Original Article

The Spectrum of Neurological Complications in Pakistani patients with Malignancies

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Abstract

Objective: To evaluate the incidence and nature of neurological complications related to malignancy in a tertiary care hospital in Pakistan.

Methods: A retrospective chart review was performed of patients with malignancy, having neurological symptoms, admitted to The Aga Khan University Hospital, Karachi, Pakistan.

Results: There were a total of 178 admissions among 152 patients, with more than half (50.5%) of them above the age of 50, with a male to female ratio of 1.34:1. Most admissions (60%) occurred within the first year of diagnosis of the malignancy. Neurological problems were the second commonest cause for admission (20%) in our study group following admissions for chemotherapy/transfusions (52%). The most common primary tumour was Non-Hodgkin's Lymphoma (16.3%), followed by breast (15.7%), Acute Myeloid Leukemia (AML), (12.9%) and carcinoma of unknown primary site (9%). The 3 most common symptoms were altered mental status (45.3%), lower limb weakness (27.9%) and seizures (17.3%). Fifteen percent of admissions were secondary to a neurological symptom as an initial presentation of the primary tumour. The commonest neurological diagnoses were brain metastasis (27%), followed by spinal cord compression (16.9%), intracerebral haemorrhage (11.2%) and metabolic encephalopathy (9%). Head imaging revealed abnormalities in 77% of patients. The most common neurological diagnosis for mortality (25.8%) was intracerebral haemorrhage (34.8%), followed by brain metastasis (26.1%).

Conclusions: This descriptive study on neurological complications amongst cancer patients from Pakistan, defines the various neurological symptoms and diagnoses in patients with malignant disorders, highlights the common tumour types, the associated characteristics and determinants of mortality in this Asian population (JPMA 58:160;2008).

Introduction

Neurological complications occur frequently in patients with systemic cancer and with the advent of more effective cancer treatment protocols, prolonging survival of these cancer patients, these are becoming even more frequent. Excluding admissions for chemotherapy, these complications are the commonest reasons for admissions to an oncology unit.[1,2] These complications may occur at or before the time of the diagnosis of the malignancy or develop later as the disease progresses. They are diverse, affecting any level of the central or peripheral nervous system. Little information is available in the literature about the incidence and nature of neurological complications in such patients in the Asian region. We present a retrospective review of neurological complications in Pakistani adults with systemic cancer, collected over a 3 year period.

Methods

The Aga Khan University Hospital is a 450 bed tertiary care hospital located in the heart of Karachi, Pakistan. Using the computerized database, maintained by the medical records unit, we retrospectively identified all cancer patients who had a neurological diagnosis on the ICD-9 CM coding system, for a three year period between January 1, 1995 to December 31, 1998. The emergency admission records and the inpatient admission medical records were then reviewed and data was collected using a standard data collection form. Data included epidemiology, course of disease, laboratory investigations, oncological histology and radiology. For the purpose of the study, each admission for a patient was considered as separate record. Only patients aged 15 and above who were admitted to the inpatient service were included in the study. Patients with primary brain tumours were excluded from the study. The data was analyzed on the statistical package Epi Info (version 8.0, CDC, Atlanta, GA) for analysis. Means are presented with $\pm$ standard error of measurement. Data was analysed for odds ratio for each risk factor, as well as a multivariate logistic regression model. A p-value of <0.05 was considered statistically significant.

Results

Between January 1995 and December 1998, 152 patients had a total of 178 admissions to the inpatient

service for neurological complications. One hundred two (102) were men, and 76 were women, with a male to female ratio of 1.34:1. The mean age for all patients was 48.8 ± 15.4 years (range 15 to 90 years), with 21.3% between the ages of 61 and 70. Other than elective admissions for cancer chemotherapy, admission for neurological complications was the second commonest reason (20%) for all admissions to the oncology service.

A total of 28 different histology types were present in the patient population (Table 1). The most common tumour seen was Non-Hodgkin's lymphoma (NHL) (16.3%), followed by breast (15.7%) and Acute Myeloid leukaemia (AML) (12.9%). Amongst AML patients, M4 staging was the most frequent. Carcinoma of unknown primary origin (CUPO) was also seen frequently (9%), majority of which were undifferentiated, followed by adenocarcinomas. In males the most common tumour was NHL (23.5%), followed by AML (13.7%) and lung (9.8%). In females the most common tumour was breast (36.8%) followed by AML (11.8%).

Neurological symptoms were the first manifestations of a tumour in 14.6% of patients. Excluding these initial presentations, 44.7% cases presented within 1 month of diagnosis of the primary tumour, 69.7% within the first 3 months of diagnosis, and 95.3% cases had presented within 1 year. The mean duration for presentation since diagnosis was 2.5 months with the longest duration of presentation being 1.5 years. All the cases of NHL with neurological complications presented within the first 3 months as compared to a lower number (37%) of breast cancer patients. Patients had received multiple modalities of previous therapy (chemotherapy, radiation and surgery) the duration of which ranged from 1 week to 11 years (data not shown). Eight patients presented with a neurological complication while still being worked up for treatment of a primary tumour.

Table 1. Primary Tumour Type in Patients admitted with Neurological diagnoses.

Tumor Type	Number of cases	%
Non-Hodgkin's lymphoma	29	16.3
Breast cancer	28	15.7
Acute Myeloid Leukaemia	23	12.9
Carcinoma of Unknown Primary Origin	16	9.0
Lung *	11	6.2
Squamous cell cancer, Head/Neck	10	5.6
Multiple Myeloma	7	3.9
Sarcoma	8	4.5
Renal cell cancer	8	4.5
Acute Lymphoid Leukaemia	7	3.9
Female genital tract cancer +	7	3.9
Chronic Myeloid Leukaemia	5	2.8
Prostate cancer	5	2.8
Gastrointestinal tract cancer ++	4	2.2
Colon and rectal cancer	3	1.7
Myelodysplastic syndrome	3	1.7
Chronic lymphoid leukaemia	2	1.1
Hepatoma	1	0.6
Hodgkin's Disease	1	0.6

* 6 squamous cell, 2 small cell, 2 large cell and 1 spindle cell; + ovary, uterus or cervix ; ++ esophagus, stomach, gall bladder or pancreas

Table 2. Neurological Diagnoses in all patients with systemic cancer.

Neurological Diagnosis	Number of cases	%
Brain Metastasis	51	28.1
Spinal Cord Compression	30	16.9
Intracranial Haemorrhage (ICH)	20	11.2
Encephalopathy	18	10.1
Leptomeningeal Metastasis	17	9.6
Cerebrovascular Disease	12	6.7
Seizure	7	3.9
Chemotherapy related Neuropathy	7	3.9
Neuropathy #	6	3.4
Base of Skull Metastasis	5	2.8
Plexopathy	3	1.7
Infections	2	1.1
Paraneoplastic Syndromes	2	1.1
Others **	9	5.1

Neuropathy otherwise incompletely worked up.
** includes radiculopathy, brachial neuritis, cauda equina syndrome, ischemic retinopathy, radiation myelopathy, subdural hemorrhage and central nervous system effects of lymphoma incompletely worked up.

Of the 152 total patients, 7.9% were in remission with no evidence of disease; 46.1% had active tumour, 24.2% had stable disease with no admissions or complications within the past 1 year, and for 21.9% the tumour status was not known (either due to being an initial presentation or having received care at another institution prior to presenting at our hospital). Metastasis to other sites in the body was present in 46.6% of patients, while 41.1% of cases had no known metastasis. The remaining 12.3% had not been worked up or had been receiving care at another institution with incomplete past records. The most common site for previous metastasis was to non-axial bony structures (23.9%), followed by liver (19.2%), lung (16.3%) and brain (10.5%). Others sites such as vertebra, spleen, skin, gastrointestinal lymph nodes and metastasis to other pelvic and abdominal viscera were also present amongst the other 29%.

The most common symptoms at presentation were altered mental status (AMS) (45.3%), followed by lower

extremity weakness (27.9%) seizures (17.3%), headache (11.2%) and backache (10.1%). Physical examination suggesting cranial nerve dysfunction was noted in 35 cases (19.6%). Amongst these patients, facial weakness was the most common (40%), followed by dysfunction of the optic nerve (31.4%). Many patients presented with multiple symptom complexes. Among patients with spinal cord compression, 50% of cases had back pain, sphincter disturbance and sensory disturbance while 96% had variable degrees of lower extremity weakness.

Brain metastasis (28.1%) was the most common neurological diagnosis, followed by spinal cord compression (16.9%) and intracerebral haemorrhage (ICH) (11.2%) (Table 2). The most common primary tumour presenting with brain metastasis and metastatic spinal cord compression was breast cancer (37.2% and 16.6% respectively), with more than half (60.7%) of these breast cancer patients having a diagnosis of brain metastasis. The most common primary tumour type presenting with leptomeningeal metastasis was NHL (70.5%) while the most common primary tumour to present with intracerebral haemorrhage was AML (45%). Hypercalcaemia and disturbances in sodium levels either hypo- or hypernatraemia were the most common causes for metabolic encephalopathy. Multiple metabolic abnormalities in patients were also common. Of the 7 patients with chemotherapy related neuropathy, 5 were identified to have received vincristine and 2 had received cisplatin as part of their chemotherapy regimens.

Of the 24 patients with platelet count less that 20,000 at admission, 14 (58.3%) suffered from ICH with a resultant 85% mortality. Seven of these patients had AML. Six patients suffered intracerebral haemorrhage but had platelet counts >20,000.

Radiology

Radiological studies were performed in a total of 117 cases of which 83 were cranial imaging studies while the rest 34 were spine imaging studies. Head imaging included CT and MRI with contrast as indicated, while spine imaging included plain X-rays, CT, MRI, and myelograms. Of the 83 head images, 77% had positive findings, the most common being brain metastasis (59.3%), followed by ICH (18.7%) and ischaemic changes (15.6%). Other findings included meningeal enhancement, skull metastasis, brain abscess, vasculitis, normal pressure hydrocephalus and subdural haemorrhage. Of the brain metastasis, 39.4% were solitary metastasis. Of the 18 breast cancer patients who had head imaging, 94.4% had a positive scan, while all lung cancer patients had a positive head image. In contrast, 58.3% of Non-Hodgkin's Lymphoma patients who had head imaging had a positive image.

Spine imaging studies were primarily done in patients with neurological symptoms indicating spinal cord compression. All of the 34 patients had a positive finding. Metastasis limited to the vertebra only was found in 14 patients, while 9 patients had both vertebral and epidural metastasis. Pure epidural metastasis was found in 4 patients, paraspinal metastasis in 5 patients, and intramedullary metastasis in 2 patients. The spinal level of spinal metastasis was lumbar in 55.9% of cases, thoracic in 52.9% of cases, sacral in 20.8% of cases and cervical in 8.8%. Multiple levels were involved in 83% of cases, the remaining were confined to a solitary level. Metastatic spinal involvement was noncontiguous in 10% of cases.

A total of 26 cases had cerebrospinal fluid (CSF) studies performed of which 17 were in patients with suspected leptomeningeal metastasis. Decreased CSF glucose was found in 15.3%, elevated CSF protein in 69.2% and elevated lymphocytes in 75% of patients, with this neurological diagnosis. Atypical malignant cells were seen in 27% of patients whose CSF samples were taken.

Mortality

The overall mortality rate in our series was 25.8%. ICH (34.8%) and brain metastasis (26.1%) were the leading neurological diagnoses in these patients. AML (28.3%), breast cancer (17.4%) and NHL (13%) were the leading

Table 3. Risk factors for mortality among cancer patients with neurological complications.

Neurological Diagnosis	Deceased (n=46)	Survivors (n=132)	OR (95% CI)	p-value
Intracerebral haemorrhage	16	4	17.07 (4.93-73.61)	< 0.001
Altered Mental Status at admission	39	41	12.37 (4.79-33.27)	< 0.001
Platelet count < 20,000 at admission	15	9	5.54 (2.03-15.37)	< 0.001
Post complication steroids	14	78	0.26 (0.12-0.58)	< 0.001
Initial Presentation with neurological symptoms	10	16	2.01 (0.77-5.23)	0.177
Presence of previous metastasis	18	65	0.69 (0.31-1.51)	0.404
Pre complication chemotherapy	33	89	1.23 (0.55-2.74)	0.72
Male Gender	25	77	0.85 (.41-1.76)	0.76
Seizure	8	23	1 (0.37-2.6)	0.852

OR - Odds Ratio, CI- Confidence interval

primary tumour diagnoses in the expired patients. Fifty-six percent of AML patients died while 21% were those with an initial neurological presentation. Multivariate logistic regression analysis for mortality showed altered mental status on admission, platelet count <20,000 on admission, presence of ICH, and absence of steroid therapy after complication to be significant predictors of mortality ($p< 0.001$) (Table 3).

Discussion

This study attempts to describe the epidemiological and clinical data about neurological complications in cancer patients, from a region of the world where little data exists on this aspect of oncology. It also illustrates the wide range of complications and their prognostic implications. It has already been recorded in western literature that aside from routine chemotherapy, neurological problems are the most frequent reason for admission of a patient with systemic cancer.[1] The incidence of cancer in Karachi is slightly lower than developed countries but at par with neighbouring countries.[3] The only other report from this region has stated an incidence of 9.9% of CNS tumours to be of secondary or metastatic in origin.[4]

The commonest tumours presenting with neurological complications were not those with the highest prevalence in the population namely lung, oral cavity and larynx in men and breast, oral cavity and gall bladder in women.[5] However the incidence of NHL is rising in the region.[6] The results may have been influenced by institutional variations; since our institution lacked facilities for radiation at times studied in this review, the frequency of lung and oral cavity tumours were low. This pattern has been described by Malik et al.[7] One reason why neurological complications in lung cancer patients was low despite a high institutional lung cancer frequency, is that our hospital, being a tertiary care center, has a referral pattern which has a strong diagnostic arm to it, but due to the lack of radiation facilities at that time, a low turn out for follow up of lung cancer patients was noted.

Lung cancer and breast cancer are the commonest tumour types to present with neurological complications as reported in the Western Literature.[1,2,8] Even though we had low numbers of lung cancer cases, all of them had a neurological diagnosis of brain metastasis consistent with other studies.

Intracranial haemorrhage was the commonest neurological diagnosis in our leukaemia patients. Although patients with acute leukaemia may die of haemorrhage due to blast crisis with markedly elevated leukocyte counts, only two of our cases had marked leukocytosis. Of these one also had simultaneous thrombocytopenia. Hence mortality can be directly attributed to blast crisis in only one patient in our series. Severe thrombocytopenia with advanced disease was commonly noted in those patients with ICH.

Carcinoma of unknown primary origin (CUPO) was observed at a higher frequency in our series when compared with other similar studies.[1] This diagnosis is reserved for those tumours in which the primary tumour is not identified despite extensive work up. Being a developing country, financial constraints are the prime reason for foregoing a complete work up, and this being confounded with socio-cultural factors linked with terminal diseases, may be a major reason for the high number of these unknown tumours. It is also possible that some of these may have been discovered later on during the course of the tumour, which happened to be after the end of the collection of this data series.

In the published literature sphincter disturbance, though never a sole presenting symptom, is present in up to 57% of patients by the time of diagnosis. We however, noted sphincter disturbance to be present in 96% of cases. We are unable to explain the huge difference in this symptomatology. In our series however we saw only half the cases presenting with pain. Socio-cultural factors may be responsible for a lower number of cases complaining of pain, and may in fact actually be a factor which also leads to delay in presentation.

Our multivariate analysis results indicate that ICH and severe thrombocytopenia are independent risk factors for mortality in such patients and should be managed as aggressively as possible. AMS, although also an independent risk factor for mortality, is a non-specific symptom but nonetheless should prompt the physician to have a high index of suspicion for advanced neurological complications. Patients who were given steroids following their neurological complication tended to have a better outcome, highlighting the fact that steroid use to decrease cerebral inflammation and swelling should be utilized and that lack of its use is an independent risk factor for mortality.

Our data has certain limitations as outlined below. The exact incidence in our hospital might not have been captured accurately in the diagnosis coding and some patients might not have been admitted for mild complications or could have been sent to home for terminal care. It is also possible that since our results are from a private institution, there is an under representation of the lower socioeconomic classes. Our data also did not include the out- patient encounters and hence we may have an underestimate of neurological diagnoses which do not require admissions, e.g.

neuropathies, plexopathy etc. While we acknowledge the inherent biases that are present in our study due to the retrospective design and selection procedures used in the study, apart from the institutional referral and services pattern, we believe that these results are reliable and the first to be reported from our region .

The incidence of CNS involvement can be expected to rise in virtually all tumours as systemic treatment continues to improve survival. We suggest that a database be established at various levels of the health care system to collect data on neurological complications apart from regular tumour incidence and prevalence as has been established in other parts of the world.[9] This would be similar to the tumour registries that are now standard in a lot of hospitals and cancer centers.[3] Further studies with larger numbers in different regions of the country with different tumour patterns are also recommended so that more statistical significant results are available which improve the overall management and treatment plans for cancer patients. Predicting and hence preventing neurological complications in various tumour groups remains the ultimate and most important aspect of this entire exercise.

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