The Development Of Brain Metastasis In Hodgkin's Lymphoma: Review And Management Of This Rare Late Stage Finding

K Slam, M Castillo-Sang, R Medel, A Medhkour

Citation

K Slam, M Castillo-Sang, R Medel, A Medhkour. *The Development Of Brain Metastasis In Hodgkin's Lymphoma: Review And Management Of This Rare Late Stage Finding*. The Internet Journal of Neurosurgery. 2005 Volume 3 Number 2.

Abstract

Overall, approximately 25% of patients with systemic cancer will suffer metastasis to the nervous system. Intracranial manifestations of Hodgkin's disease, however, are quite rare, found in less than 0.25% of patients with the disease. A patient previously diagnosed with Hodgkin's lymphoma presented to the emergency department complaining of a severe headache, and radiologic evaluation suggested a frontal lobe meningioma. She was taken to surgery where her tumor was successfully resected, but final pathologic analysis confirmed Hodgkin's disease. We review the literature on this rare finding and discuss current therapy options.

INTRODUCTION

Hodgkin's disease is a relatively rare lymphatic disorder, affecting 7500-8500 individuals yearly in a bimodal age distribution. While the exact etiology remains unknown, infection with the Epstein-Barr virus (EBV) is believed to be associated with the disease. Patients generally present with supradiaphragmatic lymphadenopathy; however, weight loss, fever, and night sweats may be the initial symptoms (B symptoms) ([1]). Diagnosis requires pathologic evaluation of a lymph node specimen, displaying a Reed-Sternberg (RS) cell surrounded by an inflammatory environment of lymphocytes, eosinophils, neutrophils, plasma cells, and histiocytes. The RS cell contains two surface antigens, CD 30 and CD 15, serving as diagnostic markers ([2]). The Ann Arbor (Cotswold) system stages Hodgkin's disease based on chest radiographs, blood counts, and CTs of the chest, abdomen, and pelvis. Stage one disease involves a single nodal area, while stage two involves two or more nodal areas contained to one side of the diaphragm. Stage three is characterized by nodal disease on both sides of the diaphragm. Extranodal disease or distant metastasis is characteristic of stage four. Bulky disease greater than ten centimeters is denoted with the suffix “X” ([3]).

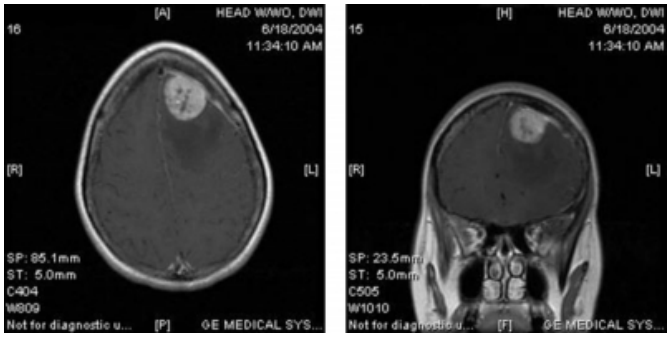
The patient's age and disease stage are most influential on long term prognosis. Early stage Hodgkin's is usually treated with radiotherapy in combination with four cycles of ABVD chemotherapy (doxorubicin, bleomycin, vinblastine, and dacarbazine); advanced stage disease is treated with six to eight cycles of ABVD or the MOPP cycle (mechlorethamine, vincristine, procarbazine, and prednisone). Relapses of Hodgkin's disease are treated high dose chemotherapy salvage followed possibly by stem cell transplantation ([4]).

CASE REPORT

A twenty-seven year old female presented to the emergency department with complaints of a severe unremitting frontal headache. Her past medical history was significant for Hodgkin's disease diagnosed two years ago and treated with chemotherapy. However, one month prior, she suffered a pulmonary recurrence of her disease and underwent a wedge resection of a right lower lung nodule. Her physical exam and laboratory profile were unremarkable, but a brain computed tomography (CT) revealed a large area of attenuation in her left frontal lobe with mass effect. MRI further delineated this as an extra-axial mass with central necrosis, avid enhancement and dural tail, radiographically suggestive of a meningioma (Figures 1 A & B).

Figure 1

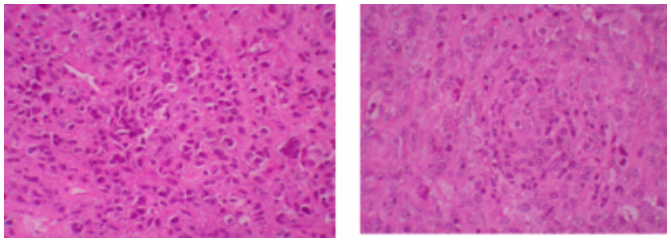
Figure 1 A and B: Axial and coronal MRI images demonstrating an extra-axial mass of superior left frontal region with avid enhancement and dural tail.



At surgical exploration, the mass was grossly found to invade her frontal bone. Successful extirpation of the tumor was accomplished and her bony defect closed via cranioplastic reconstruction. Her post-surgical course was uneventful and she was discharged home neurologically intact. Pathologic evaluation of the tumor revealed extensive tumor necrosis, sheets of large atypical cells, and a background of focal lymphocytes and scattered eosinophils (Figures 2 A & B). Immunohistochemical staining was CD 30 positive; CD 15, GFAP, and EMA negative; LCA stained only the small lymphocytes in the background; UCHL-1 stained a few of the background T cells; L26 stained a few of the background B cells. These pathologic findings are most consistent with lymphocyte-depleted Hodgkin's disease. The patient subsequently underwent post-operative radiation therapy to the tumor bed. A follow up brain MRI was obtained at two months and demonstrated a small enhancing abnormality of the left parietal lobe, possibly post-operative change versus recurrent tumor. Five months post-operatively, she was found to have multiple left chest nodules and mediastinal lymphadenopathy on chest CT, and underwent further chemotherapy. She then entered into hospice care due to continued pulmonary deterioration.

Figure 2

Figure 2 A and B: Microscopy. Poorly differentiated, large, atypical cells with bizarre mitotic figures.



DISCUSSION

Metastatic tumors to the nervous system occur in 15 to 25% of patients with solid carcinomas, typically in those with disseminated disease ([5]). The incidence and five-year risk of development of brain metastasis varies amongst different types of carcinoma (Table 1) ([7]). However, compared to solid tumors, the development of metastatic intracranial lymphoma is exceedingly rare, estimated to occur in 0.85%-3% of patients ([8], [9]). Brain metastasis of Hodgkin's lymphoma is even more exceptional, found in only 0.22% of cases all CNS neoplasms reviewed by Zimmerman ([8]). The first case of metastatic intracerebral Hodgkin's was reported in the literature by Gaelen in 1967 ([10]). It has been suggested that familial Hodgkin's disease may be a risk factor for metastasis secondary to impaired immunity ([11]). The optimal management and prognosis of these tumors are based on anecdotal evidence from case reports and extrapolation of data from the management of metastatic brain tumors from other primaries ([12],[13],[14],[15]).

Figure 3

Table 1: Brain metastasis and comparison of primary tumor site

Location	% of metastatic brain tumors	Incidence
All lymphomas	1%	? 10%
Lung	30-50%	21-64%
Breast	20-30%	2-19%
Melanoma	10-15%	4-16%
Colorectal/GI	5-10%	2-12%
Renal/GU	5-10%	1-8%
Unknown	5-15%	2-18%

(Adapted from 6, 7)

Treatment of brain metastasis includes symptomatic control of edema, elevated intracranial pressure, and seizures. Corticosteroids are typically the first line symptomatic treatment for metastatic brain tumors, possibly extending survival by several months ([7]). Definitive treatment options include craniotomy and resection; whole-brain radiation therapy (WBRT) alone or after resection; or stereotactic surgery. Two randomized studies comparing the treatment of a single metastatic brain lesion with radiotherapy alone versus surgical excision plus radiotherapy have demonstrated that the later extended survival by six months and improved neurologic function and quality of life ([16],[17]). Another randomized trial confirmed that the addition of radiation therapy to surgery improves local tumor control but not long term survival ([18]).

It has been previously noted that dural-based Hodgkin's metastases may have the initial radiologic and gross

appearance of a meningioma ([19,20,21]). Early surgical intervention is indicated in this scenario to establish a definitive diagnosis ([7]). However, because these tumors are exceedingly rare, the optimal management of a patient diagnosed pre-operatively with an intracranial Hodgkin's metastasis is less clear. Treatment with chemoradiation therapy alone, surgical therapy alone, and surgical therapy followed by chemoradiation therapy have all been reported in the literature ([10,11,12,13]). Most patients will suffer an intracranial recurrence of their disease, irrespective of initial mode of therapy.

The development of intracranial metastases generally portends a poor long term prognosis for many carcinomas, and is unfortunately quite common with many advanced stage cancers. Hodgkin's lymphoma metastatic to the brain is incredibly rare, and as such, much remains unproven about the optimal management. One might extrapolate on the data derived from trials on brain metastasis from solid organ carcinoma and conclude that surgical excision plus post operative adjuvant therapy is optimal. However, reasonable short term control via chemoradiation therapy alone, surgical excision alone, and a combination of modalities have all been reported in the literature for metastatic Hodgkin's tumors.

CORRESPONDENCE TO

Kristine Slam, MD Corresponding Author Surgical Resident Department of Surgery University of Toledo Dowling Hall 3065 Arlington Avenue Toledo, Ohio 43614 kslam@meduohio.edu 419-902-6112 (phone) 419-383-6636 (fax)

References

1. Abeloff MD, editor. Clinical Oncology, 3rd edition. Orlando: Churchill Livingstone, 2004.
2. Hoffman: Hematology: Basic Principles and Practice, 4th edition. Orlando: Churchill Livingstone, 2005.
3. Lister TA, et al. Report of a committee convened to discuss the evaluation and staging of patients with Hodgkin's disease: Cotswolds meeting. Journal of Clinical Oncology 1989. 7(11): 1630-1636.
4. Diehl V. Part 2: Hodgkin's Lymphoma-diagnosis and treatment. The Lancet, Oncology 2004 5 (1); 19-26.
5. DeAngelis LM. Metastatic disease of the nervous system. Current Treatment Options in Neurology 1999. 1: 409-416.
6. Schouten LJ, Rutten J, Huveneers, HAM, Twijinstra A. Incidence of brain metastasis in a cohort of patients with carcinoma of the breast, colon, kidney, lung, and melanoma. Cancer 2002. 94 (10): 2698-2705.
7. Nguyen T, and DeAngelis LM. Treatment of Brain Metastasis. Journal of Supportive Oncology 2004. 2(5): 405-416.
8. Zimmerman HM. Malignant lymphomas of the nervous system. Acta Neurophatholigica 1975; 6: 69-74.
9. Jellinger K, Radaskiewicz TH, Slowik F. Primary malignant lymphomas of the central nervous system in man. Acta Neuropatholgica 1975; 6: 95-102.
10. Gaelen LH, Levitan S. Solitary intracranial metastasis by Hodgkin's disease. Archives of Internal Medicine 1967; 120 (6): 740-745.
11. Ashigbi MY, et al. Intracranial Hodgkin's disease in two patients with familial Hodgkin's disease. Medical and Pediatric Oncology 1998. 28 (4): 255-258.
12. Sapozink MD, Kaplan HS. Intracranial Hodgkin's disease. A report of 12 cases and review of the literature. Cancer 1983. 52 (7): 1301-7.
13. Alvarez F, et al. Intracranial Hodgkin's disease. Report of 2 cases. Journal of Neurosurgical Sciences 1985. 29 (3): 273-277.
14. Nakayama H, et al. Brain involvement in Hodgkin's disease: Case reports and review of the literature. Radiation Medicine 2000. 18 (3): 205-208.
15. Akuyz C, et al. Intracranial involvement in Hodgkin's disease. Pediatric Hematology and Oncology 2005. 22 (7): 589-596.
16. Patchell RA, et al. A randomized trial of surgery in the treatment of single metastases to the brain. The New England Journal of Medicine 1990; 322: 494-500.
17. Vecht CJ, et al. Treatment of single brain metastasis: Radiotherapy alone or combined with neurosurgery? Annals of Neurology 1993; 33: 583-590.
18. Patchell RA, et al. Postoperative radiotherapy in the treatment of single metastases to the brain: a randomized trial. JAMA 1998; 280 (17): 1485-1489.
19. Johnson MD, Powell SZ, Boyer PJ, Weil RJ, and Moots PL. Dural lesions mimicking meningiomas. Human Pathology 2002. 33 (12): 1211-1226.
20. Johnson MD, Kinney MC, Scheithauer BW, Briley RJ, Hamilton K, McPherson WF, Barton JH. Primary intracerebral Hodgkin's disease mimicking meningioma: A case report. Neurosurgery 2000. 47 (2): 454-456.
21. Montillo M, Scarpelli M, Discepoli G, Catarini M, Rychlicki F, Leoni P. Meningioma-like cerebral relapse of Hodgkin's disease. Leukemia and Lymphoma 1994. 14 (1-2): 185-187.

Author Information

Kristine Slam, M.D.
Surgical Resident, Department of Surgery, University of Toledo

Mario Castillo-Sang, M.D.
Surgical Resident, Department of Surgery, University of Toledo

Ricky Medel, M.S. 3
Medical Student, University of Toledo

Azedine Medhkour, M.D.
Assistant Professor, Department of Neurosurgery, University of Toledo