A case of CLIPPERS syndrome responsive to tocilizumab

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Neurol Neuroimmunol Neuroinflamm 2019;6:e545. doi:10.1212/NXI.0000000000000545

Chronic lymphocytic inflammation with pontine perivascular enhancement responsive to steroids (CLIPPERS) is an inflammatory disorder consisting of (1) subacute clinical brainstem signs and symptoms, (2) characteristic punctate and curvilinear perivascular peppercorn-like gadolinium enhancement of the pons, brachium pontis, and cerebellum in MRI, (3) dense perivascular CD4+ T cell predominant inflammatory cell infiltrates in biopsy, and (4) clinical and radiologic response to steroids in the absence of alternative diagnosis.1–3 There only exists sparse data from case reports regarding the use of corticosteroid-sparing agents with a probable therapeutic efficiency for methotrexate, cyclophosphamide, hydroxychloroquine, and azathioprine.4 Use and potential efficiency of the humanized monoclonal interleukin-6 receptor antagonist tocilizumab has not yet been reported in CLIPPERS.

Case report

In early 2007, after an upper respiratory tract infection, a 34-year-old female with no pertinent medical history started to gradually develop brainstem dysfunction (double vision, vertigo, and gait ataxia) and right occipital headache over a 3-month period. She also complained of brachiofacial paresthesias and prominent facial allodynia/hyperalgesia progressing to her upper chest.

Clinical neurologic examination showed diplopia when looking to the left, left-sided facial hypesthesia, positive right Babinski and bilateral Troemner reflexes as well as appendicular and truncal ataxia with a paraspastic and ataxic gait disorder.

MR imaging showed small infratentorial lesions in the pons, bilateral middle cerebral peduncles and medulla oblongata with associated strong “salt and pepper” like Gadolinium uptake, and linear appearance suggestive of a perivascular localization as well as an upper cervical spinal cord lesion (figure, A–E). Prominent extrapontine manifestations developed during the course of the disease (figure, F–H). Brain biopsy (right temporal lesion, figure, I–N) showed extensive perivascular, less marked vascular but also parenchymal infiltration of predominantly CD4+ T-lymphocytes and few B-lymphocytes without features of vasculitis (no destruction of the vessel wall with fibrinoid necrosis, leukocytoclasia, or fibrin thrombi). These biopptic features have been noted as a hallmark in CLIPPERS.5 Few small necrotic lesions were evident. An extensive workup for known infectious, inflammatory, and neoplastic etiologies was negative.

From 2007 to 2011, the patient received multiple doses of IV methylprednisolone and intrathecal triamcinolone with clinical and radiologic improvement (figure, O). However, this always only led to a short-term improvement with subsequent evidence of disease activity even under continued oral steroid tapers.
Therefore, nonsteroidal disease-modifying therapy was initiated. Under azathioprine therapy, the patient experienced a significant increase in infratentorial and especially supratentorial Gadolinium-enhancing lesions. She was switched to cyclophosphamide, which at first lead to a significant radiologic improvement. However, symptoms progressed in 2009 under ongoing cyclophosphamide treatment, which was stabilized by addition of tacrolimus. After 13 cycles and a cumulative dose of 24,800 mg, cyclophosphamide therapy was discontinued in December 2009 with consecutive clinical and radiologic worsening.

During a trial of TNF-α blockers with monthly infliximab infusions in 2010, no new or enlarging brain lesions were
observed even though there was continuing worsening of her gait dysfunction. Treatment with infliximab was stopped after an anaphylactic reaction and a following trial with etanercept was ineffective.

After a short phase of mycophenolate mofetil therapy and a 5-day cycle of plasmapheresis, treatment with tocilizumab was initiated in October 2011 (initially 480 mg IV monthly, then 162 mg SC weekly since 2016), under which the patient’s presentation rapidly stabilized and started to continuously improve both clinically and radiologically with no further signs of relapse (observation period: 6 years, last MRI brain and clinical follow-up in September 2017). The ongoing comedication with tacrolimus was tapered down and discontinued in 2015 without any symptomatic worsening.

Discussion

Our case fulfills the published diagnostic criteria of CLIPPERS and an extensive workup did not yield an alternative diagnosis. The development of prominent extrapontine supratentorial MRI lesions in the course of diseases has been observed in the majority of patients with CLIPPERS. Given the long observation period, this case report provides valuable insight in the efficiency of different steroid-sparing agents in one single case of CLIPPERS. Its key point is the long-standing relapse-free time period associated with tocilizumab treatment, which is remarkable given the patient’s previous extensive disease course with various relapses and nonresponse to multiple agents including cyclophosphamide. Tocilizumab’s immunologic effects are thought to be a result of the induction and expansion of regulatory T cells. Although generally well-tolerated, use of tocilizumab requires a careful risk-benefit analysis, potential adverse events include severe infections and gastrointestinal perforations.

Author contribution

T. Rempe: drafting/revising the manuscript and analysis or interpretation of data. J.S. Becktepe: data acquisition. I. Metz: drafting/revising the manuscript, accepts responsibility for the conduct of research and will give final approval, and histologic analysis. W. Brück: data acquisition, drafting/revising the manuscript, accepts responsibility for the conduct of research and will give final approval, and acquisition of data. K.H. Sturner: drafting/revising the manuscript and analysis or interpretation of data. G. Deuschl: data acquisition, study concept or design, accepts responsibility for the conduct of research and will give final approval, and study supervision. D. Berg: drafting/revising the manuscript, analysis or interpretation of data, and accepts responsibility for the conduct of research and will give final approval. R. Baron: study concept or design, analysis or interpretation of data, accepts responsibility for the conduct of research and will give final approval, and acquisition of data. R. Zeuner, data acquisition, analysis or interpretation of data, accepts responsibility for the conduct of research and will give final approval, and acquisition of data. F. Leypoldt: data acquisition, drafting/revising the manuscript, study concept or design, and analysis or interpretation of data.

Study funding

No targeted funding.

Disclosure

T. Rempe reports no disclosures. J.S. Becktepe received travel funding from Ipsen Pharma. I. Metz served on the advisory board of Roche; received speaker honoraria and travel funding from Biogen, Bayer Healthcare, Teva, Serono, Novartis, and Genzyme; received research support from Biogen; and received research support from the German Ministry for Education and Research. W. Bruck served on the advisory boards of Genzyme, Novartis, MedDay, Biogen, and Teva; received speaker honoraria from Teva, Sanofi, Genzyme, Novartis, Merck Serono, Biogen, Roche, and Bayer; served on the editorial boards of Therapeutic Advances in Neurologic Disorders, MS International and Neuropathology, and Applied Neurobiology; received research support from Teva, Novartis, Biogen, Genzyme, MedDay, German Research Foundation, German Ministry for Education and Research, Tschira Foundation, and German MS Society; and was an expert witness for Teva; K.H. Sturner received travel funding and speaker honoraria from Biogen, Merck, Roche, Sanofi, and Geynzyme; and received research support from Biogen and BMBF; G. Deuschl served on the scientific advisory boards of Medtronic and Boston Scientific; received publishing royalties from Thieme; and received research support from Biogen and German Ministry of Education and Research; D. Berg served on the scientific advisory boards of Biogen, Bial, Lundbeck, and UCB Pharma; received travel funding and/or speaker honoraria from Desitin, Pfizer, Lundbeck, Boehringer, Coppenrath, Grünenthal, JPND, Apotheke Wirtschaftsdienst, Asklepios Kliniken Hamburg, Bayer Vital, BIAL Deutschland, Weser, AbbVie Deutschland, TEVA, Dekanat der CAU, Ärztekammer Schleswig-Holstein, Deutsche Parkinson Vereinigung, Janssen Neuroscience Network, Uniklinik, Humanitas Research Hospital-Mailand, Universitätsmé dizin Rostock, Deutsche Gesellschaft für Neuroologie, Universitätssüdklinikum Tübingen, Aklepios Klinik Altona, NDR Fernsehen, Seegerber Kli niken, Deutsche Parkinson Gesellschaft, Scandinavian Movement Disorder Society, and International Parkinson and Movement Disorder Society; served as an editor for Movement Disorders and a coeditor for Aktuelle Neurologie; received publishing royalties from Thieme; and received research support from Medtronic and German Ministry of Education and Research; and D. Berg served on the scientific advisory boards of Biogen, Bial, Lundbeck, and UCB Pharma; received travel funding and/or speaker honoraria from Desitin, Pfizer, Lundbeck, Boehringer, Coppenrath, Grünenthal, JPND, Apotheke Wirtschaftsdienst, Asklepios Kliniken Hamburg, Bayer Vital, BIAL Deutschland, Weser, AbbVie Deutschland, TEVA, Dekanat der CAU, Ärztekammer Schleswig-Holstein, Deutsche Parkinson Vereinigung, Janssen Neuroscience Network, Uniklinik, Humanitas Research Hospital-Mailand, Universitätsmé dizin Rostock, Deutsche Gesellschaft für Neuroologie, Universitätssüdklinikum Tübingen, Aklepios Klinik Altona, NDR Fernsehen, Seegerber Kliniken, Deutsche Parkinson Gesellschaft, Scandinavian Movement Disorder Society, and International Parkinson and Movement Disorder Society; served as a coeditor for DGNeurologie; and served on the editorial boards of Movement Disorders Clinical Practice Journal and Neurological Research and Practice; served as an associate editor for the Journal of Parkinson’s Disease; is a member of the scientific advisory
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Publication history
Received by Neurology: Neuroimmunology & Neuroinflammation September 11, 2018. Accepted in final form January 8, 2019.

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