COMMENTARY

CNS Neoplasms in Pakistan, a Pathological Perspective

Zubair Ahmad*, Huma Arshad, Sheema H. Hasan, Saira Fatima, Romana Idrees, Kanwal Aftab, M Abrar Barakzai, Arsalan Ahmed, Rashida Ahmed, Shahid Pervez, Naila Kayani

Abstract

The Section of Histopathology, Aga Khan University is the largest center for histopathology in Pakistan and is the major reporting and referral center for CNS neoplasms in the country. Over the years, a significant increase has been noted in the number of CNS neoplasms reported annually. This increase most likely represents increased number of neurosurgical procedures being performed. A major problem that we face as histopathologists is absence of clinical history or radiological films in a large number of cases.

Keywords: Central nervous system tumors - Pakistan - histopathological diagnosis - gliomas - meningiomas

Asian Pacific J Cancer Prev, **12**, 317-321

The Section of Histopathology at the Aga Khan University Hospital, Karachi is the largest center for Histopathology in Pakistan and we report over 45,000 histopathology cases per year. We are also Pakistan's premier referral center for histopathology. We receive cases from all over the country, from neighboring Afghanistan and even from places as far off as Kenya. We are also the major reporting and referral center for CNS neoplasms in Pakistan, and no other center in the country reports so many CNS neoplasms. Two of the authors (ZA and SHH) have specialty interest in CNS tumor pathology, and although all consultants in our section report cases encompassing all subspecialties of histopathology including CNS neoplasms, the large majority of CNS neoplasms diagnosed in the section are also reviewed before final sign off by one of the two authors mentioned above. These authors have attended attachments in neuropathology at major centers in U.K. and U.S.A. for various durations. Over the years we have observed a significant increase in the number of cases of CNS neoplasms that we report. Although CNS neoplasms still account for a relatively minor proportion overall of all neoplasms that we report, we have observed a significant increase in the number of CNS tumor cases submitted for histopathological examination. For example in two earlier retrospective series on CNS neoplasms that we published (Zubair et al., 2001; 2004), 1110 cases were reported over a six year period and a total of 1677 cases were reported over an eight year period or just over 200 cases per year. However, our recent data shows that we reported 597 cases in the year 2008 alone. Although we have not yet compiled the data for 2009 or 2010, we feel that the numbers increased even more in these two years compared to 2008. This increase most likely reflects increased number of neurosurgical biopsies and debulking surgeries being performed. Unfortunately, we do not have any conclusive data regarding the exact incidence of CNS neoplasms in Pakistan, although initial reports from Karachi Cancer Registry (Bhurgri et al., 2000) showed that CNS neoplasms rank at number fourteen among all malignant tumors in both sexes.

A major problem that we encounter while attempting to diagnose these tumors is that we often do not receive any clinical history, and even more importantly, in the majority of cases, we do not receive radiological films (CT scans, MRIs etc). Often patients and sometimes even neurosurgeons refuse to provide the films and insist on a diagnosis on the material submitted for histopathology, without any radiological correlation. The problem is that the large majority of our cases come from outside our hospital (from all over the country). CT Scans/MRIs are available in all of our inpatient cases, but the picture is dismal for cases from outside, which constitute the bulk of our cases as pointed out above. In 2008, out of the 597 cases that we reported, only 133 (22%) were in hospital cases, while 464 cases (78%) were outside referrals. Radiological films were available in all the in hospital cases, but were available in only 57 out of the 464 outside cases (12.2%). The importance of clinical history (such as nature and duration of neurological signs and symptoms) in helping to establish the histopathological diagnosis cannot be overemphasized. Similarly, it is essential that the neuropathologist have information about the radiological findings in all cases of suspected CNS neoplasms, so that he/she can formulate an appropriate differential diagnosis before looking at the histology, and must have the films at his/her disposal for correlation (A practical approach to the diagnosis of neurosurgical biopsies, 2002). The

*Department of Pathology & Microbiology, Aga Khan University, Karachi, Pakistan *For correspondence : zubair.ahmad@aku.edu*

fact that only 12% of our outside cases (which form the bulk of our worksload) are accompanied by radiological films shows how hampered and disadvantaged we are in our practice. For the same reason that the large majority of our cases come from outside (and many from remote and far flung areas of the country), maintaining adequate followup is a huge problem, not just for CNS neoplasms but for virtually every case we report as histopathologists. Adequate followup is only possible in the hospital cases, but unfortunately the large majority of our cases are lost to followup. This lack of followup information is another major limitation of our histopathology practice and is acutely felt in CNS neoplasms. Recently, we attempted to get followup of randomly selected outside cases of glial neoplasms through a painful process of searching out the patients through their telephone numbers, or by seeking out the surgeons through their telephone numbers (when available) or through our laboratory collection points which are located all over Pakistan. We succeeded in getting followup information in a small number of patients. This followup information was instructive and surprising and was an eye opener for us. Whereas, our in hospital patients have reasonably good survival times, it was shocking that the majority of patients who were from outside, and who underwent treatment in their respective cities / towns etc showed dismal survival times. All the patients with grade III or IV tumors, in whom followup could be obtained, were dead of their disease within one year of diagnosis. All patients with grade II lesions like diffuse astrocytomas, oligodendrogliomas, ependymomas etc were alive at the end of one year and we intend to continue following them to see the survival trends. The reasons for poor survival rates especially in cases from outside are multiple. Many patients are poor and cannot afford the expensive treatment. Governmental support is minimal if not non-existent, and many patients (or their families) decide against any form of treatment simply because they cannot afford it. In a large percentage of

Table 1. Main Features of Glial Neoplasms in the Series (n=288)

S. No	Tumor type	Tumor Grade	No.	Percentage (%)	Age Range (in years)	Mean Age (in years)	M	F	Sex Ratio	Predominant site
1	Pilocytic Astrocytoma	I	26	9.02%	5-56	11	14 (53.8%)	12 (46.2%)	1.17:1	Posterior fossa
2	Diffuse Astrocytoma	II	12	4.2%	17-76	43	8 (66.7%)	4 (33.3%)	2:1	Frontal and parietal lobes, thalamus
3	Anaplastic Astrocytoma	III	9	3.1%	7-51	36	5 (55.6%)	4 (44.6%)	1.2:1	Parietal and frontal lobes
4	Glioblastoma Multiforme	IV	70	24.3%	7-76	45	47 (67.1%)	23 (32.9%)	2:1	Frontal, parietal and temporal lobes
5	Gliosarcoma	IV	3	1.04%	56-62	59	3	-	-	Frontal, parietal and temporal lobes
6	Pilomyxoid Astrocytoma	II	1	0.3%	-	-	1	-	-	Posterior fossa
7	Subependymal Giant cell astrocytoma	II	2	0.7%	17-31	24	1 (50%)	1 (50 %)	1:1	Frontal lobe
8	Pleomorphic Xanthoastrocytoma	II	8	2.8%	12-43	26	8	-	-	Cerebral hemispheres
9	Astroblastoma	II	1	0.3%	27	27	1	-	-	
10	Oligodendroglioma	II	49	17%	13-76	39	34 (69.4%)	15 (30.6%)	2.3:1	Frontal, temporal, and parietal lobes
11	Anaplastic Oligodendroglioma	III	38	13.2%	10-66	43	29 (76.3%)	9 (23.7%)	3.2:1	Frontal, parietal and temporal lobes
12	Mixed oligoastrocytoma	II	8	2.8%	19-56	37	7 (87.5%)	1 (12.5%)	7:1	Parietal and temporal lobes
13	Anaplastic Oligoastrocytoma	IV	7	2.4%	10-43	32	6 (85.7%)	1 (14.3%)	6:1	Frontal lobe
14	Ependymoma	II	15	5.2%	9-61	30	10 (66.6%)	5 (33.3%)	2:1	Frontal lobe posterior fossa
15	Myxopapillary Ependymoma	I	6	2.1%	23-43	28	6		-	Cauda equina
16	Anaplastic ependymoma	III	16	5.6%	7-66	30	10 (62.5%)	6 (37.5%)	1.7:1	Parietal frontal temporal lobes and posterior fossa
17	Subependymoma	II	2	0.7%	20-50	35	1 (50%)	1(%)	1:1	Cerebral hemispheres
18	Oligoependymoa	II	1	0.3%	32	32	1	-	-	Frontal Lobe
19	Anaplastic oligoependymoma	III	2	0.7%	46-61	53	2	-	-	
20	Gliomas, cannot be further specified. *	*	12	4.2%	11-56	37	66.6 (8%)	4 (33.3%)	2:1	Cerebral hemispheres

*Due to scanty tissue, further subcategorization, adequate grading could not be performed.

Table 2. Main Features of Meningiomas in the Series (n=134)

S. No	Tumor type	Tumor Grade	No.	Percentage (%)	Age Range (in years)	Mean Age (in years)	M	F	Sex Ratio	Predominant site
1	Meningioma	I	106	79.1%	16-76	49	44 (41.5%)	62 (58.5%)	1:1.4	Parietal and frontal lobes
2	Atypical meningioma plus other types of higher grade	II	24	17.9%	8-69	47	11 (45.8%)	13 (54.2%)	1:1.2	Frontal and parietal lobes
3	Anaplastic meningioma	III	4	3.0%	21-56	38	4	-	-	Cerebral hemispheres

Table 3. Main Features of Non Glial, Non Meningial Neoplasms in the Series (n=175)

S. No	Tumor type	Tumor Grade	No.	Percentage %	Age Range (in years)	Mean Age (in years)	M	F	Sex Ratio	Predominant site
1	Primary CNS Lymphoma	-	29	16.6%	39-81	54	19 (65.5%)	10 (34.5%)	1.9:1	Frontal and Parietal lobes
2	Pituitary adenoma	-	14	8%	23-56	39	9 (64.3%)	5 (35.7%)	1.8:1	Sellar and suprasellar region
3	Carniopharyn gioma	-	6	3.4%	6-26	13	3 (50%)	3 (50%)	1:1	Sellar and suprasellar region
4	Schwannoma	-	31	17.8%	13-72	39	16 (51.6%)	15 (48.4%)	1.06:1	Cerebellopontine angle
5	Hemangioblastoma	-	4	2.3%	21-51	37	4 (%)	-	-	Posterior fossa
6	Medulloblastoma	IV	31	17.8%	3-44	14	23 (74.1%)	8 (25.8%)	2.8:1	Posterior fossa
7	Central neurocytoma	II	4	2.3%	11-24	18	1 (25%)	3 (75%)	0.3:1	Intraventricular
8	Choroid Plexus Papilloma		3	1.7%	4-53	23	1 (33.3%)	2 (66.6%)	0.5:1	Intraventricular
9	Neuroblastoma	IV	2	1.1%	3-6	4	1 (50%)	1 (50%)	1:1	Spinal cord
10	Ganglioglioma	II	2	1.1%	-	14	-	2	-	Posterior fossa
11	Chordoma	-	1	0.6%	-	56	1 (%)	-	-	Sellar region
12	Ganglioneuroma	II	1	0.6%	-	20	1	-	-	Spinal cord
13	Supratentorial PNET	IV	2	1.1%	6-21	13	1 (50%)	1 (50%)	1:1	Cerebral Hemispheres
14	Metastatic Carcinoma	-	45	25.7%	36-82	55	29 (64.4%)	16 (35.6%)	1.8:1	Parietal, frontal and temporal lobes.

cases, patients may decide against surgery and opt for radiotherapy only. In the remote areas, qualified and experienced neurosurgeons may not be available and so debulking or resection is often not possible. In a large and heavily populated country, with a population of nearly 170 million, there are very few qualified neurosurgeons, grossly inadequate to meet the needs of such a large population. Even radiotherapy facilities are suboptimal in most areas, and may not be available at all in others. Only the lucky patients, who can afford optimal treatment in the best centers, can hope for a better prognosis. In addition, diagnosis is too often greatly delayed. Many patients, again often due to financial reasons, consult a neurosurgeon, or even a general practitioner, for their signs and symptoms very late, and may not get imaging studies done since these are very expensive. Also, as mentioned earlier, optimum, even adequate radioimaging facilities like CT scan or MRI are not available in many places. So, the dismal survival data reflect both late diagnosis, inadequate or suboptimal treatment, or in many cases no treatment at all; non-availability of diagnostic and treatment facilities or non affordability of the patients. We are trying to collect more followup data in a much larger group of patients with CNS neoplasms, so that a clearer picture regarding patient survival may emerge. The fact that in a majority of cases, debulking or resection is not attempted is highlighted by the fact that out of the 597 cases of CNS neoplasms that we reported in 2008, 341 (57.1%) were small burrhole biopsies or small biopsies taken through open craniotomies. Resection or debulking was done in 256 (42.9%) cases. However, 105 out of these 256 cases (41%) were meningiomas. The percentage of non-meningiomatous neoplasms in which resection or debulking was attempted was much lower. Resection/debulking was performed in 105 out of 134 meningiomas (78.3%), while small biopsies alone were

performed in 29 out of 134 meningiomas (21.6%). Out of 463 non-meningiomatous neoplasms in our series of 597, resection/debulking was performed in only 150 cases (32.4%); while in the remaining 313 cases (67.6%), only small biopsy was performed. These small biopsies, in some cases, represented stereotactically directed needle biopsies, but more commonly small pieces of tumor were obtained by open craniotomy. In many parts of the country, the facilities and expertise for stereotactic biopsies are not available.

In the institutions where the authors attended clinical attachments in neuropathology, almost every neurosurgical biopsy or resection was accompanied by a request for intraoperative diagnosis (smear preparations and cryostat sections), since these centers had catchment areas and all brain surgeries for these catchment areas were performed in these centers, so that specimens could be sent to the neuropathology lab immediately for intraoperative diagnosis of CNS neoplasms. It cannot be overemphasized how important intraoperative diagnosis is in the context of CNS neoplasms. However, as our "catchment area" is huge, literally the whole country, intraoperative diagnosis is possible only in inpatient cases or cases from other hospitals in the city of Karachi. As mentioned earlier, as the bulk of our workload is from outside the hospital (464 cases or 78% of the 597 cases of CNS neoplasms that were reported in 2008 were from outside), the number of specimens for intraoperative diagnosis was very small. Out of a total of 597 CNS neoplasms reported in 2008, intraoperative diagnosis was requested in only 49 cases (8.2%). Intraoperative evaluation was requested in 38 out of the 133 in hospital cases (28.5%), and in only 11 out of the 464 outside cases (2.4%). Our concordance rate was above 95%. Examples of discordant cases included a case of reactive gliosis which was reported as low grade astrocytoma, central neurocytoma reported as oligodendroglioma etc. Our inhospital neurosurgeons usually refer cases for intraoperative examination when they suspect lymphoma, or metastatic lesions, or if they encounter a lesion which appears much more aggressive on gross examination during surgey, than they had anticipated.

Tumor grading was done according to the World Health Organization (WHO) grading system for CNS neoplasms. (5) Glial neoplasms were the commonest neoplasms in the series comprising 288 (48.2%) cases. Among the glial neoplasms, glioblastoma multiforme (astrocytoma, grade IV) was the single most common neoplasm, followed by oligodendroglioma, grade II, and anaplastic oligodendroglioma, grade III. Oligodendrogliomas grade II and III were much more common compared to astrocytomas grade II and II and ependymomas grade II and III. Even more surprisingly, even ependymomas grade II and III were more common compared to astrocytomas grade II and III (Table 1).

However, the single most common type of neoplasm in the entire series was Meningioma, grade I (18.16%). Meningiomas grade I, II and III comprised 22.4% of all neoplasms in our series (Table 2).

Out of a total of 597 cases, 370 (62%) patients were males, while 227 (38%) were females. Meningiomas were the only neoplasms in which females outnumbered males (Table 2).

Out of a total of 597 cases, 60(10%) occurred in patients upto 15 years of age. The majority of these tumors were pilocytic astrocytomas or medulloblastomas.

Although we diagnose oligodendrogliomas very frequently and both grade II and III oligodendrogliomas are more common compared to grade II and III astrocytomas, we do not have the molecular genetic analysis methods to identify genetic subsets with markedly different clinical courses especially in anaplastic oligodendroglioma (Cairncross et al., 1998; Ino et al., 2001). As is well known, allelic losses of chromosomal arms 1p and 19q are seen in about 70% of oligodendrogliomas grade II and III (Cairncross et al., 1998; Bigner et al., 1999) and are a significant predictor of prolonged survival in oligodendroglioma patients whatever the grade (Smith et al., 2000). These tumors, especially anaplastic oligodendrogliomas respond very well to PCV (Procarbazine, CCNU and vimaristine) chemotherapy (Cairncross et al., 1998). Hence, it is very important to detect these genetic alterations in oligodendroglioma patients. We suffer from this limitation. However, we hope to start this molecular analysis in the near future.

We have lately also diagnosed a number of cases of glioblastoma multiforme with oligodendroglioma component, WHO grade IV (Brat et al., 2008). We have been seeing mixed glial neoplasms with increasing frequency (Table 1). In a number of cases, the tissue received is very scanty, and although we can raise the possibility of a glial neoplasm, we are not able to sub classify or grade the neoplasm (Table 1).

Site was unknown in 122 cases (20.4%) and remained unknown as efforts to contact clinicians, obtain radiological films etc failed. So in a significant percentage of cases, we are reporting totally blindly, without any clue regarding site of neoplasms, radiological findings etc.

Among the non-glial, non meningothelial neoplasms, schwannomas (arising from cranial nervs), medulloblastomas, and primary CNS lymphomas were the most common tumor types (Table 3).

Metastatic carcinomas comprised 7.5% of all 597 neoplasms in our series. Lungs were the commonest site of primary; other common primary sites in our series included the gastrointestinal tract (including pancreatobiliary tract), kidney, urinary tract, breast etc. However, metastases were seen from female genital tract, prostate, thyroid, upper respiratory tract, salivary glands etc.

In conclusion, we hope in future to develop better links with neurosurgeons all over the country, so that we have relevant history and radiological findings at our disposal while reporting CNS neoplasms; and even more crucially to maintain adequate followup. We also hope to start molecular testing in relevant tumors such as anaplastic oligodendrogliomas (which can be of benefit to the patients); and to initiate research to determine why oligodendrogliomas are so common in our population compared to astrocytomas, grade II and III.

The government and private sector need to provide better and widespread diagnostic and treatment facilities for patients at affordable rates so that patient survival can

increase. More trained and qualified neurosurgeons need to be made available, at least at the government level, in small cities and towns. We are in the midst of an epidemic of CNS neoplasms, and need to control it before if gets totally out of hand.

References

A practical approach to the diagnosis of neurosurgical biopsies. In Ironside JW, Moss TH, Louis DN, Lowe JS, Weller RO eds. Diagnostic Pathology of Nervous system Tumors. *Churchill livingstone, Elsevier*: 17-37.

Bhurgri Y, Bhurgri A, Hassan SH, et al (2000). Cancer incidence in Karachi, Pakistan: first results from Karachi cancer registry. *Int J Cancer*, **85**, 325-9.

Bigner SH, Matthews MR, Rasheed BK, et al (1999). Molecular genetic aspects of oligodendrogliomas including analysis by comparative genomic hybridization. *Am J Pathol*, **155**, 375-86.

Brat DJ, Parisi JF, Kleinschmidt-Demasters BK, et al (2008). Surgical Neuropathology update. a review of changes introduced by the WHO classification of tumors of the central Nervous system, 4th Edition. *Arch Pathol Lab Med*, **132**, 993-1007.

Cairncross JG, Ueki K, Zlatescu MC, et al (1998). Specific genetic predictors of chemotherapeutic response and survival in patients with anaplastic oligodendrogliomas. *J Natl Cancer Inst*, **90**, 1473-9.

Ino Y, Betensky RA, Zlatescu MC, et al (2001). Molecular subtypes of anaplastic oligodendroglioma: implications for patient management at diagnosis. *Clin Cancer Res*, **7**, 839-45.

Smith JS, Perry A, Borell TJ, et al (2000). Alterations of chromosome arms 1p and 19q as predictors of survival in oligodendrogliomas, astrocytomas, and mixed oligoastrocytomas. *J clin Oncol*, **18**, 636-45.

WHO classification of Tumors of the Central Nervous System (2007). Louis DN, Ohgaki H, Wiestler OD, Cavenee WK eds. 4th Edition. *International Agency for Research on Cancer (IARC)*, Lyon, 2007.

Zubair Ahmad, Najamul Sahar Azad, Suhail Muzaffer, et al (2004). CNS Tumors at AKU: An update plus a brief discussion on intra-ventricular tumors with special emphasis on central neurocytoma. *J Ayub Med Coll Abbottabad*, **16**, 12-5.

Zubair Ahmad, Suhail Muzaffer, Naila Kayani, et al (2001). Histological pattern of Central Nervous System Neoplasms. *J Pak Med Assoc*, **51**, 154-7.