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CLINICAL REVIEW 136

Primary Lymphoma of the Pituitary: An Emerging Clinical Entity

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Pituitary masses are diagnosed with increasing frequency due to the progressive refinement of endocrine tests and imaging procedures. Pituitary adenomas are the most common cause of a mass in the sella, accounting for up to 10–15% of intracranial neoplasms (1). However, when dealing with abnormal intrasellar masses, a number of different etiologies are possible: germ cell tumor, gliomas, meningiomas, metastatic tumors, vascular lesions, granulomatous, and infectious and inflammatory processes (2).

Lymphomas originating in the parasellar region have been anedoctically reported to be among the most unusual causes of sellar masses. However, during the last decade there have been an increasing number of isolated reports describing new cases of pituitary lymphomas, including a Clinical Case Seminar recently published in *JCEM* (3). The aim of this report is to put in a clinical perspective all the available data on primary pituitary lymphomas (*i.e.* without other localization of the disease) described so far, including the features of a recent and unpublished case observed by us.

Here, we show that pituitary lymphomas are not a simple clinical curiosity but a precise, and emerging, entity likely heterogeneous in origin with possible specific risk and pathogenetic factors and distinct clinical features. We also provide elements for the clinician for the differential diagnosis and treatment of pituitary lymphomas. Finally, prognostic and outcome data on affected patients are given in this article. All these elements are put in perspective in the attempt to help endocrinologists in the understanding of pituitary lymphomas and in being prepared to deal with what we think is an emerging clinical entity.

Epidemiology

Intracranial tumors. The frequency of tumors of the central nervous system (CNS) ranges between 3.8 and 5.1 per 100,000 subjects. In the United States, CNS tumors constitute the fourth cause of death in males aged 35–54 yr. In Europe, those tumors account for only 2% of all deaths due to cancer (4). On the other hand, pituitary tumors account for about 10% of intracranial neoplasms and have an annual incidence in the general population of about 25 per million (5). Primary CNS lymphoma (PCNSL) is now thought to constitute 3% of all intracranial neoplasms (6).

Intracranial lymphomas. Non-Hodgkin's lymphoma (NHL) may involve the CNS either as a primary tumor or after spreading from an established systemic lymphoma. This occurs in 5–29% of patients with systemic lymphoma during the natural history of the disease and is usually associated with progressive widespread systemic disease (7). PCNSL is a less commonly encountered clinical entity and is defined as lymphoma limited to the cranial-spinal axis without systemic disease. In the past, PCNSL was considered a rare disorder, accounting for 1–2% of all cases of NHL and fewer than 5% of all cases of primary intracranial neoplasm (7). This frequency has largely increased because of the increasing number of patients with congenital and iatrogenic immunosuppression and acquired immunodeficiency syndrome (AIDS) (8). However, recent data also show an increase in the incidence of primary intracranial malignant lymphomas in immunocompetent individuals (6).

Lymphomas of the pituitary. As far as this last localization is concerned, 38 cases of hypophyseal lymphoma were found in an autopsy series of 165 patients (about 23%) who died of hematological malignancies, although there was no mention of hypopituitarism during life (9). Recently, some authors have carried out a clinicopathological examination of brain tissue taken postmortem from patients with PCNSL to determine the topographic involvement of the CNS. The pituitary gland was involved in 5 of 22 cases (about 25%) and particularly the posterior but not anterior lobe (10). In a recently reported series of 1120 patients undergoing transphenoidal surgery for sellar masses from January 1981 through May 1998 only a single lymphoma was diagnosed (less than 1‰) (2). Recently, several cases of PCNSL, presenting as pituitary tumor, have been described. The total number of cases reported in some detail in the literature is now 24, specifically 14 cases of apparently primary pituitary lymphoma (2, 3, 11–22) and 10 cases of secondary localization or infiltration of the sella turcica (10, 23–31). Our analysis of the main clinical features of primary pituitary lymphomas is based on the detailed description available in the literature

Abbreviations: AIDS, Acquired immunodeficiency syndrome; CHOP, cyclophosphamide, doxorubicin, vincristine, and prednisone; CNS, central nervous system; CT, computed tomography; EBV, Epstein-Barr virus; HT, Hashimoto's thyroiditis; MRI, magnetic resonance imaging; NHL, non-Hodgkin's lymphoma; PCNSL, primary CNS lymphoma.

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(Medline search, proceedings of international meetings) of 13 cases [11 available as full papers (2, 3, 11, 13–19, 22) and 2 as abstracts (12, 20)]. In fact, for one case (21) there is no possibility to obtain from the literature an adequate characterization, which was not the scope of the original publication reporting the case. Conversely, for the case observed by us, and reported so far only in abstract form (20), some details have been added to the present analysis.

Age- and sex-linked incidence. The annual incidence of malignant lymphomas ranges from 8–9 per 100,000, with about 75% due to NHL. The male to female ratio is greater than 1.1–1.3:1 for NHL. The slightly higher number of males with NHL is constant at any age and for all histological kinds. For NHL there is a first incidence peak at the age of 10, a decrease at about 20 yr of age, and a progressive increase until the age of 70 (32). PCNSL can appear at all ages, with peak incidence between the 6th and 7th decade in nonimmunodepressed subjects (33). In these subjects the male to female ratio is 3:2, whereas more than 90% of AIDS patients are males and of younger age (32).

Pituitary tumors are generally benign tumors, although they may show histological evidence of invasion of the capsule or into the surrounding structures. The peak incidence occurs between the ages of 30 and 60 yr, being somewhat earlier in women than men because of the greater frequency of prolactinomas in young women (5).

Lymphocytic hypophysitis has been reported to be predominantly a disease of females, frequently associated with pregnancy or presenting during the postpartum period (in the literature, this association was found in 63% of female patients) (34). The mean age of presentation in females is 35 yr whereas in males it is one decade later (35, 36).

Primary pituitary lymphomas have been predominantly observed in males (male of female ratio is 2:1) (Fig. 1). The peak incidence of the disease occurs around the 6th decade of age (Fig. 1). The mean age of the patients described so far is 59.46 ± 17.16 yr (mean ± SD). The age of higher incidence of NHL of the pituitary is similar to cerebral lymphomas in general as it is the male prevalence. In the only patients with AIDS reported so far (Table 1 and Ref. 11), the pituitary lymphoma appeared at a younger age than in the remaining population, reflecting a similar decrease in the age range of cerebral NHL in immunodepressed subjects.

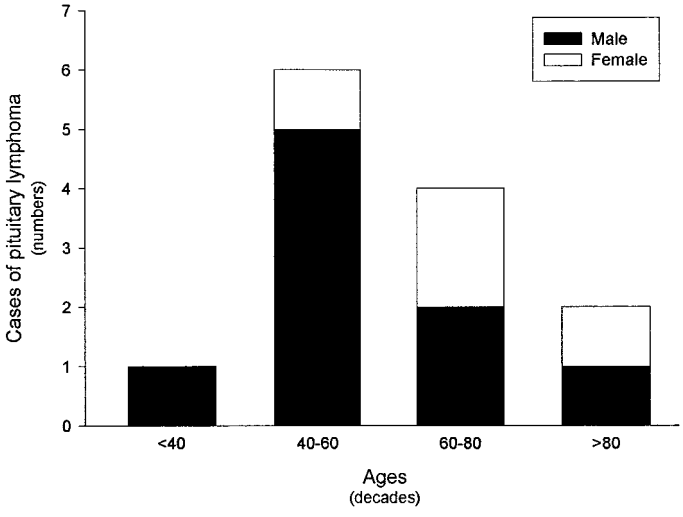

FIG. 1. Age and sex distribution of primary pituitary lymphomas.

Risk factors

Among the established or hypothetical risk factors for pituitary lymphomas are AIDS, pituitary adenomas, and lymphocytic hypophysitis.

AIDS and other immunodeficiency states. The main reason for the increase in cases of PCNSL in immunodeficient subjects is the AIDS epidemic, and it is probably due to the improved survival of AIDS patients. Two and one half percent of AIDS patients develop PCNSL (37). In autopsy studies involvement of the pituitary has been reported as a result of direct spread from adjacent structures or metastasis from extra neural sites. The tendency of primary central nervous lymphomas to grow in the brain may be explained by the decreased immune surveillance normally found within the CNS. Thus, PCNSL in the patients with AIDS may be the result of a process of uncontrolled Epstein-Barr virus (EBV)-induced B lymphocyte proliferation with possible subsequent neoplastic transformation in an immunologically privileged site in a patient with baseline impaired immune surveillance (7).

Lymphocytic hypophysitis. There has been one previous report suggesting lymphocytic hypophysitis to be a likely risk factor for the development of pituitary lymphoma (22). This possibility is also suggested by the case observed by us (20). Therefore, even with the caution suggested by the limited clinical evidence so far, it can be hypothesized, by analogy with other endocrine gland lymphomas (38), that lymphocytic hypophysitis (17) may be potentially a risk factor for pituitary lymphomas. Prospective studies on the outcome of patients with hypophysitis are needed to possibly confirm this hypothesis.

Pituitary adenomas. Patients with pituitary adenomas were reported to have an increased risk of second malignancies, including lymphoma (39). Furthermore, lymphoma cells possess endocrine hormone receptors, and growth of both T and B lymphoma cells can be stimulated by PRL and other pituitary hormones (40) (a local concentration of pituitary hormones may favor the growth of lymphoma cells). On the other hand, the breaching of the blood brain barrier by the pituitary tumor may also allow easy access of the lymphoma cells to an immunologically privileged site for rapid proliferation (19).

Pathogenesis

Several cases of PCNSL as a concomitant or secondary malignancy following intracerebral or extracerebral neoplasms are on record (41). Often, the preceding tumors had been of high malignancy and treated by chemotherapy and/or radiotherapy thought to have carcinogenic effects on hematopoietic cells (42, 43), possibly associated with genetic predisposition. This explanation is also likely to apply to malignant brain tumors occurring after radiotherapy of benign tumors. However, in the

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TABLE 1. Endocrine characteristics of 13 patients with primary pituitary lymphomas

Ref.	Age/sex	Anterior hypopituitarism	Diabetes insipidus	Hyperprolactinemia	Hormonal substitution	Concomitant endocrine disease	Endocrine and general symptoms
2	M/48	Absent	Absent	Absent			
3	F/86	Partial	Present	Absent	T_4, prednisone	Absent	Fever, weight loss
11	M/48	Absent	Absent	Absent		Absent	Fever
12	M/53	Absent	Absent	Absent		Absent	
13	M/49	Partial	Present	Present	Desmopressin		Decreased libido
14	M/28	Absent	Absent	Absent		Absent	
15	F/73	Partial	Present	Present	Hydrocortisone, desmopressin, T_4	Absent	
16	M/83	Global	Present	Absent		Pituitary adenoma	
17	M/65	Global	Absent	Present	T_4, dexamethasone, T	Absent	Decreased libido, weakness
18	M/77	Global	Absent	Absent	Hydrocortisone, T_4	Absent	Weakness
19	F/67	Global	Absent	Absent		Pituitary adenoma	
20	F/52	Global	Present	Absent	Hydrocortisone, desmopressin, T_4	Absent	Amenorrhea
22	M/44	Absent	Absent	Absent		Absent	Loss of libido

TABLE 2. Neurological findings of 13 patients with primary pituitary lymphomas

Ref.	Headache	Visual field	Cranial nerves	Others
2	Absent		Left third and sixth cranial nerve palsy	Left-sided retroorbital pain
3	Absent	Normal	Normal	
11	Present		Likely normal[a]	Meningeal irritation
12	Present	Diplopia and limitation in lateral movement of the left eye	Likely normal[a]	
13	Present		Sensorineural hearing loss on the right side	Orizontal nystagmus dysarthria
14	Present	Blind, bilateral optic atrophy, bitemporal hemianopsia	Hypoesthesia in the ophthalmic and maxillary division of the right trigeminal nerve	
15	Present	Diplopia	Sixth nerve palsy	Distal parasthesiae
16	Present	Right eye blindness, left temporal hemianopsia	Normal	
17	Absent	Normal	Normal	
18	Absent	Normal	Normal	
19	Absent	Amaurosis of the right eye	Oculomotor nerve palsy	
20	Present		Sixth nerve palsy	
22	Present	Transient blurred vision	Likely normal[a]	

[a] Not mentioned in the original description.

cases reviewed by us and in the patient observed by us no radiotherapy was recorded in the clinical history and therefore, it cannot be implicated in the development of pituitary lymphomas.

Two specific pathogenetic pathways for pituitary lymphomas may be hypothesized:

Hypophysitis in immunocompromised/immunocompetent patients. A policlonal lymphocytic inflammation (mixed T- and B-cell population) may undergo monoclonal expansion with subsequent malignant transformation, possibly triggered by an infectious agent. In fact, transient "sentinel" brain lesions have been observed in immunocompetent subjects to precede PCNSL, and histologically they included inflammatory T cells (44). Because almost all PCNSLs of immunocompromised patients contain genome of the oncogenic EBV (45), it is conceivable that polyclonal inflammatory disorders due to EBV or another herpes virus may undergo monoclonal conversion. In a previous study (22) as well as in the case of pituitary lymphoma by us observed (20) there were histological signs of inflammatory lesion even if there was not previous history of hypophysitis. Moreover, subclinical, smouldering preexisting inflammation cannot be excluded in other cases. It is interesting to hypothesize that what could take place at the pituitary level is an already well described phenomenon at the thyroid level with Hashimoto's thyroiditis (HT). Histological features of HT include, as in lymphocitic hypophysitis, diffuse infiltration of lymphoid cells usually with formation of lymphoid follicles, varying degrees of fibrosis, oxyphillic change, or squamous metaplasia in the epithelial cells (38). An etiologically important role of HT in the development of thyroid mainly B-cell lymphomas has been confirmed by epidemiological studies (46).

Pituitary adenomas. The role of pituitary adenomas in the pathogenesis of pituitary lymphomas is far to be clear, and, therefore, the possible links between these two clinical entities are somewhat hypothetical and not yet proven.

Possible pathogenetic pathways for intraadenomatous lymphoma development include monoclonal growth of T cell-infiltrates, expression of adenoma-specific adhesion molecules, and the mitogenic potential of some pituitary hormones. The expression of mutated adhesion molecule on adenomatous pituitary cells may act as lymphocyte "homing" signals to the adenoma tissue. Lymphoma development could be stimulated by hormones produced by the adenoma. Several hormones [PRL (47, 48), GH (49–51), and gonadotropins (19, 52, 53)] released by either normal or adenomatous pituitary are known to have mitogenic

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effects both on lymphoma cells and on normal human lymphocytes.

Clinical presentation

Hypopituitarism. Pituitary lymphomas, similar to pituitary adenomas, may present with symptoms of anterior pituitary hormone dysfunction. The developing hypopituitarism associated with expanding pituitary masses frequently follows a characteristic sequence involving initially diminished gonadotropin secretion, followed by GH, TSH, and ACTH deficiency (54). Although this is the classic order of deficiency, variation in the order of pituitary hormone failure may occur (55). More than 50% of patients with primary pituitary lymphomas showed at the time of diagnosis clinical and/or laboratory evidence of pituitary hypofunction. At the time of diagnosis five patients (16–20) showed global anterior hypopituitarism, whereas three patients had partial hypopituitarism (3, 13, 15): three had hyperprolactinemia (13, 15, 17) pointing to a secondary hypopituitarism presumably due to pituitary stalk compression. Of the patients with anterior pituitary failure, five also had diabetes insipidus (Table 1). Therefore, these heterogeneous endocrine findings may suggest different origins of the lymphoproliferative tissue: extrapituitary (with hypopituitarism due to pituitary stalk compression or without hypopituitarism); posterior hypophysis (with diabetes insipidus); and anterior pituitary (partial or global anterior pituitary failure).

Neurological findings. Together with hypopituitarism, the neurological signs and symptoms are those of expanding intracranial masses with headache, diplopia, and visual field defects and cranial nerve involvement. Fifty percent of patients with pituitary lymphoma had visual field defects. Varying degrees of optic chiasm involvement have been described. Two of 13 patients had bitemporal hemianopsia. Extension of the pituitary tumor into either the optic nerve or the optic tracts caused blindness in one patient; overall, three patients had variable degrees of optic nerve involvement (Table 1). Headache seems to be the most common neurological presenting symptom for expanding lymphomas of the pituitary (about 75% of patients) and results from erosion of the bony sella turcica or stretching of the diaphragma sellae. No single typical pain pattern is found in pituitary lymphoma-associated headaches, because not only occipital and retro-orbital headaches but also bitemporal patterns have been reported (Table 2). Cranial nerve involvements due to the pituitary lymphoma extending laterally into the cavernous sinus have been reported (about 40% of the patients). These findings may also have a more insidious onset, with variable presentations ranging from diminished abduction of the ipsilateral eye due to sixth nerve involvement to diplopia associated with ocular motor nerve compression, or facial pain if the first and second branches of the trigeminal nerve are affected. Interestingly, among the neurological signs, the involvement of the optic chiasm (14, 19) or even of the optic nerve seems not to have negative prognostic significance (Table 3).

Histopathological findings

Histologically, lymphomas of the CNS and sella resemble systemic lymphomas. They are almost always NHLs. Most PCNSLs are high-grade immunoblastic or diffuse large-cell type with a B-cell immunophenothype. Despite the high-grade histopathological features, many PCNSLs are arrested at relatively mature stages of differentiation (56, 57). PCNSLs are largely clonal on the basis of their monotypic expression of either κ- or λ-light chain immunoglobulin. Molecular studies have also demonstrated consistent profiles of light-chain and heavy-chain immunoglobulin gene rearrangements in primary, recurrent, and metastatic CNS lymphomas. Unfortunately, not in all cases of primary pituitary lymphomas reported in the literature is detailed histological description given. However, of those patients for whom the results of the histological examination are available (Table 4), 54% had diffuse B cell-large lymphoma

TABLE 3. Therapy and outcome of patients with primary pituitary lymphomas[a]

Ref.	Chemotherapy	Radiotherapy	Follow-up/outcome
3	Several cycles of chemotherapy		Death 3 months after neurosurgery
11			Death 11 d after the initial presentation
12		Cranial radiation	No regrowth of the residual tumor in follow-up[b]
13	High doses with methotrexate, iv and intraarterial		No regrowth of the residual tumor in follow-up[b]
14	CHOP	Cranial radiation (5000 rads)	The patient was well after 6 months of follow-up
15		Fractionated radiotherapy (4000 cGy) to sphenoid sinus and pituitary region	At least 21 months after radiotherapy tumor regression
16		Palliative radiotherapy	
17	Cytoxan, vincristine bleomycin, adriamycin after B-cell lymphoma lung metastases		At least 6 months after chemotherapy the patients was well
18			Death 2 months after the initial presentation
19		Fractionated radiotherapy of the sellar tumor region	Minimal residual tumor after 5 months was detected within the right cavernous sinus
20	Three cycles of chemotherapy	Brain radiation	Death 3 months after neurosurgery

[a] Data for patients from Refs. 2 and 22 are not available.
[b] Follow-up time was not detailed in the original description.

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TABLE 4. Radiological and histopathological findings in 13 patients with primary pituitary lymphomas

Ref.	Imaging		Diagnosis suspected	Diagnosis confirmed/histopathology	
	CT	MRI		Type of lymphoma/concomitant findings	
2		Mass involving sella sphenoid sinus and cavernous sinus		B-cell lymphoma	
3		1.2 × 1.0 × 1.25 cm sellar mass within a minimally enlarged pituitary fossa. The mass extended superiorly into the suprasellar cistern without evidence of chiasmal compression	Pituitary adenoma	B-cell lymphoma	
11	9 mm enhancing mass in the pituitary		Tubercoloma	B-cell lymphoma	
12	Extensive bony destruction	Faintly and homogeneously enhanced	Pituitary adenoma or chordoma or germinoma	T-cell lymphoma	
13	Hypothalamic tumor, suprasellar mass infiltrating contiguous structures; tissue loss in the left inferior frontal lobe	Enhancement of a suprasellar mass with infiltration of contiguous structures	Lymphoma of the brain	B-cell lymphoma	
14	A large mixed lesion in the sella, suprasellar and parasellar region extending into the sphenoid sinus. The tumor had destroyed the floor of the sella and lesser wing of the sphenoid on the right side			NHL	
15		Soft tissue mass filling the sphenoid sinus on the right and contiguous with the pituitary gland; there was thickening of the pituitary stalk and enhancing mass in the floor of the third ventricle		B-cell lymphoma	
16		Heterogeneously isointense bilobed tumor enlarging the pituitary fossa; a central hypointense hemorrhagic area is noted in the suprasellar component; the hypothalamus and optic chiasma were severely compressed	Pituitary adenoma and pituitary apoplexy	B-cell lymphoma	Pituitary adenoma; immunoreactivity to chromogranin and synaptophysin, and weak TSH positivity
17		Diffuse enlargement of the pituitary gland; the pituitary stalk was middle line, and the enlargement bowed up to the diaphragma sella but did not extend into the suprasellar cistern		B-cell lymphoma	Large lymphocytes in mitosis invading the adenohypophysis
18		Heterogeneously enhancing pituitary lesion with normal optic chiasm	Diffuse large cell NHL		
19		Large intrasellar and right parasellar lesion that invaded the right cavernous sinus	Recurring adenoma	T-cell lymphoma	Pituitary adenoma; 50% of cells were positive for FSH
20	Extensive osteolytic lesion at the front skull base	Sellar mass with suprasellar expansion that impressed the optic chiasma on top, eroded the sellar base and occupied the sphenoid sinus at the bottom and invaded the cavernous sinuses and the clivus at the side	Invasive pituitary macroadenoma	T-cell lymphoma	Focally large number of small lymphocytes, plasma cells, neutrophils and eosinophils
22		Moderately enhancing mass lesion involving sella, suprasellar and parasellar regions with infiltration of the cavernous sinus. Isointense on T1 and T2	Pituitary adenoma or granulomatous lesion or plaque meningioma	NHL	Chronic inflammation

whereas 24% had T-cell lymphoma of high malignancy (Fig. 2). In two cases (20, 22), signs of inflammation were described (Table 4). In two patients (16, 19) (Table 4), coexisting adenomatous tissue has been found with positive immunoassay for either TSH (and chromogranin) (Ref. 16 and Table 4) or FSH (50% of cells) (Ref. 19 and Table 4).

Differential diagnosis

The differential diagnosis includes pituitary and nonpituitary sellar and parasellar masses. Pituitary tumors may vary a lot in presentation. Clinical findings depend largely on whether the tumors are hormone secreting or clinically non-

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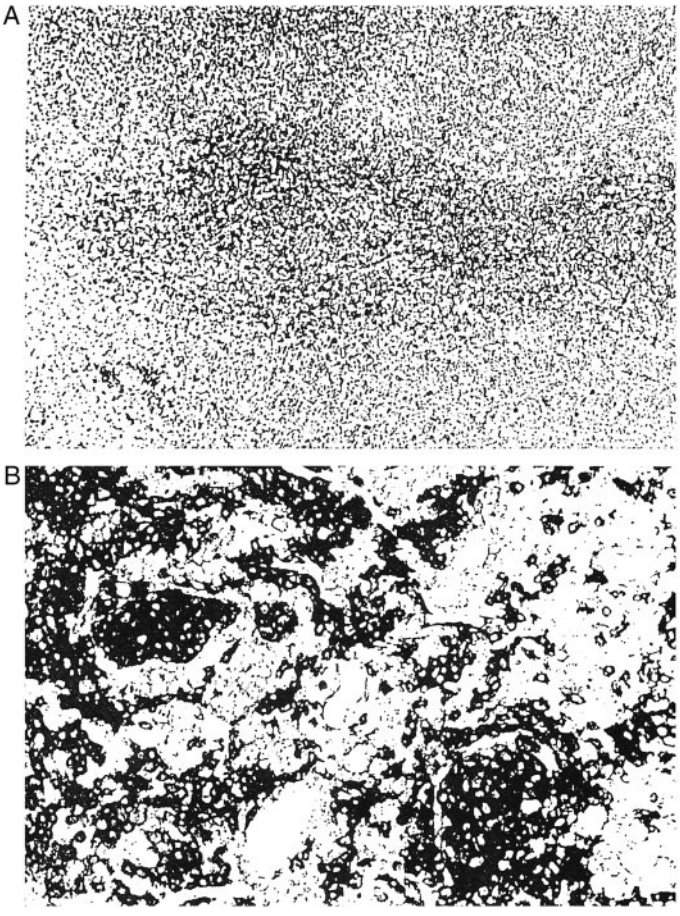

FIG. 2. Histopathological (A) and immunohistochemical (B) findings in the patient with primary pituitary lymphoma (20).

functioning, on the size and pattern of tumor growth, and on whether normal pituitary is disrupted (54). Nonsecreting pituitary tumors typically appear with visual compromise, including impairment of the visual fields and decreased acuity, signs of hypopituitarism, and nonspecific symptoms such as headache. Modest hyperprolactinemia secondary to hypothalamic-pituitary stalk compression is common (2). Pituitary lymphomas as many nonpituitary sellar and parasellar masses, and similar to pituitary adenomas, may present with symptoms of anterior pituitary hormone dysfunction. These symptoms include gonadal dysfunction, secondary hypothyroidism, and, less often, clinical adrenal cortical insufficiency. Hyperprolactinemia, which may be asymptomatic or accompanied by hypogonadism, is often found at presentation of lesions of the sellar region. Clinical diabetes insipidus at presentation is highly suggestive of a nonpituitary etiology of a sellar or parasellar mass (2). Diabetes insipidus may result from involvement or compression of the pituitary stalk, hypothalamus, or paraventricular region of the third ventricle by the lesion. In the patients examined by us, diabetes insipidus was not particularly frequent (less than 50% of patients) but a factor, when present, associated with poor prognosis. Therefore, based on clinical presentation, differential diagnosis of pituitary lymphomas is not easy at best. Severe headache without GH hypersecretion and coexisting signs of hypopituitarism with diabetes insipidus and/or cranial nerve involvement should prompt the clinical suspect of a pituitary lymphoma (but they do not exclude other causes of sellar masses). As many as 25% of patients with nonpituitary sellar or parasellar masses have impairment of cranial nerves II, III, IV, and VI (2). Headache is often a prominent symptom in patients with large tumors that produce ventricular dilatation. Similar to pituitary adenomas, many nonpituitary sellar masses may present with hypopituitarism. Differential diagnosis is difficult on magnetic resonance imaging (MRI) (Fig. 3). The sellar region enlargement is suggestive of a pituitary lesion, but the eroded bone is not particularly helpful in differential diagnosis.

In AIDS patients, pituitary lymphoma may be confused with other intracranial lesions typical of this population, such as toxoplasmosis. Brain biopsy used to be the only means of the establishing the diagnosis, but noninvasive tests can now be used with confidence to diagnose lymphoma: single-photon emission computed tomography (CT) or positron emission tomography scanning can usually discriminate PCNSL from toxoplasmosis or other infection as well as identification of EBV DNA in the cerebrospinal fluid that is sensitive and usually unique for PCNSL (58, 59).

The differential diagnosis of primary *vs.* secondary pituitary lymphomas may include a complete neurological staging, including cerebrospinal fluid examination and ophtalmological evaluation with slit-lamp examination to exclude

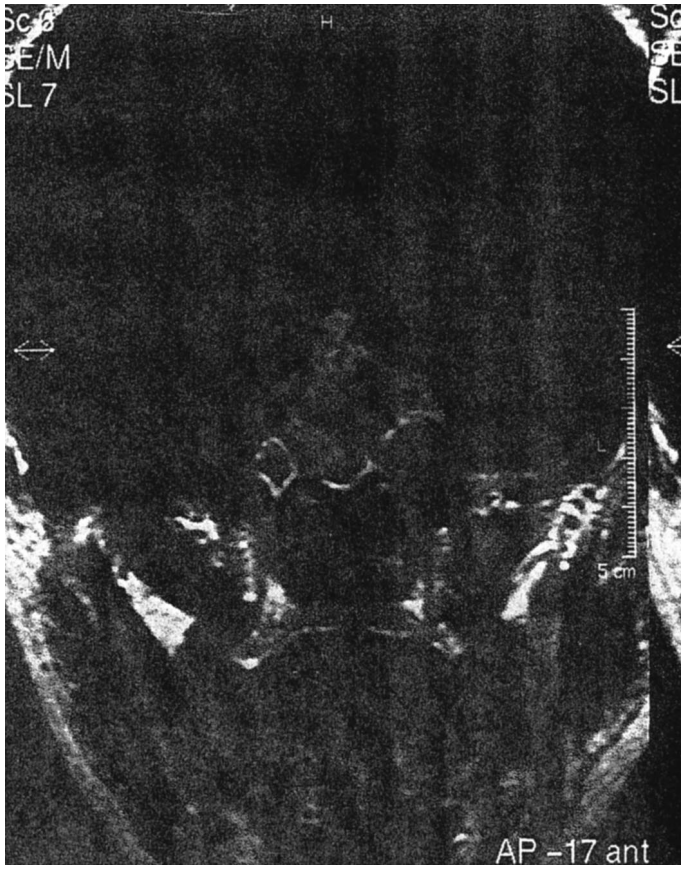

FIG. 3. MRI before neurosurgery in the patient with primary pituitary lymphoma (20).

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vitreous or retinal involvement. In addition, an abdominopelvic CT scan and bone marrow biopsy may be obtained to exclude systemic lymphoma.

In the series of patients with pituitary lymphomas examined by us, only in one case was the presumptive diagnosis lymphoma of the brain. In the large majority of cases presumptive diagnosis was pituitary adenoma. Confirmation of diagnosis was most frequently obtained with surgery (10 cases).

Treatment and outcome

Neurosurgery. In PCNSL, in general the role of neurosurgery is that of allowing the histopathological diagnosis mainly via a stereotactic biopsy. In the case of primary pituitary lymphomas the role of neurosurgery seems more important because the mass is, among all other cerebral sites, the easiest to reach via the transphenoidal approach. The clinical presentation of pituitary lymphomas may be similar to that of pituitary invasive macroadenomas. Those pituitary adenomas often cause compression of the optic chiasm and neurological deficits as well as most of primary pituitary lymphomas at presentation. We suggest that in these cases the neurosurgical removal of the mass effect (even if the resection could not be complete) may have a double advantage: to improve the clinical conditions and to allow the histopathological diagnosis. Seldom, particularly when the growing invasive mass does not involve the optic chiasm (lateral and/or inferior expansion), neurosurgical intervention is not performed because it is considered unable to obtain a complete removal of the mass and, therefore, radiation therapy is directly administered. We suggest that in the presence of such masses at least a transphenoidal biopsy should be obtained before any other interventions: this may allow a better (chemotherapy) treatment in case the mass is histopathologically diagnosed as pituitary lymphoma. In the experience obtained so far, pituitary lymphomas presented as large pituitary masses. This finding does not exclude that in the future smaller pituitary lymphomas may be diagnosed; therefore, speculatively, if the pituitary mass is not very large and there is no visual or neurological deficit, it might be appropriate to follow-up the patient and repeat short-term (*e.g.* three months) MRI and send the patient to the surgeon if a rapidly growing mass is observed. This clinical chance (follow-up) may always be taken with caution due to the almost invariably aggressive features of pituitary lymphomas.

Radiotherapy. Radiotherapy has been the primary therapy for PCNSL for many years. Radiation increases survival from 4 months with surgery alone to 12–18 months with whole brain radiotherapy (60). The Radiation Therapy Oncology Group prospectively studied 41 patients treated with 40 Gy whole brain, followed by a 20-Gy focal boost. A response was seen in 62% of patients, but the median survival was only 12.2 months. The addition of a boost to the area of bulky disease did not improve intracranial disease control or survival (60). In the examined series of patients, half of them have been given radiation therapy (Table 2).

Chemotherapy. Because PCNSL is histologically similar to systemic NHL, it seemed reasonable to try systemic lymphoma regimens for PCNSL. To date, no conventional systemic lymphoma regimen has proved effective against PCNSL. Two multicentered prospective trials tested preirradiation cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) or cyclophosphamide, doxorubicin, vincristine, and dexamethasone, followed by whole brain radiotherapy (61, 62). CHOP is the optimal combination regimen for the treatment of advanced systemic NHL. CHOP/cyclophosphamide, doxorubicin, vincristine, and dexamethasone failed to produce sustained remissions in PCNSL, and median survival rates were no better than with brain radiotherapy alone. High-dose methotrexate was found to be the only independent treatment-related factor that improves outcome (63). This has led to experimentation with different regimes, none of which have been studied in sufficient detail to determine an optimal approach. However, chemotherapy alone can produce sustained remissions in some patients, including the elderly population. Considerable improvements in survival have been accomplished by the addition of chemotherapy to cranial radiotherapy. In addition, many patients achieve substantial disease-free survival with chemotherapy alone, and survival is superior to that with radiotherapy alone (60). About half of the patients with pituitary lymphoma received chemotherapy, only in three cases (3, 13, 17) without cranial radiation. Regimens used were slightly or clearly different in the various cases reported so far (Table 2). Therefore, the data available do not allow any conclusions on the best chemotherapy regimen for pituitary lymphomas outcome. However, due to the overall good response to chemotherapy, every patient with pituitary lymphoma should be considered for this option as the first line of therapy. Subsequent cranial radiotherapy may or may not be necessary depending on the patient's clinical condition, age, and response to initial chemotherapy.

Outcome. Overall, pituitary lymphomas seem to have a better prognosis with respect to all PCNSLs. Approximately 70% of the examined patients had survived quite long (>6 months, where adequate follow-up is available) after the diagnosis, whereas in patients with cerebral lymphomas survival is often less than 6 months (although the improvement of treatment has led to an improved survival also for PCNSL, in general). As in all other malignancies, early diagnosis has to be considered the key to achieve a better outcome. In fact, among cerebral lymphomas, pituitary ones are those that allow the easiest and less invasive diagnostic approach due to the possibility of transphenoidal approach. As mentioned above, when the lesion is already too large to allow complete neurosurgical removal, we propose to obtain in any case as early as possible a sample of the sellar occupying lesion, even only with a minimally invasive transphenoidal biopsy.

Prognostic factors

PCNSL is an important lethal complication in AIDS patients. The presence of prior opportunistic infections, risk factors for AIDS, ethnicity, gender, duration of symptoms before diagnosis, and race did not influence survival. PCNSL is a neoplasm with a very poor prognosis and short survival even with CNS radiation therapy. Also for pituitary lymphomas, which seem to have a better prognosis than PCNSL

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in general, AIDS seems to be a negative prognostic factor. From the review of all the available reports of pituitary lymphomas it seems that the lesions that certainly or possibly derive from preexisting pituitary adenomas are among those with a better prognosis. Whether the apparently better prognosis of those pituitary lymphomas is due to the intrinsic characteristics of the lesions or to a better response to treatment it remains to be established.

Conclusions

Primary pituitary lymphomas are an emerging clinical entity with an increasing number of well described cases in the last decade (3, 11–20, 22), as well as reported in a large series of pituitary masses (2). This report is, to our knowledge, the first attempt to put together all the available information on this subtype of cerebral lymphoma, the main peculiarities of which are pathogenesis, clinical presentation, and even prognosis. The data reported so far suggest that pituitary lymphomas are not a unique clinical entity but that they may represent the final presentation of different processes with either hypophyseal or extra hypophyseal origin. We think that the most interesting lines of research in this field will be the understanding of the fine pathogenetic mechanisms that lead to this disease and consequently the reason of the apparently better prognosis with respect to cerebral lymphomas in general. Finally, further information from additional cases of primary pituitary lymphomas need to be collected to validate the data obtained so far and the interpretations given by us before they can be translated into the clinical practice.

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References

1. **Gsponer J, De Tribolet N, Déruaz JP, et al.** 1999 Diagnosis, treatment, and outcome of pituitary tumors and other abnormal intrasellar masses. Retrospective analysis of 353 patients. Medicine 78:236–269
2. **Freda PU, Post KD** 1999 Differential diagnosis of sellar masses. Endocrinol Metab Clin North Am 28:81–117
3. **Landman RE, Wardlaw SL, Connell RJ, Khandji AG, Bruce JN, Freda PU** 2001 Pituitary lymphoma presenting as fever of unknown origin. J Clin Endocrinol Metab 86:1470–1476
4. **Flowers A** 2000 Brain tumors in the older person. Cancer Causes Control 7:523–538
5. **Clayton RN** 1999 Sporadic pituitary tumours: from epidemiology to use of database. Baillieres Clin Endocrinol Metab 13:451–460
6. **Eby NL, Grufferman S, Flannelly CM, Schold Jr SC, Vogel FS, Burger PC** 1988 Increasing incidence of primary brain lymphoma in the US. Cancer 62:2461–2465
7. **Fine HA, Mayer RJ** 1993 Primary central nervous system lymphoma. Ann Intern Med 119:1093–1104
8. **Snider WD, Simpson DM, Aronyk KE, Nielsen SL** 1983 Primary lymphoma of the central nervous system associated with acquired immune-deficiency syndrome (Letter). N Engl J Med 308:45
9. **Buchmann E, Schwesinger G** 1979 The hypophysis and haemoblastoses. Zentralbl Neurochir 40:35–42
10. **Onda K, Wakabayashi K, Tanaka R, Takahashi H** 1999 Intracranial malignant lymphomas: clinicopathological study of 26 autopsy cases. Brain Tumor Pathol 16:29–35
11. **Gottfredsson M, Oury TM, Bernstein C, Carpenter C, Bartlett JA** 1996 Lymphoma of the pituitary gland: an unusual presentation of central nervous system lymphoma in AIDS. Am J Med 5:563–564
12. **Sakakibara Y, Matsuzawa M, Taguchi Y, et al.** 1998 A case of sellar T cell type malignant lymphoma. No Shinkei Geka 26:53–58
13. **Scully RE, Mark EJ, McNeely WF, McNeely BU** 1994 Case records of the Massachusetts general hospital. N Engl J Med 331:861–868
14. **Singh VP, Mahapatra AK, Dinde AK** 1993 Sellar-suprasellar primary malignant lymphoma: case report. Indian J Cancer 30:88–91
15. **Snaw JAM, Strachan FM, Sawers HA, Revan JS** 1997 Non-Hodgkin lymphoma with panhypopituitarism, hyperprolactinemia and sixth nerve palsy. J R Soc Med 90:274–275
16. **Au WY, Kwong YL, Shek TWH, Leung G, Ooi C** 2000 Diffuse large-cell-B lymphoma in a pituitary adenoma: an unusual cause pituitary apoplexy. Am J Hematol 63:231–232
17. **Mathiasen RA, Jarrahy R, Cha ST, et al.** 2000 Pituitary lymphoma: a case report and literature review. Pituitary 4:283–287
18. **Li JY, Chow CC, Yeung VTF, Ko GTC, Cockram CS** 1998 Adrenal and hypophyseal Non-Hodgkin's lymphoma presenting with panhypopituitarism. Int J Clin Pract 52:513–514
19. **Kuhn D, Buchfelder M, Brabletz T, Paulus W** 1999 Intrasellar malignant lymphoma developing within pituitary adenoma. Acta Neuropathol 97:311–316
20. **Spina ML, Doga M, Brighenti G, et al.** Primary lymphoma of the pituitary presenting as pituitary adenoma with hypopituitarism: a novel clinical entity. Proceedings of the International Symposium on "Neuroendocrine-Oncology: Biological and Clinical Aspects, Turin, Italy, 2000; p 76
21. **Rosenberg SA, Diamond HD, Jaslowitz B, Craver LF** 1961 Lymphosarcoma. A review of 1269 cases. Medicine 40:31–84
22. **Singh S, Cherian RS, George B, Nair S, Srivastava A** 2000 Unusual extra-axial central nervous system involvement of non-Hodgkin's lymphoma: magnetic resonance imaging. Australas Radiol 44:112–114
23. **Ramsahoye BH, Griffiths DFR, Whittaker JA** 1996 Angiocentric T-cell lymphoma associated with diabetes insipidus. Eur J Haematol 56:100–103
24. **Ashigbi MY, Venkatraj U, Agarwal V, Bello J, Wiernik PH** 1997 Intracranial Hodgkin's disease in two patients with familial Hodgkin's disease. Med Pediatr Oncol 28:255–258
25. **Shanks JH, Harris M, Howat AJ, Freemont AJ** 1997 Angiotropic lymphoma with endocrine involvement. Histopathology 31:161–166
26. **Jonkhoff AR, Huijgens PC, Schreuder WO, Teule GJJ, Heimans JJ** 1993 Hypophyseal non-Hodgkin's lymphoma presenting with clinical panhypopituitarism successfully treated with chemotherapy. J Neurooncol 17:155–158
27. **Breidert M, Schimmelpfenning C, Kittner T, Helwig A, Ehninger G** 1999 Diabetes insipidus in a patients with a highly malignant B-cell lymphoma and stomatitis. Exp Clin Endocrinol Diabetes 107:54–58
28. **Matsuda M, Hattori T, Tabata K, Seki S** 1999 A case of non-Hodgkin's lymphoma in the central nervous system, developing during treatment of galactorrhea amenorrhea syndrome. Rinsho Shinkeigaku 39:1160–1163
29. **Bunick EM, Hirsh LF, Rose LI** 1978 Panhypopituitarism resulting from Hodgkin's disease of the nasopharynx. Cancer 41:1134–1136
30. **Shibata M, Shimoda M, Sato O** 1992 A case of bilateral panophthalmoplegia caused by paranasal malignant lymphoma extending into the skull base. No Shinkei Geka 20:717–721
31. **Merlo EM, Maiolo A, Brocchieri A, Tua A, Grignani G** 1999 Hypophyseal non-Hodgkin's lymphoma presenting with diabetes insipidus: a case report. J Neurooncol 42:69–72
32. **Groves FD, Linet MS, Travis LB, Devesi SS** 2000 Cancer surveillance series: non-Hodgkin's lymphoma incidence by histologic subtype in the United States from 1978 through 1995. J Natl Cancer Inst 92:1240–1251
33. **Pels H, Deckert-Schluter M, Glasmacher A, et al.** 2000 Primary central nervous system lymphoma: a clinicopathological study of 28 cases. Hematol Oncol 18:21–32
34. **Thodou E, Asa SL, Kontogeorgos G, Kovacs K, Horvath E, Ezzat S** 1995 Clinical case seminar: lymphocytic hypophysitis—clinicopathological findings. J Clin Endocrinol Metab 80:2302–2311
35. **Bevan JS, Othman S, Lazarus JH, Parkes AB, Hall R** 1992 Reversible adrenocorticotropin deficiency due to probable autoimmune hypophysitis in a woman with postpartum thyroiditis. J Clin Endocrinol Metab 74:548–552
36. **Escobar-Morreale H, Serrano-Gotarredona J, Varela C** 1994 Isolated adrenocorticotropic hormone deficiency due to probable lymphocytic hypophysitis in a man. J Endocrinol Invest 17:127–131
37. **Baumgartner JE** 1990 Primary central nervous system lymphomas: natural history and response to radiation therapy in 55 patients with acquired immunodeficiency syndrome. J Neurosurg 73:206–211

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38. **Aozasa K, Inoue A, Tajima K, Miyauchi A, Matsuzuka F, Kuma K** 1986 Malignant lymphomas of the thyroid gland. Cancer 58:100–104
39. **Popovic V, Damjanovic S, Micic D, et al.** 1998 Increased incidence of neoplasia in patients with pituitary adenomas. The Pituitary Study Group. Clin Endocrinol (Oxf) 49:441–445
40. **O'Neal KD, Schwarz LA, Yu-Lee LY** 1991 Prolactin receptor gene expression in lymphoid cells. Mol Cell Endocrinol 82:127–135
41. **Reni M, Ferreri AJM, Zoldan MC, Villa E** 1997 Primary brain lymphomas in patients with a prior or concomitant malignancy. J Neuorooncol 32:135–142
42. **Davenport RD, O'Donnell LR, Schnitzer B, McKeever PE** 1991 Non-Hodgkin's lymphoma of the brain after Hodgkin's disease. An immunohistochemical study. Cancer 67:440–443
43. **Miller DC, Knee R, Schoenfeld S, Wasserstrom WR, Karp G** 1989 Non-Hodgkin's lymphoma of the central nervous system after treatment of Hodgkin's disease. Am J Clin Pathol 91:481–485
44. **Alderson L, Fetell MR, Sisti M, Hocheberg F, Cohen M, Louis DN** 1996 Sentinel lesion of primary CNS lymphoma. J Neurol Neurosurg Psychiatry 60:102–105
45. **Paulus W, Jellinger K, Hallas C, Ott G, Müller-Hermelink HK** 1993 Human herpes virus-6 and Epstein-Barr virus genome in primary cerebral lymphomas. Neurology 43:1591–1593
46. **Aozasa K** 1990 Hashimoto's thyroiditis as a risk factor of thyroid lymphoma. Acta Pathol Jpn 40:459–468
47. **Matera L, Cutufia M, Geuna M, et al.** 1997 Prolactin is an autocrine growth factor for the Jurkat human T-leukemic cell line. J Neuroimmunol 79:12–21
48. **Yu-Lee LY** 1990 Prolactin stimulates transcription of growth-related genes in Nb2 T lymphoma cells. Mol Cell Endocrinol 68:21–28
49. **Giustina A, Veldhuis JD** 1998 Pathophysiology of the neuroregulation of growth hormone secretion in experimental animals and the human. Endocr Rev 19:717–797
50. **Fleming WH, Murphy PR, Murphy LJ, Hatton TW, Matusik RJ, Friesen HG** 1985 Human growth hormone induces and maintains c-myc gene expression in Nb2 lymphoma cells. Endocrinology 117:2547–2549
51. **Luthman M, Wallerman E, Roos P, Werner S** 1991 Growth hormone specific stimulation of mitosis by size-fractionated serum from patients with growth hormone insufficiency: a study on the rat lymphoma cell line, Nb2. Acta Endocrinol 125:113–121
52. **Melmed S, Braunstein GD** 1983 Human chorionic gonadotropin stimulates proliferation of Nb2 rat lymphoma cells. J Clin Endocrinol Metab 56:1068–1070
53. **Costa O, Bouthet C, Sauvage P, Michel JP, Deschaux P** 1990 Age-dependent LH and FSH effect on the proliferation of women's peripheral blood lymphocytes *in vitro*. Int J Immunopharmacol 12:821–829
54. **Hennessey JH, Jackson IMD** 1995 Clinical features and differential diagnosis of pituitary tumours with emphasis on acromegaly. Baillière's Clin Endocrinol Metab 9:271–314
55. **Giustina A, Romanelli G, Candrina R, Giustina G** 1989 Growth hormone deficiency in patients with idiopathic adrenocorticotropin deficiency resolves during glucocorticoid replacement. J Clin Endocrinol Metab 68:120–124
56. **Kanavaros P, Mikol J, Nemeth J, et al.** 1990 Stereotactic biopsy diagnosis of primary non-Hodgkin's lymphoma of the central nervous system. A histological and immunohistochemical study. Pathol Res Pract 186:459–466
57. **Smith WJ, Garson JA, Bourne SP, Kemshead JT, Coakham HB** 1988 Immunoglobulin gene rearrangement and antigenic profile confirm B cell origin of primary cerebral lymphoma and indicate a mature phenotype. J Clin Pathol 41:128–132
58. **Castagna A, Cinque P, d'Amico A, Messa C, Fazio F, Lazzarin A** 1997 Evaluation of contrast-enhancing brain lesions in AIDS patients by means of Epstein-Barr virus detection in cerebrospinal fluid and ^{201} thallium single photon emission tomography. AIDS 11:1522–1523
59. **Lorberboym M, Wallach F, Estok L, et al.** 1998 Thallium-201 retention in focal intracranial lesions for differential diagnosis of primary lymphoma and non-malignant lesions in AIDS patients. J Nucl Med 39:1366–1369
60. **DeAngelis LM** 1995 Current management of primary central nervous system lymphoma. Oncology 9:63–71
61. **Schultz C, Scott C, Sherman W, et al.** 1996 Preirradiation chemotherapy with cyclophosphamide, doxorubicin, vincristine and dexamethasone for primary CNS lymphomas: initial report of radiation therapy oncology group protocol 88–06. J Clin Oncol 14:556–564
62. **O'Neill BP, O'Fallon JR, Earle JD, Colgan JP, Brown LD, Krigel RL** 1995 Primary central nervous system non-Hodgkin's lymphoma: survival advantages with combined initial therapy? Int J Radiat Oncol Biol Phys 33:663–673
63. **Blay JY, Conroy T, Chevreau C, et al.** 1998 High-dose methotrexate for treatment of primary cerebral lymphomas: analysis of survival and late neurologic toxicity in a retrospective series. J Clin Oncol 16:864–870

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