

CASE REPORT

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Intravascular CNS lymphoma: Successful therapy using high-dose methotrexate-based polychemotherapy

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Abstract

Intravascular diffuse large B-cell lymphoma limited to the CNS (cIVL) is a very rare malignant disorder characterized by a selective accumulation of neoplastic lymphocytes (usually B cells) within the lumen of CNS blood vessels but not in the brain parenchyma. In the past, treatment of cIVL with anthracycline-based regimens was unsatisfactory with very short survival times. In the case of cIVL presented here, high-dose methotrexate-based polychemotherapy according to the Bonn protocol plus rituximab therapy was successful and led to a complete clinical and MRI remission which is ongoing 29 months after diagnosis.

Keywords: Intravascular lymphoma, Intravascular CNS lymphoma, High-dose methotrexate-based polychemotherapy, Angioendotheliomatosis, Angiotropic lymphoma

Background

Intravascular lymphoma, also known as intravascular lymphomatosis or angiotropic lymphoma and formerly known as malignant angioendotheliomatosis is a rare neoplastic disorder in which tumour cells are initially confined to the vascular lumen without parenchymal infiltration. While cases of systemic intravascular lymphoma are more frequently encountered, cases of intravascular lymphoma with restricted central nervous system (CNS) involvement (cIVL) are uncommon and only few patients that had been successfully treated have been reported so far [1-4]. We here present a case with a histologically confirmed cIVL that could be successfully treated with a high-dose methotrexate (HD-MTX) and rituximab-based chemotherapy regimen.

Case presentation

A 69-year-old male Caucasian patient presented with recurrent transient amnesic aphasia and gait ataxia. Physical examination at the time of referral did not reveal

any further pathological findings. B symptoms were absent. Serum LDH levels were twice the upper limit of normal, all other serum chemistry and differential blood count was negative. Cerebrospinal fluid (CSF) analysis revealed a normal cell count, protein levels were within the reference range, no atypical cells were detected. Initial magnetic resonance imaging (MRI) revealed a contrast-enhancing lesion in the pons (Figure 1A) and additional involvement of the left temporomesial area. A stereotactic biopsy was performed and histology revealed a CD20-antigen-expressing intravascular lymphoma with high proliferative activity (Figure 2A, B). Immunohistological evaluation of B-cell differentiation markers showed a BCL-6+ and MUM-1+–status. Subsequent staging (i.e. examination of the chest, abdomen and pelvis by contrast-enhanced computed tomography (CT) scan, bone marrow biopsy, slit lamp examination of the eye, spinal tap) did not reveal any systemic or additional CNS involvement.

Chemotherapy according to the Bonn protocol was initiated in combination with rituximab therapy. The Bonn protocol comprises six 3-week courses with different combinations of HD-MTX (3 gm/m² over 24 hours), ifosfamide, procarbazine, cytarabine, vinca alkaloids, and dexamethasone (for details see [5]). Rituximab was given at

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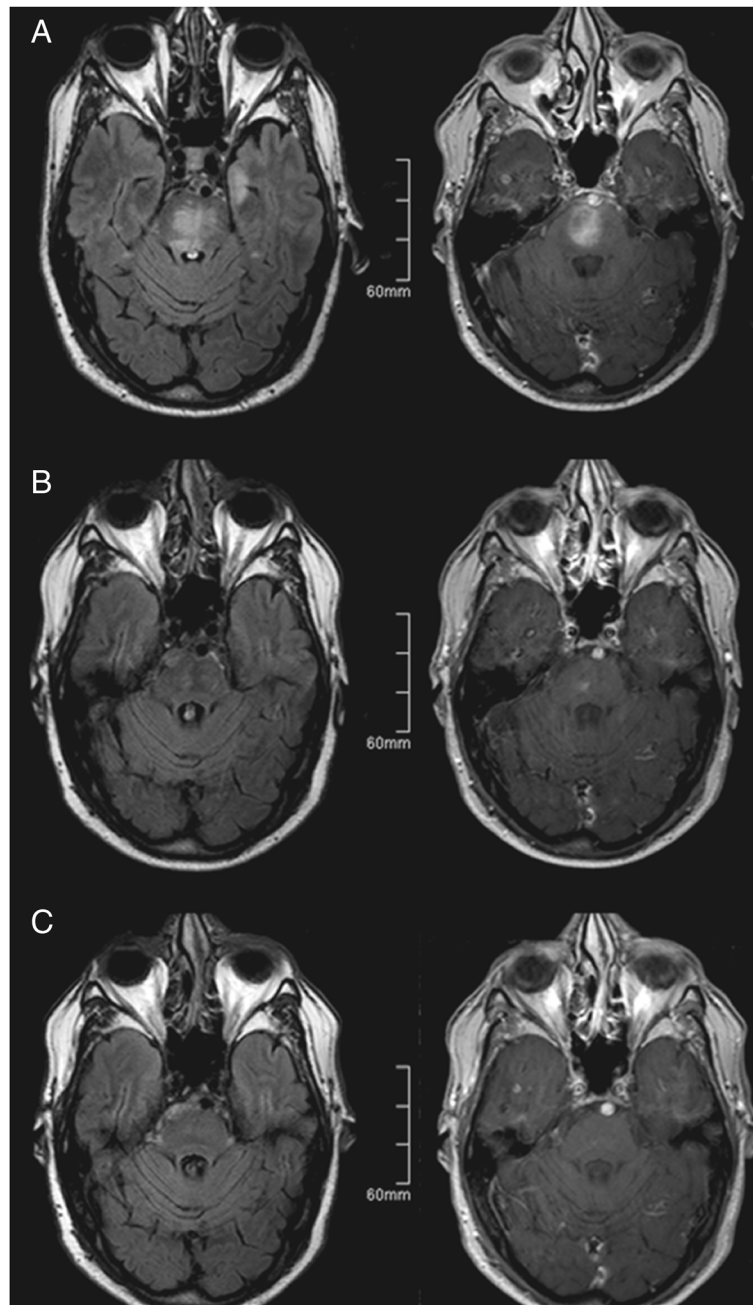


Figure 1 MR imaging prior to and after HD-MTX-based chemotherapy (left column FLAIR, right column: contrast enhanced T1-weighted imaging)MR imaging prior to therapy (A) and at follow-up imaging at the end of 6 courses of chemotherapy with a strong reduction of contrast-enhancing lesions (B). Nineteen months after initiation of treatment MR imaging showed complete regression of marked FLAIR hyperintensities and contrast enhancement in the brain stem (C).

each course one day prior to the start of the HD-MTX infusion. During the 5th course, a transient and moderate increase in serum creatinine occurred, without a need for dose reduction in subsequent treatment courses. Vincristine was removed from the treatment protocol after development of mild signs of polyneuropathy. After the second course, the contrast-enhancing lesion showed already a

partial remission; after the sixth course, only one small contrast-enhancing lesion remained that had to be qualified as unconfirmed complete remission since it further diminished in subsequent control MRIs without additional therapy (Figure 1A-C). The patient is now in complete clinical and radiographic remission 29 months after initial diagnosis of cIVL.

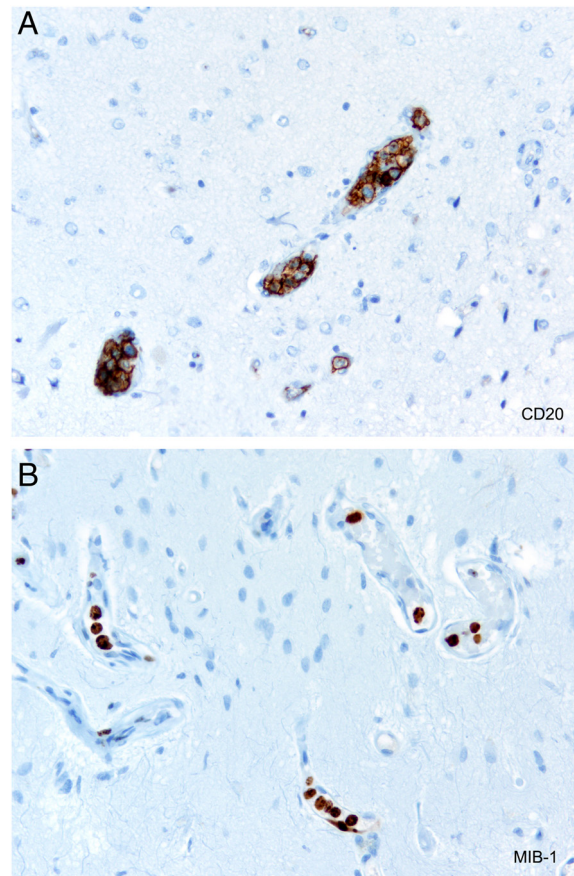


Figure 2 Histological examination of the tissue obtained by stereotactic biopsy of the brain stem. Histology revealed CD20-immunopositive intravascular lymphoma cells (A) with a very high proliferative activity in MIB-1 immunohistochemistry (B).

In this case report we demonstrate the successful therapy of a patient with cIVL, i.e. intravascular lymphoma limited to the CNS. The few reports available on the treatment of this medical condition are summarized in Table 1. All cIVL cases in which progression and death due to systemic failure was explicitly mentioned were not included here. In some cases, lymphoma-directed specific therapy was not applied or the treatment modality was not reported. In these cases, survival did not exceed 4 months [6-9]. Conventional chemotherapy with anthracycline-based protocols (i.e. CHOP in 3 patients), radiotherapy, or corticosteroid therapy was not successful [10-12]. Using anthracycline-based chemotherapy which is effective in systemic intravascular lymphoma does not penetrate the intact blood-brain barrier (BBB), overall survival rarely exceeded 6 months. Our case, on the other hand, is in line with reports demonstrating that BBB-penetrating HD-MTX-based regimens may have considerable efficacy. Seven patients treated with HD-MTX alone or in combination with CHOP survived 6–20 months [1,13,14]. In a separate study, three patients with cIVL receiving HD-MTX-based chemotherapy showed progression-free survival times of 2, 20 and

48 month [1-3]. One additional case report presented a patient receiving HD-MTX + R-CHOP followed by consolidation therapy with high-dose chemotherapy (thiotepa, busulfan, and cyclophosphamide) and autologous stem-cell rescue. This patient survived for at least 19 months after treatment [4]. It remains unclear why HD-MTX-based, i.e. blood-brain barrier (BBB)-penetrating therapy is needed for successful therapy of cIVL and which are the optimal combination partners for MD-MTX therapy. Also, it is unclear why regimens that do not penetrate the BBB but are effective in other forms of intravascular lymphoma are not successful in cIVL. This is particularly puzzling since all cIVL tumour cells are by histological definition located within the vessels and not beyond in the brain parenchyma.

Conclusion

Overall, on the base of our case and upon reviewing the literature, we recommend the use of HD-MTX-based polychemotherapy similar to HD-MTX-based protocols for primary (parenchymal) CNS lymphoma in patients with cIVL.

Table 1 Summary of all patients with intravascular lymphomatosis limited to the CNS (cIVL) reported in the literature

| Author | Site of involvement | Neurological symptoms | Treatment | Outcome |
|-------------------------|---------------------|---|--|--|
| Baehring et al. [1] | Brain | Right hemiparesis, dysarthria | HD-MTX (induction 5, consolidation 10, maintenance 2) | CR 20 months after diagnosis |
| Baehring et al. [1] | Brain, spinal cord | Proximal spastic paraparesis, psychosis | HD-MTX (induction 12) | PR 18 months after diagnosis |
| Baehring et al. [1] | Brain, nerve roots | Dysarthria, gait disturbance, allodynia | HD-MTX initially (induction 6, consolidation 4), HD-MTX salvage (6 induction, 7 consolidation) | PR until 8 months after diagnosis: PR until 12 months after recurrence |
| Baehring et al. [1] | Brain | Cognitive decline, homonymous hemianopsia, ataxia | HD-MTX (induction 1 cycle) | Died of disease progression after first cycle of chemotherapy |
| Calamia et al. [15] | CNS | NA | m-BACOD | OS 16 months |
| Calamia et al. [15] | CNS | NA | Pro-MACE-CytaBOM | OS 44 months |
| Bergmann et al. [6] | Brain | Left-sided hemiparesis | NA | OS 2 months |
| Bergmann et al. [6] | Brain | Spastic paraparesis, left arm paresis | NA | OS 2 months |
| DiGiuseppe et al. [3] | Brain | Mental status changes | Pro-MACE-CytaBOM, ifosfamide/VP-16/cisplatin & whole brain irradiation (45 Gy) | CR 48 months after diagnosis |
| Kanda et al. [16] | CNS | Aphasia, apraxia | CHOP, VEMP, radiotherapy | OS one month |
| Aznar et al. [7] | CNS | Distal paresthesia of the lower limbs, paraparesis | NA | OS few months |
| Passarin [8] | Brain | Progressive cognitive deterioration, tetraparesis | NA | OS 3–4 weeks |
| Natali-Sora et al. [17] | CNS | Generalized tonic-clonic seizures | Cyclophosphamide, mitoxantrone, BCNU, methylprednisolone | CR 46 months after diagnosis |
| Liow et al. [18] | CNS | NA | CHOP | OS 13 months |
| Albrecht et al. [9] | Brain | Cognitive deterioration, aphasia | NA | OS few weeks |
| Ferreri et al. [10] | CNS | NA | CHOP (3 patients), CVP (one patient) | OS less than 4 months |
| Holmøy et al. [12] | Brain | vertigo, diplopia, left-sided hearing loss, aphasia | high-dose corticosteroid pulse therapy | OS 18 weeks |
| Momota et al. [14] | Brain | Left-sided hemiparesis | HD-MTX, whole brain irradiation | OS 6 months |
| This case | Brain | Transient amnesic aphasia, gait ataxia | Bonn protocol + rituximab | CR 29 months after diagnosis |

Abbreviations: HD-MTX: high dose methotrexate; CR: complete remission; PR: partial response; NA: not available; OS: overall survival; m-BACOD: cyclophosphamide, doxorubicin, vincristine, bleomycin, dexamethasone, methotrexate; Pro-MACE-CytaBOM: prednisone, methotrexate (with leucovorin rescue), doxorubicin, cyclophosphamide, etoposide, cytarabine, bleomycin, vincristine; VP-16: etoposide; CHOP: cyclophosphamide, doxorubicin, vincristine, prednisolone; VEMP: vincristine, cyclophosphamide, mercaptopurine, prednisolone; CVP: cyclophosphamide, vincristine and prednisone; Bonn protocol: HD-MTX, ifosfamide, procarbazine, cytarabine, vinca alkaloids, dexamethasone.

Consent

Written informed consent was obtained from the patient for publication of this Case report and any accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal.

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

Conceived and designed therapy: UH MG. Performed neuroradiologic analysis: HU MN. Neuropathological diagnosis: KK PN. Wrote the paper: SK UH. Performed treatment and participated in collecting data: SK YK ST MS FM NS. All authors read and approved the final manuscript.

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