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Hypertrophic Pachymeningitis with Persistent Intrathecal Inflammation Secondary to Neurosarcoidosis Treated with Intraventricular Chemotherapy: A Case Report

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Keywords

Hypertrophic pachymeningitis · Neurosarcoidosis · Intraventricular chemotherapy · Cytokines · Case report

Abstract

Hypertrophic pachymeningitis (HP) is a rare immune-mediated disease characterized by thickening of the dura mater with consecutive cranial neuropathy. While HP is usually treated with systemic immunotherapies, response to therapy is variable and may be limited by insufficient drug concentrations in the brain. We report on a 57-year-old patient with HP manifesting with vision and hearing loss who had sustained clinical progression despite various systemic immunotherapies. Intraventricular chemotherapy with methotrexate, cytarabine, and dexamethasone was initiated. We present clinical, imaging and cerebrospinal fluid (CSF) findings, including cytokine levels before and after intraventricular treatment: rapid decrease

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of cell count, lactate and profibrotic cytokine levels in the CSF following intraventricular chemotherapy was paralleled by a mild reduction of dura thickness in MRI. The already severely impaired visual acuity and hearing loss did not progress further. Treatment was complicated by exacerbation of previously subtle psychiatric symptoms. Follow-up was terminated after 6 months as the patient suffered from a fatal ischemic stroke. Autopsy revealed neurosarcoidosis as the underlying cause of HP. This case report suggests that intrathecal chemotherapy can reduce the inflammatory milieu in the CNS and should be considered for treatment-refractory HP before irreversible damage of cranial nerves has occurred.

Introduction

Hypertrophic pachymeningitis (HP) is a rare immune-mediated disease that typically presents with headache and cranial neuropathy [1]. Characteristic MRI findings include thickening of the dura mater with gadolinium enhancement [2]. HP can develop secondary to IgG4-related disease, myeloperoxidase antineutrophil cytoplasmic antibody (MPO-ANCA)-associated vasculitis, neurosarcoidosis or infectious diseases. If no underlying condition can be identified, it is termed idiopathic HP (iHP) [1, 3, 4]. Treatment for HP includes systemic corticosteroids, rituximab, and other immunosuppressants, but response to therapy may be poor, potentially related to insufficient drug concentrations in the brain. We report on a patient with progressive sensorineural hearing and visual loss initially diagnosed with iHP after extensive diagnostic assessment including dural biopsy, who had marked cerebrospinal fluid (CSF) inflammation and was treated with intraventricular chemotherapy.

Case Presentation

A 57-year-old man first presented to our hospital in 2014 due to progressive hearing and visual loss over the previous 3 years. Except for a history of recurrent anterior uveitis of both eyes and secondary glaucoma on the left, his past medical history was unremarkable. On examination, vision on the right eye was intact but on the left eye he could only distinguish light and darkness. Hearing was impaired on both sides (left>right). The remaining neurological exam was normal and he denied having any headache or nausea.

Brain MRI showed retroclival and tentorial pachymeningeal gadolinium enhancement as well as enhanced cranial nerves V, VII, and VIII. There were no further imaging signs of intracranial hypotension, such as venous engorgement or subdural collection. CSF analysis revealed a marked lymphocytic pleocytosis (844 cells/μL; ref. <5/μL) and increased lactate (34.4 mg/dL; ref. <22 mg/dL). Blood-brain barrier permeability was disturbed as evidenced by an elevated CSF protein (1485 mg/L; ref. 150–450 mg/L) and albumin quotient (Q_{Alb} = 21.4; ref. <4.07 based on Q_{Alb} = (4+age)/15). Reiber diagrams revealed an intrathecal IgG and IgA synthesis (15% and 39%, respectively). Soluble interleukin-2 receptor was elevated in CSF (287 IU/mL; ref. <50 IU/mL).

Extensive rheumatologic studies, including ANA screening, rheumatoid factor, antineutrophil cytoplasmic antibodies and HLA-B27 genotyping, remained negative. Serum immunoglobulin G subclasses 1–4, CD4/8 ratio in blood and CSF, serum angiotensin converting enzyme and serum soluble interleukin-2 receptor were normal. *M. tuberculosis* CSF PCR and interferon-gamma release assay of peripheral blood were negative.

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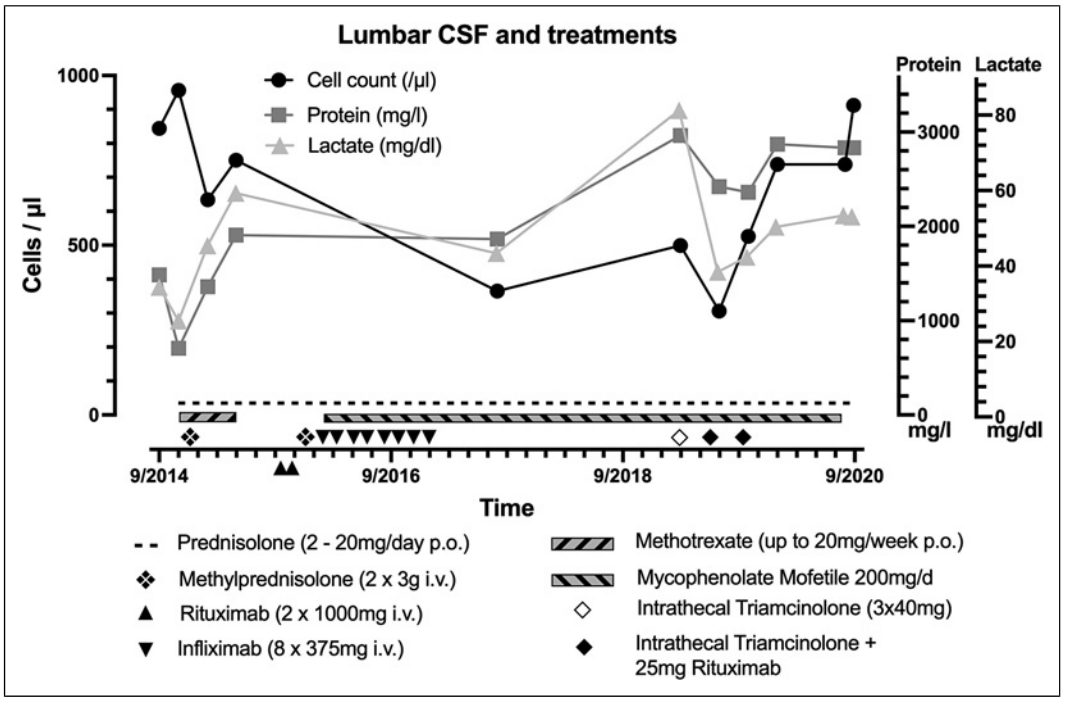

Fig. 1. Lumbar CSF findings during disease course and treatment over time. Note, that the first Y-axis on the right refers to protein in mg/L, the second to lactate in mg/dL.

Thoracic and abdominal-pelvic CT scan was normal. Dural biopsy obtained from right parietal burr-hole surgery showed typical dense connective tissue with low density of cells. There were no signs of inflammation, no granulomas, or signs of vasculitis and *M. tuberculosis* PCR from biopsy was negative. As known causes of HP could not be identified at this timepoint, a diagnosis of iHP was made.

Treatment was initiated with a pulsed intravenous methylprednisolone followed by oral prednisolone and oral methotrexate (up to 20 mg/week). Methotrexate had to be interrupted due to severe lymphocytopenia. Oral prednisolone was maintained throughout the years (2–20 mg/d). Despite treatment with various further immunosuppressants (for synopsis, see Fig. 1), symptoms slowly worsened over the years and inflammatory markers remained elevated.

In 2020, he was blind in the left eye and visual acuity was 0.4 in the right one. He had received a cochlea implant left in 2017 and audiogram revealed a severe sensorineural hearing impairment in the right ear. No further neurological signs were present. Furthermore, he was depressed and expressed suicidal thoughts due to loss of autonomy. His partner noted he was increasingly suspicious of strangers.

After informed consent, an Ommaya reservoir was implanted and treatment with 40 mg cytarabine, 15 mg methotrexate and 4 mg dexamethasone initiated and instilled 4 times over 2 weeks. At the fifth and last treatment session, dexamethasone was left out due to suspected corticosteroid-induced psychosis.

During the course of intrathecal treatment, CSF cell count and lactate levels decreased (Fig. 2a). Furthermore, an 18-plex immunoassay of CSF detected several cytokines before treatment (IL-6, IL-10, IL-17A, IL-27, TNF-α, GM-CSF) that were not present in CSF of 3 control patients with neurodegenerative diseases (Fig. 2c). After treatment, CSF levels of the pro-inflammatory, profibrotic cytokines IL-6 and IL-10 decreased. In addition, follow-up cerebral

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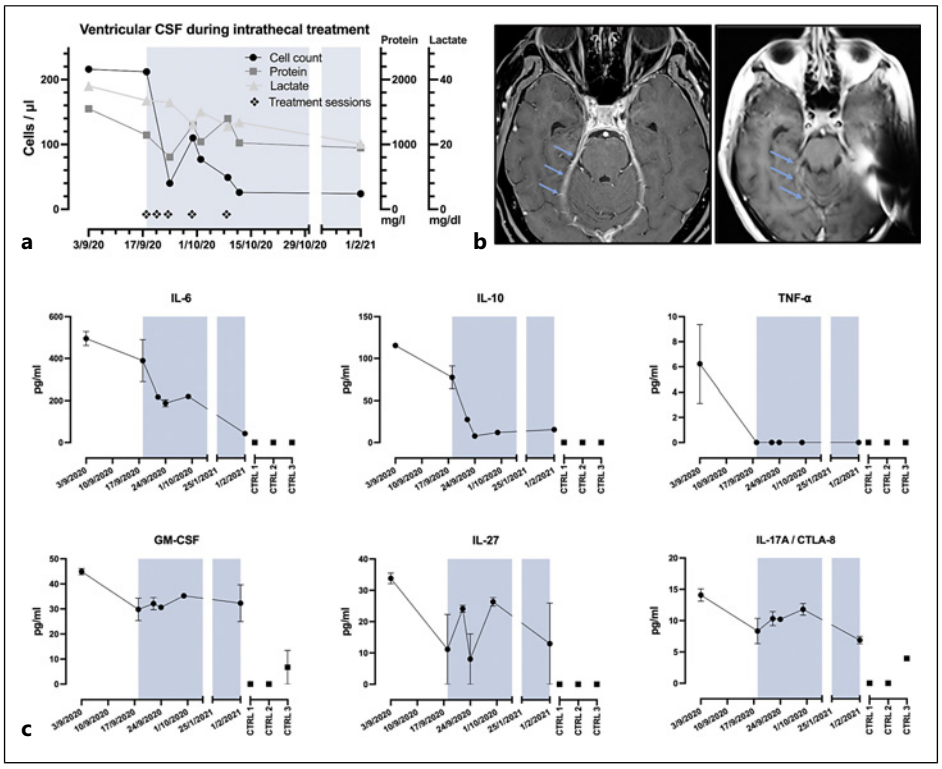

Fig. 2. Ventricular CSF parameters, radiological findings, and cytokine levels during intraventricular treatment. After beginning of intraventricular treatment (blue background, treatment sessions as diamonds), a falling trend was seen for cell count and lactate (**a**). In (**a**), the first right-bound Y-axis corresponds to protein in mg/L and the second to lactate in mg/dL. T1-contrast dural enhancement in MRI remained constant over the years (left side, image from 2017) and a slight improvement followed intraventricular treatment as demonstrated here for the tentorium in January 2021 (**b**). Note that comparability is limited as images were acquired in different scanners (T3 vs. T1.5) due to cochlea implant and that this device accounts for an artifact in the posttreatment images. In (**c**) cytokine levels detected in CSF are depicted. Cytokine levels were measured with an 18-plex immunoassay (Invitrogen™; https://www.thermofisher.com/order/catalog/product/EPX180-12165-901). Each point represents the average of three technical replicates ± standard deviation. The CSF of three patients with neurodegenerative diseases served as controls (CTRL 1-3). The first two values in all graphs are (1) at reservoir implantation and (2) immediately before the first intraventricular instillation. Blue background represents time from first instillation.

MRI 3 months after intraventricular chemotherapy showed reduced meningeal enhancement (Fig. 2b), as far as comparable due to artifacts after cochlear implantation in the posttreatment images. At a follow-up visit 3 months after treatment interruption, audiogram revealed an unchanged hearing impairment. Visual impairment at clinical examination also remained static.

Over the first weeks of intraventricular treatment, the patient developed psychotic symptoms (hallucinations, delusion, fear), necessitating medication with haloperidol and risperidone as well as a 2-day stay in a closed psychiatric ward. Corticosteroid-induced psychosis was suspected and intrathecal treatment consecutively discontinued. Ommaya reservoir infection was excluded through negative CSF cultures and viral/bacterial PCRs. There were no signs of toxic encephalopathy on cerebral MRI. At last follow-up – 4 months after the last treatment session – psychiatric symptoms had regressed to the initial (pretreatment) status.

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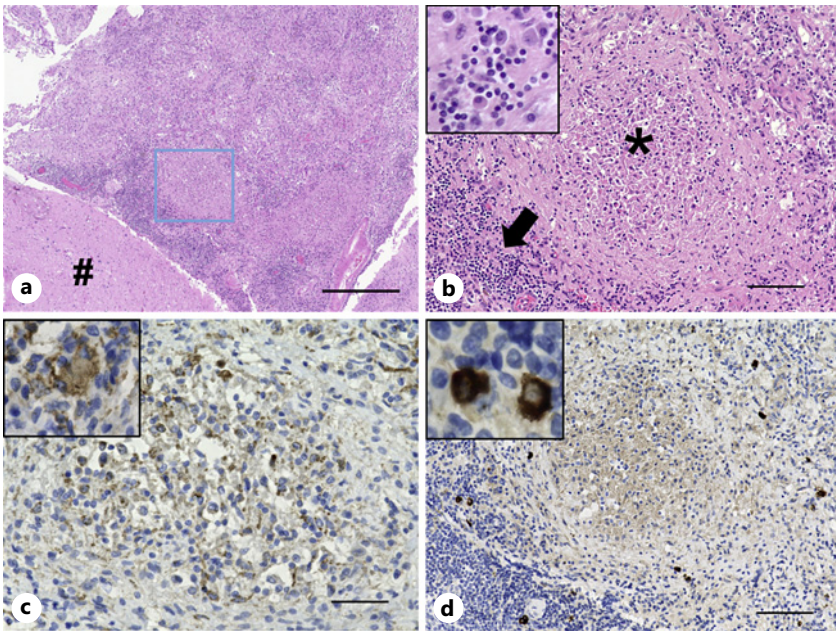

Fig. 3. Cerebral autopsy showed granulomatous inflammation in the meninges around the brainstem. Here, leptomeninges are shown around the medulla oblongata (marked with # in **a**). We identified meningeal non-necrotizing granulomas with central histiocytes (marked with * in **b**) surrounded by dense lymphocytic and plasma cell infiltrates (arrow in **b** and inlay). Central histiocytes show expression of CD68 (**c**) as well as multinucleated cells. Infiltrates included only scattered IgG4-positive plasma cells (**d**). Scale bars: 500 µm (**a**); 100 µm (**b** + **d**); 50 µm (**c**).

Six months after the last intrathecal chemotherapy, the patient died of a large embolic stroke. Cerebral autopsy revealed pronounced chronic inflammatory changes around the brainstem and basal leptomeninges as well as prominent fibrotic changes of the residual tissue and distinct meningeal proliferation. Inflammatory changes included granulomatous formations without necrosis and mixed infiltrations with clusters of lymphocytes, plasma cells, macrophages and eosinophilic granulocytes, typical of sarcoidosis (Fig. 3). Based on the postmortem histopathological findings, a final diagnosis of neurosarcoidosis with secondary HP was made [5]. The remainder of the body was not examined for systemic sarcoidosis, as the patient's life partner (and appointed representative by the patient) only consented for cerebral autopsy.

Discussion

We present a case of secondary HP with progressive deafness and blindness followed over 7 years with persistently high lymphocytic pleocytosis refractory to several immunosuppressants. During treatment with intraventricular chemotherapy, various CSF inflammatory markers decreased. Dural enhancement in contrasted MRI revealed signs of regression, indicating a treatment response despite the advanced disease. However, there were no changes in hearing capacity or visual acuity.

Throughout the years, systemic treatments either led to severe side effects or failed to stop or decelerate the ongoing meningeal inflammation. We hypothesized that the latter was due to insufficient distribution of the active substance in the CNS. Intraventricular

chemotherapy is established for treatment of meningeal neoplastic disease [6]. Compared with lumbar administration, installation via Ommaya reservoir allows more reliable drug distribution in CSF [7]. A previous case report described a 28-year-old man with iHP and marked lymphocytic pleocytosis refractory to systemic immunosuppressant treatment whose disease stabilized after intraventricular treatment with cytarabine [8]. In our case, this specific triple intrathecal therapy was chosen based on current treatment regimens for proliferative CNS involvement in leukemia/lymphomas [9].

The marked pleocytosis since initial presentation seen in our patient is untypical for iHP and pointed to a secondary HP form due to persistently active chronic inflammation [4]. Increased CSF pro-inflammatory cytokine levels have been described in MPO-ANCA-related HP as well as in iHP and neurosarcoidosis [4, 10]. In our case, treatment resulted in decrease of IL-6 and IL-10 levels below the high-sensitivity detection threshold. In how far cytokine profiles are indicative of a specific etiology or if they are suitable to monitor disease activity remains to be investigated.

In HP, treatment is guided by pathophysiological concepts: HP secondary to neurosarcoidosis is expected to respond to infliximab whereas combining prednisolone with cyclophosphamide or rituximab is beneficial in MPO-ANCA-related HP [3, 4]. Poor response to treatment with infliximab in neurosarcoidosis has been associated with longer disease duration before treatment initiation [11]. Furthermore, more intensive treatment protocols have been used in other centers for stronger affected patients – e.g., every 4 weeks after an induction phase or up to 7 mg/kg instead of 5 mg/kg every 8 weeks as proceeded in this case. In the presented case, decision to escalate treatment was prompted by the patient's progressive and severe clinical symptoms and aimed to suppress inflammation as the putative driver of the observed structural meningeal changes. It remains speculative, if we would have made the same therapeutic decision if we had known the underlying diagnosis of neurosarcoidosis at the time we started intraventricular treatment. Nevertheless, as the patient had not responded to targeted therapies considered effective for neurosarcoidosis and given the severity of the patient's symptoms, we consider it very likely that we would have evaluated alternative treatment options, including treatment escalation with intraventricular chemotherapy.

This case report further highlights the challenges of etiological investigation in HP, as clinical presentation was misleading (high pleocytosis, ineffective systemic immunosuppressive treatment, and time course not suggestive of neurosarcoidosis) and initial biopsy inconclusive. Histopathological inflammatory changes revealed by autopsy were most prominent around the brainstem and basal leptomeninges, areas not suited for biopsy due to high risk of complications. Incongruent findings between dural biopsy and clinical presentation in cases of HP due to (probable) neurosarcoidosis have been described before [12, 13].

Since intraventricular chemotherapy is applied locally and lower doses are used, systemic side effects such as myelosuppression and cardiotoxicity are less common. However, distribution of medication in the whole body is possible. Thus, not only local complications (e.g., neurotoxicity or complications related to the reservoir) but also potential systemic side effects must be discussed with the patient before treatment [14]. Our patient developed psychosis during intraventricular treatment, most likely associated with glucocorticoids and in context of preexisting psychiatric symptoms and acquired blindness, a potential risk factor for hallucinations [15]. Consequently, intrathecal treatment may be considered earlier in the disease course as to avoid secondary complications. The CARE Checklist has been completed by the authors for this case report, attached as online supplementary material (for all online suppl. material, see https://doi.org/10.1159/000531229).

Conclusion

This report illustrates the diagnostic and treatment challenges in a case of HP. We conclude that sustained chronic inflammation as reflected in long-lasting marked pleocytosis and increased profibrotic cytokines may be associated with secondary HP. Accordingly, intraventricular chemotherapy may have the potential to appease the inflammatory milieu and interfere with the natural course of disease. We therefore suggest considering this treatment earlier to avoid irreversible nerve damage through inflammation. To what extent clinical impairments can be reversed or symptom progression halted must be addressed in further studies with longer follow-up periods and clinically less advanced disease. A thorough selection of patients with severe intrathecal chronic inflammation might be useful to predict treatment efficacy while potential risks of intraventricular treatment must always be discussed.

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Statement of Ethics

According to the Ethics Committee of Charité – Universitätsmedizin Berlin, no specific ethical approval is required for publication of a case report. Written informed consent was obtained from the patient's life partner for publication of the details of the medical case and any accompanying images.

Conflict of Interest Statement

The authors report no conflicts of interest regarding this study. K. Ruprecht has received research support, unrelated from this work, from Novartis Pharma, Merck Serono, German Ministry of Education and Research, European Union (821283-2), Stiftung Charité (BIH Clinical Fellow Program), Arthur Arnstein Foundation, and Guthy Jackson Charitable Foundation and travel grants from Guthy Jackson Charitable Foundation. K. Ruprecht is a participant in the BIH Clinical Fellow Program funded by Stiftung Charité. A.L. de A. Marcelino is a fellow in the BIH Charité Junior Clinician Scientist Program funded by Stiftung Charité.

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Author Contributions

A.L.A.M., K.R., and H.P. were involved in clinical care of the patient; A.L.A.M., K.R., and H.P. conceptualized and wrote the manuscript; A.L.A.M. acquired and analyzed the data; S.S. and

H.R. performed the neuropathological exams, wrote and revised the manuscript; M.A.H. quantified and analyzed the cytokines; H.-C.B. reviewed the radiological findings. All authors reviewed and approved the manuscript.

Data Availability Statement

All data generated or analyzed during this study are included in this article and its online supplementary material. Further inquiries can be directed to the corresponding author.

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