Virchows Arch. A Path. Anat. and Histol. 370, 345–362 (1976)

Involvement of the Central Nervous System in Malignant Lymphomas

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Received January 17, 1976

Summary. A retrospective histologic study of 145 consecutive autopsy cases of systemic malignant lymphomas (including lymphatic leukemias) was performed. The classification followed the Kiel Classification (Gérard-Marchant et al., 1974). There was an overall secondary CNS involvement in 26.2% of the total or in 30.4% of the non-Hodgkin's lymphomas including ALL, with intracranial lesions in 21.4 and 26.1%, respectively, and spinal epidural spread in 5.5 (5.1)%. Peripheral nerve involvement was seen in almost 40% of the examined cases. Ten further cases were isolated ("primary") intracranial lymphomas without evidence of extraneural deposits or systemic lymphatic disease. The CNS complications in non-Hodgkin's lymphomas were diffuse meningeal and/or perivascular infiltration with or without invasion of the nervous parenchyma, and did not differ from those in CNS leukemia. Isolated solid mass lesions in the brain were only present in 7% of the secondary CNS lymphomas, but were seen in all instances of "primary" cerebral lymphomas. The incidence of CNS complications was highest in lymphoblastic lymphomas including ALL (39%), CLL (31%), immunocytic lymphoma (29%), less frequent in immunoblastic (18.7%), and centrocytic lymphomas (16.6%). No intracranial lesion was observed in centroblastic-centrocytic and centroblastic lymphomas which only produced epidural spread. Bone marrow involvement was present in 92.8% of the cases with secondary CNS lesions, and in 83.2% of the epidural lymphomas. Leukemic conversion, present in 44% of the total (52% with ALL), was demonstrated in 83.3% of the cases with secondary brain lesions, but was hardly combined with epidural spread. The histologic pattern of CNS lesions in non-Hodgkin's lymphomas and their frequent association with leukemic conversion suggest the importance of *hematogenous dissemination* rather than of direct spread from bone marrow or local manifestation in multisystem disease. Isolated ("primary") lymphomas of the CNS which are morphologically identical with the extraneural lymphomas may represent a primary, often lethal manifestation of a multisystem disease with or without secondary generalization.

Introduction

Malignant lymphomas may involve the central nervous system (CNS) (1) as part of a generalized disseminated disease, (2) as a "primary" lesion confined to the CNS, and (3) due to secondary CNS complications. Except for epidural lymphomas of the spinal cord, meningeal and intracerebral involvements are recognized. While CNS affection in leukemia has been reported to be demonstrable in 50–78% of the cases with the highest incidence in acute childhood leukemia (Aur et al., 1972; Price and Johnson, 1973; Pochedly, 1975; Möbius et al., 1976), several postmortem studies indicate that CNS involvement in generalized malignant lymphomas occurs in 10–21% of the cases (Table 1). Additional spinal epidural spread is observed in 5–7% (Verity, 1968). Recently, Bunn et al. (1976) reported a 27% clinical incidence of CNS lymphoma in 52 patient with diffuse histiocytic and undifferentiated lymphoma, and positive CNS

Table 1. CNS involvement in malignant lymphomas (ML) (Autopsy series)

Author, Year	Generalized ML No. of cases	CNS No.	Involvement percent
Sparling et al. (1947)	188	19	10.1
John and Nabarro (1955)	93	9	9.7
Buerger and Monteleone (1966) 700 autopsies	17	2	11.7
Scholtze and Jänisch (1971) 29,423 autopsies	124 RCS (+ prim. CNS	16 11)	11.9
Griffin et al. (1971)	140	15	10.7
Schaumburg et al. (1972) 25,200 autopsies	121 RCS (+ prim. CNS	13 23)	10.8
Jänisch et al. (1975a)	49 (28 Non-HML	10 6)	20.4 21.4
Jänisch et al. (1975b)	86	16	18.3
Reznik (1975) 6,000 autopsies	17 RCS (+ prim. CNS	3 9)	17.6
Law et al. (1975)	172 Non-HML	20	11.7
Present series	145 ML (+ ALL)	31	21.4
	epidural	8	5.5
	(+ prim. CNS	10)	
	108 Non-HML	31	28.7

RCS = reticulum cell sarcoma; Non-HML = non-Hodgkin's M.L.; Prim. CNS = primary CNS lymphoma

findings at postmortem in 9 of 14 cases of this series. Isolated ("primary") intracranial malignant lymphomas referred to as cerebral reticulum cell sarcoma/microglioma have been reported to represent 0.3–1.5% of all intracranial neoplasms (cf. Zimmerman, 1975; Jellinger et al., 1975).

The purpose of this paper is to analyze retrospectively the incidence and nature of CNS involvement in each histologic type of malignant lymphoma, with special reference to non-Hodgkin's lymphomas, in a retrospective autopsy series.

Materials and Methods

Among 6080 autopsies performed from January 1, 1972 until July 1, 1975, at the Department of Pathology, University of Vienna Medical School, there were 145 proven cases of systemic (extraneural) malignant lymphomas including 30 cases of Hodgkin's disease, 98 cases of non-Hodgkin's lymphomas, 17 cases of ALL, and 10 additional cases with non-Hodgkin's lymphomas confined exclusively to the brain. All cases had complete autopsies and postmortem histologic examination of the lymph nodes and viscera. All patients had studies of peripheral blood, and in almost all cases the bone marrow was investigated during life and/or at autopsy. In more than half the cases previous biopsies of lymph nodes and/or organs were available.

Paraffin sections of autopsy and biopsy materials were stained with H. & E., Giemsa, PAS, and Gomori's silver impregnation. In many cases enzyme-cytochemical studies for

peroxidase, acid and alkaline phosphatase, nonspecific esterase, and naphthol-ASD-chloroacetate esterase were performed according to the methods reported by Leder (1967).

All biopsy and autopsy materials were reviewed without knowledge of the prior diagnosis or clinical course of the patients. The malignant lymphomas were reclassified according to the Kiel Classification (Gérard-Marchand et al., 1974; Lennert, 1975). Therefore, cases of chronic lymphatic leukemia (CLL) and acute lymphoblastic leukemia (ALL) were included, while plasmacytomas were excluded from this study. The criteria for lymphomas with leukemic conversion were infiltration of the bone marrow and the demonstration during life and/or at autopsy of neoplastic cells in the peripheral blood (Mathé et al., 1975). Most of the patients had received one or several courses of radiation and chemotherapy, the latter administered as a single agent or, more often, in combination regimes. Several patients with ALL had received whole brain irradiation, and some also had received intrathecal methotrexate.

Neuropathologic studies. The brain was histologically examined by piecemeal and semiserial section techniques in each case; the spinal cord, spinal ganglia, nerve roots, and peripheral nerves were investigated in 56 cases. The involvement of the cerebrospinal dura and skeletal muscles were not evaluated as they were available for histologic studies only in a small number of cases.

Routine stains—H. & E., cresyl violet, luxol fast blue, Giemsa, PAS, Masson-Goldner, van Gieson's, and Gomori's methods—and, in some cases, methyl green-pyronine (pH 3.4 and 4.4), Hortega-Penfield's, and Gallyas' impregnation techniques for demonstration of microglia, and the above-mentioned cytochemical methods were performed.

All cases classified as *primary* cerebral lymphomas had also complete autopsies and postmortem histologic examination of the viscera and/or lymph nodes in order to exclude extraneural lymphoproliferative disorders. In none of the 10 cases were neoplastic cells found in the peripheral blood or bone marrow. In four of these cases both brain biopsy and autopsy were available. The cerebral lymphomas were also classified according to Lennert's cytologic criteria. Some of these cases were previously reported by Jellinger et al. (1975).

Results

The histologic types of malignant lymphomas and the incidence of nervous system involvement as well as of secondary CNS complications are summarized in Table 2. There were three groups of nervous system affection with documented postmortem lesions: (1) secondary intracranial and/or peripheral nerve involvement; (2) epidural spinal spread; and (3) isolated (primary) intracranial malignant lymphomas without evidence of systemic or other extraneural lymphoproliferative disease.

Intracranial affection was demonstrated in 30 cases of systemic malignant lymphomas, i.e., in 21.4% of the total series or of the non-Hodgkin's lymphomas (excluding ALL), and in 26.1% of the non-Hodgkin's lymphomas including ALL. If further 10 cases of isolated (primary) cerebral lymphoma were included, the overall incidence of brain involvement in the total group of 155 malignant lymphomas was 25.8%, and 32.0% among the 125 cases of non-Hodgkin's lymphomas including ALL.

Additional *epidural spinal spread* was present in 5.5% of the total or 5.1% of the non-Hodgkin's lymphomas. As one case showed combined intracranial and epidural lesions, the total incidence of *secondary CNS involvement* was 26.2% or 30.4% in the group of non-Hodgkin's lymphomas including ALL.

Peripheral nerve involvement (neoplastic invasion) was observed in 39.3% of the histologically examined cases or in 41.2% of the non-Hodgkin's lymphomas including ALL.

Table 2. Nervous system involvement in malignant lymphomas (ML) (Inst. of Pathology, Univ. Vienna 1. 1. 1972–1. 7. 1975: 6080 autopsies)

Extraneural lymphoma	*n*	Brain involvement *n*	Epidural spinal *n*	Nerve roots/peripheral nerves *n/n*	Intracranial hemorrhage *n* %		Secondary CNS complications—infections, gliosis, etc.			
							n %		*n* %	
Hodgkin's disease	30	1	2	1/5	2		6		7	
C.L.L.	26	6	—	2/10	6		6		7	
M.F., Sézary syndrome	3	3	—	1/2	—		1			
M.L. immunocytic	21[a]	6	1[a]	4/10	4		1		12	
M.L. centrocytic	6	1	1	1/5	—		2		2	
M.L. centroblastic/cyt.	12	—	1	1/4	1		—		2	
M.L. centroblastic	3	—	2	—/3	—		—		2	
M.L. lymphoblastic	11	2	—	3/6	1		2		3	
A.L.L.	17	9	—	6/10	6		5		6	
M.L. immunoblastic	16	3	1	3/6	—		1		5	
Total	145	31	8	22/56	20	13.7	24	16.6	48	33.1
Non-Hodgkin's M.L.	98	21	6	15/41	12	12.2	13	13.1	35	35.5
Non-Hodgkin's M.L. + A.L.L.	115	30	6	21/51	18	15.6	18	15.6	41	35.6
Primary cerebral ML		10								

[a] Combined affecton *n/n* = affected/examined cases

Secondary CNS complications included intracranial hemorrhage in 13.7% of the total or 15.6% of the non-Hodgkin's lymphomas, and secondary infections in 16.6 and 15.6%, respectively. Other CNS lesions, e.g., diffuse gliosis with occurrence of Alzheimer type II glia (Herdin et al., 1974), were seen in 33.1 and 35.6%, respectively. Other complications of treated CNS leukemia and lymphoma, e.g., disseminated necrotizing leukoencephalopathy (Norrell et al., 1974; Rubinstein et al., 1975; Price and Jamieson, 1975) or intracranial calcification (Michotte et al., 1975; Flament-Durand et al., 1975) were not observed in this series.

As in Hodgkin's disease brain and spinal epidural lesions were limited to 3 cases (=10%), only the CNS lesions in *non-Hodgkin's lymphomas* will be further considered.

1. Secondary CNS Lymphomas

Clinical Features. Intracranial involvement in systemic non-Hodgkin's lymphomas was seen in 19 males and 10 females ranging in age from 1 to 84 years, with a mean age of 58.7 years. Only six patients were under 16, four of whom suffered from ALL. Most cases developed intracranial dissemination during the advanced or final stages of their illness (duration before development of neurologic signs between 4 months and 15 years), except for 3 children with ALL who demonstrated relapsing cerebral manifestations during the course of the disease

Table 3. CNS involvement in Non-Hodgkin's Lymphomas. Incidence of leukemic conversion and bone marrow involvement (BMI)

Extraneural Lymphoma		n/leukemic conversion	Brain involved n/leukemic	Spinal epidural n/leukemic	Brain involved n/BMI	Spinal epidural n/BMI	Primary CNS lymphoma
C.L.L.		29/27	9/7	—	8[a]/7	—/—	—
Immunocytic		21/6	6/4	1/1	6/5	1/1	4
Centrocytic		6/2	1/1	1/0	1/1	1/0	—
Centroblastic/cytic		12/0	—	1/0	—	1/1	—
Centroblastic		3/0	—	2/0	—	2/2	—
Lymphoblastic		11/6	2/2	—	1[a]/1	—	1
(A.L.L.)		(17/17)	(9/9)	—	(9/9)	—	—
Immunoblastic		16/2	3/2	1/0	3/3	1/1	5
Non-Hodgkin's	*n*	98/43	21/16	6/1	19[a]/17	6/5	10
Lymphomas	%	43.9	21.4/37.2	6.2/2.5	89.0	83.2	9.5
Non-Hodgkin's	*n*	115/60	30/25	6/1	28[a]/26	6/5	10
M.L. + ALL	%	52.0	26.1/41.7		92.8	83.2	8.0

[a, b] In 2 cases bone marrow not examined

(duration 2 months–4 years). *Epidural spinal spread*, usually manifested by paraparesis, was seen in 3 males and 3 females ranging in age from 33 to 76 years, with a mean age of 60.3 years. It occurred both as initial manifestation of the disorder and in the late course of the illness.

Cerebrospinal cytology which has been reported to give positive results in 50–100% of the primary and secondary lymphomas of the CNS (Rawlinson et al., 1975; Billingham et al., 1975; Bunn et al., 1976) was positive in 75% of the 19 examined cases of the present series with secondary CNS involvement.

The *prognosis* of secondary CNS affection was poor; the majority of the patients with non-Hodgkin's lymphomas except for ALL died within a few days to 3 months after the onset of neurologic signs indicating CNS affection. In the patients with spinal epidural spread the survival ranged from 2 months to 2.2 years.

Postmortem Findings. At autopsy all cases with intracranial and epidural spread disclosed multiple involvement of lymph nodes and/or viscera. *Bone marrow involvement* was present in 26 of the 28 adequately examined cases of non-Hodgkin's lymphomas with intracranial affection (=92.8%), and in 5 of 6 cases with epidural spinal spread (Table 3).

Leukemic conversion was observed in 42% of the total series of malignant lymphomas and in 43.9% of the non-Hodgkin's lymphomas except ALL; after inclusion of ALL the incidence of postmortem demonstration of neoplastic cells in the peripheral blood rose to 52.0%. Brain involvement among the cases of non-Hodgkin's lymphomas with leukemic conversion was seen in 37.2% and, after inclusion of ALL, even in 41.7%, while epidural spread was only present in 2.5% of this group (Table 3). Leukemic conversion was seen in 25 or 83.3% of the adequately examined cases of non-Hodgkin's lymphoma (including ALL) with intracranial involvement. Among the cases with epidural spread terminal leukemic conversion with additional leptomeningeal spread was only present in one case of generalized immunocytoma with paraproteinemia.

Table 4. Types of CNS involvement in malignant lymphomas (with/without leukemic conversion)

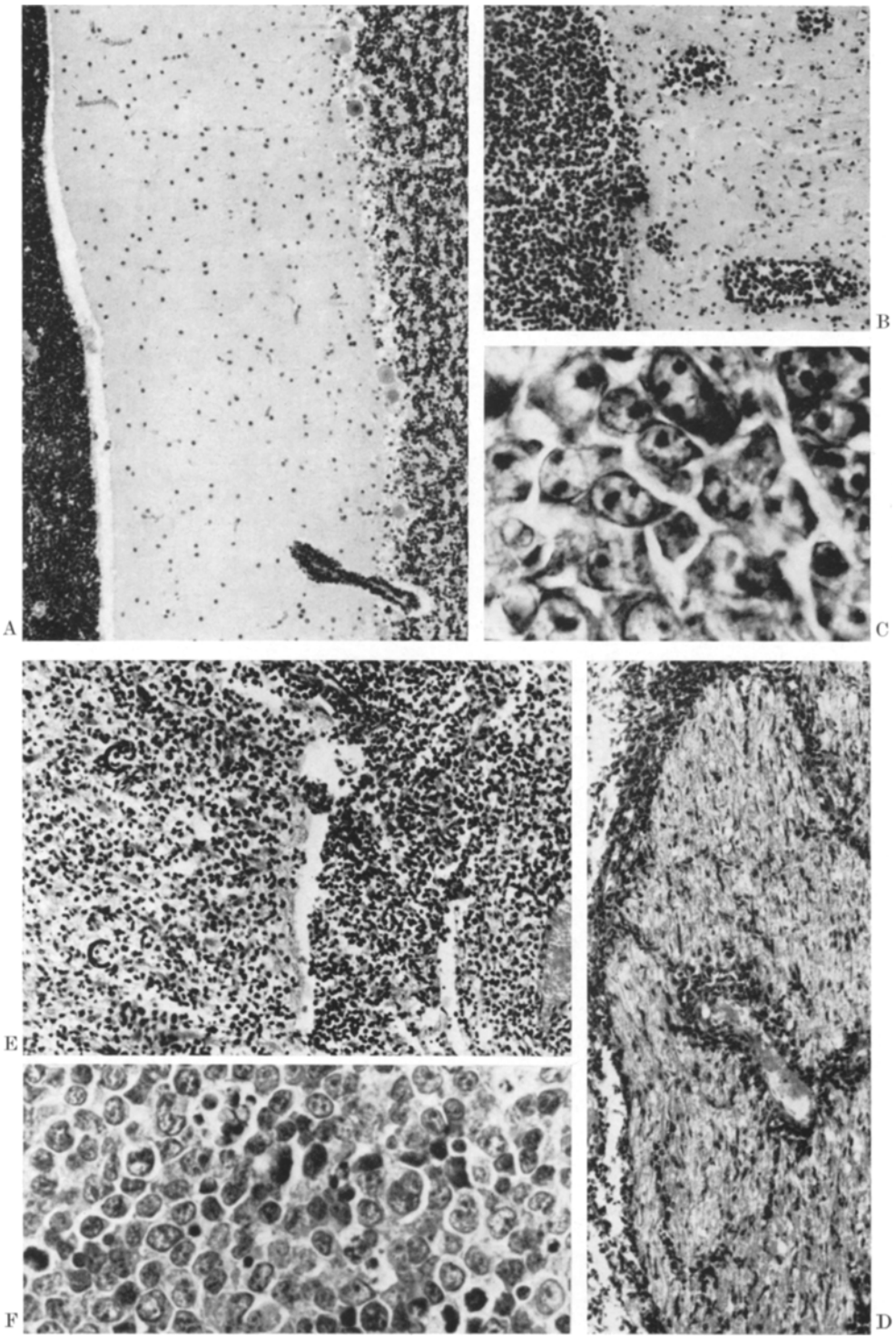
Type of CNS lesion	Total n/leukemic conversion	Arachnoid n/leukemic	Perivascular n/leukemic	Arachnoid + perivascular n/leukemic	Parenchyma (+tumor) n/leukemic	Total brain involvement n/leukemic	%	Spinal epidural n/leukemic	%
Hodgkin's disease	30/2				1(1)0	1/0	3.6	2/0	7.0
C.L.L./M.f.	29/27	2/2	2/0	2/2	3(1)3	9/7	31.0	—	—
Immunocytic	21/6	1[a]/1	1/0	2/1	2(1)2	6/4	27.6	1[a]/1	5.0
Centrocytic	5/2			1/1	—	1/1	16.6	1/0	20.0
Centroblastic/cyt.	12/0			—	—	—	—	1/0	8.3
Centroblastic	3/0			—	—	—	—	2/0	66.6
Lymphoblastic	11/6			—	2/2	2/2	18.2	—	—
(A.L.L.)	17/17	2		3	4	9	56.2	—	—
Immunoblastic	16/2	1/1		—	2/1	3/2	18.7	1/0	6.7
Non-Hodgkin's lymphomas	98/43 43.9%	4/4	3/0	5/4	9(2)/8	21/16	20.8 36.6	6/1	6.2
NH-lymphomas + A.L.L.	115/60 52.0%	6/6	3/0	8/4	13/12	30/25	25.3	6/1	5.4

[a] Combined lesion

Neuropathology. The morphologic findings in cases with secondary CNS involvement are summarized in Table 4. Gross focal lesions were found in only two brains (Fig. 2). The histologic changes included meningeal and/or perivascular infiltration with or without involvement of the adjacent nervous parenchyma (Fig. 1), infiltration of cranial and spinal nerve roots (Fig. 1 D), and skeletal muscle.

Meningeal infiltration was generally diffuse, involving many areas of the brain and spinal cord, but occasionally the neoplastic lesion was isolated to or predominantly affecting the cerebellar, cerebral, or spinal meninges. Arachnoidal infiltration without concomitant CNS involvement was present in 6 cases (4 non-Hodgkin's lymphomas and 2 ALL), one with epidural spread. *Perivascular infiltration* of intracerebral vessels without invasion of the adjacent parenchyma was present in 3 cases without leukemic conversion (2 cases of mycosis fungoides

Fig. 1 A—E. Secondary CNS lymphomas with arachnoid and perivascular infiltration. (A) Dense infiltration of cerebellar leptomeninges and occasional perivascular cuffs without parenchymal invasion. Male aged 74 with generalized immunoblastic lymphoma. H. & E. × 90. (B–D) Leptomeningeal and perivascular infiltration with neoplastic invasion of cortical parenchyma (B-Giemsa × 90), and perineural and perivascular infiltration of cranial nerve root (D.-H. & E. × 90). Female aged 81 with generalized immunoblastic lymphoma, composed of large, strongly basophilic cells with clear nuclei and large nucleoli (C-Giemsa × 900). (E, F) Extensive arachnoid infiltration with diffuse invasion of subpial cortex (*c*). H. & E. × 100. Male aged 73 with generalized immunocytic lymphoma without macroglobulinemia. (E) Tumor shows mixed cellularity with lymphoid and plasmacytoid cells. PAS × 370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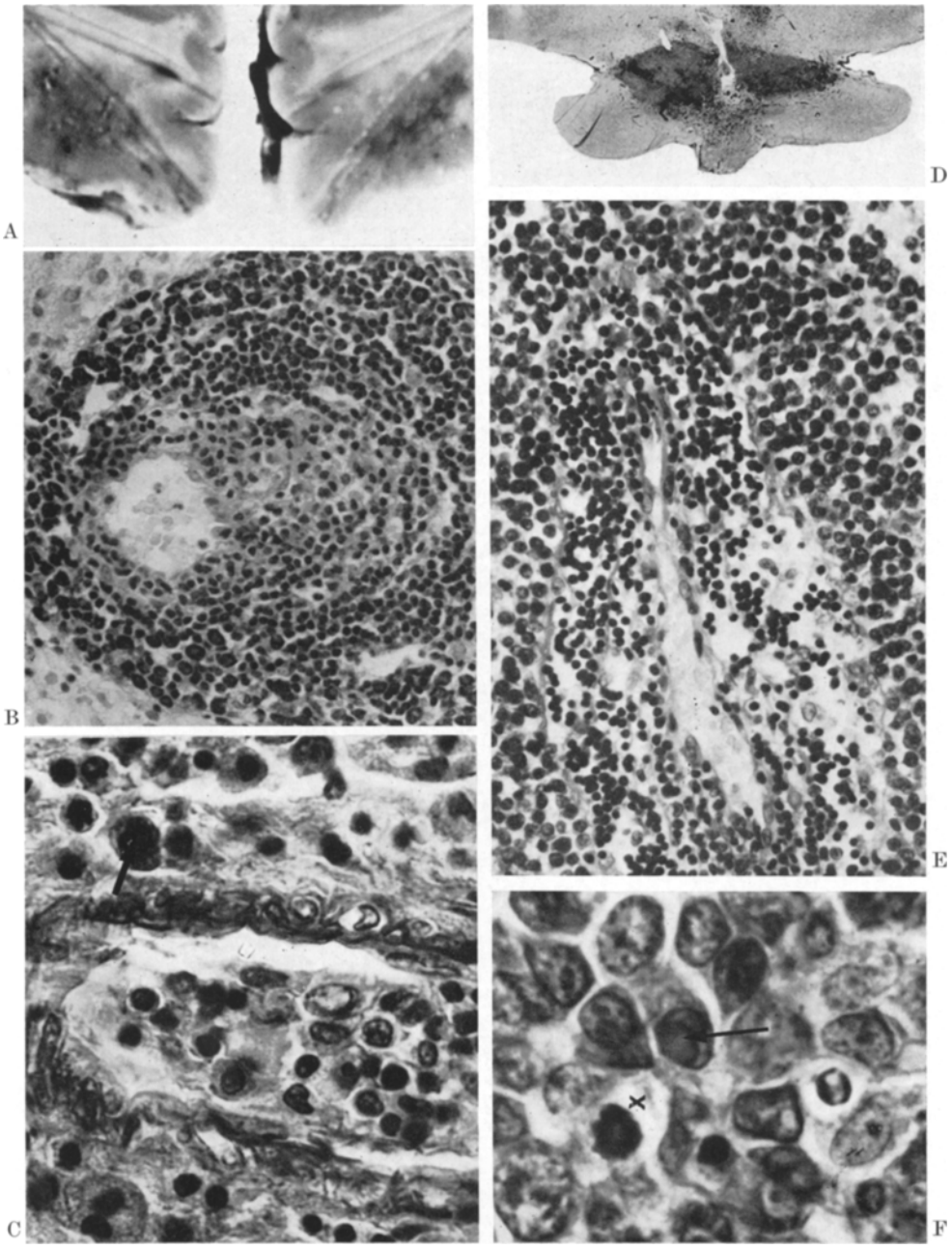

Fig. 2 A—F. Secondary cerebral lymphomas with solid mass lesions. (A–C) Sézary syndrome in male aged 72 years. (A) Small bilateral tumor foci in frontobasal region. (B) Perivascular arrangement of tumor cells forming concentric whorl. Giemsa × 230. (C) Intraluminal and perivascular accumulation of lymphoid cells, some with irregular nuclei (arrow). PAS × 550. (D–F) Hypophyseal-hypothalamic involvement in generalized immunocytic lymphoma with diabetes insipidus. (D) Focal tumor-like invasion of anterior hypothalamus. (E) Hypothalamic vessel cuffed by lymphocytes (inner collar) and tumor cells invading parenchyma (Giemsa × 400). (F) High power view of tumor showing mixed cellularity with plasmacytoid cells with occasional PAS positive nuclear inclusion (arrow) and mitosis (*x*). PAS × 600

without bone marrow involvement, and one immunocytic lymphoma with bone marrow infiltration). Combined *meningeal and perivascular* infiltrations *without* parenchymal involvement (Fig. 1A) were demonstrated in 8 cases—3 cases of ALL, 2 cases of CLL, one centrocytic lymphoma with leukemic conversion, and 2 cases of immunocytic lymphoma, one of which was without leukemic conversion or bone marrow involvement. The most frequent type of CNS lesion was arachnoidal and perivascular infiltration *with* parenchymal invasion (Fig. 1B, F), which was seen in 13 cases, i.e., 4 cases of ALL, three with CLL, and 2 cases each of lymphoblastic, immunoblastic, and immunocytic lymphomas, *all* showing leukemic conversion (Table 4). In only two of them single or multiple *gross lesions* were present.

A male aged 72 with Sézary syndrome and terminal confusional state presented small bilateral focal lesions in the frontobasal regions (Fig. 2A–C). In a 52-years-old male with generalized immunocytic lymphoma presenting with diabetes insipidus a small lesion involved the hypophyseal-hypothalamic region (Fig. 2D–F). In another male with Sézary syndrome not included in this series, typical polymorphous lymphocytes with clefted nuclei were demonstrated in the CSF and in the biopsy specimen of a parietal mass lesion (Gerstenbrand et al., 1976). In spite of brain irradiation and cytostatic treatment the patient recently died, 1 year after neurosurgical intervention. Autopsy disclosed multifocal visceral and brain lesions.

Spinal root and/or *peripheral nerve infiltrations* were seen in at least 13 of the 29 cases with intracranial involvement (Table 2). Other patients showed combined affection of the CNS, peripheral nerves, and skeletal muscle, e.g., 2 cases of generalized immunocytic lymphoma without macroglobulinemia.

The highest incidence of CNS involvement was observed in lymphoblastic lymphoma including ALL (39.3%), with intracranial affection of 56.2% in ALL alone. Brain involvement in CLL (and mycosis fungoides) and in immunocytic lymphoma was 31 and 29%, respectively. It was less frequent in immunoblastic lymphoma (18.7%), solid lymphoblastic lymphoma (18.2%), and centrocytic lymphoma (16.6%). No intracranial lesions were seen in centroblastic-centrocytic lymphoma and centroblastic lymphoma which, however, presented epidural spinal spread (Tables 3 and 4). Lymphoblastic and immunoblastic lymphomas were often associated with widespread infiltration of the CNS parenchyma, while all the other histologic types of non-Hodgkin's lymphomas showed both meningeal and parenchymal dissemination (Table 4).

2. Isolated Intracranial Lymphomas

Gross cerebral mass lesions were prominent in 10 cases of non-Hodgkin's lymphomas presumably confined to the brain. As there was no clinical or postmortem evidence of systemic or extraneural lymphoproliferative disease, these cases were classified as *isolated* (primary) intracranial lymphomas (see Table 5) There were 6 males and 4 females ranging in age from 47 to 76 years with an average of 61 years, who presented nonspecific signs of space-occupying intracranial lesions. The mean duration of symptoms from onset to the time of diagnosis was 2.6 months; the time of survival ranged from 2 days following neurosurgery to 8 months after radiotherapy. CSF cytology gave positive results in three of the 7 examined cases.

Table 5. Primary isolated cerebral malignant lymphomas

Case	Age, Duration/ sex survival	Neurologic symptoms	CSF	Therapy	Periph- eral blood	Bone marrow	General autopsy	Brain tumor localization	Histology
270–72	68, ♂ 2 months/4 months	OBS, hemiparesis	280 Prot. 0 TuC	Poly chem	norm	norm	hypernephroid carcinoma	multiple	immuno- cytic M.L.
191–72	61, ♀ 1 month/1 week	OBS, aphasia	n.e.	Op	norm	n.e.	pneumonia	frontal bil + cerebellum	same
157–72	46, ♀ 8 months/1 month	OBS, hemiparesis	140 Prot. 80% TuC	—	norm	norm	cholelithiasias uterine myofibroma	thalamus bil	same
335–72	71, ♀ 3 months/2 days	similar	n.e.	Op	norm	norm	renal cysts thyroid adenoma ly. inf. gallbladder	frontal lft	same
186–72	76, ♂ 6 months/6weeks	similar	200 Prot. 95% TuC	—	norm	norm	pulm. emboliasm prostat. adenoma gen. sclerosis	frontal lft	immuno- blastic M.L.
596–74	59, ♂ 1 month/3weeks	OBS, aphasia hemiparesis	n.e.	—	norm	n.e.	pneumonia coronary sclerosis	temporo occip. lft	same
83–75	49, ♂ 3 weeks/5 weeks	hemiparesis	80 Prot.	Op	norm	norm	pneumonia myocard. fibros.	multiple	same
221–75	74, ♀ 1 month/3weeks	Brainstem syndrome	136 Prot. 22/3 TuC	—	norm	norm	pyelitis ren. angiolo- sclerosis	diencephalon + pons	same
115–75	60, ♂ 2 months/1week	OBS, paresis	norm	—	norm	norm	thyroid adenoma hypertr. prostat.	multiple	same
367–74	68, ♂ 1 month/8months	Aphasia hemiparesis	130 Prot. 0 TuC	60 Co 6,000 rd	norm	norm	pneumonia pulmon. emboliasm	multiple	lympho- blastic M.L.

OBS = organic brain syndrome; CSF = cerebrospinal fluid; Prot. = protein; TuC = tumor cells; n.e. = not examined

Grossly, the brain was involved by single or multiple lesions of the cerebral hemispheres, basal ganglia, and cerebellum often resembling malignant gliomas (Fig. 3E) or metastases (Fig. 3A). Their histologic patterns were comparable with those of extraneural lymphomas of the diffuse, nonfollicular type, showing apparent perivascular arrangement of the tumor cells with or without proliferation of stromal and reticulin fibers and diffuse invasion of the parenchyma and/or meninges (Fig. 3C, D). In 4 cases the cytologic appearance was that of pleomorphic lymphoplasmacytoid immunocytoma (Fig. 3B); 5 cases were classified as immunoblastic lymphoma or reticulum cell sarcoma (Fig. 3F), while one case was considered as lymphoblastic lymphoma (Fig. 3C, D).

Discussion

Involvement of the CNS in malignant lymphomas can be due to hematogenous or epidural spread, separate involvement of the brain in systemic or multicentric disease, or as a lesion confined to the CNS. Both the epidural lymphomas of the spinal cord and the isolated (primary) cerebral lymphomas referred to as reticulum cell sarcoma/microglioma have been well described (Kernohan and Uihlein, 1962; Schaumburg et al., 1972; Ebels, 1972; Rubinstein, 1972; Henry et al., 1974; Stefanko and Moffie, 1974; Littman and Wang, 1975; Hubert, 1975; Reznik, 1975; Vuia, 1975; Olvera Rabiela et al., 1975; Valsamis et al., 1976; Friedman et al., 1976).

Meningeal and secondary intracerebral involvements, well documented in CNS leukemia, have rarely been recognized in non-Hodgkin's lymphomas. The overall incidence of CNS complications varies with different institutions (see Table 1). Postmortem studies indicate a CNS involvement in 10–21% of systemic (extraneural) lymphomas. Only in American Burkitt's lymphoma were CNS complications observed in 46.5% (Banks et al., 1975). Recently, an increased incidence of meningeal and intracerebral disseminated lesions was reported with various types of non-Hodgkin's lymphomas (Griffin et al., 1971; Watanabe et al., 1973; Magrath et al., 1974; Olson et al., 1974; Law et al., 1975; Bunn et al., 1976). Our data revealed secondary intracranial involvement in 20.2% of the non-Hodgkin's lymphomas—26.2% including ALL—and epidural spread in 5.1% i.e., *secondary CNS involvement in 30.4% of the non-Hodgkin's lymphomas* (including ALL), and peripheral nerve invasion in about 40% of the examined cases, while 10 cases (about 8% of the non-Hodgkin's lymphomas) were primary intracranial lymphomas confined to the brain.

The CNS complications were usually found in the advanced stages of the disease. Except for children with ALL showing relapsing neurologic signs, and epidural lymphomas occurring as early manifestations of a multisystemic disease, most patients revealed CNS infiltrations as a terminal event. At autopsy, there was usually multiple involvement of the lymph nodes and/or visceral organs. Bone marrow infiltration was demonstrated in 92.6% of the cases with intracranial dissemination, and in 83.2% of those with spinal epidural spread. These findings are in agreement with recent reports indicating the increased incidence of CNS and bone marrow involvement with non-Hodgkin's lymphomas (Griffin et al., 1971; Watanabe et al., 1973; Law et al., 1975), although bone marrow infiltrations are not considered a prerequisite for CNS dissemination (Clausen

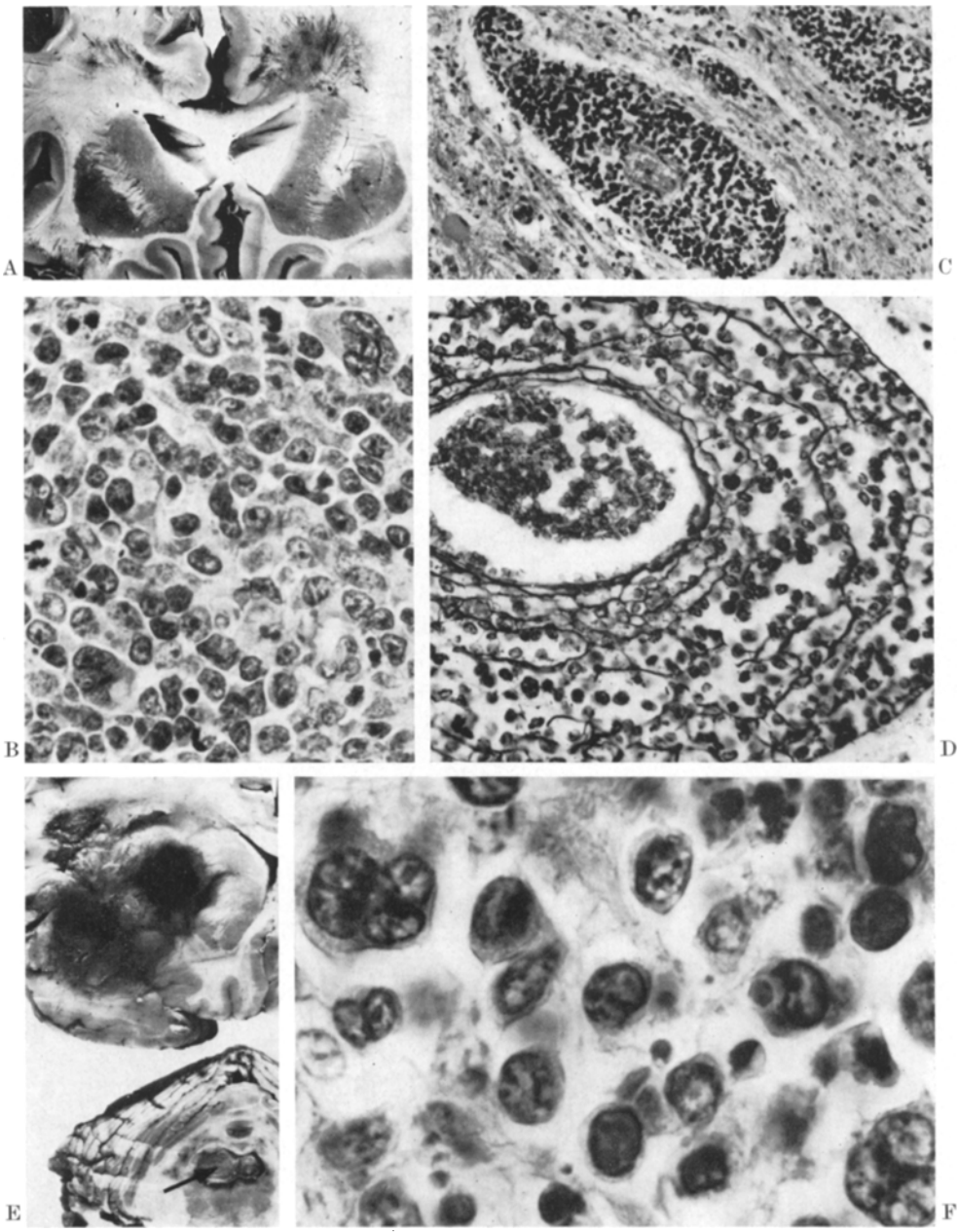

Fig. 3A—F. Multifocal "primary" cerebral lymphomas. (A, B) Multiple necrotic foci in both frontal lobes of male aged 68 with immunocytic lymphoma, showing mixed cellularity with lymphoid and plasmacytoid cells, and occasional giant cells. PAS × 370. (C, D) Lymphoblastic lymphoma in periventricular white matter of male aged 68, showing perivascular arrangement of tumor cells forming concentric whorls with increased reticulin fibers. (C) Giemsa × 90, (D) Gomori × 250. (E, F) Large left hemispheral tumor and small lesion in cerebellar vermis (arrow) in male aged 49, with the pleomorphic histologic picture of immunoblastic lymphoma with Reed-Sternberg-like giant cells. H.-E. × 1,000

et al., 1956; Hyman et al., 1965; Jones et al., 1972). Only one of the 14 patients with meningeal infiltration reported by Bunn et al. (1976) had no bone marrow involvemenet.

The common neuropathologic lesions of secondary CNS affection in non-Hodgkin's lymphomas were diffuse meningeal and/or perivascular infiltrations with and without invasion of the cerebral parenchyma or neuromuscular infiltration. They were not different from the types of lesion in CNS leukemia (Moore et al., 1960; Thomas, 1965; Price and Johnson, 1973; Pochedly, 1975) and from leukemic infiltration of skeletal muscle (Buerger and Monteleone, 1966).

Leukemic conversion, clinically reported in 10–70% of non-Hodgkin's lymphomas (Gendelman et al., 1969; Aur et al., 1971; Watanabe et al., 1973; Mathé et al., 1975), was present in 51.2% of our autopsy series of non-Hodgkin's lymphomas including ALL, part of which showed terminal spreading of neoplastic cells. The increased incidence of CNS involvement in lymphoma-leukemic conversion has been recognized (Gendelman et al., 1969). While in two recent reports on comparable but smaller postmortem samples leukemic conversion was demonstrated in only one-third of the cases of non-Hodgkin's lymphomas with CNS affection (Griffin et al., 1971; Law et al., 1975), in our series 75% of these cases—and even 85% with inclusion of ALL—were in a leukemic phase or showed post mortem evidence of circulation of neoplastic cells in the peripheral blood. These data highly suggest that the intracranial dissemination was rare without leukemic conversion. Eighty-three percent of the cases with meningeal and intracerebral infiltrations showed signs of leukemic conversion and thus were indicative of hematogenous spread. Conversely, epidural spread and pure infiltration of cerebral perivascular spaces without meningeal or parenchymal invasion were not associated with leukemic conversion. These latter findings appear of interest, since perivascular space as a primary metastatic focus has been suggested in meningeal carcinomatosis (Globus and Meltzer, 1942; Willis, 1952).

CNS affection in the present series was most frequent in lymphoblastic lymphoma plus ALL, followed by CLL and immunocytoma, and less frequent in centrocytoma and immunoblastic lymphoma. The absence of primary and secondary intracranial involvement in centroblastic-centrocytic and centroblastic lymphomas is in agreement with the results of other authors (Griffin et al., 1971; Olson et al., 1974; Law et al., 1975). While Law et al. (1975) reported prominent meningeal seeding in poorly differentiated lymphocytic lymphoma with frequent leukemic conversion in contrast to a more invasive propensity in diffuse histiocytic lymphoma, we were unable to find any differences in the CNS lesions between the various histologic types of non-Hodgkin's lymphomas. However, both lymphoblastic and immunoblastic lymphomas showed a more invasive propensity than the other types which were associated with all kinds of meningeal and parenchymal involvement.

The *pathogenesis* of intracranial affection in malignant lymphomas is controversial. The relative absence of lymphatic system in the CNS and the frequent demonstration of leukemic conversion in M.L.s with CNS lesions suggest that intracranial affection may be by *hematogenous dissemination*. Similar mechanisms are believed to be operative in CNS leukemia (Price and Jonson, 1973; Nadel and Nelson, 1975; Graham and Willoughby, 1975) and in metastatic brain disease

(Rubinstein, 1972). Rarely, intracerebral dissemination via intraspinal perineural sheaths, as in carcinomatous meningitis (Griffin et al., 1971), or direct spread from the bone marrow along the (perforating vessels and nerves, through dura and into arachnoid space, have been suggested (Bunn et al., 1976; Calvo and Hoelzer, 1976). Other authors stressed the rarity of blood-borne CNS metastases in malignant lymphomas (Schaumburg et al., 1972; R. Adams, 1975) and suggested local rather than metastatic development of the CNS lesions due to synchronous neoplastic transformation of lymphoreticular cells within and outside the CNS (Jänisch et al., 1975). This may hold true for rare instances of separate development of cerebral mass lesions unconnected with extraneural lymphoma (Ljungdahl et al., 1965; Plafker et al., 1972; J. Adams, 1975; Jänisch et al., 1975). This latter type of solid CNS lesion which may represent a non-blood borne manifestation of a multisystem disease, however, was seen in only two cases of our series (Hodgkin's disease and generalized immunocytic lymphoma), i.e., in less than 7% of the total, while the vast majority revealed meningeal and/or parenchymal invasion. Bunn et al. (1976) reported CNS involvement in 9 of 14 autopsy cases of non-Hodgkin's lymphomas, all of which showed arachnoid infiltrations with cerebral lesions in five, but there was no instance of isolated foci of CNS tumor.

The *origin* of *primary* (isolated) intracranial lymphomas is also uncertain. Recent cytochemical and electron-microscopic studies in this group of neoplasms, referred to as "primary cerebral reticulum cell sarcoma/microglioma" (Rubinstein, 1972), confirmed their *morphologic identity with extraneural non-Hodgkin's lymphomas* (Horvath et al., 1969; Hirano et al., 1975; Cravioto, 1975; Ishida, 1975; Johnson, 1975). The demonstration within these brain tumors of the whole spectrum of cell transformation encountered in extraneural immunocytomas and immunoblastomas of suggested B-cell type (Stein et al., 1974; Glick et al., 1975; Henry, 1975) is in favor of a common morphogenesis of these types of malignant lymphomas (Jellinger et al., 1975b). It should be emphasized, however, that in 7.2–42% of the primary cerebral lymphomas incidental visceral deposits of neoplastic cells or evidence of systemic lymphatic disease have been reported (Russel et al., 1948; Henry et al., 1974; J. Adams, 1975; Barnard and Scott, 1975). In a small number of cases cerebral "microglioma" similar to or identical with immunocytic lymphoma was combined with paraproteinemia (Gunderson et al., 1971; Vuia and Mehraein, 1972; Lambert et al., 1974). It is tempting to consider the possibility that multiple organ lesions or association with dysglobulinemia represent part of a multifocal lymphatic disease with *primary manifestation in the CNS.*

This is demonstrated by two observations: A 67-years-old man developed a frontal mass lesion which was removed 3 years before systemic manifestation of Hodgkin's disease and 5 years prior to death. In a male aged 74 not included in this series a small frontal tumor histologically akin to immunocytic lymphoma was removed and irradiated 2.5 years before death. The patient was well without clinical evidence of systemic disease for 1.5 years when cutaneous and intestinal lesions developed. Autopsy confirmed generalized immunocytoma but failed to demonstrate any further CNS lesions.

The prognosis of primary CNS lymphomas is poor (Littman and Wang, 1975; Jellinger et al., 1975a). The initial location in the brain and associated fulminant clinical course may preclude the development of extensive generalized lymphoma

due to early demise. Other interpretations of CNS lymphoma with incidental extraneural deposits include the possibility of visceral micrometastases from the CNS primary or, conversely, metastases to the CNS from an occult visceral primary lymphoma. However, in all our cases referred to as isolated CNS lymphomas the lesion seemed to occur exclusively in the brain, and we have no proof as to whether they would ultimately become generalized. Although the cytologic identity of the malignant lymphomas arising in extraneural sites or as "primary" lesion in the CNS is now generally agreed upon, the problem of their origin particularly within the CNS needs further elucidation.

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