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Prolonged Corticosteroid-Induced Remission in Primary Central Nervous System Lymphoma: Report of a Case and Review of the Literature

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In primary central nervous system lymphomas (PCNSL) recent studies have shown a prolongation of survival from 12–25 months with radiotherapy to 33–42 months with radiochemotherapy [1]. Histological confirmation of PCNSL is a prerequisite of aggressive treatment. Many patients, however, receive corticosteroid treatment prior to biopsy. This often obscures histology as short-term partial or complete tumor remission is seen in 20–60% of the cases [1,2]. We have seen a patient with a 6.5-year history of PCNSL until biopsy and two complete long-term remissions after short-term application of corticosteroids. This unusual case prompted us to review the literature regarding the time course of corticosteroid-induced remissions of PCNSL.

Case

In August 1988, a 61-year-old patient presented to his physician with slowly increasing unsteadiness of gait, vertigo and diplopia. CT scan and MRI disclosed a space-occupying lesion within the right cerebellar peduncle (fig. 1a). Without treatment the symptoms improved slightly within 1 month. Three days prior to a second CT scan

Fig. 1. Course of the disease according to contrast-enhanced CT scans; **a** Lesion in the right cerebellopontine angle in September 1988 prior to any therapy; **b** Complete remission on control scan November 1988 three days after starting corticosteroid treatment; **c** Recurrent lesion in March 1993 prior to corticosteroids; **d** Complete remission 1.5 months after the beginning of corticosteroid treatment in May 1993. **e** Recurrent lesion in February 1995 prior to stereotactic biopsy and radiochemotherapy.

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corticosteroid treatment was started with 24 mg dexamethasone daily. The lesion was no longer detectable on CT scan (fig. 1b). The clinical symptoms resolved completely and dexamethasone was tapered off within 11 days.

In February 1993, the patient developed right-sided hemiparesis and impairment of psychomotor functions. CT scan showed a space-occupying lesion extending from the medial wall of the left lateral ventricle into the corpus callosum (fig. 1c). Already suspecting PCNSL his physician treated him again with dexamethasone 16 mg daily which was tapered off within 2 weeks. One and a half months later the tumor (fig. 1d) and clinical signs and symptoms had resolved again.

In July 1994, October 1994 and January 1995 the patient himself treated three episodes of severe headaches and slowing of psychomotor functions with dexamethasone for about 2 weeks starting with 16 mg (7/94), or 24 mg (10/94 and 1/95). No CT scans were obtained on these occasions.

In February 1995, the patient presented to our clinic with papilledema, mild right-sided hemiparesis, and psychomotor slowing. CT scans showed a left frontal lesion of 3 cm in diameter (fig. 1e). Histology from macroscopically complete tumor resection revealed a high-grade malignant B-cell lymphoma. The patient was started on corticosteroids and radiochemotherapy according to DeAngelis et al. [3]. He is doing well.

Discussion
Many clinical studies have analyzed the outcome of surgical, radiotherapeutic, and radiochemotherapeutic treatment of PCNSL usually including corticosteroids [1]. Few authors have looked at treatment results with corticosteroids alone prior to definitive treatment with chemo- and/or radiotherapy [2, 4, 5, 7]. They usually have not specified dosage and duration of corticosteroid treatment. Prior to diagnosis corticosteroids are applied to treat brain edema or PCNSL lesions misdiagnosed as inflammatory CNS disease. PCNSL treatment protocols include corticosteroids because of their direct apoptotic effect on lymphoma cells [6]. Corticosteroid sensitivity of PCNSL defined as any reduction of tumor volume on CT is reported in 20–60% of the cases [1,2]. Hochberg et al. [7] observed 43% complete remissions within only 10 days of treatment with 24 mg dexamethasone daily without giving data on partial remissions. This transitory effect of corticosteroids on PCNSL is comparable to the 40–80% response rate in systemic lymphoma [8].

Clinical improvement usually occurs within 2–3 days after the start of dexamethasone, 8–32 mg daily, and is partially due to the resolution of brain edema. Complete or incomplete tumor regression occurs over a period of 10 or more days. In rare cases such as ours complete regression of the tumor on CT may be observed even within a few hours or days. After discontinuation of corticosteroids partial or complete remission of PCNSL lesions usually last for weeks to months but may be as short as 1 week [7]. Ongoing corticosteroid therapy does not seem to prevent recurrences. There are two reports on patients who had recurrences under continuous corticosteroid therapy 2 months after complete remission on CT scan [9, 10]. Long-term remissions of more than 1 year are exceptional. Two patients are reported with remissions of 17 [11] or 30 months [12], respectively; the latter after 4 months’ treatment with dexamethasone 5 mg daily. Apart from ours only 1 patient has been reported with a remission lasting 5 years after 2 months of dexamethasone treatment. He eventually died after 7 years [13]. Another patient had 5 years of complete remission following corticosteroid treatment and tumor resection [14]. His long-term remission, however, may also be attributed to the application of corticosteroids as resection alone does not markedly prolong survival in PCNSL [1, 2].

In the rare cases with several remissions, including ours, the time in remission progressively decreases with repeated corticosteroid treatment. We suppose that corticosteroids induce a selection of lymphoma cell clones with low functional glucocorticoid receptor expression as has been shown in in vitro experiments [15]. Alternatively, there might also be a selection of cell clones with increased bcl-2 gene expression which is reported to protect lymphoma cells from apopto-sis induced by corticosteroids [16].

At the first recurrence of a PCNSL an increase of the corticosteroid dose may increase its efficacy [2] but in the long run corticosteroids become ineffective. There is no clinical evidence that previous short- or long-term corticosteroid application impairs or increases the sensitivity of PCNSL to subsequent radiochemotherapy but this issue has not been analyzed systematically.

Corticosteroids should be an integral part of any PCNSL treatment protocol and high-dose corticosteroids are included in current protocols of radiochemotherapy. In patients with suspected PCNSL, however, corticosteroids should be withheld and replaced by osmotherapy in the treatment of brain edema, until the diagnosis has been confirmed by biopsy.

Multiple enhancing lesions diagnosed as inflammatory foci which recur rapidly after reducing or tapering off corticosteroids, and lesions considered as metastases, or gliomas which rapidly and completely remit upon corticosteroid therapy are always suspicious of PCNSL. In these cases corticosteroids should be tapered off and biopsy performed at the time of recurrence.

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