ELSEVIER

PRIMARY SPINAL EPIDURAL NON-HODGKIN'S LYMPHOMAS: A CLINICAL STUDY

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BACKGROUND
The spinal epidural space is an uncommon presenting site in primary non-Hodgkin's lymphoma. The occurrence of spinal epidural disease ranges from 0.1%–6.5% among patients with non-Hodgkin's lymphoma.

METHODS
We report a retrospective study regarding 19 patients with primary epidural non-Hodgkin's lymphomas analyzing the factors influencing prognosis of this tumor, with emphasis on treatment.

RESULT
Ten patients were females and nine males. The neurologic conditions of patients were assessed preoperatively and postoperatively according to Shaw's classification for neurologic disability. All cases underwent surgery accompanied by radiotherapy in 16 cases as well as chemotherapy in 13 cases. Histologically, the tumor proved to be a low-grade non-Hodgkin's lymphoma in three cases, intermediate-grade in four cases and, high-grade in 12 cases. At average follow-up of 7.2 years (range 5–15 years), 15 patients had died after an average interval of 31 months from treatment (range 3–130 months) and four patients are alive after an average interval of 61 months (range 32–86 months).

CONCLUSION
It appears that the outcome in these patients depends on the gravity of preoperative deficits, whereas the survival is influenced by the type of treatment.

KEY WORDS
Primary lymphoma, spinal cord compression, extradural spaces.

Epidural lymphomas account for 9% of epidural spinal tumors and 0.1%–3.3% of all lymphomas [7,11]. Non-Hodgkin's lymphomas have a spinal localization in 0.1–6.5% of cases [1,16,18–19].

We report 19 cases of primary epidural non-Hodgkin's lymphomas (PENHLS) and analyze the factors influencing prognosis of this tumor, with emphasis on treatment.

PATIENTS AND METHODS

Nineteen patients with PENHLS were operated on in the Department of Neurological Sciences of Rome University "La Sapienza" between 1975 and 1987.

Histologic classification of the tumor followed the NCI Working Formulation [17].

The neurologic conditions of patients were assessed preoperatively and postoperatively according to Shaw's classification for neurologic disability [21]: grade 1: able to walk normally; grade 2: weak legs but able to walk unaided; grade 3: walking but with aid; grade 4: unable to walk but able to move the legs; and grade 5: paraplegic.

Before or after surgery all patients were thoroughly evaluated to identify any other systemic lesions (e.g., total body CT, bone scintigraphy, bone marrow examination). All patients had their disease staged according to the Ann Arbor classification.

Epidural lymphoma was detected by myelography, myelo-CT, and MRI with gadolinium. Surgical treatment consisted either of laminectomy or a combined transthoracic or transabdominal approach. The prognostic factors considered were the histologic aspect of the tumor, patient age, clinical condition, and the type of treatment.

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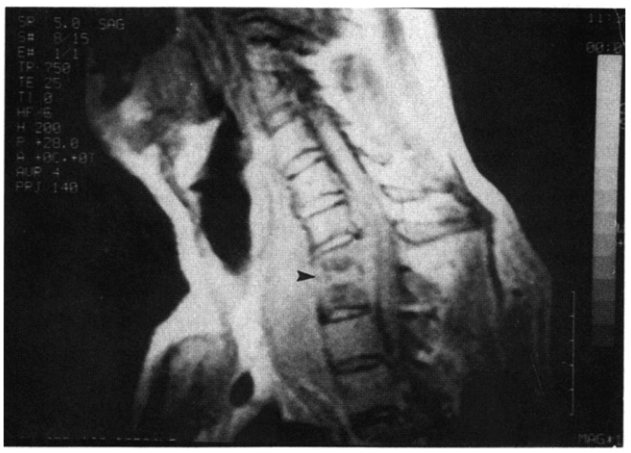
1 Characteristics of 19 Patients with Epidural Lymphoma

Pt No	Sex/Age	Site	Preop Grade	Stage	Treatment Dose of Rxt	Postop Grade	Histology	Status, Survival Cause of Death
1	m/42	Do	1	IE	S/C R = 40 Gy	1	H	A 32 months
2	f/51	Do	2	IE	S	1	L	D 3 months Rel within CNS
3	m/52	Ce	3	IE	S/R = 40 Gy	1	I	D 51 months Syst/Tr
4	f/51	LS	5	IE	S/C R = 40 Gy	5	H	D 32 months Syst
5	m/48	LS	3	IE	S	2	I	D 7 months Syst/Tr
6	m/46	LS	4	IE	S/C R = 40 Gy	3	H	A 86 months
7	f/53	Do	1	IE	S/R = 40 Gy	1	I	D 51 months Syst
8	f/47	Do	2	IE	S/C R = 40 Gy	1	H	D 13 months Rel within CNS
9	m/48	LS	5	IE	S	5	L	D 5 months Syst
10	f/48	Do	4	IE	S/C R = 40 Gy	4	H	D 19 months Syst
11	m/47	Do	4	IE	S/C R = 40 Gy	4	I	D 39 months Syst/Tr
12	f/56	LS	2	IE	S/C R = 40 Gy	1	H	A 54 months
13	m/55	Do	3	IE	S/R = 40 Gy	1	L	D 38 months Syst
14	4/51	Do	4	IE	S/C R = 40 Gy	3	H	D 19 months
15	m/52	Do	4	IE	S/C R = 40 Gy	3	H	D 22 months Syst
16	f/51	Ce	3	IE	S/C R = 40 Gy	1	H	A 72 months
17	m/53	Do	4	IE	S/C R = 40 Gy	3	H	D 12 months Syst
18	f/53	Do	4	IE	S/C R = 40 Gy	2	H	D 32 months Syst
19	m/55	Do	4	IE	S/C R = 40 Gy	3	H	D 12 months Rel within CNS

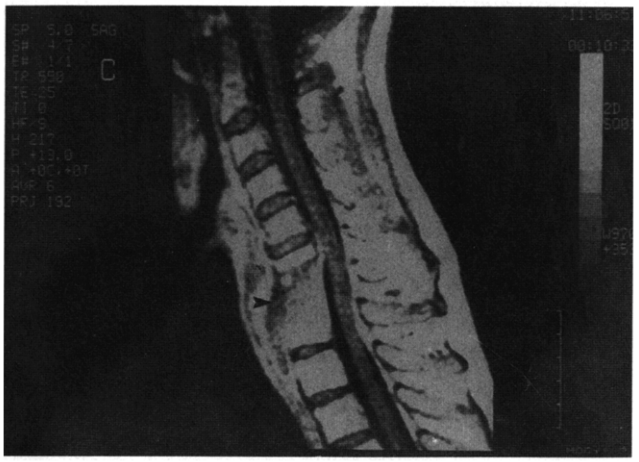
Abbreviations: A = alive; C = chemotherapy; Ce = cervical; D = died; Do = dorsal; f = female; H = high-grade; L = low-grade; LS = lumbosacral; I = intermediate-grade; m = male; no = number; Preop = preoperative; Postop = postoperative; Pt = patient; R = radiotherapy; Rel = relapse; S = surgery; Syst = systemic progression; Tr = histologic transformation.

Result

Ten patients were females and nine males (M/F ratio: 1.1:1) (Table 1). Average age was 51 years (median 53 years; range 42–63 years). In nine cases the duration of symptoms was shorter than 3 days; in five cases from 3 days–1 month; in four cases from 1–2 months; and in one case more than 2 months. Pain was a common feature in all 19 cases. There was a motor deficit of the lower limbs in 17 cases, sphincter disturbances in 13 cases (urine retention in 10 and urine incontinence in three) and 19 patients had a level of hypoesthesia. The patients' neurologic status on admission was grade I in two cases; grade II in three cases; grade III in four cases; grade IV in eight cases; and grade V in two cases. Neuroradiologic investigation showed an osteolitic lesion of the vertebral bodies in two cases (10.5%). Myelography, performed in nine cases, documented a total block in seven and a partial block in two cases. Myelo-CT with sagittal and coronal reconstruction always showed an isodense lesion displacing the spinal cord with moderate enhancement and in two cases displayed erosion of the vertebral body. MRI with gadolinium, performed in four cases, showed a hyperintense lesion in T_1-weighted images with moderate enhancement



1 Preoperative MRI showed an extradural cervical hyperintense lesion and vertebral body destruction.



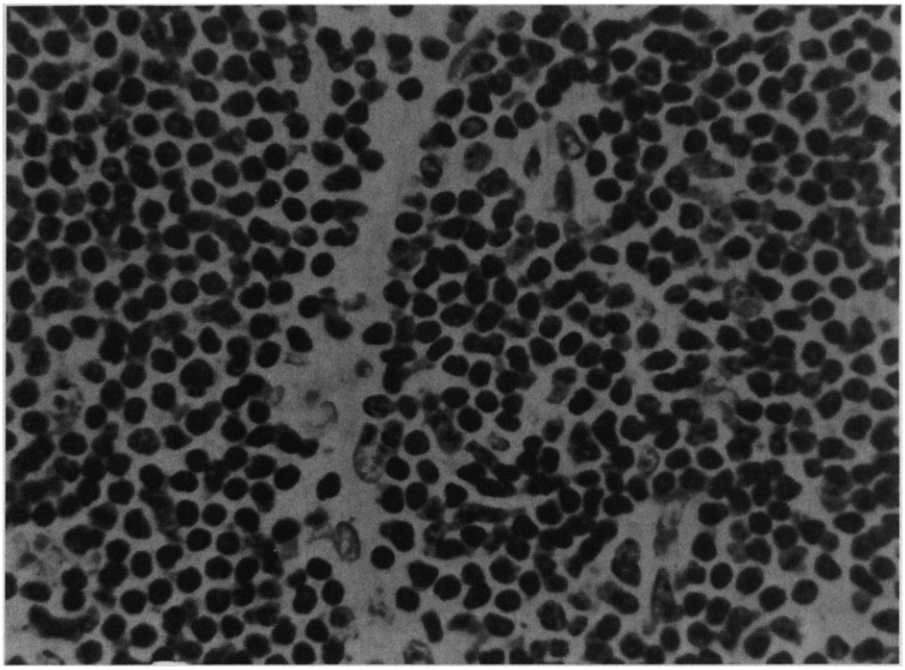
2 Postoperative MRI showed subtotal removal of cervical lymphoma.

(Figure 1). The site of the tumor was thoracic in 12 cases, lumbosacral in five and cervical in two. Surgical removal of the lesion was subtotal in all 19 patients. In eight cases the approach was anterior or anterolateral with surgical stabilization. Sixteen patients underwent local radiotherapy (40 Gy in 4 weeks), 13 patients were also given polychemotherapy (MACOP-B in seven; BACOP in six). In two of the 13 patients given chemotherapy hemopoietic factors were also administered (GSF-GM) to treat leukopenia (granulocytopenia).

Histologically, the tumor proved to be a low-grade non-Hodgkin's lymphoma in three cases, intermediate-grade in four, and high-grade in 12 cases. At average follow-up of 7.2 years (range 5–15 years), 15 patients had died after an average interval of 31 months from treatment (range 3–130 months) and four are alive after an average interval of 61 months (range 32–86 months). Death was due to systemic progression of the disease in 13 patients and relapse within the CNS in two patients. In three of the 15 patients who died the lymphoma had undergone transformation from low-grade to high-grade. Neurologic conditions evaluated in the 15 patients who died, before the disease reappeared, and in the four survivors improved in 10 cases and were unchanged in nine. In the latter, the duration of preoperative symptoms was at least 1 month. Favorable prognosis depended on good preoperative neurologic status grade II–III. Combined treatment with surgery, radiotherapy, and chemotherapy increased survival times but did not significantly influence prognosis. Average survival was 5 months in the three patients treated by surgery alone, 21 months in those treated by surgery and radiotherapy, and 43 months in those treated by chemotherapy. Moreover, surgical treatment improved the preoperative deficits in 13 cases (68%) while radiotherapy and chemotherapy did not have any effect on postoperative deficits.

Discussion

The origin of PENHLS is still unknown. Rubinstein [20] believes that it derives from the lymphatic tissue present in the epidural space. However, other authors [13] support the hypothesis that PENHLS originates from the paravertebral lymph nodes or from the vertebral body, later extending to the epidural space. Recent immunocytochemical and electron microscope studies have shown that the tumor most frequently originates from the B lymphocytes [19]. In our series, PENHLS was diagnosed on the basis of absence of other systemic localizations; brief clinical history (average 20 days); and no, or only secondary, erosion of the vertebral body. PENHLS usually presents in the 4th–5th decade of life and occurs most often in the male sex (66%–76% of cases) [6,10]. In our series, PENHLS affected the fifth decade of life and had an almost equal incidence in both males and females. Both the mass effect of the tumor and the compression it exerts on the medullary vessels contribute to the symptomatology of PENHLS [2,6,9,21]. The most affected site was the thoracic spine [2,4,5]. Some authors [2,4,19] consider this to be a result of both the greater length of the thoracic portion in relation to others and to the particular lymphatic drainage of the vertebral column. The cervical localization of PENHLS observed in two of our cases was an exceptional finding [4,5,22]. The neurologic symptoms present in our patients were typical of spinal epidural neoplasm: back pain in all patients



3 Photomicrography reveals a diffused, mixed, small cleaved and large NHL (× 200).

and motor impairment in 89%, ranging from slight spasticity to serious flaccid paraplegia. A sensory level was always present and bladder control impairment occurred in 68% of our patients.

Treatment of PENHLS is based not only on surgery but also on radiotherapy and recently on chemotherapy [3,12]. Previously, some authors [5,6] have suggested that radiotherapy and chemotherapy be used in all cases to eradicate clinically occult disease; other authors [19,22] retain useful subtotal removal of PENHLS because of a disproportionate number of relapses and deaths in patients treated with either therapy alone. We think that a simple decompression of the cord is useful for neurologic improvement and histologic diagnosis, though we must avoid complete removal or multilevel decompression, once the diagnosis of PENHLS has been established. Local radiotherapy and polychemotherapy are considered the treatment of choice, because the tumor is particularly sensitive to these modalities. Surgery ameliorated the preoperative motor deficits in 13 of our cases (68%), especially in patients operated within 72 hours from onset of symptoms (100%). Radiotherapy and polychemotherapy helped to consolidate the patients' clinical improvement. Average survival in patients with PENHLS is about 3 years. Cappellani [2], in his series of 17 patients treated by surgery and radiotherapy, reports an average survival of 31 months and 40% survival rate at 4 years from treatment. Eeles [5], in a study of 20 patients who underwent surgery, radiotherapy and chemotherapy (the latter not in all cases), gives average survival as 42 months (20% at 5 years). In his series of five patients, Epelbaum [6] noted that average survival in patients treated by surgery and radiotherapy was 26 months while in those who also received chemotherapy it was 33 months. In our series average survival was 36 months (24% at 5 years). In three of our cases, the tumor, firstly a low-grade, became high-grade, a rare occurrence in the literature [5]. Prognosis in our series was significantly influenced by preoperative neurologic condition. In fact, in the 9 grade I–III patients, average survival was 46 months compared to 25 months in the 10 grade IV–V patients. It is worth noting that in patients with similar neurologic status, average survival differed according to whether they were treated by surgery and radiotherapy alone or whether chemotherapy was used.

Conclusion

This study shows that the outcome in patients with PENHLS is essentially related to preoperative deficits, while for the survival, combined treatment (surgery, radiotherapy, and chemotherapy) ensures the best results.

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COMMENTARY

Dr. Salvati and his colleagues provide a very nice review of this relatively rare pathology. It is important to note that, in their series, approximately 50% of the patients (9/16) had symptoms of three days' duration or less. Surgery resulted in an improvement in preoperative symptoms in all patients who underwent surgery within 72 hours of clinical presentation, but in only 69% of the patients who were surgically treated after that period. Therefore, it should be recognized that surgery is more efficacious in providing immediate symptomatic relief in patients in whom some neurological function remains, if performed within a fairly limited temporal window.

In addition, all three patients who had surgery alone died of systemic disease during the follow-up period, whereas the long-term survivors (4/19) were those who had a combination of surgery, chemotherapy, and radiation therapy, confirming the value of these adjunctive measures for achieving a long-term success in controlling the systemic illness.

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The treatment of epidural spinal cord compression presented in the paper by Salvati et al differs from what is currently practiced in most medical centers in this country. When the nature of the pathology is known and the cancer is radiosensitive as is non-Hodgkin's lymphoma, radiotherapy will be the first rung of treatment. Exceptions will be rapid onset (<24 hours) of neurological deficit or progression during or after treatment with radiation.

This course of treatment is unfortunately not based on prospective randomized studies which are lacking in this important area. Many clinicians believe that the most expeditious way to reverse neurological deficit and achieve best results in