Disseminated necrotizing leukoencephalopathy eight months after alemtuzumab treatment for multiple sclerosis

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To the editor

We report a case of disseminated necrotizing leukoencephalopathy (DNL) occurring after alemtuzumab treatment for multiple sclerosis (MS). A 33 year-old female patient with a 14-year history of highly active, relapsing-remitting MS despite treatment with interferons, natalizumab and fingolimod was administered 12 mg of alemtuzumab for five consecutive days. Alemtuzumab is a humanized monoclonal antibody directed against the CD52 antigen that significantly reduces relapses, MRI activity and the rate of sustained accumulation of disability [1]. Autoimmune disorders such as autoimmune thyroid disease occur in up to 28 % of patients after alemtuzumab therapy and are associated with the phase of immune reconstitution [2, 3]. In addition, respiratory infections are well known side effects observed in 60 % of patients [2]. Eight months after treatment, during a phase of clinically stable MS, the patient was admitted to the hospital due to anemia with low hemoglobin which was observed in her for the first time, and warm autoimmune hemolytic anemia was diagnosed. The hemoglobin dropped as low as 2.4 g/dl, requiring therapy with corticosteroids, intravenous immunoglobulins, plasma separation, cyclophosphamide and erythrocyte substitution. The anemia could not be stabilized. A lower respiratory tract infection with consecutive septic shock developed. The patient lost consciousness and required intubation. No focal neurological deficits were documented, and due to the fulminant disease course no MRI was performed. The patient died six days after admission and a brain autopsy was performed.

Autopsy revealed, besides characteristic inactive MS lesions, numerous small, round, disseminated and necrotizing lesions in the supratentorial white matter, the cerebellum and the brain stem including the pons. These lesions were characterized by numerous axonal spheroids and a pronounced macrophage infiltrate in the absence of lymphocytes, consistent with DNL (Fig. 1) [4, 5].

Severe autoimmune hemolytic anemia has been reported after alemtuzumab therapy, and may be caused by an immune dysregulation with the development of autoimmunity following drug application [6, 7]. Paradoxically, alemtuzumab is also used to treat autoimmune hemolytic anemia [6, 8].

The etiology of DNL is still unknown. It was first described in patients with brain tumors treated with high-dose, methotrexate-based chemotherapy and whole brain irradiation [4, 5]. DNL has been found in immunosuppressed patients, including HIV patients [1]. Single case reports described DNL occurring with infectious diseases and sepsis, suggesting an excessive inflammatory response as etiologic factor [9]. Symptoms occur directly after therapy or many months later [4]. Thus, DNL in our patient may be related to the direct effects of alemtuzumab, e.g. immunosuppression, or it could be linked to side effects of alemtuzumab infusions such as the respiratory tract infection with sepsis or the warm hemolytic anemia and its immunosuppressive treatment. The autopsy showed acute necrotizing lesions, suggesting they developed simultaneously with the sepsis and hemolytic anemia.

Clinical symptoms of DNL include irritability, somnolence, rapidly progressive subcortical dementia and coma with fatal outcome. Neuroimaging may be normal...
in early stages and show white matter lesions, often calcified, in later stages [4]. The observed loss of consciousness in our patient may have been related to DNL. DNL can be difficult to recognize clinically and is thus easily overlooked.

In conclusion, the clinician should be aware of DNL as a possible direct or indirect side effect of alemtuzumab treatment in MS that is rare but severe, and has never before been described in the literature.

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