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CNS Non-Hodgkin Lymphoma in a Patient Previously Treated for Systemic Hodgkin Disease

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Current therapy for Hodgkin disease has resulted in a 5-year survival rate of approximately 90% for individuals with asymptomatic stage I and II disease and nearly a 60% survival rate for those with symptomatic stage IV disease [1]. This improvement in survival has created an increase in the number of second malignancies occurring after successful treatment of the original disease, a complication that is of particular concern in children because of their longer life expectancy. The development of a non-Hodgkin lymphoma after treatment for Hodgkin disease is one such described complication, with an estimated risk of 1.6% at 15 years [2]. Non-Hodgkin lymphoma occurring as a second malignancy usually exhibits aggressive histology, frequent abdominal involvement, and an apparent relation to immunosuppression, augmented by therapy for Hodgkin disease [1, 3, 4]. Six cases of primary CNS non-Hodgkin lymphoma arising as a second malignancy in patients initially treated for Hodgkin disease have been described [3, 5–7]. CT findings are described in three of these cases [5, 6].

We present a case of intracranial non-Hodgkin lymphoma, complete with CT and MR imaging findings, that arose 5 years after successful treatment of non-CNS Hodgkin disease to reemphasize that this rare sequence of events can occur.

Case Report

In 1984, a 12-year-old girl was diagnosed as having stage IIA (Ann Arbor modification of Rye staging system) nodular sclerosing Hodgkin disease. Diagnosis was made by supraclavicular lymph node biopsy. At the time of diagnosis, thoracic CT revealed mediastinal and bilateral internal mammary adenopathy. A lymphangiogram showed only mediastinal adenopathy. A gallium scan showed increased tracer uptake in the left neck and mediastinum, but was negative below the diaphragm. Bone scan and liver/spleen scan were negative. Staging laparotomy demonstrated no disease below the diaphragm. One dose of prednisone, procarbazine, and vincristine was administered, and chemotherapy was then discontinued in view of the patient's adult body habitus and the risks of combined modality treatment.

Subsequent treatment consisted of mantle and Waldeyer ring irradiation to a total mantle dose of 4250 centigray (cG) with a boost

of 680 cG to the area of original involvement (left supraclavicular node) over a period of 30 days. After a 3-week interval, 3570 cG were given to the paraaortic nodes and splenic pedicle over an additional 30 days.

The patient was followed at regular intervals by physical examination, complete blood count, and chest radiographs and was thought to be in complete remission until 4 years later when a relapse occurred with left supraclavicular and left axillary disease. A CT scan at this time showed a left supraclavicular mass and an increased number of retroperitoneal lymph nodes, not pathologically enlarged by CT criteria. A bone marrow biopsy was negative. This relapse was treated with alternating cycles of mechlorethamine, vincristine, procarbazine, and prednisone (also known as "MOPP" combination chemotherapy) and doxorubicin, bleomycin, vinblastine, and dacarbazine (also known as "ABVD" combination chemotherapy) for a period of 9 months. During this time, the patient developed restrictive lung disease, which was treated with corticosteroids.

Five years after the initial diagnosis of Hodgkin disease and only a few days after completing her most recent course of chemotherapy, she was admitted to the hospital after two episodes of seizurelike activity associated with profound lethargy. She reported several weeks of headaches, nausea and vomiting, diplopia, and progressive short-term memory loss. Physical examination demonstrated bilateral ptosis, difficulty with upward gaze, and sluggishly reactive pupils. Cranial postcontrast CT scan (Fig. 1A) demonstrated hydrocephalus; a large partially enhancing mass in the left frontal lobe; and a second lesion centered in the splenium of the corpus callosum with extension into the medial parietal lobes bilaterally, the tectum of the midbrain, and the posterior diencephalon. An MR examination (0.35-T imager; Diconics, Milpitas, CA) better localized these mass lesions and confirmed midbrain compression/invasion as the probable cause of the hydrocephalus (Fig. 1). The findings were considered compatible with recurrent lymphoma. A ventricular shunt was inserted and CSF obtained at this time yielded atypical lymphocytes, suspicious for lymphoma.

The patient was treated with Decadron, phenytoin, and a 12-day course of cranial irradiation for presumed CNS lymphoma. Chemotherapy was refused. Follow-up CT scans demonstrated decreased hydrocephalus but no significant change in the previously described mass lesions. The patient rapidly deteriorated and died 3 weeks after the intracranial disease was discovered.

Physical examination, chest radiographs, and chest CT scan during the patient's final hospital admission demonstrated no evidence of

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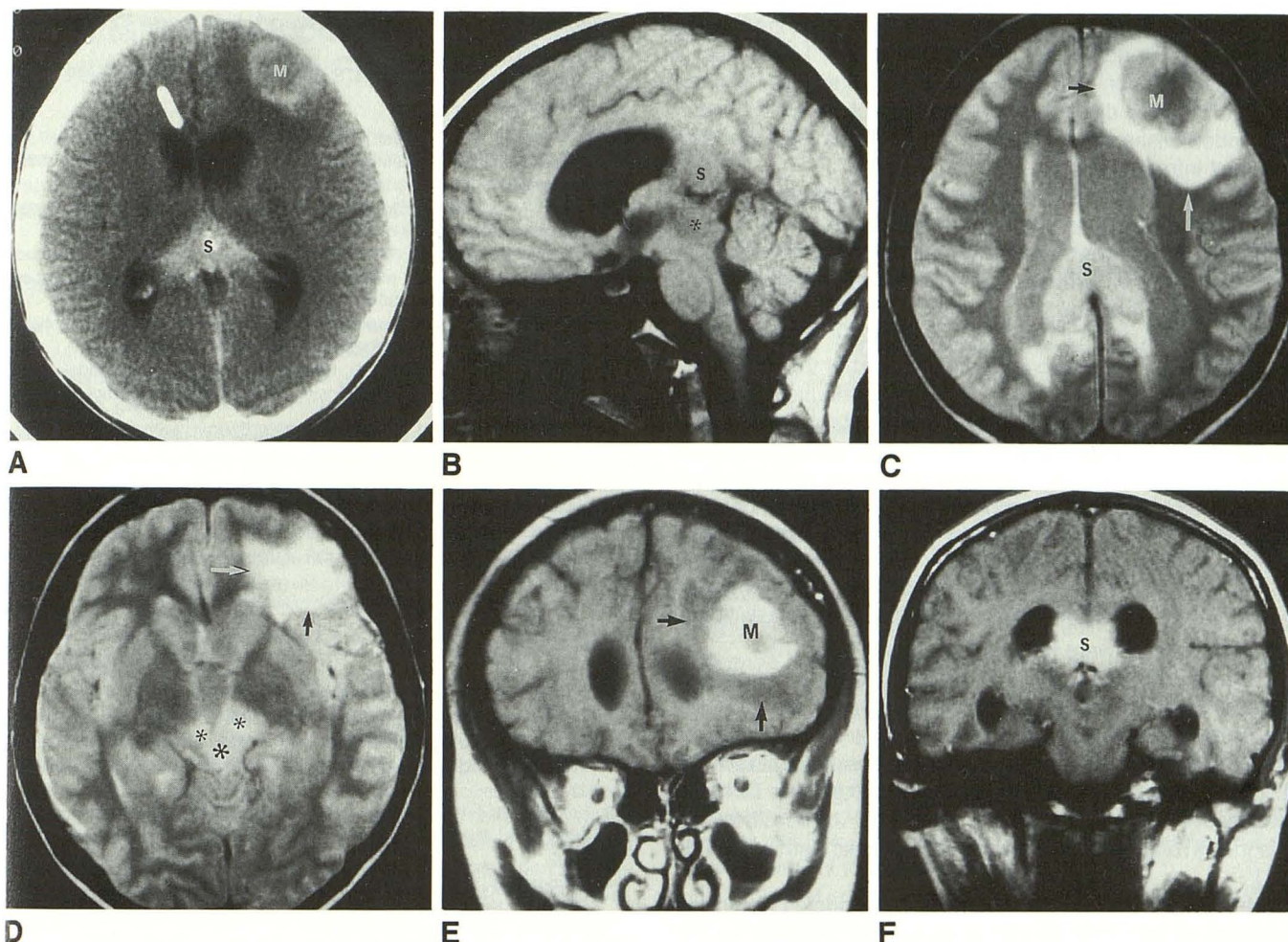


Fig. 1.—12-year-old girl with CNS non-Hodgkin lymphoma who was previously treated for systemic Hodgkin lymphoma. Noncontrast CT scan (not shown) revealed an isodense mass in left frontal region associated with moderate mass effect and edema. A second mass was centered in the region of the splenium of the corpus callosum and extended into the midbrain and posterior diencephalon.

A, Postcontrast CT scan shows enhancement of a portion of the left frontal lobe region mass (M) and also the majority of the more midline (splenium and vicinity) lesion (S). A right ventricular shunt catheter is also seen.

B, Sagittal T1-weighted MR image (500/30/2) shows splenic mass (S) with brainstem extension (asterisk).

C and D, Axial T2-weighted images (2000/60/2) show partially necrotic left frontal lobe mass (M) with local mass effect/edema (arrows) and also the splenic mass (S) extending into the midbrain and posterior diencephalon (asterisks).

E and F, Coronal contrast-enhanced T1-weighted images (500/30/2) also demonstrate the two masses. M = left frontal lobe mass, arrows = local mass effect/edema, S = splenic mass.

recurrent systemic Hodgkin disease. At necropsy, primary non-Hodgkin large-cell lymphoma of the B cell type was found in the left frontal lobe and also extensively involved the splenium of the corpus callosum, the posterior third ventricle region, the forceps major, and the tectum of the mesencephalon. Focal involvement of the meninges of the upper posterior pons and invasion of the third and lateral ventricles were also seen.

Discussion

Primary CNS non-Hodgkin lymphoma represents less than 1% of all non-Hodgkin lymphomas and less than 1–2% of all brain tumors [7–11]. There is a well known relationship between CNS non-Hodgkin lymphoma and immunosuppressive states. Previously described immunosuppressive states that

appear to predispose to development of CNS non-Hodgkin lymphoma include organ transplants, AIDS, congenital immunodeficiency, and drug- or disease-induced immunosuppression [4, 7, 10–12]. The increased risk of non-Hodgkin lymphoma following Hodgkin disease has not been shown to be related to any specific treatment, but rather is thought to be related to the immunosuppression accompanying the Hodgkin disease itself, which is exacerbated by the chemotherapy and radiotherapy used in its treatment.

The time interval between diagnosis of Hodgkin disease and development of subsequent non-Hodgkin lymphoma ranges from 3 to 10 years, with an average interval of 4 to 5 years [13], as was seen in our case. The risk of developing non-Hodgkin lymphoma as a second malignancy after successful treatment of Hodgkin disease is estimated at 0.5–

4.4% at 10 years, with CNS non-Hodgkin lymphoma being rare among the non-Hodgkin lymphomas [2-4, 14]. The prognosis for CNS non-Hodgkin lymphoma after successful treatment of Hodgkin disease is poor, with five of the six previously described cases dying 3 weeks to 14 months after the diagnosis of intracranial disease [3, 5, 7].

Hodgkin disease recurring intracranially is rare and generally occurs in the meninges. It rarely recurs as an isolated parenchymal brain lesion. In the rare cases with intracranial findings [15, 16], extracranial lesions are usually present. Primary CNS non-Hodgkin lymphoma has a predilection for the brain parenchyma, with the basal ganglia, thalamus, corpus callosum, and periventricular white matter the most common sites of disease [7, 9, 10, 17]. This distribution of lesions is the same regardless of whether the neoplasm arises in the setting of AIDS, organ transplant, or immunosuppression. In 21-60% of cases, multiple intracranial lesions are described, usually involving the basal ganglia [7, 10, 17]. On noncontrast CT scans, the lesions are usually isodense to slightly hyperdense. After contrast administration, they commonly enhance homogeneously. Mass effect is generally mild, with a variable amount of surrounding edema [7, 9, 10, 12, 18]. The majority of these findings were present in our case (Fig. 1A).

The differential diagnosis in a patient with the above-described intracranial lesions includes abscess, metastatic disease, glioma, meningioma, and radiation necrosis. However, an isodense, homogeneously enhancing lesion located in the corpus callosum in addition to the basal ganglia is highly suggestive of lymphoma, as other lesions in the differential diagnosis rarely demonstrate this topographic distribution [10, 17].

MR imaging of primary intracranial non-Hodgkin lymphoma appears to add little additional specific information to that provided by CT, except for improving anatomic localization, which is important for biopsy purposes. On MR scans, the imaging characteristics of non-Hodgkin lymphoma are non-specific; hypointense relative to brain parenchyma on T1-weighted images and hyperintense relative to brain parenchyma on proton-density and T2-weighted images, with minimal mass effect and variable edema [12, 18]. Our case differs only slightly from this pattern, as the center of the frontal lobe

lesion was slightly hypointense on the more T2-weighted images (Fig. 1C).

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