartis, Sanofi, Teva and Synthon for consulting services. Ziemssen received additional financial support for research activities from Bayer, Biogen Idec, Novartis, Teva and Sanofi Aventis.

Consent

The authors confirm that any aspect of the work covered in this manuscript that has involved human patients has been conducted with the ethical approval of all relevant bodies (institutional review board of the University Hospital of Dresden, EK348092014). The patient provided written informed consent for publishing this case report in an international medical journal.

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