NERVOUS SYSTEM INVOLVEMENT IN HODGKIN'S DISEASE PATIENTS AT MARMARA UNIVERSITY HOSPITAL BETWEEN 1989 AND 1995

(Received 30 January, 1997)

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ABSTRACT

Objective: Nervous System involvement in Hodgkin's disease is a very uncommon occurrence at presentation and during the course of the disease. This paper analyzes the incidence and the clinical manifestations of nervous system involvement of all cases of Hodgkin's disease seen at Marmara University Hospital.

Methods: The records of all cases of Hodgkin's Disease patients seen at Marmara University Hospital, were examined to determine whether nervous system involvement had occurred at any time during the course of the disease between 1989 and 1995.

Results: Neurologic complications were observed in four of 23 total cases in our series of Hodgkin's Disease, giving an overall incidence of 17%. All four patients presented with neurological findings had evidence of advanced disease at presentation with B symptoms. Two of the patients had clinical paraneoplastic syndrome and the other two were determined to have paraspinal masses.

Conclusion: These figures represented here probably do not reflect the true incidence in the country, since Marmara University Hospital is a reference hospital in Istanbul and those patients with advanced disease or patients at a later stage of their disease are referred to our Hematology Department.

Key Words: Nervous System, Hodgkin's disease

INTRODUCTION

Neurological manifestations of Hodgkin's disease (HD) and other lymphomas have long been regarded as relatively uncommon occurrences (1), although lymphomas in general involve the nervous system (NS) in about 10-25% of cases sometime during the course of the illness. They involve the nervous system as part of a generalized disseminated process, or, less frequently, as a primary disease. The ratio of intraspinal to intracranial involvement is about 2:1 to 3:1.

The purpose of this paper is to analyze retrospectively the incidence and the nature of nervous system involvement in Hodgkin's disease patients at Marmara University Hospital.

MATERIALS AND METHODS

A total of 23 cases of HD were hospitalized in the hematology service at Marmara University Hospital between September 1989 and August 1995 (Table I). All patients had biopsy-confirmed disease and were classified according to the histopathologic criteria of Rye. Patients were clinically staged according to the Ann Arbor Staging. Two of the patients had undergone exploratory laparotomy for their staging. The records of all 23 patients with HD were examined to determine whether NS involvement had occurred at any time during their course of the disease. Neurological involvement was observed in four of 23 HD patients. Two of the patients had clinical paraneoplastic syndrome and the other two were determined to have paraspinal masses.

RESULTS

A total of 23 HD cases with a mean age of 31 (range: 16 to 61) years are illustrated in Table I. 14 of the patients were male and 9 were female. Most patients had advanced disease at their first presentation to our clinic. 16 of 23 patients had Stage III or Stage IV disease with 'B' symptoms.

Neurological complications were observed in four of 23 total cases (Table II) in our series of HD giving an overall incidence of 17%. One of them was female and the other three were male. Their mean age was 38 years with a range of 20 to 53 years. Sites of NS lymphomatous involvement is evident in two of the four cases presented here. All four patients with neurological findings had evidence of advanced disease at first presentation. All had "B" symptoms, one had Stage III disease and the other three had Stage IV disease at the time of initial diagnosis of their systemic illness by virtue of their extranodal lymphomatous involvement. The histologic diagnoses of the patients who developed neurological symptoms and signs are presented in Table II. Three patients had nodular sclerosis and one had lymphocyte-depleted subtype of histopathological classification. Leptomeningeal or focal cerebral lymphomatous involvement were not evident clinically in any other HD patients.

Case 1: This 53 year old male first presented to our clinic with five-months history of weakness of the lower extremities, and decreased sensation of pain and temperature. Neurological examination revealed distal muscle atrophy, loss of deep tendon reflexes,distal hypoesthesia, loss of deep sensation, and sensory ataxia. Electromyography (EMG) was consistent with motor and sensory polyneuropathy primarily affecting axonal compenent, with decreased amplitudes of motor and sensory action potentials and signs of distal axonopathy. He has no previous drug or alcohol history that would cause polyneuropathy. The patient was not diabetic, and renal or hepatic failure was not demonstrated. His plasma vitamin B12 and folic acid levels were normal. Then, he was determined to have Stage III-SB HD and received a standard alternate C-MOPP-ABVD chemotherapy protocol, without vinca alkaloids, following diagnosis. After five courses of chemotherapy, regression of neurological manifestations was observed.

Case 2: Back pain and paresthesia with weak lower extremities were the initial nervous system findings in this 48 years old male. Since he had upper motor neuron signs at the lower extremities with hyperactive deep tendon reflexes, paraparesis and hypoesthesia in pain and temperature sensation below the level of T7, electrophysiological test was not done, but thoraco-lumbar Magnetic Resonans Imaging (MRI) of the spine was preferred T8 vertebral pathological fracture and lytic lesions with an additional paravertebral mass were identified on MRI. Biopsy of the paravertebral mass revealed HD. After standard alternate C-MOPP-ABVD chemotherapy and radiotherapy, neurologic findings disappeared completely.

Case 3: A 20 year old male, presented with low back pain radiating to his left leg and without any neurologic deficit or sphincter dysfunction, was determined to have Stage IV-B HD. There was no electrical evidence of a peripheral neuropathy or a root involvement on EMG. A L4-S1 epidural mass was evident on spinal MRI (Fig.1). Complete regression of radiologic and neurologic findings occurred following alternate chemotherapy.

Case 4: A 30 year old female patient was referred to our clinic complaining of diffuse weakness of her both upper and lower extremities. She was determined to have Stage IV-B HD with liver and bone marrow involvement. Spastic quadriparesis, hyperreflexia and pathological reflexes bilaterally were identified on her neurological examination. Cranial Computed Tomography (CT) with contrast and cervical, thoracolumbar MRI were normal. Cerebrospinal fluid was negative for infection and malignant infiltration. Her paraneoplastic myelopathy responded to two courses of standard C-MOPP-ABVD chemotherapy. But, she developed bilateral foot drop after two and half months while she was on therapy. Vinca alkaloid was thought to be responsible for her peripheral neuropathy and her treatment was continued for additional 4 courses without Oncovin. Complete disappearance of her neurological findings together with the remission of the disease was confirmed with EMG study.

DISCUSSION

The complications of HD involving the NS may be divided into two categories: complications related to the metastatic involvement and complications occurring in the presence of tumor elsewhere in the body.

Tumoral involvement of brain was observed in 1.7% and of the cranial nerves in 1.2% of HD (2) None of the patients seen at our institution showed any evidence of intracerebral or leptomeningeal involvement or any cranial nerve abnormality.

HD is very rarely associated with NS disease except for the direct sequelae of growth within the epidural

spaces of the vertebral column and skull (3). Invasion of the spinal canal is the most common type of NS involvement. The frequency of cord compression in HD, either at presentation of during the course of disease varies between 3.0 to 7.6% in different series of HD (2,4-6). There are only a few cases in the literature that describe the spinal cord compression as the initial manifestation of HD as in our second and third cases(7,8). The earliest symptom of spinal cord involvement is back or radicular pain as in our two cases, and this is present for a median duration of five to six months, either alone or in combination with other symptoms, followed by weakness and superficial sensory loss below the involved area. Sphincter dysfunction appears later. After these symptoms have been present for a certain time, paraplegia may ensue (2). Early detection of spinal epidural lymphoma avoids serious complications of cord compression such as paraplegia and sphincter dysfunction. Our cases with paraspinal mass did not evolve to the point of serious complications. Mechanical compression of the cord by epidural tumor is usually the major factor in producing the neurologic deficit and since tumor growth along the intervertebral foramina is believed to be the most common route of spread to the epidural space (5), occlusion of radicular arteries may be important in the pathologenesis of spinal cord compression. Concomitant vertebral bone involvement has been observed in 32-42% of the cases (4,9). Most unusual in HD is spinal cord parenchymal invasion; only a few cases of HD with intramedullary spinal cord metastasis has been described (10).

Table I. Summary of 23 HD patients

Case	Age	Sex	Clinical Stage¶	Extranodal Lymphomatous Involvement	Hitopathologic Classification*	NS Involvement
1	20	M	IV-B	Liver and bone marrow	Nodular sclerosis	No
2	39	M	III-SB	No	Lymphocyte-predominant	No
3	24	M	IV-B	Liver and lung	Nodular sclerosis	No
4	16	F	IV-B	Lung	Lymphocyte-predominant	No
5	25	M	IV-B	Liver and bone marrow	Nodular sclerosis	No
6	28	M	III-B	No	Mixed cellularity	No
7	30	F	IV-B	Liver and bone marrow	Lymphocyte-depleted	Paraneoplastic syndrome
8	20	M	IV-A	Thyroid	Nodular sclerosis	No
9	61	F	II-A	No	Lymphocyte-predominant	No
10	18	M	IV-B	Lung and liver	Mixed cellularity	No
11	23	F	II-A	No	Nodular sclerosis	No
12	53	M	III-SB	No	Nodular sclerosis	Paraneoplastic syndrome
13	34	F	IV-B	Lung	Nodular sclerosis	No
14	33	M	II-A	No	Nodular sclerosis	No
15	39	M	IV-B	Liver	Mixed cellularity	No
16	29	M	III-B	No	Nodular sclerosis	No
17	30	F	II-B	No	Lymphocyte-predominant	No
18	51	F	IV-B	Lung and bone marrow	Nodular sclerosis	No
19	29	M	I-A	No	Nodular sclerosis	No
20	48	M	IV-B	Bone and paraspinal mass	Nodular sclerosis	Paraspinal mass
21	20	M	IV-B	Paraspinal mass	Nodular sclerosis	Paraspinal mass
22	20	F	IV-B	Liver	Nodular sclerosis	No
23	29	F	II-A	No	Nodular sclerosis	No

¶ Ann Arbor staging

* Histopathologic criteria of Rye

Table II. Summary of clinical and neuropathologic findings in 4 patients with Hodgkin's disease

Case No.	Age, years	Sex	Symptoms and Signs	Onset	Documentation	Histopathologic subtype*	Stage¶
1	53	M	weak lover extremities with decreased sensation of pain and temperature	at diagnosis	EMG: polyneuropathy	Nodular sclerosis	III-SB
2	48	M	back pain and paresthesia, weak lower extremities	at diagnosis	MRI: T8 vertebral pathologic fracture and lytic lesions with an additional paravertebral mass Biopsy: HD	Nodular sclerosis	IV-B
3	20	M	low back and left leg pain	at diagnosis	MRI: L4-S1 epidural mass	Nodular sclerosis	IV-B
4	30	F	diffuse weakness of upper and lower extremities; paraneoplastic myelopathy	at diagnosis	Cranial CT and spinal MRI were negative, CSF: negative	Lymphocyte-depleted	IV-B

EMG = electromyography, MRI = magnetic resonance imaging, CT = computed tomography, CSF = cerebrospinal fluid
* Histopathologic criteria of Rye
¶ Ann Arbor staging

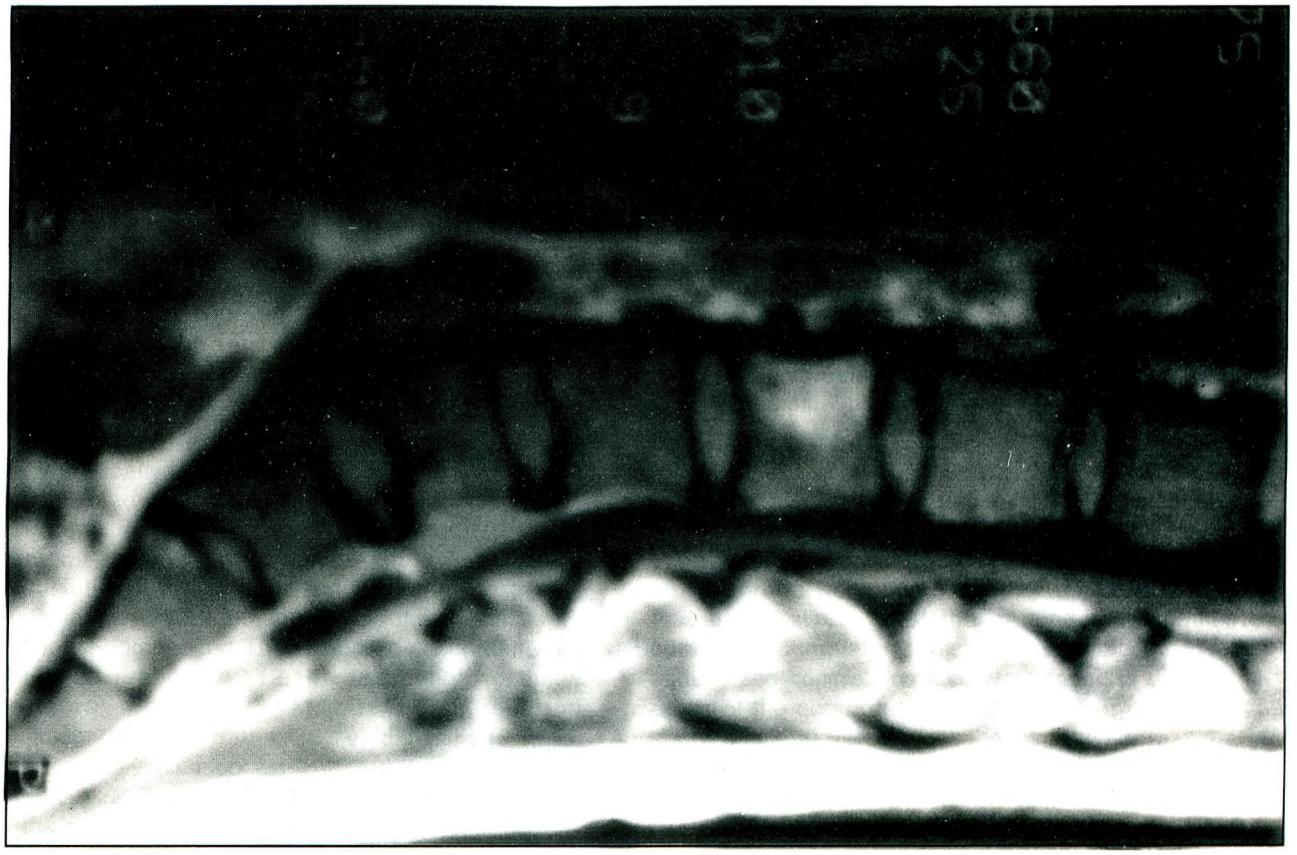

Fig. 1.: T1-weighted sagittal spin-echo image shows epidural extension of the soft tissue lesion towards the spinal canal and compression of the spinal cord.

Intraspinal involvement by lymphomas may occur in a variety of fashions: 1) epidural deposits may occur as a result of direct extension through the intervertebral foramina of tumors in the posterior mediastinum or retroperitoneal space; 2) pressure on the spinal cord occurs from collapse of vertebrae following invasion of bone; 3) occlusion of segmental arterial supply to the spinal cord by retroperitoneal or posterior mediastinal tumors is probably one of the more frequent causes of spinal cord lesions when no compression is evident; 4) toxic myelitis, or myelomalacia for wihich no other nearby cause can be demonstrated, does occur in persons with malignant lymphomas; 5) occasionally a diffuse meningeal lymphomatous involvement will produce a clinical picture of meningitis; 6) rarely, necrosis of the spinal cord occurs following irradiation treatment for intraspinal lymphomas.

Another category of complications of HD involving the NS is nontumoral CNS and peripheral nerve complications (2). Optic neuritis and peripheral neuropathies not associated with neoplastic infiltration have been described. Electrophysiological studies with HD and other lymphoproliferative disorders disclosed impairment of motor and sensory nerve conduction consistent with generalized neuropathy. The pathologic and electron microscopic abnormalities were those of axonal degeneration and segmental demyelination indicating a disorder of the nerve and Schwann cells. The mechanism is still unclear; although it is thought to be toxic or metabolic. Peripheral neuropathy (motor and sensory), visual disturbances, cranial nerve deficit (III, V, VI, VII), alterations of taste, constipation, ileus, difficulty in initiating micturition, general weakness, malaise, and depression have been listed as toxic manifestations affecting neurologic function.

Four of the total 23 HD cases revealed evidence of neurologic involvement with an overall incidence of 17%. These figures probably do not reflect the true incidence in this country since Marmara University Hospital is a reference hospital in Istanbul and those patients with advanced disease or patients at a later stage of their disease are referred to our Hematology Department.

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