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THE CENTRAL NERVOUS SYSTEM LEUKEMIA

A CLINICAL AND PATHOLOGICAL STUDY

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An increasing number of patients with central nervous system leukemia (CNSL) are now being observed. This has been attributed to lenghtening survival since the advent of effective antileukemic therapy [4,5,26,27]. CNSL may occur as an initial manifestation of systemic leukemia [10]. Most often, however, it appears during either the active or the hematologic remission [25]. The development of CNS involvement usually represents a poor prognosis [26].

The present communication reports on clinical and pathological findings in 18 patients with CNSL.

MATERIALS AND METHODS

Clinical data on 18 patients from Saint Louis University Hospital with diagnosis of CNSL were reviewed including age, sex, date of diagnosis, morphological type of leukemia, neurological signs and symptoms, hemogram, myelogram, cerebrospinal fluid findings, status of the systemic leukemia at onset of the CNS involvement (28); interval between the onset of the disease and CNS involvement; total survival and survival after CNS involvement. Autopsy descriptions and histologic slides of CNS were reviewed in each case. Special emphasis was placed on amount and location of leukemic cells and hemorrhage. Other lesions including edema, demyelination, infarct, infection and calcification were also evaluated. One or more slides were generally examined from each of the following sites: frontal, parietal and occipital cortex; internal capsule and basal ganglia; hippocampus, midbrain, pons, medulla and cerebellum. Sections form at least three levels of spinal cord were also examined in most instances.

Intracranial hemorrhage was classified according to Phair (22) in: A. Intracerebral — 1. petechial and of no clinical significance; 2. focal, either single or multiple but less

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than 2.0 cm in greatest diameter and so located as to probably not to be related to the patient's death; 3. diffuse or massive, either single or multiple, but greater then 2.0 cm in greatest diameter and probably related to the patient's death. B. Subarachnoid -- 1. primary: a. petechial; b. focal, c. diffuse; 2. secondary. C. Subdural.

Leukostasis was defined as the degree of clogging of vascular lumina by leukemic cells (17,22) and was graded as (22): 0 normal; 1+ equivocal; 2+ slight; 3+ moderate; 4+ marked. Perivascular and parenchymal infiltrates were similarly rated. Meningeal infiltrates were considered of leukemic origin when consisted of less than 100 cells/high power field in the most concentrated regions. The term meningeal infiltrates indicates involvement of the leptomeninges since the dura matter was not always available.

RESULTS

The incidence of CNSL for the four main morphological groups of leukemia is shown in table 1. The same incidence (22.2%) was seen in acute and chronic lymphocytic leukemia (ALL and CLL respectively), a slightly lower (16.6%) was found in acute myelogenous leukemia (AML) and a notably higher (38.8%) incidence in chronic myelogenous leukemia (CML). There were 10 males and 8 females. The age ranged from 10 to 87 years with a median age of the 52 years. The interval from diagnosis of leukemia to recognition of CNS involvement ranged from 2 to 2,239 days (6 years and 49 days) with a median of 147 days. At the time of CNS manifestation minimal clinical evidence of systemic leukemia was found in 2 cases (status II — mild disease). In 10 patients the systemic leukemia was in moderate relapse (status III — moderate disease) — whereas in 6 cases it was in advanced relapse (status IV — advanced disease). None of the patients was in complete hematologic remission (status I — no apparent disease) (Table 2).

Types of leukemia	Patients (%)
Acute lymphocytic leukemia	22.2
Chronic lymphocytic leukemia	22.2
Acute myelenogenous leukemia	16.7
Chronic myelogenous leukemia	38.8

Table 1 — Types of leukemia in patients with central nervous system involvement.

Status of systemic leukemia	Nº Patients	%
I. No apparent disease	0	0
II. Mild disease	2	11.1
III. Moderate disease	10	55.6
IV. Advanced disease	6	33.3

Table 2 — Status of systemic leukemia at onset of CNS manifestations.

The principal CNS signs and symptons are recorded in table 3. Disturbances of the mental status as lethargy, disorientation, delirium, stupor and coma were the most common signs. Cranial nerves dysfunctions were next in frequency, most commonly anisocoria, ptosis, diplopia and facial paralysis. Ocular pain, upward gaze palsy, dysphagia and dysarthria were also seen. Other signs and symptoms included retinal hemorrhage, convulsions, headache, nuchal rigidity, decerebrate rigidity, vomiting, paresthesia, hemiparesis and paraplegia. In three autopsy-proved cases of CNSL no clinical manifestation was found. Analysis of the leucocyte count nearest to death revealed that 89% of the patients had less than 50,000 leukocytes/cu.mm. In the remaining 11% it ranged from 50,000 to 100,000 leukocytes/cu.mm. Analysis of the platelet count nearest to death, is shown in table 4. In only 12.5% of the cases the platelets

Signs and symptons	Nº Patients	%
Mental status disturbances		
Lethargy	8	44.4
Desorientation	5	27.8
Delirium	3	16.7
Stupor	3	16.7
Coma	2	11.1
Cranial nerves dysfunction		
Anisocoria	3	16.7
Ptosis	3	16.7
Diplopia	3	16.7
Facial paralysis	2	11.1
Upward gaze palsy	1	5.6
Ocular pain	1	5.6
Dysphagia	1	5.6
Dysarthria	1	5.6
Others		
Retinal hemorrhage	4	22.2
Convulsions	3	16.7
Headache	2	11.1
Nuchal rigidity	2	11.1
Decerebrate rigidity	2	11.1
Vomiting	1	5.6
Paresthesia	1	5.6
Hemiparesis	1	5.6
Paraplegia	1	5.6

Table 3 — Clinical findings in central nervous system leukemia.

Platelets (per cu.mm)	Nº Patients	%
Less than 1,000	0	0
1,000 - 10,000	2	12.5
10,000 - 25,000	3	18.8
25,000 - 50,000	2	12.5
More than 50,000	9	56.2

Table 4 — Platelet count in patients with CNS leukemia.

were below 10,000/cu.mm. In three patients platelet counts were available. Bone marrow findings (28) at the onset of CNS signs and symptoms suggested no evidence of leukemia in 6 patients, moderate leukemic involvement in 5 and marked involvement in 6 (Table 5). Bone marrow was not examined in one patient whose death occurred within 24 hours after admission. Lumbar puncture was performed in 8 patients. The cerebrospinal fluid (CSF) was normal in three cases. Initial pressure higher than 150 mm of water was seen in four cases. Pleocytosis of mononuclear cells was found in two cases (18 and 726 cells/cu.mm respectively) and of hematias in three cases (30, 40 and 371 cells/cu.mm respectively). Protein levels exceeded 50 mg% in three cases, the highest value being 330 mg% whereas glucose levels were normal (45-60 mg%) in all patients. The total survival time ranged from 8 to 2,250 days with a median of 300 days. The survival time after CNS involvement ranged from 1 to 180 days with a median of 21 days.

Marrow rating *	Nº Patients	%
1. No evidence of leukemia	6	35.3
2. Moderate leukemic involvement	5	29.4
3. Marked leukemic involvement	6	35.3

Table 5 — Bone marrow findings at onset of CNS involvement. (*) Acoording to Sullivan et al. 28.

Analysis of the pathological findings showed that edema as well as uncal and tonsillar herniation were present in 28% of the cases. Intracranial hemorrhage was seen in all but one patient. Parenchymal hemorrhage occurred in 61% of the brains, 36% of them being petequial and the remaining were focal hemorrhages. Fifty-five per cent of the patients had subarachnoid hemorrhage (Fig. 1), 20% of them were just petequial and 35% were focal. Ischemic infarct was present in 17% of the cases.

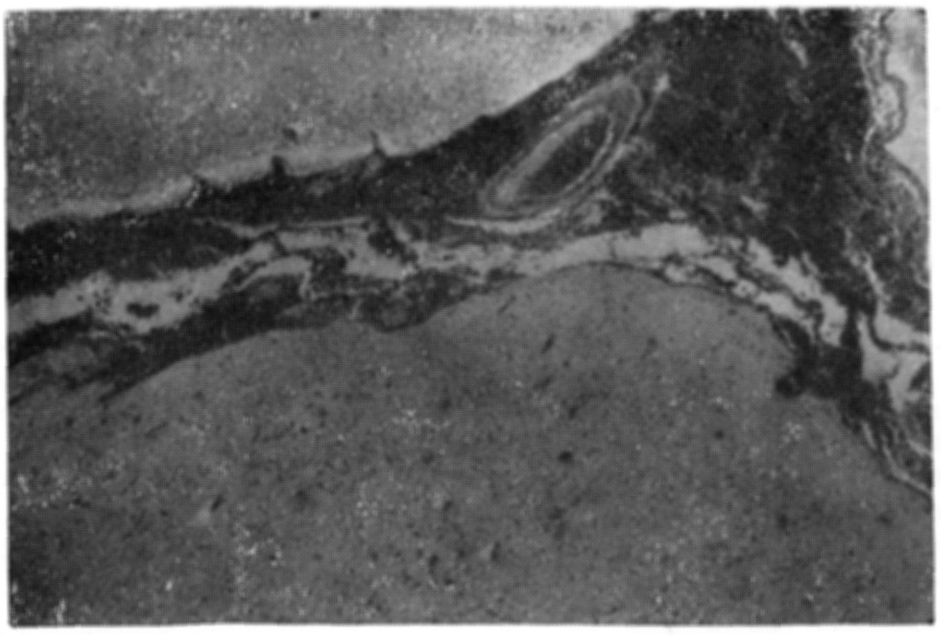

Fig. 1 — Diffuse subarachnoid hemorrhage (H.E.; 100 X).

Leukemic parenchymal infiltrates (Fig. 2) were seen in 22% of the brains. They were usually masses of densely paked leukemic cells mostly perivascular in distribution and occasionally intermixed with hemorrhage. They ranged from 1+ to 4+. Meningeal infiltrates were present in 44% (Fig. 3). They were twice as frequent among patients with lymphocytic leukemia as among those with myelogenous leukemia. Leukostasis was found in 28% ranging from 1+ to 4+. Demyelinated areas were present in the cerebrum and brainstem of 10% of the cases. These areas showed reduction in number of oligodendroglia and bizarre enlargement of astrocytes which were often multinucleate. Macrophages laden with neutral fat were also found. At the margins of the demyelinated

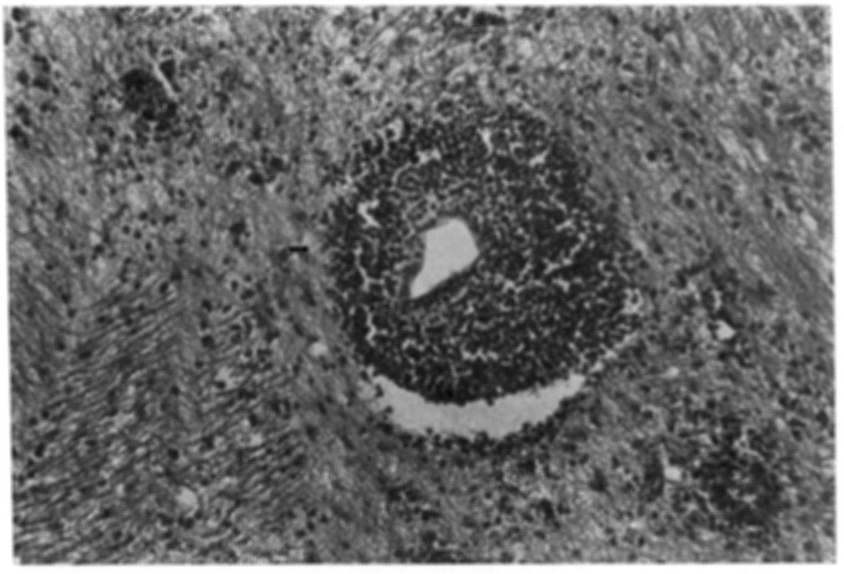

Fig. 2 — Marked (4+) leukostasis and slight leukemic perivascular infiltration (H.E.; 400 X).

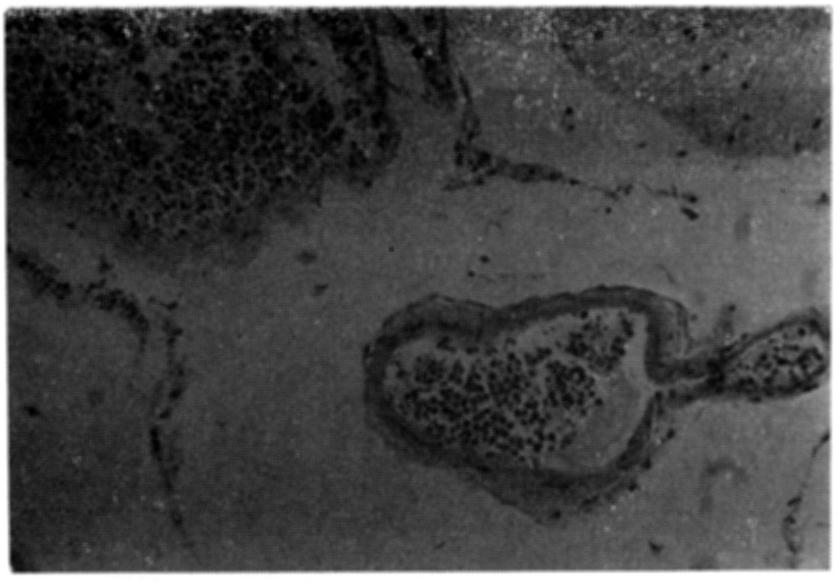

Fig. 3 — Moderate (3+) menigeal infiltrate (H.E.; 400 X).

foci abnormal oligodendrocytes were common. Their nuclei were larger than normal and occasionally contained eosinophilic inclusions. Intracerebral calcifications, seen in the deeper layers of the cerebral cortex and in the underlying white matter, were found in 5% of the patients (Fig. 4). Meningitis was also found in 5% of cases. The most common central nervous system lesions found in the different morphological types of leukemia are summarized in table 6. Subarachnoid hemorrhage was most frequently found in acute myelogenous leukemia (22.2%) while parenchymal hemorrhage predominated in acute lymphoblastic leukemia (22.2%). Leukemic infiltrates, both parenchymal and meningeal, were more commonly seen in lymphoblastic than in myelogenous types of leukemia, whereas leukostasis was predominantly found in chronic myelogenous leukemia (11%).

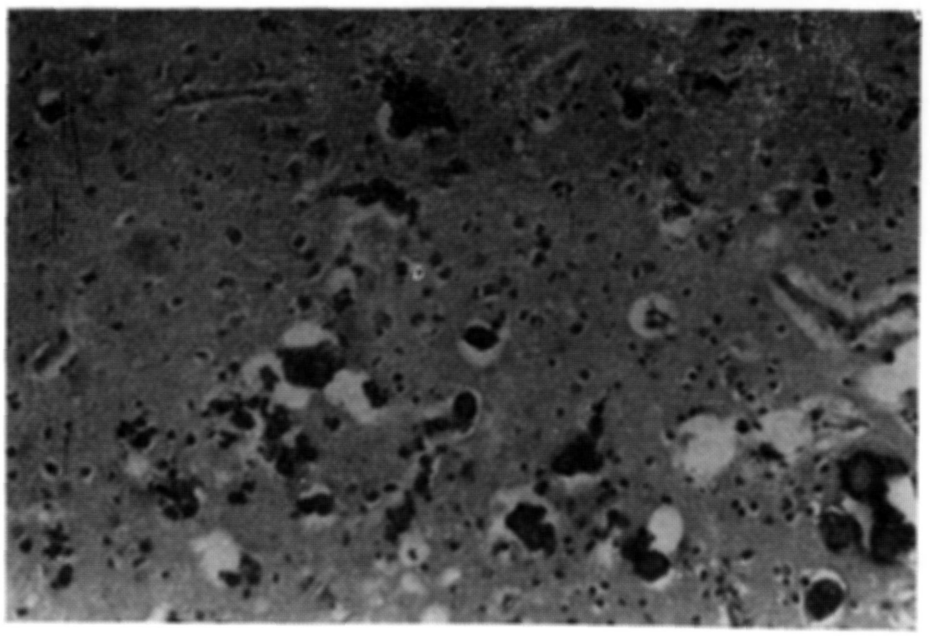

Fig. 4 — Intracerebral calcifications (H.E.; 400 X).

Types of leukemia	Significant lesions (%)				
	Parenchymal hemorrhage	Subarachnoid hemorrhage	Parenchymal infiltration	Meningeal infiltration	Leukostasis
ALL	22.2	11.1	11.1	11.1	5.5
CLL	11.1	11.1	11.1	11.1	5.5
AML	11.1	22.2	—	5.5	—
CML	16.7	11.1	5.5	5.5	11.1

Table 6 — Relationship between significant lesions and types of leukemia: ALL, acute lymphocytic leukemia; CLL, chronic lymphocytic leukemia; AML, acute myelogenous leukemia; CML, chronic myelogenous leukemia.

COMMENTS

This autopsy study reveals that the involvement of the CNS is more commonly found in chronic myelogenous leukemia (CML) than in the other types of leukemia. In some clinical series [4,15,31] acute lymphocytic leukemia (AAL) has been found responsible for the great majority of cases with CNS lesions. This discrepancy might be attributed to a lower clinical suspiction of CNSL in CML [31]. There was no significant difference of CNSL for the two sexes as seen in other series [15,20,22,29,30] although some authors [25,31] have found a higher incidence in males. CNS involvement was found to occur throughout the course of the disease from early as two days after the clinical diagnosis of systemic leukemia to as late as 6 years. At the time of diagnosis of CNSL most patients were in status III (moderate disease). A similar finding was observed by Hyman et al. [15]. In other series [23,25] CNS manifestations of leukemia occurred mostly while the systemic disease was apparently under therapeutic control (stage I and II). Bone marrow examination at the time of diagnosis of CNSL has shown no evidence of leukemia in 33.3% of the cases further indicating the CNS lesions may occur in other than the terminal phase of the systemic disease. A wide variation of symptoms and signs was present in our cases avoiding the formulation of any specific diagnostic criteria. CSF examination is frequently helpful in establishing a diagnosis of CNS involvement. Changes in CSF pressure, number of cells and protein content were found in about 63 per cent of the patients in whom lumbar puncture was performed. In the remaining patients no CSF abnormality was detected, confirming the finding of other authors that CSNL may be associated with normal CSF [15,25]. As leukemic cells may often be seen in the CSF when appropriate tecniques of cytology are employed [11] a reducing number of normal lumbar punctures may be expected as those techniques become routinely used.

The pathogenesis of CNSL [19] is related to the diffuse leukemic cell infiltration of the arachnoid [21,23,25]. Leukemic involvement initially becomes apparent in the walls of the superficial arachnoid veins. The leukemic cells in the arachnoid originate either from migration of circulating cells through venous endotelium or from transformation of preexisting undifferentiated germinal elements in venous walls [24]. As the number of leukemic cells increases there is rupture of the arachnoid trabeculae and contamination of CSF. Eventually they extend in the perivascular spaces in hemispheric gray and white matter. The direct infiltration of neural tissue occurs when in association with advanced deep perivascular arachnoid leukemia there is disruption of the pia-glial membrane [24]. Severe compression of blood vessels by leukemic cells in the perivascular spaces may cause ischemic infarcts or hemorrhages. A direct correlation between diffuse intraparenchymal hemorrhage and the magnitude of peripheral leukocyte count has been noticed [7,8,20]. It appears that fatal parenchymal hemorrhage occurs when the white cell count is greater than 100,000/cu.mm. in the presence of a normal platelet count. On the other hand fatal subarachnoid hemorrhage has been related to low platelet count (less than 10,000/cu.mm.) in the presence of normal or low leukocyte count [7,20,24].

Demyelinated plaques are thought to represent progressive multifocal leucoencephalopathy, a common pathological finding in lymphoproliferative disorders. Papova-like virus has been demonstrated in the CNS in these conditions [32] and correspond to the eosinophilic nuclear inclusions seen in oligodendrocytes. Wether the disease results from activation of virus residing in a latent form in the brain or invasion of the brain by virus normally residing in a harmless manner in extraneural tissues, or a primary infection by Papova-virus is not known. Cerebral calcifications have been described previously in CNS [2,6,21] and found to represent complications of X-ray therapy and intrathecal methothrexate treatment.

The development of CNSL is usually thought to indicate a poor prognosis [4,12,13,23,25]. Evans et al. [4] showed that the median survival predicted for those who develops CNS symptoms is 8 months; for those who do not, it is 24 months. However Hyman [15] suggests that there is no shortening of the survical time when CNS leukemia is early and correctly treated. In an attempt to prevent or delay involvement of CNS by leukemia cranial irradiation and intrathecal methotrexate are usually added to combination chemotherapy (vincristine, prednisone, 6-mercaptopurine, methotrexate, cyclophosphamide) [1,3,9,14,15,18,25]. Dearth et al. [3] still recommend additional utilization of leukapharesis [16] in order to reduce the blast cell population to safe levels.

SUMMARY

Post-mortem clinical and pathological study of 18 cases of central nervous system leukemia showed that this complication occurred mostly in chronic myelogenous leukemia (38.8%). No diagnostic criteria was found. The great majority of signs and symptoms were related to either d sturbances of the mental status or cranial nerves dysfunction. Cerobrospinal fluid may be found normal. CNS involvement may occur at any time during the course of systemic leukemia, when the disease is under apparently good therapeutic control as well as during relapse. Pathological findings in order of decre sing frequency were: parenchymal hemorrhage (61%); subarachnoid hemorrhage (55%); meningeal infiltrates (44%); leukostasis (28%); edema and herniation (28%); parenchymal infiltrates (22%); ischemic infarcts (17%); progressive multifocal leucoencephalopathy (10%); calcifications (5%); meningitis (5%). Total survival time ranged from 8 to 1980 days a median of 300 days. Survival time after CNS involvement ranged from 1 to 180 days with a median of 21 days.

RESUMO

Leucemia do sistema nervoso central: estudo clínico e patológico.

Estudo postmortem abrangendo os aspectos clínicos e patológicos de 18 casos de leucemia do sistema nervoso central mostrou que esta complicação ocorreu com mais frequência na leucemia mielógena crônica (38,8%). Não

houve um quadro clínico típico, mas na grande maioria dos casos os sinais e sintomas estavam relacionados ou a alterações do estado mental ou à disfunção de nervos cranianos. O líquor pode ser normal. Os achados patológicos em ordem decrescente de frequência foram: hemorragia intraparenquimatosa (61%); hemorragia subaracnóidea (55%); infiltrados meníngeos (44%); leucostase (28%); edema e herniação (28%); infiltrado n parênquima (22%); infarto isquêmico (17%); leucoencefalopatia progressiva multifocal (10%); calcificações (5%); meningite (5%). O tempo total de sobrevida variou de 8 a 1.980 dias, com uma mediana de 300 dias. O tempo de sobrevida após acometimento do sistema nervoso central variou de 1 a 180 dias com uma mediana de 21 dias. O acometimento do sistema nervoso central pod ocorrer em qualquer época durante o curso de leucemia sistêmica, mesmo quando a doença está aparentemente sob bom controle terapêutico, mas é mais comum durante os seus relapsos.

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