Journal of Neuroimmunology 334 (2019) 576997

Contents lists available at ScienceDirect

Journal of Neuroimmunology

journal homepage: www.elsevier.com/locate/jneuroim

Short communication

Intrathecal rituximab in immunoglobulin G4-hypertrophic pachymeningitis

Carolina Soares[a,b,*], Diana F. Martins[c], Roberto Pestana-Silva[c], Mrinalini Honavar[e], Olinda Faria[d], Pedro Abreu[a,b], Andreia Costa[a,b]

[a] Department of Neurology, Centro Hospitalar Universitário de São João, E.P.E., Porto, Portugal
[b] Department of Clinic Neurosciences and Mental Health, Faculty of Medicine of University of Porto, Porto, Portugal
[c] Department of Anatomic Pathology, Centro Hospitalar Universitário de São João, E.P.E., Porto, Portugal
[d] Department of Ophthalmology, Centro Hospitalar Universitário de São João, E.P.E., Porto, Portugal
[e] Department of Anatomic Pathology, ULS de Matosinhos - Hospital de Pedro Hispano, Matosinhos, Portugal

ARTICLE INFO

Keywords:
IgG4 disease
Hypertrophic pachymeningitis
Intrathecal rituximab

ABSTRACT

We describe the case of a 69-year-old man who presented with symptoms of headache and severe vision loss due to G4 immunoglobulin (IgG4) hypertrophic pachymeningitis (HP). The patient was initially responsive to corticotherapy, but vision loss progressed when steroid therapy was first tapered. No improvement was noticed with intravenous rituximab. The patient showed clinical and radiological improvement after intrathecal rituximab, which can be an efficacious alternative treatment option.

1. Report of a case

In 2017, a 69-year-old man with well-controlled type 2 diabetes developed progressive right ptosis and vision loss, with moderately intense fronto-orbital headache.

First neurologic examination revealed right eye exotropia and impaired adduction with a right Marcus-Gunn pupil. Progressive decrease of visual acuity of the right eye was demonstrated, 20/30 OD on the first assessment with progressive deterioration towards finger counting. Brain CT scan depicted a right basal expansive lesion with homogeneous enhancement, and erosion of frontal and ethmoidal bones extending to paranasal sinuses and orbit. Brain MRI confirmed a right fronto-basal lesion, hypointense in T1 and T2-weighted images, without restriction on diffusion study, with hypersignal in the right frontal lobe on T2-fluid attenuation inversion recovery and meningeal thickening and dural enhancement along the falx and right frontal area in T1-weighted images (Fig. 1A–C).

An exhaustive laboratory study for inflammatory/autoimmune, neoplastic and infectious diseases, including serum G4 immunoglobulin (IgG4) was negative. CSF analysis showed a total cell count of 5 leukocytes/uL, a slight increase of total protein count (0.89 g/L), elevated IgG level (9.10 mg/dL), positive extra bands in the CSF and cytology negative for malignant cells.

Thoracic and abdominopelvic CT and gallium scintigraphy were normal. Positron emission tomography revealed no extracranial hypermetabolic areas.

The patient received empirical corticotherapy with good response. However, as steroid therapy was tapered, bilateral progressive deterioration of visual acuity occurred with bilateral increase of the meningeal thickening and parenchymal edema on brain MRI. A meningeal biopsy showed a lymphoplasmacytic infiltrate and fibrosis arranged in a storiform pattern with an increased number of IgG4-expressing plasma cells (more than 10 cells/per high-power field), consistent with IgG4-related disease (Fig. 2I–L).

Despite optimizing treatment with PO corticosteroids, four months later the patient presented almost blind, which failed to improve a 5-day course of IV methylprednisolone at 1000 mg/day, followed by PO prednisolone (1 mg/kg/day). Subsequently, treatment with IV rituximab (375 mg/m^2 in two perfusions 2 weeks apart) was performed and CD19+ lymphocytes count in CSF and peripheral blood (PB) were monitored by flow cytometry to evaluate treatment response (Fig. 1H). Intravenous rituximab failed to induce clinical and radiologic improvement (Fig. 1D–E). Follow-up optical coherence tomography (OCT) depicted bilateral optic fiber atrophy, with a very modest improvement in visual acuity in the left eye. Additionally, PB CD19+ lymphocytes were suppressed during four months, while those in CSF increased: 50 vs 156 CD19+/ml before and after rituximab (Fig. 1H). Consequently, administration of intrathecal rituximab (2 infusions according to protocols adopted for CNS lymphomas (Rubenstein et al., 2003) was initiated. One month later, PB and CSF CD19+ lymphocytes were both suppressed (Fig. 1H). Vision improved, with recognition of faces in photographs, finger counting at 1 m in the left eye (20/800 OE) and

* Corresponding author at: Alameda Professor Hernâni Monteiro, 4200-319 Porto, Portugal
E-mail address: carolina.soares@chsj.min-saude.pt (C. Soares).

https://doi.org/10.1016/j.jneuroim.2019.576997
Received 14 April 2019; Received in revised form 29 May 2019

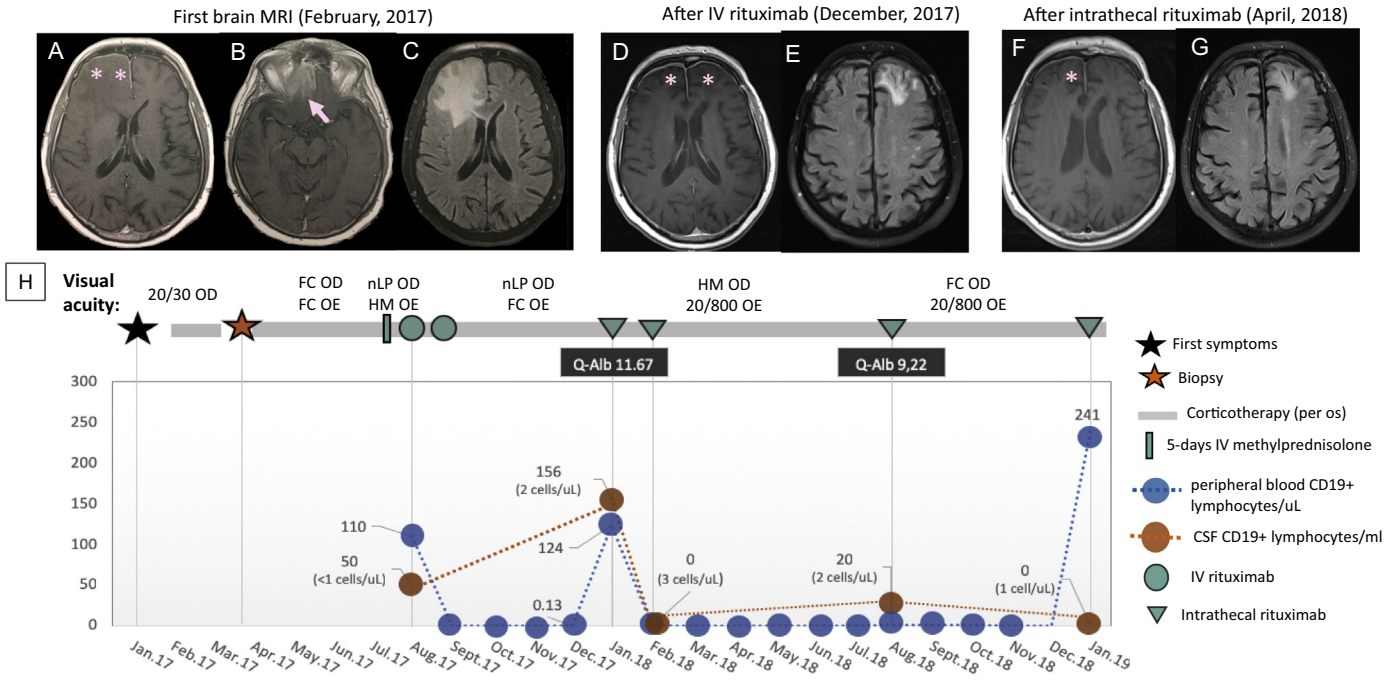

Fig. 1. Imaging and counting of serum and CSF CD19+- expressing B cells.
A. Post gadolinium T1-weighted imaging on axial MRI: diffuse thickening and enhancement of right frontal dura mater and falx (*). B. Post gadolinium T1-weighted imaging on axial MRI: right fronto-basal lesion with homogeneous enhancement indicated by arrow. C. T2-fluid attenuation inversion recovery on axial MRI showing a hypersignal of white mater of right frontal lobe corresponding to cerebral edema. D. Post gadolinium T1-weighted imaging on axial MRI: bilateral thickening and enhancement of frontal dura mater. E. T2-fluid attenuation inversion recovery on axial MRI showing cerebral edema of left frontal lobe. F. Post gadolinium T1-weighted imaging on axial MRI: decrease of left frontal thickening and enhancement. G. T2-fluid attenuation inversion recovery on axial MRI showing cerebral edema decrease of left frontal lobe. H. Counting of PB and CSF CD19+ expressing B-cells during treatment with rituximab and visual acuity assessment; total cell count in CSF by cytomorphologic examination is in parentheses, VA (visual acuity), FC (finger counting), nLP (no light perception), HM (hands movement), Q-Alb (CSF/serum albumin ration).

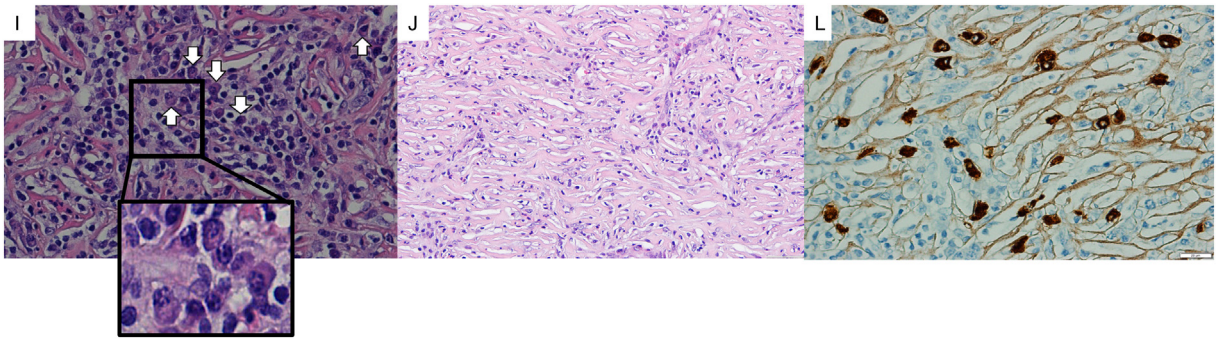

Fig. 2. Histology/immunohistochemistry.
I. Lymphoplasmacytic infiltrate with plasma cells indicated by arrows (hematoxylin–eosin stained slide, 400×). J. Fibrosis arranged in a storiform pattern; there were no signs of obliterative phlebitis (hematoxylin–eosin stained slide, 200×). L. More than 10 IgG4-expressing plasma cells per high power field (Mouse monoclonal antibody, MRQ-44, Roche, 400×).

perception of hands movement in the right eye. OCT maintained bilateral temporal optic fibers loss, however brain MRI showed improvement with a decrease in left frontal meningeal thickening, brain edema and diminished involvement of paranasal sinuses and orbit (Fig. 1F–G). Six months later, an increase of CD19+ count in CSF (20 CD19+/ml) were noticed and a third infusion of intrathecal rituximab was performed, showing subsequent sustained PB and CSF CD19+ suppression and the patient was able to count fingers at 1 m with right eye (Fig. 1H).

2. Data availability statement

Anonymized data relating to this case will be made available by the authors upon request from a qualified physician or investigator. The patient provided her written consent to publish his case.

3. Discussion

We describe a case of IgG4-HP that potentially demonstrates intrathecal administration of rituximab as an alternative therapy in aggressive and resistant relapsing form of the disease.

IgG4-related disease is a recently recognized fibro-inflammatory condition that has been described in virtually every organ system and its spectrum encompasses IgG4-HP (Lu et al., 2014; AbdelRazek et al., 2018). The diagnosis and management of IgG4-HP can be challenging, requiring a meticulous exclusion of infectious, inflammatory/

autoimmune and neoplastic causes. It must be borne in mind that serum IgG4 can be normal in up to 30% of patients with biopsy proven IgG4-related disease (AbdelRazek et al., 2018), as in our patient. Brain MRI shows dural thickening, but our patient also had cerebral edema, bone erosion and paranasal sinuses and orbit involvement, which are more rarely described in literature and depict the aggressive nature of the active inflammatory process (Lu et al., 2014; AbdelRazek et al., 2018).

The pathophysiologic mechanism remains unknown, but crucial interactions occur between B-cells (B lymphocytes and plasmablasts) and CD4+ T lymphocytes (T-follicular helper cells and cytotoxic T lymphocytes), culminating in potential targets for therapy (AbdelRazek et al., 2018). An international consensus statement recommends glucocorticoids as first-line treatment (Khosroshahi et al., 2015), nevertheless steroids often fail to induce durable remissions and morbidity from lengthy courses is considerable. These considerations justify the use of B-cell depletion with rituximab and there is an emerging literature about its intravenous administration in IgG4-HP, which seems to be effective as second line therapy in refractory and severe IgG4-related disease (Khosroshahi et al., 2012; Shapiro et al., 2012; Liao et al., 2014; Carruthers et al., 2015; AbdelRazek et al., 2018; Mageau et al., 2018).

Our patient, who was steroid-unresponsive, started intravenous rituximab (a total of two perfusions 2 weeks apart). We assessed treatment response by serial neurological and ophthalmological observations, orbits and brain MRI findings, and monitoring of PB and CSF CD19+ cells before and after treatment (Khosroshahi et al., 2010; Wallace et al., 2015). Rituximab has a high molecular weight which impairs penetrance through blood-brain barrier after intravenous infusion, usually reaching 0,1% of serum concentration in the CSF (Rubenstein et al., 2003; Liao et al., 2014; Della-Torre et al., 2018). In our patient, CD19+ B-cells in CSF were not as effectively depleted as their PB counterparts and after 2 infusions of IV rituximab the CD19+ count in CSF doubled (Fig. 1H). CD19+ B cells were depleted in PB within 1 month after IV rituximab. However, the PB CD19+ B-cell population was reconstituted within 5 months after rituximab therapy (124 CD19+/uL), indicating that the inhibitory effect of rituximab on peripheral B cells was temporary.

Recently, *Della-Torre* and colleagues (Della-Torre et al., 2018) advocated intrathecal administration of rituximab in patients who fail to improve after its intravenous administration. Due to the active and severe inflammation in the intrathecal compartment and no response to systemic immunosuppressive treatment, we decided to administer rituximab intrathecally, after obtaining patients' informed consent and ethical approval.

Before intrathecal administration of rituximab, cytomorphologic examination of CSF revealed 2 cells/uL, corresponding to 156 CD19+/ml in flow cytometry (18.20%), increased protein count (1.13 g/L) and high CSF/serum albumin ration (Q-Alb), reflecting blood-CSF barrier damage and active intrathecal inflammation (Fig. 1H). Six months after intrathecal administration of rituximab, our patient had 20 CD19+/ml in CSF (2.4%), a decrease in total protein count (0.82 g/L) and normal Q-Alb. Our patient reported visual improvement and brain and orbits MRI depicted a decrease in meningeal thickening, parenchymal edema and orbit involvement. Interestingly, intrathecal administration of rituximab induced a more sustained suppression of peripheral B-cells when compared to IV administration. It is a common misconception that a drug injected into CSF distributes deep into brain tissue. In fact, when injected into the CSF drugs distribute to the ependymal surface of brain or spinal chord, but not to the deeper parenchyma, and are quickly and preferentially distributed to the blood circulation (Pardridge, 2016). We suggest that the observed therapeutic effects are probably mediated in the periphery, after the intrathecally rituximab has been redistributed to the blood circulation a few hours after administration.

To our knowledge, only one successful case on intrathecal administration of rituximab in a patient with IgG4-HP was reported (Della-Torre et al., 2018). We report a clinical, radiological and immunological response to intrathecal rituximab in refractory IgG4-HP that reinforces its role as an efficacious alternative treatment option.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jneuroim.2019.576997.

Study funding

None.

Declaration of Competing Interests

None.

Acknowledgment

The authors thank the patient for cooperation and encouragement for publication.

References

AbdelRazek, M.A., Venna, N., Stone, J.H., 2018. IgG4-related disease of the central and peripheral nervous systems. Lancet Neurol. 17 (2), 183–192.

Carruthers, M.N., Topazian, M.D., Khosroshahi, A., Witzig, T.E., Wallace, Z.S., Hart, P.A., Deshpande, V., Smyrk, T.C., Chari, S., Stone, J.H., 2015. Rituximab for IgG4-related disease: a prospective, open-label trial. Ann. Rheum. Dis. 74 (6), 1171–1177.

Della-Torre, E., Campochiaro, C., Cassione, E.B., Albano, L., Gerevini, S., Bianchi-Marzoli, S., Bozzolo, E., Passerini, G., Lanzillotta, M., Terreni, M., Callea, M., Trimarchi, M., Mortini, P., Tresoldi, M., Acerno, S., Dagna, L., 2018. Intrathecal rituximab for IgG4-related hypertrophic pachymeningitis. J. Neurol. Neurosurg. Psychiatry 89 (4), 441–444.

Khosroshahi, A., Wallace, Z.S., Crowe, J.L., Akamizu, T., Azumi, A., Carruthers, M.N., Chari, S.T., Della-Torre, E., Frulloni, L., Goto, H., Hart, P.A., Kamisawa, T., Kawa, S., Kawano, M., Kim, M.H., Kodama, Y., Kubota, K., Lerch, M.M., Lohr, M., Masaki, Y., Matsui, S., Mimori, T., Nakamura, S., Nakazawa, T., Ohara, H., Okazaki, K., Ryu, J.H., Saeki, T., Schleinitz, N., Shimatsu, A., Shimosegawa, T., Takahashi, H., Takahira, M., Tanaka, A., Topazian, M., Umehara, H., Webster, G.J., Witzig, T.E., Yamamoto, M., Zhang, W., Chiba, T., Stone, J.H., G. R. D. Second International Symposium on Ig, 2015. International consensus guidance statement on the management and treatment of IgG4-related disease. Arthritis Rheum. 67 (7), 1688–1699.

Khosroshahi, A., Bloch, D.B., Deshpande, V., Stone, J.H., 2010. Rituximab therapy leads to rapid decline of serum IgG4 levels and prompt clinical improvement in IgG4-related systemic disease. Arthritis Rheum. 62 (6), 1755–1762.

Khosroshahi, A., Carruthers, M.N., Deshpande, V., Unizony, S., Bloch, D.B., Stone, J.H., 2012. Rituximab for the treatment of IgG4-related disease: lessons from 10 consecutive patients. Medicine (Baltimore) 91 (1), 57–66.

Liao, B., Kamiya-Matsuoka, C., Fang, X., Smith, R.G., 2014. Refractory IgG4-related intracranial hypertrophic pachymeningitis responded to rituximab. Neurol. Neuroimmunol. Neuroinflamm. 1 (4), e41.

Lu, L.X., Della-Torre, E., Stone, J.H., Clark, S.W., 2014. IgG4-related hypertrophic pachymeningitis: clinical features, diagnostic criteria, and treatment. JAMA Neurol. 71 (6), 785–793.

Mageau, A., Shor, N., Fisselier, M., Aboab, J., Lecler, A., Rebours, C., Adle-Biassette, H., Gout, O., Deschamps, R., 2018. Rituximab for corticosteroid-resistant relapsing IgG4-related intracranial pachymeningitis: report of two cases. Pract. Neurol. 18 (2), 159–161.

Pardridge, W.M., 2016. CSF, blood-brain barrier, and brain drug delivery. Expert Opin. Drug Deliv. 13 (7), 963–975.

Rubenstein, J.L., Combs, D., Rosenberg, J., Levy, A., McDermott, M., Damon, L., Ignoffo, R., Aldape, K., Shen, A., Lee, D., Grillo-Lopez, A., Shuman, M.A., 2003. Rituximab therapy for CNS lymphomas: targeting the leptomeningeal compartment. Blood 101 (2), 466–468.

Shapiro, K.A., Bove, R.M., Volpicelli, E.R., Mallery, R.M., Stone, J.H., 2012. Relapsing course of immunoglobulin G4-related pachymeningitis. Neurology 79 (6), 604–606.

Wallace, Z.S., Mattoo, H., Carruthers, M., Mahajan, V.S., Della Torre, E., Lee, H., Kulikova, M., Deshpande, V., Pillai, S., Stone, J.H., 2015. Plasmablasts as a biomarker for IgG4-related disease, independent of serum IgG4 concentrations. Ann. Rheum. Dis. 74 (1), 190–195.