Intracranial malignant lymphoma

Report of 30 cases and review of the literature

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Although primary malignant lymphoma is a rare entity in the gamut of intracranial tumors, it is more frequently seen than the secondary intracranial spread of a primary extracranial lymphoma. In general, the occurrence of lymphomas seems to be provoked by immunosuppression, as with medication (predominantly after transplantation) or with immunodepressive disease such as acquired immunodeficiency syndrome (AIDS). The usual age of onset of this disease is 55 to 65 years; and the male:female patient distribution is roughly 2:1.

Characteristically, computerized tomography (CT) scans of lymphomas show a mass which is often large with regular contours, moderate mass effect, and hyper- or isodensity with marked and often homogeneous enhancement. In the series of 30 patients reported, the locations of lesions, in order of decreasing frequency, were the frontocallosal and temporal regions, the basal ganglia, and the cerebellum. Multiple lesions were present in 15% of these cases (20% to 40% in the literature). The following features should raise the suspicion of intracranial lymphoma: mirror lesions of the basal ganglia, bilateral subependymal infiltration, and leptomeningeal involvement contiguous with an intracerebral mass.

According to the literature, the angiographic finding typical of lymphoma is an avascular tumor. A blush or vascular encasement of the mass seems to be rare, and the present series was in accordance with other reports in this respect. Differential diagnostic consideration should include meningioma, glioblastoma, metastatic disease, and focal infectious lesions such as toxoplasmosis or multifocal progressive leukencephalitis, particularly in immunodepressed subjects. Diagnosing lymphoma from CT scans offers the alternative of substituting stereotaxic biopsy and neuropathological diagnosis for the more aggressive open surgical approach, since radiation therapy and possibly chemotherapy usually prove to be the treatment of choice.

KEY WORDS • lymphoma • brain neoplasm • stereotaxic biopsy • immunosuppression
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FIG. 1. Age and sex distribution among 30 patients with intracranial malignant lymphoma. Horizontal axes: age in years; vertical axes: number of cases. The front diagram shows primary lymphomas, the back diagram represents secondary lymphomas. Shaded columns indicate males and white columns females.

posed: Rappaport, Kiel, Lennert, Lukes-Collins, Dorfman, British National Lymphoma Classification, and the Working Formulation of Non-Hodgkin’s Lymphoma. For the present report the principles of Kiel and the Working Formulation have been adopted.

Computerized tomography (CT) plays a major role in the neuroradiological evaluation of possible ICML. It will not only detect a mass lesion and define its topography but will often reveal features of differential diagnostic significance, facilitating a more or less specific diagnosis. Based on the CT findings, neuropathological diagnosis of ICML can be made by biopsy either via a classical stereotaxic approach or by needle puncture monitored by CT. Such management avoids the hazard of more aggressive open surgical intervention in cases where irradiation and chemotherapy will constitute the major elements of treatment, which can then be started at an early stage.

Clinical Material and Methods

The present series comprises 30 cases of ICML. The patients’ ages ranged from 14 to 78 years, and the male:female ratio was 2:1. There were 26 cases of primary ICML (17 males and nine females); 16 (62%) of these were aged between 55 and 65 years (Fig. 1). The remaining four cases (three males and one female, aged 35 to 65 years) had secondary ICML; the two youngest of these had Hodgkin’s lymphoma.

The majority of patients were admitted to the hospital for evaluation of neurological symptoms suggesting an intracranial expanding lesion. The duration of symptoms is summarized in Fig. 2. In all patients CT examination was carried out before and after intravenous injection of contrast material. Serial subtraction angiography was undertaken in 20 patients and technetium isotope brain scanning in 20. In the group of 26 cases of primary ICML, the histopathological diagnosis was established following surgical removal of the lesion in 11 cases and from stereotaxic biopsy material in 15 cases. In the four patients with secondary ICML, stereotaxic biopsy yielded diagnostic material in one case, and the diagnosis was extrapolated from biopsy results of an extracranial lesion in three. Histologically, according to the classifications of the Working Formulation and Kiel, 14 (54%) of the patients with primary ICML had an immunoblastic lymphoma and 11 (42%) had a lymphoblastic lymphoma.

Results

In the present series of patients with primary ICML no immunosuppressive condition was found, nor were there any other predisposing factors. With the supratentorial lesions, the clinical signs at presentation were (in order of decreasing frequency): disturbance of intellectual functions and behavior problems, progressive hemiparesis, intracranial hypertension, and epileptic seizures. The infratentorial lesions were associated with cranial nerve symptoms, with or without a cerebellar syndrome, depending on the tumor site (Table 1). In

**TABLE 1**

<table>
<thead>
<tr>
<th>Symptoms &amp; Signs</th>
<th>No. of Cases</th>
</tr>
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<tbody>
<tr>
<td>disturbance of behavior &amp; intellect</td>
<td>15</td>
</tr>
<tr>
<td>progressive hemiparesis</td>
<td>14</td>
</tr>
<tr>
<td>intracranial hypertension</td>
<td>9</td>
</tr>
<tr>
<td>epileptic seizures</td>
<td>7</td>
</tr>
<tr>
<td>cerebellar syndrome</td>
<td>3</td>
</tr>
<tr>
<td>cranial nerve deficit</td>
<td>3</td>
</tr>
</tbody>
</table>

* Several patients presented with two or more of the signs listed above.
FIG. 3. Computerized tomography scans, non-enhanced (left) and enhanced (right) images, showing multiple nodular primary intracranial malignant lymphomas mimicking metastatic tumor.

Of the 26 cases of primary ICML, 22 had supratentorial and three had infratentorial lesions; one patient had lesions at both levels. A further three cases of primary ICML had multiple lesions in the supratentorial compartment (Fig. 3). Thus, in total, four of the 26 primary cases were multiple. In the four cases of secondary ICML, the lesions were all supratentorial in location; two of these patients had multiple lesions (Fig. 4). Depending on whether only primary or all cases of ICML are considered, the incidence of multiple lesions ranged between 15% and 20%.

From a topographic point of view (Table 2), by far the most frequent sites of lesions were the frontal lobes (40%) (Fig. 5), with or without involvement of the corpus callosum, followed by the temporal lobes (17%) and the central gray nuclei (16%). Leptomeningeal extension of lesions (Fig. 6) was demonstrated in five cases (17%), and subependymal infiltration (Fig. 4) was evident in two cases. Of the four patients with lesions in the posterior fossa, one had an ICML located in the cerebellopontine angle stimulating a neuroma, two had a paramedian lesion of the cerebellar hemisphere, and in the fourth the lesion invaded the leptomeningeal space.

The majority of patients had spontaneously hyperdense (66%) or isodense (30%) lesions; in one case a supratentorial secondary Hodgkin's lymphoma was spontaneously hypodense relative to the surrounding brain. The intravenous injection of contrast material elicited a homogeneous enhancement of the lesions in 90% of cases; enhancement was marked in 86%. The four cases of secondary ICML all showed moderate enhancement. The lesions were rounded and regular in shape in about 70% of cases; three lesions were polylobular. As a rule, perifocal white matter edema was not extensive, and the mass effect was usually small compared to the volume of the lesion.

Angiography was performed in 20 patients and typically yielded only signs of an avascular mass. However, three cases of primary ICML had further angiographic findings: a discrete late blush in two cases (Fig. 5) and an intense early blush in the central gray nuclei, persisting in the late venous phase, in one case. One secondary ICML with leptomeningeal extension manifested a persistent blush on selective external carotid angiograms.

<table>
<thead>
<tr>
<th>Location</th>
<th>Primary Lymphoma</th>
<th>Secondary Lymphoma</th>
</tr>
</thead>
<tbody>
<tr>
<td>frontal</td>
<td>11*</td>
<td>1</td>
</tr>
<tr>
<td>temporal</td>
<td>5</td>
<td>0</td>
</tr>
<tr>
<td>parietal</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>occipital</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>basal ganglia</td>
<td>4</td>
<td>1</td>
</tr>
<tr>
<td>posterior fossa</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>leptomeningeal</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>subependymal</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>multiple</td>
<td>3</td>
<td>2</td>
</tr>
</tbody>
</table>

* Three were of a "butterfly" configuration (see Fig. 5).
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Discussion

Pathology
In recent years, the increase in frequency of primary as well as secondary ICML's has promoted the development of theories concerning the cytological origin of these lesions, in particular stimulated by progress in immunocytochemistry.\textsuperscript{19,20,48} For a number of years, a multitude of classifications of this disease have been used. According to the classical concept, this type of neoplasm originates in the perivascular cells of the leptomeningeal vessels, invading the adjacent cerebral tissue at a later stage, extending into the perivascular space of the perforating vessels, and finally involving even deep hemispheric structures.\textsuperscript{1,2,19,59} Actually, the origin of primary ICML seems to be related to the proliferation of neoplastic B lymphocytes, with or without a concomitant deficit of T lymphocytes.\textsuperscript{26,35,57,58} This neuropathological basis is helpful in explaining the various neuroradiological features observed, in particular the location of lesions close to the meninges. The high cell density of ICML's, comprising cells with nuclei of a large size relative to the cytoplasm, explains the capacity of these lesions for spontaneous hyperdensity with reference to the surrounding brain tissue. The perivascular extension is associated with a focal disturbance of the blood-brain barrier, manifested by marked contrast enhancement without neovascularization. Furthermore, this mode of spread probably explains the irregularity of vascular contours (encasement) at angiography, which has been reported with primary ICML's,\textsuperscript{6,33} although it was not observed in the present series.

Incidence
A review of the literature allows a comparison of the results derived from the present series with those published during the past 20 years. A study of 25 series\textsuperscript{2,5,7,13,14,19,21,23,26-30,32,39,42,45,47,48,50,52,55,56} yielded a total of 241 cases of primary ICML with a peak age incidence between 55 and 65 years (Fig. 7), which is identical to the age group most affected in the present series; there was also a male:female ratio of 1.4:1 compared with 2:1 in the present series. The sex difference appears to be most marked in the age group between 35 and 45 years (Fig. 1). According to a number of reports,\textsuperscript{14,21,26,29,34} as in our present work, the immunoblastic form of lymphoma is more frequent than the lymphoblastic type, in particular in immunodepressed subjects.

Symptomatology
From a clinical point of view, although no specific symptomatology exists, several authors have reported the frequent deterioration of intellectual function and alteration of behavior patterns in ICML presentation (Table 1), the morphological correlate being the prevalence of a frontal, frontocallosal, or temporal location of these lesions;\textsuperscript{19,21,29,30} this agrees with the findings in the present series. A favorable effect of steroid treatment in ICML has been confirmed clinically as well as on CT scans.\textsuperscript{7,40,52} In one patient in the present series, neurological symptoms appeared after discontinuation of steroid treatment that had been instituted for a Wissler-Fanconi syndrome.

![Fig. 5. Upper: Computerized tomography scans of a primary intracranial malignant lymphoma, bilateral frontocallosal "butterfly" type. The tumor shows spontaneously hyperdense with massive enhancement (right) and moderate perifocal edema. A clear separation is seen between the enhanced lesion and the falx (right); this appearance is significant in the differential diagnosis from a meningioma. Lower: On angiography the lesion presents as an intra-axial avascular mass.](image)
Diagnostic Considerations

The usefulness of cerebrospinal fluid (CSF) analysis has been discussed by several authors. In the present series, CSF was sampled by lumbar puncture but diagnostic information in terms of neoplastic cells was obtained in only one case. In secondary ICML, the diagnostic approach is guided by the clinical presentation: the involvement of multiple lymph nodes and splenomegaly as well as blood tests frequently give clues to the final diagnosis. A diagnosis of intracranial Hodgkin's lymphoma was established in one of our patients, presenting as a primary lesion; such a presentation is extremely rare.

Computerized Tomography Diagnosis

Most cases of primary as well as secondary ICML present as single lesions. In this series, 15% of patients had multiple lesions as compared to 20% to 40% reported by others. The predominance of a frontotemporal location of these tumors has already been discussed. On CT scans, ICML typically appears as a relatively large mass, spontaneously hyper- or isodense, with a regular shape and contours. However, polyglobular lesions may be encountered. The mass is usually markedly enhanced by intravenous injection of contrast material; with few exceptions, enhancement is homogeneous in character.

Perifocal edema was not often a prominent feature in the present series or in others, resulting in an apparent discrepancy between the large volume of the lesion and the moderate mass effect elicited. Certain CT features have been considered to be particularly indicative of ICML: these include bilateral subependymal infiltration of the periventricular tissue (detected only after intravenous injection of contrast material (Fig. 4)), and a mirror-image bilateral distribution pattern of lesions in the regions of the central gray nuclei. Certain CT features have been considered to be particularly indicative of ICML: these include bilateral subependymal infiltration of the periventricular tissue (detected only after intravenous injection of contrast material (Fig. 4)), and a mirror-image bilateral distribution pattern of lesions in the regions of the central gray nuclei.

Infiltration of the leptomeningeal compartment, demonstrated on CT scanning, has rarely been reported in the literature but was a relatively frequent finding in this series (17% of cases). In our opinion, it may be considered as a characteristic feature of ICML, particularly when associated with infiltration of adjacent nervous tissue (Fig. 6). Leptomeningeal infiltration is typically seen on plain CT images as a hyperdense corticomeningeal structure that enhances less densely than does the intracerebral lesion after injection of contrast material. Leptomeningeal infiltration is a constant finding at autopsy of ICML cases, if carefully sought, even if not macroscopically evident. In our opinion, the statement of anatomopathologists that infiltration of the cerebral tissue is more characteristic of primary ICML whereas leptomeningeal infiltration is typical of secondary ICML does not extend to the CT diagnostic situation. A differentiation between primary and secondary ICML does not appear to be feasible on CT scans. This is amply illustrated by the case in Fig. 6.

Angiography

The usual mode of presentation of ICML on angiography is that of an avascular mass. The presence of irregularly constricted vessels, which has been described by some authors, appears to be a relatively infre-
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quent finding. In the present series, angiography was carried out in 20 patients and did not reveal any vascular encasement. A tumor blush has not been reported as a frequent finding; however, a blush was present in four of our 20 cases: an early intense blush in one case; a late and less marked blush in two cases of primary ICML; and a persistent blush on the external carotid angiograms in one case of secondary ICML associated with a focal erosion of bone at the same site.

Differential Diagnosis

On the suspicion of ICML, the most likely alternative entity to eliminate is noncalcified meningioma, for which angiography is usually diagnostic. In parasagittal lesions, meningioma is usually adherent along the falx when falcial in origin; absence of this sign supports the diagnosis of ICML, unless a high convexity meningioma is considered (Figs. 5 and 8). One patient in the present series displayed features suggesting a meningioma en plaque along the edge of the tentorium; however, angiography was negative, and the diagnosis of primary ICML was finally established at operative biopsy.

In case of tumor heterogeneity, with a more or less hypodense center, the differentiation of ICML from glioblastoma is not feasible by CT. Again, the angiographic features are helpful: the classical neovascularization with arteriovenous shunting and blush of a glioblastoma contrast with the absence of neovascularity in ICML, and the blush, if present, is usually weak in cases of ICML. However, glioblastoma may present as an avascular mass, and intense angiographic blush has been reported with ICML, although rarely.

The differentiation between ICML and metastatic disease, particularly when multiple lesions are present, remains a challenge, because patients affected are much the same age. If angiography yields only signs of one or several avascular lesions, it is not helpful; however, only one case of primary ICML with multiple hypervascularized nodules has been reported.

Finally, the possibility of an infectious focal lesion, mainly in immunodepressed subjects and particularly in AIDS patients, should be eliminated. Neither intracerebral abscess nor the virus-induced multifocal progressive leukencephalitis (which are not visible on CT images) are readily confused with ICML. However, the CT appearance of acute intracerebral focal manifestation of toxoplasmosis with iso- or hyperdense nodular lesions, strongly enhancing, with or without associated diffuse ependymitis, may exactly mimic ICML. If this possibility exists, in the absence of definitive improvement on specific antiparasitic therapy, as monitored by frequent CT scans, only biopsy may provide the diagnosis. In this context, the usefulness of the stereotaxic approach for biopsy should be strongly emphasized: more than half of the cases in the present series were classified histologically on the basis of material obtained from a stereotaxic biopsy. The particular advantage of this approach is that any subregion of interest within the lesion can be sampled based on the CT image, if it is considered suitable for biopsy. In this series, there were no complications during or after the biopsies, which were performed according to Talairach's method.

Conclusions

Computerized tomography is the diagnostic approach of choice in patients suspected of having an ICML and may be strongly suggestive of the specific diagnosis. If necessary, the CT scans will constitute the basis for a biopsy, permitting definitive diagnostic classification by histopathology. This method offers a suitable therapeutic choice, without delay and without more invasive surgical intervention. Cerebral angiography seems to be useful only in differential diagnosis or as a preoperative measure, in case surgical exeresis of the lesion is considered. The differentiation of primary from secondary ICML's by neuroradiological means does not appear feasible, because of the similar appearance of the two types of ICML on CT scans and angiograms. Differential diagnosis in a wider sense should comprise meningioma, glioblastoma, metastatic disease, and toxoplasmosis in the immunodepressed subject. The usefulness of stereotaxic biopsy is empha-
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Manuscript received December 12, 1985.
Accepted in final form April 28, 1986.
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