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CRANIOCEREBRAL INVOLVEMENT IN LYMPHOMA

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SUMMARY — Nine-hundred-eighty-nine patients with lymphoma were studied. Fifty-three cases (5.3%) had lymphomatous craniocerebral infiltration. The principal factors of risk for this complication were: advanced stage of the lymphoma (III or IV), diffuse histiocytic, diffuse poorly differentiated lymphocytic, or mixed cellularity lymphoma histological type, bone marrow involvement, and previous systemic chemotherapy. Thirty-two per cent of the cases of meningeal lymphomatous infiltration were asymptomatic and represented autopsy findings. CT-scan was an useful test to detect brain focal parenchymatous infiltration, as opposed to meningeal infiltration. Mean survival time in patients with lymphomatous meningeal infiltration was 4.3 months, following the combined use of systemic chemotherapy, radiation therapy and intrathecal methotrexate. Two cases had primary cerebral lymphoma, although without associated immunodeficiency Twenty patients (2%) had intracranial hemorrhage, in clear relationship with platelet alterations. Fifteen patients (1.5%) had CNS infection, caused by common bacteriae or opportunistic agents. In 7 cases, the diagnosis was made at autopsy. Thirty-six autopsies were performed. In 8 cases (22%), pathologic findings such as, demyelination, microcalcifications, coagulative necrosis, or gliosis, suggested complications from treatment.

Infiltración linfomatosa craneocerebral.

RESUMEN — Fueron estudiados 989 pacientes con linfoma. Tuvieron infiltración linfomatosa craneocerebral 53 casos (5.3%). Los principales factores de riesgo para esta complicación fueron: a. estado avanzado del linfoma (III o IV); b. las formas difusas histiocíticas, difusa pobremente diferenciada o celularidad mixta; c. el compromiso de la medula osea y de la quimioterapia sistémica previa. En el 32% de los casos la infiltración meníngea linfomatosa fué asintomática y representó hallazgos de autopsia. La tomografía cerebral fué de utilidad para detectar infiltraciones parenquimatosas focales, no así para las infiltraciones meníngeas. El tiempo medio de sobrevida en pacientes con infiltración meníngea linfomatosa fué de 4.3 meses, siguientes al uso combinado de terapia radiante a craneo total, quimioterápia sistémica y/o intratecal con methotrexate. Dos casos con linfoma cerebral primario no estuvieron asociados con inmunodeficiencia. Hemorragias intracraniales se observaron en 20 pacientes (2%), en relación con alteraciones plaquetarias. En 15 casos hubo infección del SNC (1.5%), causada por bacterias comunes o por agentes oportunistas. En 7 de esos casos el diagnóstico se hizo por autopsia. En 8 de 36 casos autopsiados (22%) se observaron desmielinización, microcalcificaciones, necrosis coagulativa o gliosis, sugestivas de complicaciones por los tratamientos efectuados.

In recent years, advances in the treatment of lymphoma have permitted a longer life expectancy, and consequently the appearance of neurological complications in more advanced stages of the disease. Most of the drugs used in the treatment of lymphoma have difficulties penetrating the blood-brain barrier. For that reason, lymphomatous cells localized in the central nervous system (CNS) may not be reached by chemo-

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therapeutic agents, and may proliferate at that level. Bone marrow involvement from lymphomatous invasion, medication toxicity, or both, can determine abnormalities in the number and function of platelets, with subsequent occurrence of hemorrhagic phenomena. The use of chemotherapeutic agents and radiation therapy (RT) has also brought about new complications. Chemotherapy or RT can have direct toxic effects on the CNS which, in turn, can produce necrotic lesions, demyelinating microangiopathy, or a subacute necrotizing leukoencephalopathy. Secondly, treatment can produce immunodepression superimposed to the immunological deficiency caused by the lymphoma, thus creating conditions for the development of opportunistic infections.

In the present study, we assess the different craniocerebral lesions caused by the above mentioned mechanisms in patients with lymphoma.

SUBJECTS AND METHODS

Four-hundred-twenty-four inpatients were studied prospectively between 1984 and 1987 in the Neurology and Hematology Departments of the José María Ramos Mejía Hospital of Buenos Aires. They all had a diagnosis of lymphoma. In a small proportion of patients, initial neurological symptoms led to the subsequent diagnosis of lymphoma. At the same time, 565 outpatient charts were reviewed, all of them with diagnosis of lymphoma. This made a total of 989 cases. Five-hundred-sixty-three cases corresponded to non-Hodgkin's lymphoma (NHL), while the remaining 426 to the Hodgkin's type (HL). In our population, 73 patients (7.4%) had evidence of craniocerebral involvement consisting of lymphomatous infiltrations, hemorrhages, infections or complications from treatment. The diagnosis of CNS lymphomatous infiltration was based on either: (a) the presence of signs and symptoms of craniocerebral involvement in patients with diagnosis of lymphoma, in whom there was evidence of structural abnormalities shown by ancillary methods such as CT scan of the head, brain radionucleide scan or plain X-Rays of the skull, and in whom there was improvement or disappearance of the pathological images and of the clinical symptoms after treatment with chemotherapy, RT, or both; or (b) cerebrospinal fluid (CSF) cytology, brain biopsy, or autopsy.

Analysis of the clinical picture included age of the patient, sex, duration of the disease, histological type of lymphoma, clinical stage, bone marrow involvement, CSF study, ancillary methods, treatment administered, and response. Treatment included RT at doses from 2400 to 5000 Rads over 15 to 20 sessions, systemic chemotherapy (SCh), intrathecal methotrexate administration (IT Mtx) followed by leucovorin rescue, or a combination of them. The only patients who underwent surgery were those who had neurological involvement as the initial clinical picture, i.e., a space-occupying mass, and in whom diagnosis of lymphoma was unknown yet. Hemorrhagic phenomena were demonstrated by means of CT scan or autopsy, when the latter was performed. Diagnosis of CNS infection was based on Hooper's criteria for immunosuppressed patients [26]. Complications from treatment were included when verified by pathological studies in patients that received RT, SCh, or IT Mtx. A total of 36 autopsies were performed. NHLs were classified according to the histological criteria of Rappaport [51]. For the HLs, Luke's criteria were used [41]. Clinical stage was established according to the recommendations of the Ann Arbor Conference [5]. One case of Burkitt's lymphoma was also included.

RESULTS

INFILTRATIONS — Meningeal, brain, or skull lymphomatous infiltrations were seen in 53 patients (5.3%). There were 39 cases with NHL, 12 with HL, 1 with Burkitt's lymphoma, and 1 with a T-cell type lymphoma. In the NHL group, there were 25 men and 14 women. Their mean age was 48 $\pm$ 17.3 years. Duration of the disease, from the time of diagnosis of lymphoma until the appearance of the first neurological symptom, was 26.4 months (range 1-108 months). In 5 patients (13%), the neurological picture was the first manifestation of the disease. In the HL group, there were 7 men and 5 women. Their mean age was 37 $\pm$ 16 years. Duration of the illness, at the time of the neurological complication, was 52.9 months (range 1-84 months). The lymphoma histological types are summarized in Table 1. There was a clear relationship between the clinical stage of the lymphoma and the occurrence of CNS lymphomatous infiltration. Eleven per cent of the cases with lymphomatous infiltrations were on stages II A or B, 22.7% on stages III A or B, and 66% on stages IV A or B.

Thirty-one patients had leptomeningeal lymphomatous infiltrations. In 19 cases, there were brain parenchymatous infiltrations. Ten patients had infiltration either circumscribed

Non-Hodgkin's Lymphoma		Hodgkin's Lymphoma	
	Nº of cases		Nº of cases
D-PDLL	15	MC	8
D-HL	14	LD	3
D-ML	9	NS	1
NHL	1		

Table 1 — Histological classification of lymphoma in patients with craniocerebral infiltrations (one patient with Burkitt's lymphoma and another with T-cell lymphoma are not included in this table). D-PDLL, diffuse poorly differentiated lymphocytic lymphoma; D-HL, diffuse histiocytic lymphoma; D-ML, diffuse mixed lymphoma; NHL, nodular histiocytic lymphoma; MC, mixed cellularity; LD, lymphocyte depletion; NS, nodular sclerosing.

to the orbit or extending to adjacent areas. Finally, four patients had infiltration of the skull. In 11 cases, there was a combination of brain parenchymatous lymphomatous infiltration with either meningeal or orbital involvement. Ten cases of lymphomatous meningeal infiltration were diagnosed at autopsy, without any prior indication of such an involvement. Two cases corresponded to primary cerebral lymphomas (PCL) of the diffuse histiocytic type. Their age at onset was 57 and 52 years, and their survival time was 8 and 11 months, respectively. None of them had associated immunodeficiency. Eight patients with brain meningeal infiltration had concomittant spinal cord involvement. Forty-five patients with craniocerebral infiltration underwent a bone marrow biopsy, which showed lymphomatous infiltration in 70% of them. However, when considered separatedly, patients with HL and craniocerebral infiltration had bone marrow involvement in all cases. The commonest symptoms and signs are summarized in Table 2.

Symptoms and signs	Nº of cases	Percentage
Headache	23	43.0
Visual disturbances	17	32.0
Confusion	13	24.5
Nausea-vomiting	8	15.0
Paresthesiae	4	7.5
Photophobia	4	7.5
Psychiatric disturbances	3	5.0
Gait disturbances	3	5.0
Cranial nerve dysfunction	23	43.0
Focal weakness	13	24.5
Nystagmus	10	18.0
Meningeal signs	9	17.0
Seizures	8	15.0
Cerebellar signs	4	7.5

Table 2 — Symptoms and signs in patients with craniocerebral lymphomatous infiltration.

CSF study revealed lymphoma cells in only 14 of 18 patients in whom a subsequent autopsy showed craniocerebral lymphomatous infiltration. In 21 patients with meningeal infiltration, the CSF study showed elevated protein and the presence of lymphomatous cells in 82% of the samples. Twenty-three per cent of the cases also had low glucose in CSF.

In all cases with brain parenchymatous or skull lymphomatous infiltration, positive findings were seen on the CT scan. In 55% of the cases, there were single hyperdense images, which enhanced homogeneously after contrast administration. In the remaining cases, the images were isodense but enhanced after contrast administration. In all cases, they had varying degrees of surrounding edema and mass effect, depending on their size. They were contiguous to either the cortex or the ependymum. On these studies images either correlated with the pathological findings or disappeared after specific treatment. Nevertheless, CT scans of the head were negative in patients with lymphomatous meningitis except for one case, where there was periependimal contrast enhancement suggesting meningeal involvement.

Fourteen patients with CT scan images consistent with focal brain infiltration were treated with RT. There was subsequent disappearance of the lesions in 9 patients (64%). Twenty-one cases of lymphomatous meningeal infiltration were treated with a combination of RT at doses of 2400 to 4000 Rads, SCh, and IT Mtx. None of them showed a satisfactory response to treatment. Their survival time had a mean of 4.3 months from the onset of symptoms.

HEMORRHAGES — Twenty patients (2%) had intracranial hemorrhages. Among them, 18 had abnormalities in the platelet count or function. Two cases had an elevated platelet count, and they had intracranial hemorrhages secondary to platelet function abnormalities. The types of the intracranial hemorrhages were: diffuse suffusions (60%), petechiae (26%), or parenchimatous hematomas (26%). In 12% of cases, two or more of these findings occurred combined.

INFECTIONS — Fifteen patients (1.5%) had CNS infections. In most cases, the etiological agent was a bacteria or a virus, either in the HL or the NHL group (Table 3). All the infections occurred in patients on advanced stages of the lymphoma. The clinical pictures corresponded to meningoencephalitis or meningitis in 7 cases. One patient had a brain abscess caused by Staphylococcus aureus. In the remaining patients, the clinical picture consisted of confusion and focal findings without meningeal irritation signs. Diagnosis was made at autopsy in these cases.

Agent	Nº of cases		
	NHL	HL	Total
Herpes zoster virus	3	3	6
Cryptococcus neoformans	2	—	2
Pseudomonas aeruginosa	—	2	2
Listeria monocytogenes	1	1	2
Haemophilus influenzae	—	1	1
Staphylococcus aureus	1	—	1
Trypanosoma cruzi	—	1	1
Total	7	8	15

Table 3 — Etiologies of brain and meningeal infections in patients with lymphoma. NHL, non-Hodgkin's lymphoma; HL, Hodgkin's lymphoma.

COMPLICATIONS FROM TREATMENT — Thirty-six autopsies were performed. Lesions that can be related to treatment, i.e., circumscribed or diffuse demyelination areas, microcalcifications, coagulative necrosis or gliosis, were seen in 8 patients (Table 4). One patient, who had been treated with RT alone, had cerebral microcalcifications. In this case, lesions can be ascribed to RT. In the other cases, it was not possible to single out a definitive relationship between the pathological findings and treatment, since more than one of the therapeutic agents used could have caused demyelination.

Nineteen patients had two or more forms of craniocerebral involvement. The most frequent associations were: hemorrhage with lymphomatous infiltration (8 cases), and infiltration with infection (4 cases).

Case	IT Mtx	RT	SCh	Pathological findings
1	+	+	COPP/BACOPP	Diffuse demyelination
2	—	+	—	Microcalcifications
3	+	+	Cy-Pred	Focal demyelination Gliosis
4	+	+	Cy-Pcb-Pred	Focal demyelination
5	+	+	Vnb-Leuk	Focal demyelination Coagulative necrosis
6	+	+	Cy-Vnc-Pcb	Focal demyelination Gliosis
7	+	+	Cy-Pred	Focal demyelination
8	+	+	BACOPP	Focal demyelination Coagulative necrosis

Table 4 — Complications from treatment in patients with lymphoma. IT Mtx, intrathecal methotrexate; RT, radiation therapy; SCh, systemic chemotherapy; Cy, cyclophosphamide; Pred, prednisone; Pcb, procarbazine; Vnb, vinblastine; Leuk, leukeran; Vnc, vincristine; COPP, cyclophosphamide, vincristine, predisone, and procarbazine; BACOPP, blocamycine, adryamicine, cyclophosphamide, prednisone, vincristine, and procarbazine.

COMMENTS

Different series reported varying incidences of brain and meningeal lymphomatous infiltration in patients with lymphoma. Figures varied between 2 and 29% in patients with NHL[4,21,29,34,40,53,66]. In the case of HL, there have been either few reports or series with a small number of patients [8,43,56,61]; Sapozinck and Kaplan reported an incidence of 0.5% [56]. In our series, 6.9% of the NHL and 2.8% of the HL patients had evidence of craniocerebral lymphomatous infiltration. In the HL group, this complication occurred at a 10-year younger age than in the NHL group, perhaps reflecting the earlier age of onset of HL. However, the duration of the hematological disease, at the time of the CNS infiltration, was twice as long in the HL group (52.9 vs 26.4 months, respectively). Neurological involvement was the first manifestation of the disease in 13% of cases of NHL. On the contrary, no case of HL had neurological involvement at the onset, in agreement with other series [33,56,60]. Generally, brain lymphomatous infiltration is seen on advanced stages of the lymphomas, and is associated with histological types like diffuse histiocytic lymphoma (DHL) and diffuse poorly differentiated lymphocytic lymphoma (DPDLL)[4,21,34,37]. Brain infiltration is infrequent in patients with HL or NHL of nodular type [4,17,21,34,37,40], although it may occur in the latter after transformation to a diffuse form [34,37,66]. Meningeal lymphomatous involvement has been reported in pathological studies of up to 76% of patients with Burkitt's lymphoma with early relapse of the disease after treatment (within 3 months)[27,36,67]. Sixty-five per cent of the patients with brain infiltration were on advanced stages of the disease, i.e., IV A or B. In patients with NHL, DPDLL accounted for 38% of the cases and, DHL for 36%, in agreement with other authors [34,37,66]. In the group of patients with HL, we found a greater incidence of histological types of mixed cellularity (66.6%). There have been controversial results in this regard in the different published series [8,11,56]. Between 9.5 and 73% of the lymphomatous meningeal infiltrations are asymptomatic and are diagnosed at autopsy [17,24,66]. In our series, 32% of meningeal infiltrations fell into this category.

Lymphomatous orbital involvement may occur isolated or combined with widespread disease. Lazzarino et al.[35] found orbital infiltration in 2.4% of patients with NHL. All these cases represented immunologically monoclonal B-cell proliferations. Sixty-two per cent of these patients had systemic involvement expressed as cutaneous or suocutaneous nodules. There was a much lower incidence of systemic involvement in our series (1%), perhaps reflecting a predominance of nodular or low grade malignant forms (60%). Patients with DHL or DPDLL, and orbital infiltration were on stages III or IV of the disease. They had orbital erosion in 50% of the cases, which represented a sign of poor prognosis, in agreement with other series [1,32,35] Bone marrow lymphomatous infiltration is seen in 60 to 100% of patients with brain

infiltration [17,37,40]. This association suggests dissemination from the bone marrow to the dura, subarachnoid space, and subsequent invasion to the Virchow-Robin space. The incidence of bone marrow infiltration in patients with early DHL is significantly lower than in patients with nodular forms (15 vs 40%, respectively). However, meningeal involvement in the former is frequent [17]. There is no clear explanation for this fact [4]. We found bone marrow involvement in 70% of the cases of lymphoma with craniocerebral infiltration. In the case of HL with brain and meningeal infiltration, the bone marrow was involved in all cases. In the cases of brain and meningeal infiltration without bone marrow involvement, the initial lymphomatous infiltration occurred in the nasal cavum, orbit, or spinal nerve roots, from where the disease disseminated to the CNS.

Lymphoma cells could be demonstrated in 78% of the CSF studies of patients with craniocerebral infiltration. According to different series [2,21,42,66], lymphoma cells can be seem in the CSF study in 70 to 88% of the patients with craniocerebral infiltration when these studies are performed with cytocentrifugation techniques. However, these figures can drop to 50%, if only one CSF sample is drawn [42,66]. Most authors recommend the study of at least three samples of CSF when looking for lymphoma cells. The study of surface markers, the identification of deoxynucleotidyltransferase, and the use of immunocytochemical techniques on CSF lymphocytes decrease the number of false positive results due to viral or mycotic infections [13,14,16,25,39]. The CT scan of the head is not a very useful test to detect meningeal lymphomatous infiltrations. Even using larger doses of contrast, enhancement similar to that occurring in patients with infectious or carcinomatous meningitis is not frequently seen [3,12,48]. On the contrary, brain focal parenchymatous infiltrations tend to appear as iso or hyperdense masses in contact with the cortical surface or the ependymum. This fact would suggest dissemination to the brain parenchyma from the dura and CSF [48]. In patients with orbital infiltrations, enlargement of the optic nerve can be seen on the CT scan [3]. In our series CT scan findings were similar to those reported by others. In only one case of meningeal infiltration, was periependymal contrast enhancement observed on the CT scan. Conversely, the CT scan was very useful in revealing brain focal parenchymatous infiltrations.

Different conditions have been considered as risk factors predisposing to brain involvement in lymphomas. Specifically, the presence of a DPDLL, a diffuse indifferentiated histological type, prior treatment with SCh, bone marrow involvement, age below 35 years, or extranodal involvement, have been singled out as risk factors [34,40]. The combination of these factors permits the prediction of the risk of CNS infiltration for each patient through a multivariable regression model. With the above mentioned data, Litam et al.[40] proposed a table that would group patients as having low, medium, or high risk of infiltration of the CNS. In our series, 95% of the patients met the criteria for inclusion in the high risk group for craniocerebral infiltration.

The lack of a uniform protocol for the treatment of these patients, as well as the different clinical forms observed, did not allow us to draw valid conclusions on the efficacy of any single therapeutic approach. However, there are two important observations. In the first place, when using combined SCh, RT, and ITMtx for the treatment of meningeal lymphomatous infiltrations, we observed a mean survival time of 4.3 months. In other series it is reported [52] a mean survival time of 8 months with the use of Ommaya reservoirs for the intrathecal administration of chemotherapeutic agents, along with RT in the same situation. Therefore, this would suggest the possible usefulness of the administration of chemotherapy with this technique. Secondly, consideration should be given to chemotherapeutic prophylactic treatment in patients at high risk for brain and meningeal lymphomatous infiltrations [29,40,49], since 80% of these occur within 5 months following treatment. Thus, prophylaxis should start early in the course of treatment, e.g., in the first three months [40].

In our series, there were two cases of PCL, both documented with pathological studies. Even though PCL used to represent only 0.3 to 1.5% of all brain tumors [26,59], there has been an increase of its incidence because of the higher current number of patients with immunodeficiency [20,26,28,38,46]. These conditions increase up to 350 times the chance of developing PCL [20,26,46]. Our two cases did not have immunodeficiency. Other authors have related PCL in patients without imunodeficiency to Epstein-Barr virus infection [18,23]. Unfortunately, we did not look for that contigency in our two patients. Hemorrhagic phenomena were observed in 2% of patients. Except for two cases, there was a clear relationship between the presence of hemorrhage and abnormalities in the platelet function or count. This suggests that brain bleeding in

patients with lymphoma is related to bone marrow involvement from lymphomatous infiltration or from chemotherapy toxicity. As opposed to intracranial hematomas, brain suffusions and petechiae are more frequently an autopsy finding, as previously suggested [9]. Patients with lymphoma are well-known for their predisposition to infections. Opportunistic agents, the association of different infectious agents compromising the same host, or the appearance of several infectious foci, are a frequent occurrence in these patients [26,54]. According to Hooper et al.[26], 2.7% of patients with HL and 0.6% of those with NHL develop some kind of CNS infectious complication in the course of their disease. In our series, the incidence of such complication was 1.9 and 1.2% in each group, respectively. Because of their poor symptomatology, early diagnosis of the CNS infection is frequently difficult in these patients [54]. In 7 cases (46%), diagnosis of CNS infection was made at autopsy, in agreement with other series [7]. Common bacteriae, as well as opportunistic agents, are capable of causing CNS infections in immunocompromised patients at varying frequencies [6,7,26]. In our series, we observed a predominance of bacterial and viral agents, even though we also found Trypanosoma cruzi, a parasite, causing one case of meningoencephalitis. This last entity was initially described in 1911 [62], and was subsequently seen in patients with immunodeficiency from different etiologies [30,45].

Previous work has reported neurotoxicity from IT Mtx, RT, and less frequently, from SCh [10,15,19,31,44,47,50,55,57,58,63-65]. Lesions are much more frequent in the white matter of the brain and consist of foci of oligodendrocyte loss with severe reactive astrocyte proliferation, coagulation necrosis of the vascular endothelium, fibrinoid degeneration, and vascular thrombosis [57,58,63]. Occasionally, there are associated calcifications [15,19,47,55]. The clinical picture corresponds to a progressive encephalopathy with confusion, seizures, spasticity, ataxia, coma, and death [10,31,44]. In 22% of the autopsies, we found elements suggesting lesions secondary to treatment, i.e., focal or diffuse demyelination, microcalcifications, coagulative necrosis, or gliosis. In only one case, could the use of RT as the only treatment, be held responsible for the observed demyelinating lesions. In the remaining cases, the lesions could have been caused by the combination of different therapeutic agents, while being difficult to single out the predominance of anyone of them in the origin of the process.

The current longer life expectancy in patients with lymphoma determined an increase in the appearance of the different types of craniocerebral involvement, most of which carry a severe prognosis. Awareness can lead to an early diagnosis and prompt treatment, which may provide relief and a longer survival time. Therefore, patients at high risck for lymphomatous infiltration should be considered for early prophylatic treatment. However, this point awaits further definition.

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