

CLINICAL RESEARCH

Primary Non-Hodgkin Brain Lymphomas. A Retrospective Clinicopathological Study of 18 Patients

Beynin Birincil Non-Hodgkin Lenfomaları. Onsekiz Hastanın Retrospektif Klinikopatolojik İncelenmesi

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Abstract: Eighteen patients with primary non-Hodgkin brain lymphomas without a history of any acquired or congenital immunodeficiency syndrome or organ transplantation were reviewed retrospectively. Cases were selected from 2633 primary intracranial malignancies encountered between the years of 1987 and 1995. Eleven were male, seven were female with a mean age of 55 years (range 40-74; male predominance 1.57:1). All patients presented with neurological symptoms without any signs of extracranial lymphomatous disease. Radiological examination revealed mostly multiple lesions often located in the deep nuclei, corpus callosum and the intraventricular region. The diagnoses were made by stereotactic biopsy (7 cases), subtotal resection (6 cases), and surgical biopsy (5 cases). Histologically the most frequent type was centroblastic malignant lymphoma (50%), 72 percent of lymphomas being high-grade. Seventeen patients were treated with radiation therapy and corticosteroids. Six patients underwent subtotal resection, five received systemic chemotherapy. Three recurrences were observed, one of which was an extracranial metastasis to the clavicle and distal humerus. One year survival rate was 75% (median 21.5 months). Among 11 cases diagnosed by surgical biopsy or subtotal resection, there were four cases of leptomeningeal invasion which could be detected histologically, but were not detected by radiological means. This is clear evidence that these lesions may be more widespread than found radiologically.

Key Words: Brain neoplasms, clinical pathology, lymphoma

Özet: Edinsel veya doğumsal bağışıklık yetmezliği veya organ aktarımı öyküsü bulunmayan onsekiz birincil beyin lenfoması olgusu geriye dönük olarak incelendi. Olgular 1987-1995 yılları arasında saptanan 2633 birincil kafaiçi malignite arasından seçildi. Olguların onbiri erkek yedisi kadındı, ortalama yaş 55 olarak bulundu (yaş aralığı 40-74, erkek kadın oranı 1.57:1). Tüm olgular ekstrakraniyal lenf sistemi hastalığı olmaksızın nörolojik semptomlarla başvurdu. Radyolojik incelemede çoğunlukla derin çekirdekler, korpus kallozum ve ventrikül içinde çoklu lezyonlar saptandı. Tanı stereotaktik biyopsi (7 olgu), subtotal rezeksiyon (6 olgu) ve açık biyopsiyle (5 olgu) konuldu. Histolojik olarak en sık görülen tip sentroblastik malign lenfoma olarak bulundu (% 50): olguların % 72'si yüksek dereceliydi. Onyediy hasta radyoterapi ve kortikosteroidlerle tedavi edildi. Altı hastaya subtotal rezeksiyon yapıldı, beşi sistemik kemoterapi aldı. Üç nüks olgusu gözlemlendi; birinde klavikula ve distal humerusa ekstrakraniyal metastaz biçimindeydi. Bir yıllık sağkalım oranı % 75 olarak bulundu (ortalama 21.5 ay). Açık biyopsi veya subtotal rezeksiyonla tanı konulan 11 olgunun dördünde histolojik olarak gösterilen ancak radyolojik olarak saptanamayan leptomeningeal yayılım vardı. Bu durum, beyin lenfomalarının radyolojik verilere oranla daha yaygın olduklarının açık bir delilidir.

Anahtar sözcükler: Beyin tümörleri, klinik patoloji, lenfoma

INTRODUCTION

Primary brain lymphomas (PBL) account for less than 1% of all primary brain tumours and for 0.7%-1.5% of all non-Hodgkin lymphomas (NHL).

Their incidence has increased threefold when compared with that of the 1960s (19).

A considerable increase in PBL prevalence is found in patients with acquired or congenital

immunodeficiency, in those who receive significantly long and heavy immunosuppressive treatment, and in recipients of kidney transplantation (3, 4, 6, 7, 8, 9, 14, 17, 21, 30, 34, 35). Moreover, attention is directed to the role of immunosuppression caused by chronic disease and recently to the role of Epstein Barr virus infections (4, 10, 19, 20, 25, 40).

Most of the PBL are of B-lymphocyte, few are of T-lymphocyte in origin (1,2, 5, 12, 16, 19, 22, 28, 29, 35, 41). A widely accepted view is that a deficiency in the suppressor T-lymphocyte system leads to an excessive proliferation in B-lymphocytes, thus causing neoplasms of B cell clones (26).

However, it is a recent significant observation that the incidence of PBL is also on the increase in immunologically normal subjects (11).

In this retrospective study, a review of eighteen patients with PBL was made with a comparison of reported series. These cases did not have a history of acquired or congenital immunodeficiency, nor were they recipients of organ transplantation.

MATERIALS AND METHODS

Among 2633 primary intracranial malignancies diagnosed in the Neuropathology Department of İstanbul Faculty of Medicine from 1987 to 1995, there were 29 cases of central nervous system lymphomas. We selected 18 cases as primary brain lymphomas according to the following criteria: 1) patients with neurological complaints, 2) radiologically confirmed intracranial lesion(s), 3) absence of extracranial or systemic lymphomas, 4) histopathological diagnosis confirmed by immunohistochemical methods. Epidural lymphomas were not included in the study.

Data concerning age, sex, symptoms, interval between onset of symptoms and diagnosis, past and present patient history and clinical findings were obtained from patient records. We carried out necessary inquiries into the patients' status through mail and telephone.

According to computerized tomography (CT) and magnetic resonance (MR) findings, the lesions were classified as unifocal lesions (in a single lobe or in a single anatomical location confined to one hemisphere), multiple lesions (in more than one lobes or anatomical locations confined to one hemisphere), and multicentric lesions (lesions involving both hemispheres).

Cerebrospinal fluid (CSF) investigations were carried out at the beginning of the treatment protocols.

Material for histopathological evaluation was obtained through subtotal resection, surgical biopsy, and image-guided stereotactic biopsy (Leksell stereotactic system, Elekta AB, Stockholm, Sweden) in six, five, and seven cases, respectively. Immediate intraoperative diagnoses during stereotactic biopsy were made through smears stained with hematoxylin eosin (HE). Materials obtained for histopathologic examination were first routinely fixed in 10% formalin, then 5µm sections prepared from paraffin embedded tissue samples were stained with HE, Giemsa, periodic acid-Schiff (PAS) with and without digestion, and Gomori reticulum. In all cases, leucocyte common antigen (LCA, monoclonal) and epithelial membrane antigen (EMA, monoclonal) were examined immunohistochemically (Strept A-B, Universal Kit, EURO/OPC, Llanberis, UK). In some cases monoclonal antibodies to immunoglobulin light chains kappa and lambda were applied. Materials from 15 cases were re-examined through the light microscope, then classified according to the "Updated Kiel Classification (1991)" (23). In the remaining three cases evaluation was based on data from histopathological reports.

All cases were assessed with respect to perivascular small lymphatic infiltrations in the tumour stroma, necrosis, invasion patterns, and presence of leptomeningeal invasion. However, their associated prognostic relevance as a parameter was not statistically analysed due to the small size of the series.

RESULTS

Eighteen PBL cases in our series accounted for 0.68% of all primary intracranial malignancies (2633) diagnosed in our department from 1987 to 1995, the annual incidence being 2.25 cases per year. Of these eighteen cases, 11 were male and seven female. The ratio of male to female was 1.57:1. The average age was 55.08 years (range 40-74). The average age in males and females were 55.90 and 53.71 years, respectively.

Clinical Findings

All patients sought treatment for their neurological complaints. Initial examinations revealed neurological deficits (16 patients; 88.88%), headache, vomiting, and nausea (13 patients; 72%),

higher cortical function deficiencies (12 patients; 66%), seizure disorders (2 patients; 11.11%), and papilledema (5 patients; 27.77%) (Table I). The interval between symptom onset and diagnosis varied from 15 days to 1.5 years (average 3.5 months, median 1.5 months).

Table I: Clinical findings of 18 cases found in the initial examination

| Findings | Number of patients | % |
|------------------------------------|--------------------|------|
| Headache | 13 | 72.0 |
| Impaired consciousness | 9 | 50.0 |
| Memory disorder | 9 | 50.0 |
| Progressive hemiparesis/hemiplegia | 8 | 44.4 |
| Disturbance in balance | 6 | 33.3 |
| Vomiting and nausea | 5 | 27.7 |
| Gait disturbance | 5 | 27.7 |
| Papilledema | 5 | 27.7 |
| Personality change | 4 | 22.2 |
| Urinary incontinence | 4 | 22.2 |
| Foot drop | 3 | 16.6 |
| Dizziness | 2 | 11.1 |
| Cerebellar signs | 2 | 11.1 |
| Weight loss | 2 | 11.1 |
| Seizures | 2 | 11.1 |
| Insomnia | 1 | 5.5 |
| Parosmia | 1 | 5.5 |
| Visual symptoms | 1 | 5.5 |
| Facial nerve palsy | 1 | 5.5 |
| Quadriplegia | 1 | 5.5 |
| Hemihypoalgesia | 1 | 5.5 |

Data on past medical histories were available in 15 cases. We did not encounter a history of organ transplantation, nor any congenital or acquired immunodeficiency syndromes. Two patients had a history of resolved meningitis; a 40-year-old woman who had meningitis during infancy (3 months), and a 69-year-old man with meningitis preceded by rhinorrhea as a complication of a paranasal sinus operation 15 years ago. The latter had long-term treatment, his symptoms subsided except for headaches and he developed PBL 15 years later. Another two patients presented with a history of erythema-squamous skin disorders, one of whom was a 47-year-old man. He had suffered from wide-spread, eczematoid, and pruritic lesions for the past 10 years, which disseminated in the previous year resulting in erythroderma. Peripheral blood smears, bone marrow biopsy and the repeated cutaneous biopsies did not yield atypical cells, nor did clinical and radiological examinations reveal lymphadenomegaly or

hepatosplenomegaly. He then had gait disturbances a year after erythroderma had been recognized, after which a diagnosis of multicentric brain lymphoma was made. The other was a 62-year-old man who had a history of eczematoid skin disorders 42 years ago. Other past histories were peripheral facial nerve palsy (2 cases), essential hypertension (2 cases), eye and chest injuries (2 cases), angina pectoris, nephrolithiasis, diabetes mellitus, degenerative joint disease, and chronic bronchitis.

Radiological Findings

Fourteen of the cases were supratentorial (77.77%), two were infratentorial (11.11%) and two supra- and infratentorial (11.11%). The presenting lesions were classified as unifocal (7 cases, 38.89%), multiple (5 cases, 27.78%), and multicentric (6 cases, 33.33%). Most commonly involved regions were deep nuclei, corpus callosum, and the periventricular and intraventricular regions (Figure 1). The frequency of involvement for parietal, frontal, temporal, occipital, and insular lobes were 7 (38.38%), 4 (22.22%), 4 (22.22%), 3 (16.16%), and 1 case(s)(5.55%), respectively. The midbrain was involved in two and pons in only one case.

CT appearances of the lesions were hyperdense (40%; n=4), isodense (20%), and hypodense (40%). Computerized tomography scans with contrast enhancement helped to identify hyperdense lesions in 14 cases (87%).

Pathological Findings

Among the eighteen diffuse type primary brain lymphomas, nine were centroblastic (50%) (six monomorphic, three multilobated), four were immunoblastic (22.22%), three were centroblastic-centrocytic (16.16%), and one was lymphocytic lymphoma (5.55%). Histological evidence was not sufficient for diagnosis in one case. Thirteen of the cases were high-grade lymphomas (72.22%).

In all cases we observed infiltration of neoplastic lymphocytic cells into the white matter. Invasion of the white matter was considerably destructive in centroblastic and immunoblastic types, moderate in centroblastic/centrocytic types (Figure 2), and minimal in lymphocytic type. Perivascular pattern was observed in eight cases giving the characteristic "onion-skin" appearance of the reticulin network in Gomori's reticulin stain (Figure 3). Necrosis was seen in 50% of

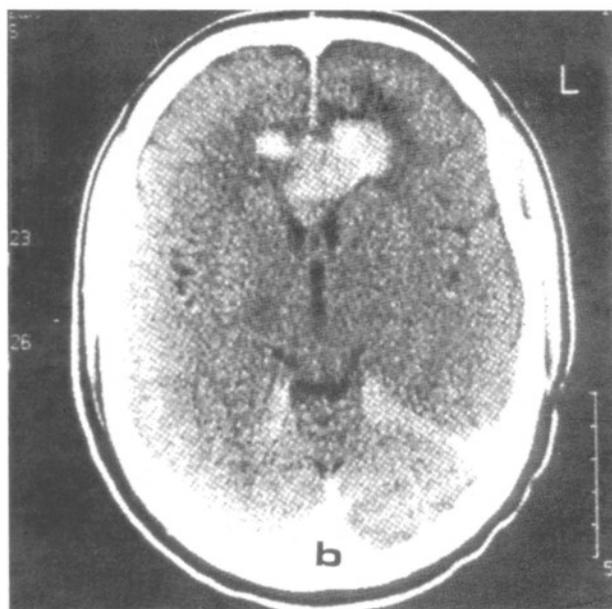
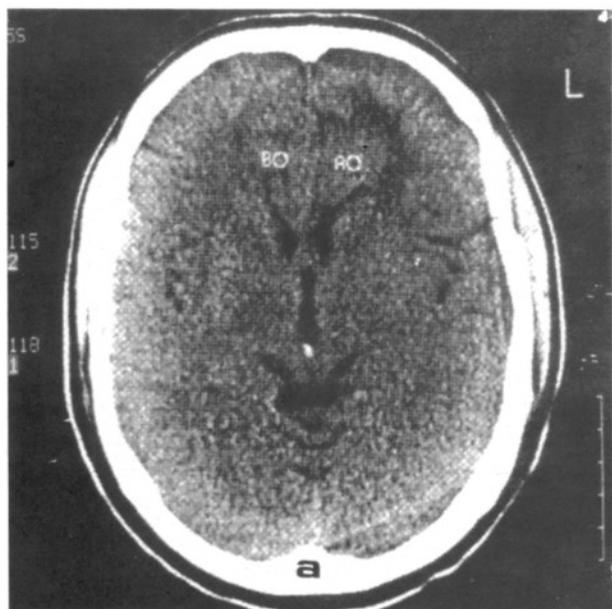


Figure 1: Axial CT scans demonstrate lesions anterior to the both frontal horns with surrounding edema. Isodense non-contrast (a), homogeneously hyperdense post-contrast (b).

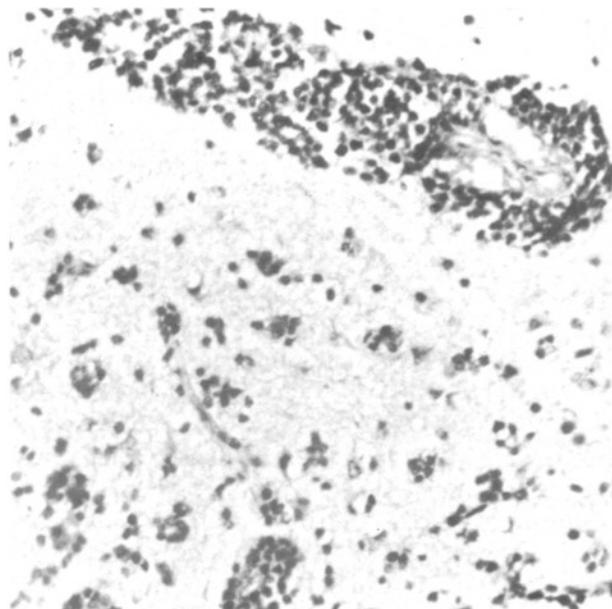


Figure 2: Centroblastic-centrocytic lymphoma. Expansion of the Virchow Robin's spaces by lymphoma cells and infiltration of the white matter. (H&E,X200)

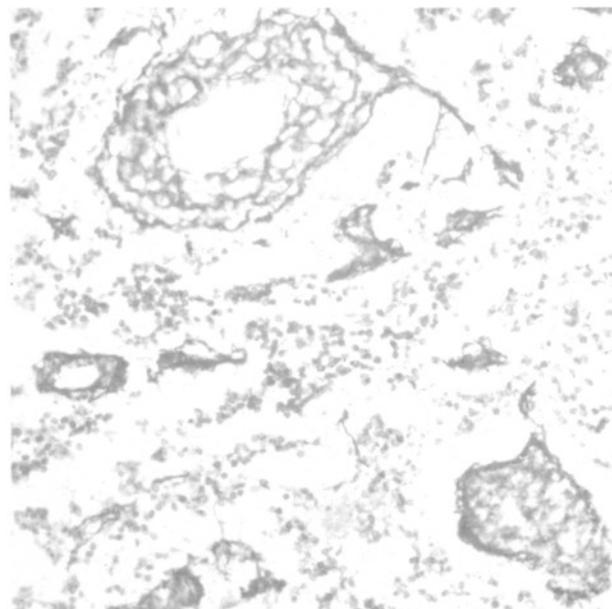


Figure 3: Characteristic "onion-skin" appearance of the reticulin network.(Gomori's reticulin stain,X200)

the eighteen cases, especially in high-grade lymphomas. Tingible body macrophages were typically universal in centroblastic lymphomas both in histological sections and in smears. Perivascular reactive small lymphocytic infiltrations were detected in eight cases, being mild to moderate in general. Owing to the previous administration of

corticosteroids there were reactive astrogliosis and microcystic cavitations in the white matter, often in the periphery of tumoral regions (Figure 4). We detected leptomenigeal invasion in four cases (three were minimal, one was mild) (36%), in which surgical biopsy and subtotal resection were performed (Figure 5). It is remarkable that, in these cases, we failed to

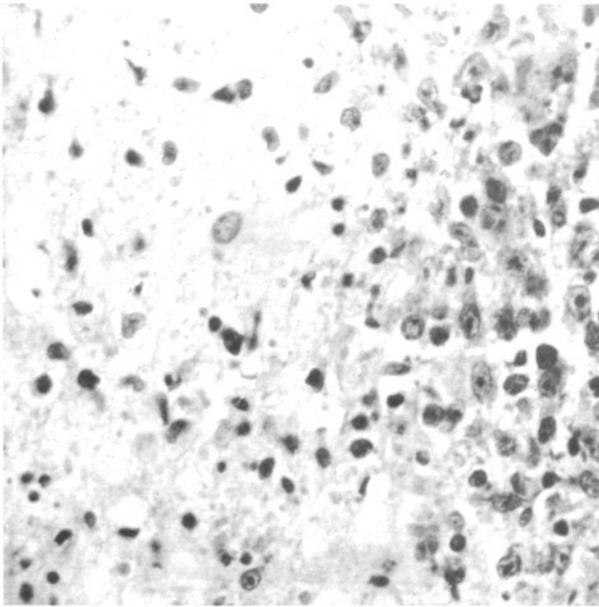


Figure 4: Immunoblastic lymphoma. Reactive astrogliosis and microcystic cavitations. (H&E,X400)

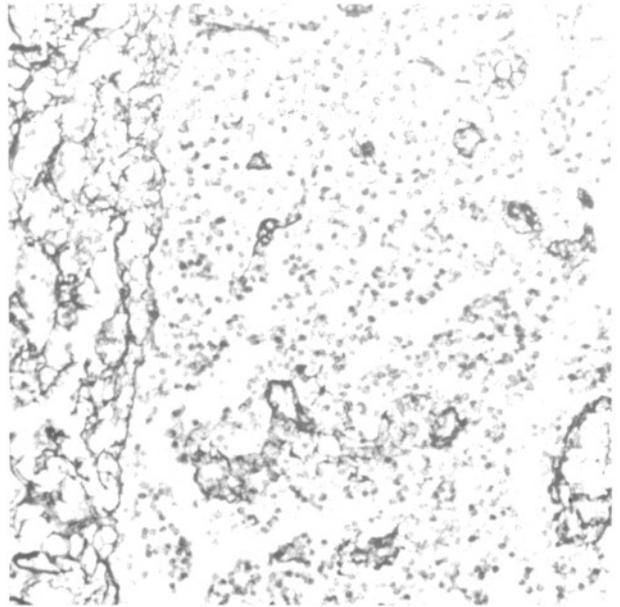


Figure 5: Leptomeningeal invasion. (Gomori's reticulin stain,X200)



Figure 6: Branching vessels surrounded by neoplastic lymphocytes invading parenchyma. Specimen obtained from the immediate stereotactic procedure. (H&E,X200)

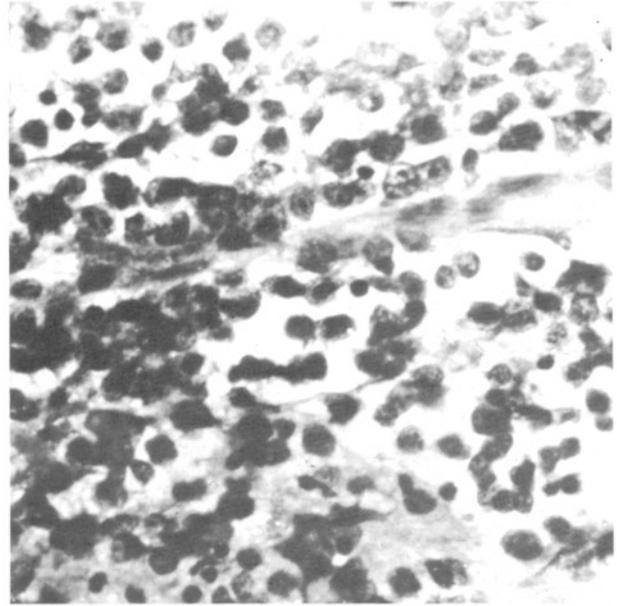


Figure 7: Neoplastic lymphocytes with prominent nucleoli surrounding small blood vessels without endothelial proliferation. Specimen obtained from the immediate stereotactic procedure. (H&E,X400)

encounter any radiological evidence of leptomeningeal involvement.

In H&E stained smears (7 cases) prepared during the stereotactic biopsy, characteristic findings were infiltration by the noncohesive round cells with vesicular nuclei and prominent nucleoli, often

obliterating neuropil and reactive astrocytes, tingible body macrophages, plasmocytes, and small lymphocytes. In addition, in thick smear preparations enclosure of the thin-walled branching vessels by neoplastic lymphocytes was seen with the absence of endothelial proliferation within the vessels (Figures 6, 7).

Cerebrospinal fluid (CSF) investigations did not yield any atypical cells.

Treatment and follow-up

Treatment procedures employed in this series were subtotal resection (6 cases), surgical biopsy (5 cases), radiotherapy (RT) in combination with corticosteroids (17 cases), and systemic chemotherapy (BACOP: bleomycin, doxorubicin, cyclophosphamide, vincristine, prednisone) (5 cases). Radiotherapy was applied for 3 to 4 weeks in equivalent doses with a total dose ranging from 3000 cGy to 9100 cGy depending upon the patients' status (total cranium irradiation 3000-5000 cGy+spinal 2000-3600 cGy+ boost 900-1000 cGy). Two patients received spinal irradiation. Of the eighteen patients in the series, only nine (50%) could be followed up, the upper limit being 42 months. Three of these patients developed recurrences after 7 months, 8 months, and 28 months of treatment, respectively, and were given 1500 cGy of radiotherapy. The first patient developed extracranial metastasis in the right clavicle and humerus one month after the recurrence. Nine patients that could be followed up had a median survival of 21.5 months; one-, two-, and three-year survival rates being 75%, 37.5%, and 12.5 % respectively.

DISCUSSION

Eighteen primary brain lymphomas in this series accounted for 0.68% of 2633 cases diagnosed as primary intracranial neoplasms between 1987 and 1995. Primary brain lymphomas are reported to have an incidence rate of 0.7% to 1.6%, which rises in immunologically normal subjects as well as in patients with AIDS (19, 34, 35). The yearly incidence in our series varies between 0.25% and 1.32%.

Compared with the literature data on ages ranging (6, 17) between 16 days and 90 years, the age range of our cases was 40-74 years. The average age of patients was 55 years. This is consistent with the average ages of 54 and 55 reported by Braus et al. for a PBL group of 54 sporadic patients and by Feiden et al. for 54 patients most of whom were non-AIDS cases (5, 12). Similarly, our male to female ratio of 1.57:1 is very near to the average ratio of 1.5:1 which ranges in literature from 3:1 to 3:4 (9, 15, 18, 31, 34).

Although such risk factors as AIDS, organ transplantation, and congenital immunodeficiency

syndromes are known, etiological factors in sporadic cases of PBL are still not clear. The general belief is that chronic inflammatory stimulation with or without autoimmune nature may be a pathogenetic factor (2). In our series two patients had a history of meningitis dating back to 40 and 15 years. In one of the patients with erythematous-squamous skin disorders, the development of lesions suggested Sezary syndrome though we were not able to detect any evidence favouring the diagnosis. Although reported in other series we did not encounter a history of uveitis or iritis in our patients (2, 24, 33, 36).

In patients with PBL the interval between the onset of symptoms and diagnosis varies from one month to 24 months, with an average of two months (2, 5, 17, 19). This interval in our series varied from 15 days to 18 months with an average of 3.5 months. It is probable that administration of corticosteroids may have delayed diagnosis in some cases.

Focal neurological deficits were found in 88.88%. The most commonly encountered symptom was headache (72.22%). Papilledema was encountered in 27.77% (5 cases) compared to 44% reported by Hardwidge et al. (16) Higher cortical function disorder was 66.66%, which ranged in literature between 30% and 70% (5, 16, 18). Multiplicity or multiple localization have been reported up to 86% whereas we had 61.11% (5, 9, 16, 37). The supra-infra tentorial localization of the lesions varies between 1:1 and 9.5:1 (17): this ratio was 7:1 in this series.

In our study high grade PBLs accounted for 72.22% compared to a range of 26-88% from reported sporadic or mainly sporadic PBL series (2, 5). Centroblastic lymphomas constituted the widest group (50%: n=9) in our series, which is consistent with many reported series (1, 12, 16, 17, 19, 35, 39). It is of interest that three of the nine cases were multilobated centroblastic lymphomas. This type was first reported in brain lymphomas by Kanavaros et al. in a series of 29 cases one of which was multilobated centroblastic lymphoma and another two were rich in multilobated centroblastic cells (22).

Although radiological findings did not reveal leptomenigeal invasion, we detected this phenomenon in four cases (4/11, 36%) in which histological material was obtained by incisional biopsy and resection. Among these, three cases showed minimal invasion and one case showed

marked invasion. On the other hand, relatively high rates of leptomeningeal involvement in autopsy series have been reported (1, 17, 33, 38). This study shows that lesions in PBL may be more widely distributed with leptomeningeal invasion at the initial clinical presentation.

In our cases cytologic examination of the CSF failed to give any diagnostic evidence. We noted that the diagnostic accuracy of cytologic examination depended on the stage of the disease. Where there is considerable leptomeningeal invasion, cytologic examination may provide precise evidence. It has been reported that CSF examinations yielded positivity of up to 70% in secondary (15, 17, 27) and 40% in primary (17, 33) central nervous system lymphomas. From this standpoint, our experience with CSF involvement is that CSF examination yields secondary infiltration rather than primary tumors.

We based our diagnosis on the following criteria; round cells with vesicular nucleus and prominent nucleoli surrounding thin-walled vascular canals without endothelial proliferation, tingibile body macrophages, plasma cells, lymphocytes, and individual cell necrosis (12, 22, 32, 37). These findings were obtained from immediate intraoperative smears during the stereotactic procedure, which were defined by many authors as a very helpful method in providing ease and access to a detailed cytologic examination as well as to additional histological evidence.

We noted that most of our patients had received corticosteroids at the time of referral to our centre. Though corticosteroids were discontinued before the stereotactic procedure the cytolytic action of corticosteroids especially in high grade lymphomas was still obvious. The replenishment of neoplastic lymphoid cells has been reported to occur within five days (13).

In PBL extracerebral metastasis is not unusual; involvement of the axilla, lungs, eyes, testicle, and retroperitoneum have been reported (1, 17). We encountered extracerebral metastasis in the right clavicle and humerus in only one case 8 months after treatment.

If left untreated PBL may cause death within three weeks. However, radiation therapy or a combination of radiotherapy and chemotherapy may give a considerably favourable outcome (6, 18, 40). Irradiation of over 5000 cGy is reported to have better

results (31). In our series the patients were given whole brain irradiation of 3000 cGy to 6000 cGy in 3 to 4 weeks. We did not encounter any sign of necrosis. A three years survival has been achieved in PBL as a result of combined therapy (31, 39, 40). Our survival rates for 1, 2, and 3 years were 75%, 37.5%, and 12.5%, respectively. The longest period of survival was in a lymphocytic lymphoma case (39 months), the shortest being in a centroblastic multilobated lymphoma case (3.5 months).

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