Primary Hodgkin’s disease of the CNS in an immunocompetent patient: A case study and review of the literature

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Primary Hodgkin’s disease limited to the CNS is exceedingly rare. Little is known regarding etiologic risk factors, optimal management, and prognosis. A case of Hodgkin’s disease confined to the CNS, with cerebrospinal fluid negative for cytology, is described in an immunocompetent patient previously treated for hyperthyroidism with 131I. The patient underwent craniotomy, with resection of two lesions in close proximity within the parenchyma of the temporoparietal lobe. Histopathology revealed classic nodular sclerosing Hodgkin’s disease, without evidence of Epstein-Barr viral infection. Treatment included radiation to the whole brain with a boost to the tumor bed. The patient made a full neurologic recovery and remains free of disease recurrence 21 months after treatment. A literature review has identified only 9 additional cases. Seven of 8 evaluable patients remain alive and free of recurrence with a median follow-up of 13 months. The risk factors for this presentation remain undefined. Although follow-up is short, radiotherapy alone appears to provide excellent disease-free survival. Chemotherapy may be reserved for patients with positive cerebrospinal fluid, extracranial disease, or subsequent relapse. Neuro-Oncology 2, 239–243, 2000 (Posted to Neuro-Oncology [serial online], Doc. 00-028, September 6, 2000. URL <neuro-oncology.mc.duke.edu>)

Hodgkin’s disease with CNS involvement is uncommon, even in the HIV-positive population, and usually occurs in the setting of advanced or recurrent disease. Reports of primary Hodgkin’s disease confined to the CNS are exceedingly rare. We describe a case of primary CNS Hodgkin’s disease in a patient previously treated with 131I for Grave’s hyperthyroidism and review the literature with respect to potential risk factors, management, and treatment outcomes.

Case Study

A 52-year-old right-handed male truck driver developed sudden onset of headache and confusion. He presented to the emergency department 2 days later with mild disorientation and receptive aphasia. Functional inquiry was negative for fatigue, weight loss, pruritis, fever, and night sweats. Physical examination revealed proptosis, but no evidence of peripheral adenopathy or hepatosplenomegaly. Assessment of cranial nerves, power, sensation, and coordination revealed no abnormalities.

Past health included a history of Grave’s hyperthyroidism with ophthalmopathy 4 years earlier. The patient was treated with radioactive iodine at a total dose of 229 mBq (6.2 mCi) administered orally. There was a 40-pack-year smoking history. Medication on admission was limited to L-thyroxine, 0.125 mg per day. Family history was negative for cancer.

Initial investigations revealed a normal complete blood cell count, peripheral blood smear, electrolytes, blood urea nitrogen, creatinine, random glucose, and international normalized ratio. Serum lactate dehydrogenase and erythrocyte sedimentation rate were not performed. A CT scan with contrast of the head revealed a contrast-enhancing 1.0 cm left temporoparietal lesion, with significant edema and mass effect (Fig. 1).

Received 18 April 2000, accepted 19 June 2000.

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2Abbreviations used are as follows: CSF, cerebrospinal fluid; HIV, human immunodeficiency virus.
Treatment was initiated in the emergency department with phenytoin and dexamethasone. Craniotomy with tumor resection was performed 2 days later. Two mass lesions measuring $8 \times 6 \times 4$ mm and $2 \times 2 \times 1$ mm were removed without complications. The larger lesion was parenchymal, with the smaller adjacent mass adherent to the arachnoid mater.

Pathologic work-up included histologic and immunohistochemical studies, as well as in situ hybridization for Epstein-Barr virus RNA. The surgical specimen was fixed in 10% neutral buffered formalin and embedded in paraffin, and sections were stained with hematoxylin and eosin. For immunohistochemical staining, commercially available antibodies and the biotinylated-streptavidin horseradish peroxidase technique were used. In situ hybridization for Epstein-Barr virus RNA was performed using the EBER-1 probe (Novocastra Laboratories, Newcastle upon Tyne, U.K.).

Examination of the hematoxylin- and eosin-stained tissue demonstrated a mixed infiltrate composed of lymphocytes, plasma cells, numerous eosinophils, and large pleomorphic malignant cells separated into vague nodules by fibrous tissue. Numerous multinucleated cells with classic features of Reed-Sternberg cells were present (Fig. 2a). Lacunar variants and mononuclear variants were frequently identified. The Reed-Sternberg cells were CD30- (Fig. 2b) and CD15-positive. They were negative for CD45, CD20, and CD3, although the reactive component revealed a mixed infiltrate of T cells and B cells. Reed-Sternberg cells and lymphocytes were negative for Epstein-Barr virus LMP-1 protein and RNA using the EBER-1 probe.

The patient's postoperative course was uneventful, and the dexamethasone was successfully tapered. He achieved full neurologic recovery and was discharged on phenytoin with no documented seizures.

Subsequent staging work-up included a normal bone marrow aspirate and biopsy. A lumbar puncture yielded clear CSF characterized by normal white cell count, normal protein level, and slightly elevated glucose. The CSF was negative for malignant cells. Ultrasound of liver and CT scan of thorax, abdomen, and pelvis revealed no significant abnormality. A whole-body gallium scan was within normal limits. Thyroid ultrasound revealed a small coarse gland with no significant abnormality. HIV testing was negative.

The patient was classified as Ann Arbor stage IEA. Radiation planning was begun 10 weeks after surgery. The target volume included the whole brain and meninges. The patient was treated supine, immobilized in

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Fig. 1. Contrast-enhanced CT scan of the head, demonstrating a parenchymal lesion in the left temporoparietal region.

Fig. 2. Histopathology of CNS lesion. A. Histology of polymorphous infiltrate composed of numerous eosinophils, small lymphocytes, and occasional classic binucleate Reed-Sternberg cells (hematoxylin and eosin, original magnification ×400). B. Prominent perinuclear Golgi staining of Reed-Sternberg cell with CD30. (Dako primary, diaminobenzidine chromogen, hematoxylin counterstain, original magnification ×600).
a plastic shell. A lateral parallel pair was used to deliver a
dose of 3000 cGy in 17 fractions to midplane on cobalt-
60. The eyes were shielded throughout therapy. A
weighted lateral parallel pair was used to boost original
sites of gross disease with a margin of 2 cm to a dose of
500 cGy in 3 fractions. Radiation was well tolerated.

Follow-up CT scans at 1, 6, 12, and 20 months post-
treatment revealed no evidence of recurrence. At 21
months from completion of radiation treatment, the
patient remains well with no evidence of local or systemic
Hodgkin’s disease.

Discussion

CNS Hodgkin’s disease has been described in patients
with disseminated disease, particularly those with relapse
involving extranodal sites (Cutner et al., 1979; Dujovny
et al., 1980; Sapozink and Kaplan, 1983). Primary Hodg-
kin’s disease isolated to the CNS is exceedingly rare
of the literature over the past 50 years reveals only 9 well-
documented cases of Hodgkin’s disease confined to the
craniospinal axis at presentation (Table 1). Tumors have
been described as isolated cerebral or cerebellar masses
or, less commonly, parenchymal disease with attachment
to the dura or bone. In two cases, disease was confined to
the dura (Bender and Mayernik, 1986; Nagashima et al.,
1980). In one report, the primary CNS lesion was treated
3 months before lung involvement was ultimately discov-
ered (Deckert-Schloter et al., 1998). Other case reports
(Bertelsen, 1970; Burstein et al., 1963; Henry et al.,
1974; Zimmerman, 1975) provide inadequate diagnostic
information or have been reclassified as non-Hodgkin’s
lymphoma, an unsurprising finding given the evolving
pathologic classification and staging methods over the
period of this review.

Patients with immunodeficiency are at increased risk
of malignancy, including Hodgkin’s disease (Gatti and
Good, 1971; Rabkin et al., 1991). An increased risk of
Hodgkin’s disease has been confirmed in those infected
with HIV (Hessol et al., 1992; Levine, 1998; Schoeppel et
al., 1986; Serraino et al., 1997; Straus, 1997). HIV-
infected patients with Hodgkin’s disease are more likely
to present with B symptoms, mixed cellularity histology,
extranodal involvement, and advanced stage of disease
(Carbone et al., 1991; Tirelli et al., 1992). Epstein-Barr
virus infection is common in this population, particularly
in those aged 50 years and older (Tirelli et al., 1995).
Primary CNS malignancies including high-grade non-Hodg-
kín’s lymphoma and Kaposi’s sarcoma have been associ-
ated with the low CD4+ count of HIV infection (Petruckevitch et al., 1999; Rubio, 1994). A similar asso-
ciation has not been established for CNS Hodgkin’s dis-
ease. However, as HIV-related Hodgkin’s disease cases
accumulate, a propensity for primary CNS involvement
may emerge.

Interest in radiation-induced cancers has grown in
recent years as the number of long-term survivors has
increased. The results of epidemiologic reviews are of par-
ticular interest in this case because of the possible rela-
tionship between I311 exposure and development of
Hodgkin’s disease. A number of population-based studies
from the United States and Sweden have examined cancer
incidence in patients undergoing diagnostic I311 scans
and therapeutic doses of I311 for hyperthyroidism or thyroid
cancer. These studies have reported an increased risk of
some solid tumors (Goldman et al., 1988; Hoffman et al.,
1982) and chronic myeloid leukemia (Shimon et al.,
1995; Walgraeve et al., 1991). An increase in the inci-
dence of lymphoma or acute leukemia has not been
observed (De Vathaire et al., 1997; Hall et al., 1992;
Holt et al., 1991). Large population-based reviews have
not identified an increase in the relative risk of death from
hematopoietic or lymphoreticular malignancy among
patients treated with I311 (Franklyn et al., 1998; Ron et al.,
1998). The weight of the evidence suggests that I311 expo-
sure is unlikely to be related to the pathogenesis of Hodg-
kín’s disease in this case.

The optimum management of primary CNS Hodgkin’s
disease is not known. The role of chemotherapy is under
active investigation in primary CNS lymphoma because of
disappointing results with radiotherapy alone (Laperriere

<table>
<thead>
<tr>
<th>Case</th>
<th>Year, author</th>
<th>Patient (age/sex)</th>
<th>Disease site</th>
<th>Treatment</th>
<th>Outcome at last follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1946, Sparling and Adams</td>
<td>53/M</td>
<td>L frontal</td>
<td>None</td>
<td>Died 5 days postop</td>
</tr>
<tr>
<td>2</td>
<td>1955, Schicker and Smith</td>
<td>45/M</td>
<td>R temporal</td>
<td>RT 1500 r</td>
<td>NED–36 mo.</td>
</tr>
<tr>
<td>3</td>
<td>1980, Nagashima</td>
<td>60/M</td>
<td>Falx cerebri</td>
<td>None</td>
<td>Unknown</td>
</tr>
<tr>
<td>4</td>
<td>1986, Bender and Mayernik</td>
<td>34/M</td>
<td>R frontal dura/bone, spinal meninges</td>
<td>RT+CT</td>
<td>NED–12 mo.</td>
</tr>
<tr>
<td>5</td>
<td>1987, Dooryl et al.</td>
<td>51/M</td>
<td>L cerebellum</td>
<td>RT 3000 cGy WB boost 1500 cGy</td>
<td>NED–12 mo.</td>
</tr>
<tr>
<td>6</td>
<td>1988, Ashby et al.</td>
<td>62/M</td>
<td>R frontoparietal</td>
<td>RT 4000 cGy; IT CT</td>
<td>NED–14 mo.</td>
</tr>
<tr>
<td>7</td>
<td>1990, Sickler et al.</td>
<td>84/F</td>
<td>R parieto-occipital</td>
<td>RT 3500 cGy</td>
<td>NED–8 mo.</td>
</tr>
<tr>
<td>8</td>
<td>1992, Clark et al.</td>
<td>53/F</td>
<td>R cerebellum</td>
<td>RT 4500 cGy</td>
<td>NED–6 mo.</td>
</tr>
<tr>
<td>9</td>
<td>1999, Klein et al.</td>
<td>54/M</td>
<td>R occipital</td>
<td>RT 3600 cGy WB boost 1400 cGy+IT</td>
<td>NED–16 mo.</td>
</tr>
<tr>
<td>10</td>
<td>Current report</td>
<td>52/M</td>
<td>L temporoparietal</td>
<td>RT 3000 cGy WB boost 500 cGy</td>
<td>NED–21 mo.</td>
</tr>
</tbody>
</table>

Abbreviations: M, male; F, female; R, right; L, left; RT, radiation therapy; CT, chemotherapy; r, roentgens; cGy, centigray; WB, whole brain; IT, intrathecal; NED, alive with no evidence of disease; mo, months.
Although 3 of the 9 reported cases were treated with chemotherapy, there is insufficient data to recommend the routine use of adjunctive intrathecal or systemic chemotherapy without evidence of positive CSF cytology or extracranial extension. It is not clear if whole-brain irradiation is required to prevent intracranial relapse. Conclusions regarding treatment efficacy are clearly limited by small numbers and lack of long term follow-up.

In summary, primary Hodgkin’s disease limited to the CNS is exceedingly rare. The risk factors for this presentation remain undefined. Although follow-up is short, radiotherapy alone appears to provide excellent disease-free survival. Chemotherapy may be reserved for patients with positive CSF, extracranial disease, or subsequent relapse.

References


