Clinical Features of Primary Central Nervous System Lymphoma

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Abstract **Objective** The authors present a retrospective analysis of 35 surgical patients with primary central nervous system lymphoma (PCNSL) treated at West China Hospital, Sichuan University between January 1997 and October 2002. **Methods** Our analysis of patients with PCNSL documents the clinic features, neuroimaging findings, and histological characteristics in PCNSL. The histological diagnosis was obtained after surgical resection in 32 patients, with the remainder undergoing biopsy sampling only, for which preoperative computerized tomography and magnetic resonance studies were available. **Results** The cohort included 19 men and 16 women whose median age at diagnosis was 52 years old (range 26 to 72 years old). The duration of symptoms was less than 4 weeks in 20(57%) and 8 weeks in 27 (77%) of the patients. Symptom groups included increased intracranial pressure, arm and leg weakness or palsy, neuropsychiatric symptoms, and focal neurological deficit. There are no pathognomonic presenting symptoms or signs in PCNSL. No patient had antecedent of human immunodeficiency virus positively or acquired immunodeficiency syndrome. A total of 52 tumors were seen in 35 patients: the most common sites were in frontal lobes(14 patients), temporoparietal (7 patients), and basal ganglia (5 patients); multiple lesions were reported in 16 patients. In 29 (83%) of these patients, the majority of the tumors were in a supratentorial location. There were 34 B-cell lymphomas (97%) and only one T-cell lymphoma (2.85%). Of the 28 large cell (82%) and the six immunoblastic lymphomas (18%) that were successfully phenotyped, all were of B-cell lineage. **Conclusion** The evaluations of pathologic features in PCNSL are useful and practical for diagnostic purposes, but cannot delineate distinctive morphologic subtypes. Characteristic imaging features of PCNSL are isodense hyperdensity in non-enhanced CT, significant contrast uptake in CT and MR, absence of calcification, hemorrhage, or cystic change, localization in the periventricular region or in the corpus callosum, and moderate or mild perifocal edema. Acute onset presents with poor prognosis. The optimal therapeutic strategy remains to be determined.

Key Words primary central nervous system lymphoma; brain neoplasm; non-Hodgkin´s lymphoma

Primary central nervous system lymphoma (PCNSL) is a type of densely cellular, aggressive non-Hodgkin´s (NHL) lymphoma. It originates in the brain, leptomeninges, spinal cord, or eyes and in most cases does not spread outside the nervous system.[1] It is a previously rare tumor of the central nervous system (CNS), accounting for less than 2% of all primary brain tumors and having an estimated annual incidence of 1.83 per 1,000,000 people. Over the past decade, the incidence of PCNSL has increased in both immunosuppressed and immunocompetent patient populations beyond that which can be accounted for improved diagnostic capabilities, or the changes in tumor classification. Furthermore, the increase in PCNSL exceeds the increasing frequency of systemic NHL.[1,2,3]

Although PCNSL develops in the CNS and in most cases does not spread elsewhere, its pathological findings are similar, if not identical, to those of systemic non-Hodgkin´s lymphoma.[3] However, the results of multiple radiation, chemotherapy, and combined treatment trials have shown that the fate of patients with PCNSL is very different from that of patients with lymphoma occurring at other extranodal sites.[3] Thus, the treatment of this tumor continues to be a formidable challenge and will need to develop a clear understanding of this disease and more effective therapies. To that end, in this retrospective study we examined the clinical and neuroimaging findings and the histological features of 35 primary CNS lymphomas at West China Hospital, Sichuan University between January 1997 and October 2002.

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MATERIAL AND METHODS

Patient Characteristics

35 patients with histologically proven primary

CNS lymphoma at West China Hospital, Sichuan University from January 1997 to October 2002 were reviewed retrospectively. Tumor tissues were obtained by craniotomy with tumor resection, open brain biopsy or stereotactic biopsy. Testing (a full clinical examination, complete blood count with white cell differentiation and platelet count, liver function test, bone marrow aspirate and trephine, chest x-ray, chest and abdominal CT scans, abdominal ultrasonic) was performed to rule out systemic lymphoma for all cases identified as PCNSL. These tests varied somewhat according to the time of diagnosis and the standard practice of attending neurosurgeon. Nineteen patients were male and 16 were female, The ages of patients ranged from 26 to 72 years old (mean 52.31). No patient in this group infect with the human immunodeficiency virus (HIV) or of AIDS.

Neuroimaging and Radiological Reports

In all patients, the number and the locations of lesions were determined from evaluations of computed tomography(CT) brain scan and magnetic resonance (MR) imaging studies and on the basis of radiology reports in patient records. Preoperative CT scans were available for 29 patients and preoperative MR images for 11 patients. The lesions were studied for: number, location, size and shape, mass effect, perifocal edema, and appearance before and after injection of contrast agent.

Histological Studies

A pathologist and a neuropathologist to verify the diagnosis of lymphoms and to classify the lymphomas according to the criteria of the World Health Organization Classification of Tumors reexamined hematoxylin and eosin-stained slides from all histological specimens.[4] New sections were obtained from formol-fixed specimens that embedded in paraffin.

RESULTS

Patient Characteristics

The mean time between appearance of the first symptom and admission was 32 days in all the patients. There are no pathognomonic symptoms or signs in PCNSL. We found an equal percentage of focal neurologoical deficits and more general signs as increased intracranial pressure or neuropsychiatric symptoms. Symptoms at presentation included signs of increased intracranial pressure, arm and leg weakness or palsy, neuropsychiatric symptoms, and focal neurological deficit. There was absent of seizures upset in this group of patients. No single physical finding was characteristic of this disease. Surgical resection was performed in 32 of the cases, with the remainder undergoing biopsy only. The cut surface is yellow-white and granular, and the tumor soft. PCNSL appears as a solitary, bulky, and irregular mass merging into the surrounding edematous brain tissue. There may be areas of focal necrosis or hemorrhage but cystic change is rare.

Neuroimaging Studies

A total of 52 tumors were reorded in 35 patients. Multifocal lesions were reported in 45.71% (16 patients) of PCNSL. A bilateral mirror pattern was found in 12 patients (34%). The location of the 52 lesions encountered included frontal lobe (23), temporoparietal lobe (13), basal ganglia (5), corpus callosum (3), cerebellum (5), occipital lobe (2), and spinal cord (1). In 29 (83%) of these patients, the majority of the tumors were in a supratentorial location. Among the 35 patients analyzed, the most frequent locations of PCNSL were the cerebral hemispheres: frontal (14 patients), temporoparietal (7 patients), basal ganglia (5 patients) and followed by corpus callosum (3 patients). One patient presented with a primary lymphoma of the cervical spinal cord.

On analysis of CT and MR studies, we discovered that lesion borders were sharply circumscribed in 83% of cases and ill-fined in 17%, almost all lesions were either isodense or hyperdense to gray matter on noncontrast CT scans and that varying degrees of peritumoral edema was present in 85% of lesions. Among the 52 lesions, 88% of whose tumor sizes were larger than 1 cm, the maximum dimension ranged from 8 to 85 mm. Mass effect were present in almost all patients. Cranial CT images in PCNSL usually reveal solitary or multiple paracentral, isodense or hyperdense mass lesions that enhance homogeneously with contrast medium. No patient´s scan displayed calcification, hemorrhage, or cystic change.

Histological Studies

Microscopic examination usually demonstrates tumor infiltration well beyond the microscopic margin. The tumor invades along perivascular spaces

with perivasular cuffing and vessel wall infiltration. This cuffing is most prominent at the tumor margin and for a distance beyond. There may be an associated astrocytic reaction accompanied by the presence of tingible body macrophage. Most often, the neoplastic cells produced destructive parenchymal masses with variable angiocentricity and expansion of Virchow–Robins spaces. In some cases, tumor was only in a perivascula distribution. Tumor cells contain few organelles, abundant free ribosomes, large nucleoli, and scant cytoplasm. Tumor necrosis was not present.

There were 34 B–cell lymphomas (97%) and only one T–cell lymphoma (2.85%). of the 28 large cell (82%) and 6 immunoblastic lymphomas (18%) that were successfully phenotyped were of B–cell lineage. The neoplastic cells are large with round nuclei, dispersed chromatin, multiple nuclcoli apposed to nuclear membranes, and a modest amount of cytoplasm in large B–cell phenotype. In immunoblastic phenotype, the neoplastic cells are large with round to irregular nuclear outlines, marginated heterochromatin, and single central prominent nucleoli. There is massive infiltration of the brain and expansion of the Virchow–Robins spaces by a monomorphous population of small lymphocytes with markedly irregular hyperchromatic nuclei, and sparse cytoplasm.

DISCUSSION

Primary CNS lymphoma (PCNSL) is an extranodal non–Hodgkin´s lymphoma (NHL) confined to the CNS in the absence of systemic malignancy, which has been known by many other names, including reticulum cell sarcoma, diffuse histiocytic lymphoma, perithelial sarcoma, microglioma, and others.[1,5] It was Bailey who initially described it as perivascular sarcoma in 1929; the proliferation of names reflects initial uncertainty about the cell of origin. PCNSL is now known to be a high–grade diffuse non–Hodgkin´s neoplasm, usually large cell or immunoblastic type. Intracerebral parenchymal lymphoma is the most frequent manifestation of PCNSL. Other anatomical sites of involvement include infiltration of the posterior vitreous of the retina, or spinal cord, and rarely spread outside the nervous system. PCNSL originates in the CNS and typically fails there.[1,4,5]

The median age at diagnosis of PCNSL is 52 years in our study. The presenting neurological symptoms have usually been present for less than 2 months, and include signs of increased intracranial pressure (such as headache, nausea, and vomiting), arm and leg weakness or palsy, neuropsychiatric symptoms, and focal neurological deficit, there was absent of seizures upset in this group of patients. The clinical presentation was similar to that reported in the literature, with the frequency of these findings at presentation varies slightly.[3,5,6,11,12] The typical presenting symptoms or signs which characteristics of this disease is difficult to establish, because there was an equal percentage of focal neurological deficits and global neurological deterioration more typical of a diffuse infiltrating process. The low frequency of seizures in this group of patients probably relates to the subcortical location of most of these tumors. The high concentration of neuropsychiatric symptoms in our PCNSL patients may relate to the large numbers of frontal lobe tumors and also to the involvement of other areas of the brain which are important in affective behavior such as the septal region and hypothalamus.

The neuroimaging studies employed accurately displayed the tumor´s site (s), number, associated phenomena (mass effect, meningeal contrast enhancement, hydrocephylus, and so forth).[5,7] Radiographic imaging may be suggestive of the diagnosis of PCNSL.[8] In our series, patients with PCNSL presented with an isodense or hyperdense lesion (90%) on nonenhanced CT scans, significant contrast uptake in CT and MR, absence of calcification, hemorrhage, or cystic change, this is different from other primary brain tumors or metastatic lesions that produce solitary or multiple enhancing lesions on CT scanning, which are usually hypodense on nonenhanced imaging. Following contrast administration, more than 90% of PCNSLs enhance on CT and MR, and 50% do so homogeneously. The location of the lesion may also provide a clue to the diagnosis, since the majority of these lesions occur in a periventricular regien, usually involving the corpus callosum, basal ganglia, or thalamus. In our series, the frontal lobe was involved in 14 (40%) of the 35 cases, a frequency similar to that reported by other authors. This large percentage has been attributed to the fact that the frontal lobes, which would be expected to be the part most affected, volumertrically represent a substantial part of the brain. Multifocal lesions with bilateral mirror pattern are also strongly suggestive of a lesion of lymphomatous origin.

MR imaging is now the radiologic investigation of choice for PCNSL. Despite typical appearances, the findings cannot be construed as diagnostic. The lesions are usually hypointense to isointense on T1-weighted images and isointense to hypointense on T2-weighted images. Higher signal intensity can be achieved following an intravenous injection of gadolinium-DTPA. The lesions may be multiple and are generally sharply demarcated with a small rim of surrounding edema. The lesions are frequently large, with more than 75% being greater than 2 cm in diameter but, surprisingly for the size of the lesions, the mass effect may be relatively small. For definitive diagnosis in immunocompetent patients biopsy is required, because metastases, gliomas and inflamatory lesions may present identical imaging findings.[9,10]

PCNSL had pathologic features comparable with the spectrum of systemic lymphoma. However, the macroscopic appearance of PCNSL may vary considerably between patients. Most commonly, PCNSL appears as a solitary, bulky, and irregular mass merging into the surrounding edematous brain tissue. The most common histololgic subtypes are diffuse large cell lymphoma and diffuse immunoblastic lymphoma based on the World Health Organization Classification of Tumors. Diffuse large cell lymphoma characterized by large cells containing abundant cytoplasm, prominent nucleoli, and dense nuclear chromatin, was the predominant cell type noted in this study, accounting for 82% of cases. The percentage is high than that report by Elizabeth A[6] and Tiwari MK[10] but is in keeping with other report.[5,11,12,13] Our criteria for the classification of a lymphoma as immunoblastic type are rigidly defined, thus some tumors diagnosed in other series, as immunoblastic type would have been classified as large cell type in our study. Our study also confirms other reports that T-cell lymphomas are rare in the CNS.[5,9,14]

Over the last decade, the incidence of PCNSL has increased significantly which cannot be entirely explained by changes in tumor classification, or improved diagnostic capabilities. The rise in incidence was attributed to factors: AIDS epidemic, the extensive use of immunosuppressive therapy, organ transplantation, and role of the Epstein-Barr virus (EBV).[14] However, the data presented in this study and other published series in China to date does not provide support for it[12].

The mechanism of PCNSL is not clear. There are several hypotheses to explain the origin of B-cell PCNSL but no definitive data, which explain their pathophsiology. B-cells may transform outside the CNS and then "home" into the CNS where they grow in a relatively immunoprivileged environment. This mechanism would suggest that these tumor cell have unique surface markers which would induce migration into the CNS; however PCNSL cells have the same cell surface receptors as standard systemic NHL cells and no unique markers have been identified to date. Alternatively, a B-cell passing through the CNS, even intravascularly, become transformed during this passage and then remains in the brain, developing into PCNSL.[6,15,16]

Current therapeutic options include surgery, corticosteroids, radiotherapy, and chemotherapy. If PCNSL is suspected, then the institution of corticodteroid therapy should be delayed until a definitive biopsy has been performed unless cerebral herniation is imminent. The immediate introduction of corticosteroids prior to diagnosis is tempting in the face of symptoms and focal intracerebral lesions. However, the early use of corticosteroids may make histological assessment difficult due to the exquisite sensitivity of PCNSL to the drug. In fact, radiological disappearance of the tumor can occur rapidly after the commencement of corticosteriods. The response is due to tumor cell lysis rather than the resolution of cerebral edema. As a consequence of this rapid lysis, cerebral biopsies may be non-diagnositic or misdirect definitive therapy.[1,17,18]

The results of this study and other studies in the lecture confirm the fact that the survival in patients with this tumor is dismal, resembling that of patients with glioblastoma multiforme.[5,12] Biopsy, rather than resection, is the recommended approach for PCNSL, because aggressive resection of these highly diffusely infiltrative neoplasms may worsen neurological deficits and does not affect the prognosis.[12] Recognizing PCNSL by imaging criteria is therefore essential to avoid steroid medication and to facilitate attempts to biopsy rather than resection. Ninety percent of the patients in our series underwent craniotomy with tumor resection. This high percentage may be explained by the fact that preoperative imaging findings were typical but not diagnostic of cerebral lymphoma. In conclusion, it is preferable to diagnosis a primary cerebral lymphoma based on results of CT or MR studies to orient the approach for a stereotactic biopsy procedure. The method of biopsy with the attendant risks

of craniotomy needs to consider both operative risk and the success of obtaining satisfactory specimens to allow accurate diagnosis.

Open brain biopsy may be necessary in those patients who have lesions located in areas of the brain that are difficult to access (e.g. brain stem). If possible, the procedure should be performed before corticosteroids have been administered. Chest and abdominal CT scans should be performed because small minorities of immunocompetent patients (only a dozen or so reported in the literature so far) have an extraneural source for their cerebral lymphoma. Common sites are abdomen and breast. Therefore, after the establishment of a definitive diagnosis of PCNSL, these staging procedures should be performed. Staging investigation of extent of extraneural lymphoma has a higher yield in patients with AIDS.[1,17]

Radiation therapy has historically been standard treatment for this disease.1 Although postoperative radiotherapy results in high response rates and improved survival rates, compared with supportive therapy, response duration is short and the median survival time with radiotherapy alone is 10 to 18 months.[17] The use of chemotherapy appears to change the nature history of this tumor, with significantly prolonged survival in some groups of patients.[17,18] The optimal agents, dose, schedules, routes of administration, and need for radiation therapy, however, remain undefined.[17]

Because of the relative rarity of PCNSL, the design and performance of clinical trials will remain a challenge and will require collaboration and compromise among investigators. Hopefully, data from this Chinese survey provides a reasonable basis for the treatment of PCNSL, further studies are in progress and will aid in the design of more effective treatment schemes in the future.

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