

Successful therapy with rituximab in three patients with probable neurosarcoidosis

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Abstract

Background: Neurosarcoidosis occurs in about 5–15% of patients with sarcoidosis. Therapy with corticosteroids is generally accepted as the first-line medication, followed by various immunomodulating and cytotoxic agents or combined therapy. However, some patients show an unsatisfactory outcome or have adverse events and require novel treatment strategies.

Methods: We describe three patients with systemic sarcoidosis and central nervous system involvement who received CD20-targeted B-cell depletion with rituximab.

Results: Treatment with rituximab was well tolerated and followed by marked remission in patients nonresponsive to other immunosuppressive agents.

Conclusion: Rituximab may be used for patients with neurosarcoidosis who are nonresponsive to established treatment regimes.

Keywords: B-cell depletion, CD-20, infliximab, neurosarcoidosis, sIL-2R

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Introduction

Sarcoidosis is a clinicopathological syndrome of unknown etiology characterized by noncaseous epithelioid granulomas which show a predilection for the lungs, skin and lymph nodes, but may affect any other organ.¹ Usually the disease starts between the ages of 20–40 years. The prevalence of central nervous system (CNS) involvement (neurosarcoidosis; NS) is about 5–15%.^{2,3} Clinical features of NS include, among other things, cranial neuropathy, seizure, aseptic meningitis, hydrocephalus and myelitis.^{2–4}

The most commonly used diagnostic criteria for NS were proposed by Zajicek and colleagues.⁵ The gold standard is histopathological confirmation from biopsy tissue; however, CNS tissue is rarely biopsied due to the risk of bleeding and subsequent neurological deterioration. Thus, diagnosis of NS may be challenging and is often made by exclusion of other entities using a combination of clinical presentation, imaging and laboratory work-up. Magnetic resonance imaging (MRI) often shows leptomeningeal involvement of the basilar meninges but virtually any portion of the CNS may be

affected.^{2,4} Currently, no reliable serologic marker exists. Laboratory testing includes serum angiotensin converting enzyme and soluble interleukin-2 receptor (sIL-2R) but both may also be negative in patients with biopsy proof of NS.² In contrast, cerebrospinal fluid (CSF) sIL-2R value was found to have a high sensitivity in NS.⁶

Corticosteroids are generally accepted as the first-line therapy. In severe and recurrent cases or in cases of steroid resistance immunomodulating or cytotoxic agents such as azathioprine (AZA), methotrexate (MTX), mycophenolate mofetil, chloroquine, and cyclophosphamide (CYP) can be considered as monotherapy or in combination with corticosteroids. Furthermore, the monoclonal immunoglobulin (Ig)G1 antibody, infliximab, has been employed in patients not responsive to other treatment strategies.

Here we report on three patients with progressive CNS sarcoidosis consecutively and successfully treated with rituximab. So far, only isolated case reports have described beneficial effects in patients who are refractory to first-line therapy.^{7,8}

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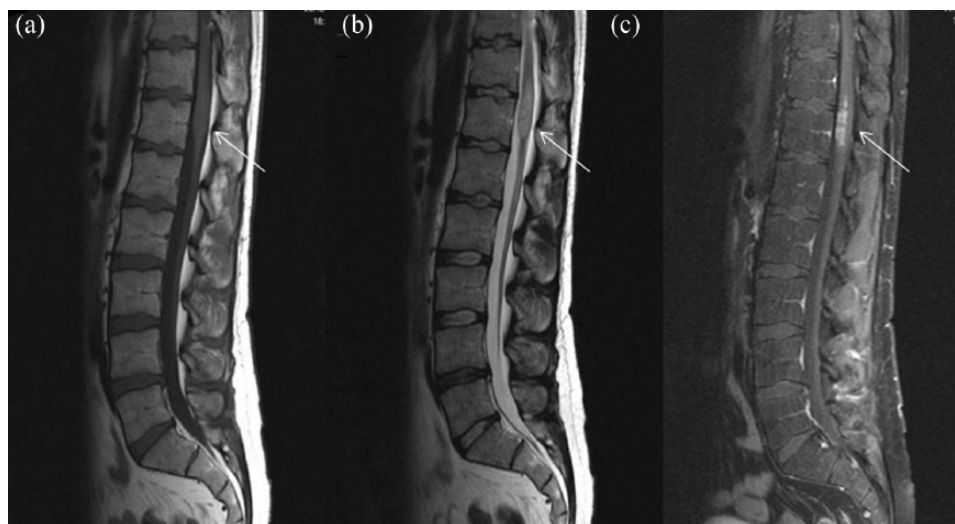


Figure 1. MRI of patient 2: Sagittal T1- (a) and T2-weighted (b) MRI depicts a new lesion in the thoracic cord (arrow) with contrast enhancement on the corresponding T1-weighted images (c). MRI, magnetic resonance imaging.

Patients and methods

Between 2013 and 2017 three patients diagnosed with definitive systemic sarcoidosis and consistent neurological involvement underwent B-cell targeted therapy with the anti-CD20 antibody, rituximab. Routine laboratory testing, including serological markers of other immune disease, were without pathological findings. Other viral or bacterial infections were excluded in the CSF and serum.

CD20 is a transmembrane protein present on the surface of most B-cell lymphocytes.⁹ Patients were treated and followed at the Department of Neurology at St. Josef Hospital Bochum, Germany and at the Department of Neurology at Katholische Kliniken Ruhrhalbinsel, Essen Germany. Inclusion criteria were clinical and histological proof of sarcoidosis and a probable diagnosis of NS based on the diagnostic criteria proposed by Zajicek and colleagues.⁵ All patients did not respond to first-line therapy with corticosteroids nor to alternative treatment regimes, nor showed adverse events. In one case treatment was changed because of the detection of anti-infliximab antibodies accompanied by a low serum drug concentration. There is no consensus about the optimum rituximab administration scheme and especially in patients who previously received other immunosuppressive agents, there is a potential risk of severe infections with the use of rituximab. After microbial screening and urine analysis, all patients received one 500 mg rituximab infusion systematically together with methylprednisolone 100 mg, paracetamol

and antihistamine single-shot premedication. In all patients, rituximab led to a complete B-cell depletion, defined as CD19 count <1%, and was followed by maintenance rituximab infusions (250–500 mg) every 6–9 months before CD19 repopulation occurred, because B-cell repopulation increases the risk of relapse.

The present case series was discussed with the responsible ethics committee of the Ruhr-University in Bochum, Germany. The ethics committee did not consider an ethical application necessary owing to the small number of patients included and the retrospective nature of the analysis. All participants provided written informed consent before undergoing any procedures and provided written informed consent for publication of the data in an international medical journal. The data concerning this study were stored separately from the hospital charts of the patients.

Case reports

Case 1

A 51-year-old woman with a history of pulmonary sarcoidosis and a syringomyelia (initial diagnose in 2002) between Th₄ and Th₅ presented in 2012 with dizziness, headache, left thigh hypoesthesia and progressive fatigue. Her treatment regime included AZA (100 mg/day) and MTX (5 mg/week). Neurological examination on admission confirmed a mild left thigh hypoesthesia without dermatome

reference. A cerebral MRI demonstrated numerous T2-hyperintense lesion in proximity of the frontal horn of the left and right ventricle. Thoracic MRI was unchanged to previous MRI examinations. Syringomyelia was unrelated to NS.

Under the suspect of CNS involvement her treatment regime was changed to AZA (100 mg/day) and infliximab (5 mg/kg body weight) which led to a clinical and radiological stability over 24 months.

In 2014 a severe increase of serum transaminases forced treatment discontinuation. Following normalization of serum transaminases treatment was changed to infliximab (5 mg/kg body weight every 4 weeks) and dimethyl fumarate (DMF; 5 mg/kg body weight). However, recurrent infections like a sacroiliac joint infection and a plantar fasciitis again necessitated treatment interruption.

The authors decided to finish treatment with infliximab and to initialize treatment with rituximab. Subsequent to rituximab, the patient was progression-free and reported on a significant amelioration of fatigue. So far, she received 500 mg rituximab three times. At the last visit (September 2017) clinical stability was constantly demonstrated and neuroradiological screening also did not reveal disease progression. Additionally, the patient was free of recurrent infections.

Case 2

A 50-year-old woman with a known sarcoidosis mimicking a vasculitis presented in 2011 with sensory disturbances of both legs described as a feeling of heaviness and clumsiness. Neurological examination on admission revealed a mild gait disturbance. At that time, an immunosuppressive therapy with corticosteroids (60 mg/day) was already ongoing. MRI showed an intramedullary lesion in the cervical and thoracic cord between C₂ and Th₃ vertebrae. The lesion was mostly isointense on T2-weighted sequences and showed contrast enhancement (Figure 1). The diagnosis of NS was considered and treatment with infliximab (5 mg/kg body weight, every 4 weeks) started. Follow-up examinations every 4–6 weeks after the beginning of infliximab showed a progressive clinical improvement until an almost complete remission after eight treatment cycles. For some reason, treatment with infliximab was not continued in the course and apart from corticosteroids (60 mg/day)

no other immunosuppressive medication was started. A few weeks after the suspension of infliximab, the patient developed the same gait disturbances as at the first presentation. An externally induced immunosuppression with AZA (200 mg/day) was without any beneficial effect and the patient reported progressive sensory disturbances in both legs. Neurological examination revealed an ascending hypoesthesia of both legs and gait ataxia. The patient was unable to walk >500 m without rest. The authors decided to interrupt AZA and to reuptake therapy with infliximab (5 mg/kg body weight). Again, infliximab led to a significant neurological improvement.

At the 13th infusion after the restarting of infliximab, anti-infliximab antibodies were detected in the serum. In parallel, the infliximab serum concentration was low ($\leq 0.1 \mu\text{g/ml}$). At that point in time, the patient showed neither clinical nor neuroradiological signs of disease progression. Nevertheless, infliximab therapy was switched to rituximab followed by maintenance rituximab infusions (500 mg) every 6–9 months. Following rituximab, there was continuous neurological stability. To date, the patient has received rituximab 500 mg three times. At the last follow up (October 2017) the patient demonstrated no neurological deficits and reported being well. The neuroradiological screening was also inconspicuous and no adverse events occurred.

Case 3

A 57-year-old man with an history of pulmonary sarcoidosis presented in March 2012 with a residual left facial paralysis and a right hemiparesis after left middle cerebral artery stroke in January 2012.

At hospitalization, his medication included AZA (100 mg/day). A cerebral T2-weighted MRI revealed a left parietal high-intensity lesion, unchanged to previous examination. A subsequent catheter angiography showed a segmental multiple narrowing in the distal part of the middle cerebral artery and multiple venous occlusions in the affected parietal area, high consistent with the hypothesis of a vasculitis associated with NS. In addition to AZA, infliximab (5 mg/kg body weight every 4 weeks) was started. Apart from that, the patient received aspirin 100 mg/day and underwent cardiologic work-up, including transesophageal echocardiography and continuous halter electrocardiograph monitoring.

Under combined therapy, the patient developed several adverse events like fever, fatigue, hip bone pain and ischemic strokes in September 2012, with the involvement of cranial nerves. Therefore, treatment with CYP (cumulative dose 670 mg/m²) was initiated instead of AZA with neurological and neuroradiological stability over a year.

In November 2013, a progressive third nerve palsy was reported. Due to disease progression and after microbial screening, we initiated treatment with rituximab. A decent clinical improvement was demonstrated. Currently, the patient receives rituximab (250–500 mg) every 6 months depending on his B-cell count, aiming to remain 0–5 cells/ μ l. No further ischemic strokes occurred and at the last visit the patient was still neurologically and neuroradiologically progression-free.

Discussion

Despite great efforts, sarcoidosis is still a disease of unknown etiology. Current pathogenetic concepts assume an exaggerated immune response which occurs in genetically susceptible individuals following exposure to a yet unidentified pathogenic antigen. While formation of noncaseating granulomas at sites of ongoing inflammation was basically considered as an antigen-mediated Th1 response, the involvement of Th17 inflammatory cascades, B cells and different cytokines is now obvious.¹² A Th1 response, promoting by cytokines like interferon gamma, is basically based on a proinflammatory cascade aimed to kill intracellular parasites.¹³ This process is able to start an autoimmune response and to keep it going. In order to avoid uncontrolled tissue damage, Th2 cytokines yield an anti-inflammatory response.¹³ Interleukin-17 and its cascade also play a strong role in the inflammatory process, producing CD4+ T cells and differentiating from classic Th1 and Th2 responses.¹⁴ B cells play a role in the humoral immunity by secreting antibodies, presenting antigens and secreting cytokines.¹⁵

In NS, noncaseating granulomas mostly affect the CNS even if there are few cases of a primary involvement of the peripheral nervous system (PNS).^{2,3} In CNS, granulomas have tropism for meninges, more rarely for pure cerebral tissue, in PNS for spinal root sheaths, which are an extension of pachymeninges.

In contrast with other organs, NS is less likely to spontaneously remit. Usually patients are treated with second- and third-line agents, including infliximab, early during disease.² Although blockage of tumor necrosis factor (TNF)- α with infliximab is effective in many patients, ongoing disease progression, development of anti-infliximab antibodies and adverse reactions may warrant treatment modification. In our case reports, infliximab was discontinued because of (a) recurrent infections, (b) disease progression and (c) detection of anti-infliximab antibodies. Anti-infliximab antibodies are thought to be the result of an immunological process, whereby, in the course of therapy, the patient mounts an immune response to infliximab. However, detection of anti-infliximab antibodies does not necessarily have to be followed by treatment failure and treatment discontinuation, because patients with high infliximab and low anti-infliximab antibody trough levels often maintain a clinical benefit. However, in the contrary case (high anti-infliximab antibody and low infliximab trough level) the predisposition for therapeutic failure grows.^{16,17}

All patients were switched to rituximab. Treatment with rituximab led to neurological improvement in two cases and to disease stabilization in one case and was generally well tolerated. No severe infections or malignancies were recorded during the whole follow up.

In literature, there are solely two case reports of refractory NS successfully treated with rituximab with variable dosing regimens.^{7,8} Rituximab is a monoclonal IgG1 chimeric antibody that selectively targets the protein CD20 expressed on the surface of B-cell lymphocytes. Treatment with rituximab induces depletion of circulating CD20+ B cells.^{10,11} The US Food and Drug Association and European Medicines Agency approved rituximab for the treatment of non-Hodgkin's lymphoma and rheumatoid arthritis but given the probably autoimmune-inflammatory etiology and limited therapies available, especially in aggressive forms of NS, rituximab might be an interesting alternative. In line, rituximab is used off-label in various inflammatory-autoimmune disorders of the CNS such as multiple sclerosis and neuromyelitis optica.^{18,19} The mechanisms of action by which rituximab exerts its effects in immunological disease and sarcoidosis are manifold. B cells produce autoreactive antibodies, act as antigen-specific antigen-presenting cells for T cells and secrete cytokines

and costimulatory molecules that activate macrophages, induces Th1 and Th2 differentiation and stimulate further B-cell proliferation.^{18,19} Moreover, B-cell depletion with rituximab reduces the local Th17 response, which in turn reduces inflammation.

Our results support the hypothesis that rituximab is beneficial and well tolerated in managing refractory NS. We propose that B-cell-directed therapies may become an attractive option. Further controlled studies are needed to confirm the efficacy and safety of rituximab in NS patients.

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Conflict of interest statement

The authors declare that there is no conflict of interest.

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