Original Article

The spectrum of malignancies presenting with neurological manifestations: A prospective observational study

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Abstract

Introduction: A neurological consultation is needed in nearly 45% of patients suffering from cancer. The present study was planned to evaluate the clinical, radiological and histopathological spectrum of patients with an underlying malignancy and presenting with a neurological complaint. **Materials and Methods:** We prospectively evaluated all patients provisionally diagnosed either with a primary or secondary malignancy of the brain on the basis of clinical, radiological and/or histopathological features. **Results:** A total of 155 patients were enrolled from a total of 4893 admissions done from January 2015 to July 2016. The common presenting symptoms were headache, back pain and paraparesis. Around 26% of patients presented with an altered sensorium, 19.4% with seizures and 21% had at least one cranial nerve involvement. The most common site of involvement was the brain noted in 49.7% of patients. Primary malignancies constituted 78 cases (50.7%) while secondary malignancies included 77 cases (49.3%). Magnetic resonance imaging (MRI) revealed 92 (59.4%) intra-axial lesions and 59 (38.1%) extra-axial lesions, with five cases having both. The most common diagnoses were intra-cerebral metastases and glioblastoma (intra-axial), and vertebral metastases and meningioma (extra-axial). Histopathological confirmation was obtained in 59 patients (38.1%) with 12 primary and 47 secondary lesions. Ten (6.45%) patients had an unknown primary with secondary metastases. The three most common histopathologically confirmed diagnoses were adenocarcinoma lung, plasma cell dyscrasia and adenocarcinoma prostate. **Conclusion:** Primary neurological consultations with an unknown primary are common hence a high index of suspicion can prevent an inadvertent delay in the diagnosis and appropriate treatment of a malignant lesion. Developing a neuro-oncology register may help us in gaining more insight into such situations.

Keywords: Carcinoma lung, central nervous system, glioblastoma multiforme, metastasis, neuro-oncology

Introduction

One of the most frequent and debilitating complications of cancer is the involvement of the nervous system, with nearly 45% of these patients requiring evaluation of a neurological problem. Neurological complications are the most common reason for emergency admissions of patients with cancer as well as the most common and primary reason for admission, besides chemotherapy administration.[1] Most studies dealing with this subject have been conducted in oncology settings, with analysis of the neurological referrals that may result in an under-reporting of neurological manifestations in cancer patients. It has been reported that approximately 15% of the patient population in an oncology centre

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was seen by a neurologist.[2,3] The National Cancer Registry in India was set up in 1981 and as late as 2009 there was no mention of a neuro-oncology society.[4,5] This is in contrast to the Netherlands, where a neuro-oncology register (NOR) was established nearly three decades ago and in the USA where a law was passed in 2004 making the reporting of nervous system tumours compulsory at a national level.[6,7] It has been observed that nearly one-third of patients seek neurological consultation for brain metastasis without any prior malignancy.[8,9] The clinical presentations in such patients may vary from subtle hypoactive delirium to quadriparesis and any delay in diagnosis may be catastrophic.[10,11]

The objective of our research was to study the clinical, radiological and histopathological spectrum of patients presenting with a neurological complaint to a neurology specialist, as the first manifestation of an underlying malignancy.

Materials and Methods

This was a prospective observational study conducted in the Department of Neurology, King George's Medical University, Lucknow, from January 2015 to July 2016. This study was approved by the Institutional Ethics Committee (IEC). Written informed consent was obtained from each subject or their legal guardian, prior to enrolment.

Inclusion criteria

All patients provisionally diagnosed with either primary or secondary malignancies, based on clinical, radiological and/or histopathological features, were included in the study.

Exclusion criteria

All patients below the age of 18 years or with a diagnosed malignancy were excluded.

Evaluation

All included patients underwent a detailed clinical evaluation followed by imaging relevant to each case. All enrolled patients were subjected to routine blood tests. Patients with suspected metastases underwent further work up directed at finding the primary site of origin. This included a detailed urological and gynaecological examination, contrast-enhanced computed tomography (CECT) of the chest/abdomen (as indicated), radionuclide scan, FDG-PET, estimation of tumour markers (such as prostate-specific antigen, carcino-embryonic antigen and alpha-fetoprotein), serum immunoelectrophoresis and histopathological confirmation (as feasible) with the biopsy of the relevant tissue.

Neuroimaging

Brain/spine magnetic resonance imaging (MRI) was performed on a Sigma Excite 1.5 Tesla scanner (General Electric Medical Systems, Milwaukee, WI, USA). An experienced neuroradiologist blindly reviewed the MRI scans in terms of lesion characteristics on different sequences, perilesional oedema, contrast-enhancement, necrosis and mass effect.

Histopathological examination

Histopathology slides, whenever available, were examined independently by an expert neuro/oncopathologist and in relevant cases, immunohistochemistry staining was also performed.

Diagnostic categories

Primary malignancies were provisionally diagnosed based on findings from their characteristic imaging while metastases were diagnosed on the basis of typical MRI findings of circumscribed contrast-enhancing lesions with disproportionate perilesional oedema and mass effect along with evidence of malignancy at another site. These cases were diagnosed as 'definite' or 'histopathologically proven' cases [Figure 1].

'Probable' or 'imaging' diagnoses of primary nervous system malignancies were based on neuroradiological features when the biopsy was not possible. The lesions were classified as extra-axial if they had a majority of these imaging features (cerebrospinal fluid cleft between brain and lesion, vessels interposed between brain and lesion, cortex between mass and oedematous white matter, dura (meninges) between (epidural) mass and brain). The rest were classified as intra-axial.

The origin of secondary malignancies were diagnosed as 'probable' or termed 'imaging diagnosis' if one of the following was noted: an abnormal CT scan (chest or abdomen), bone scan or positron emission tomography (PET) scan, suggesting the primary site of origin for nervous system metastasis, and the systemic workup being otherwise unremarkable and

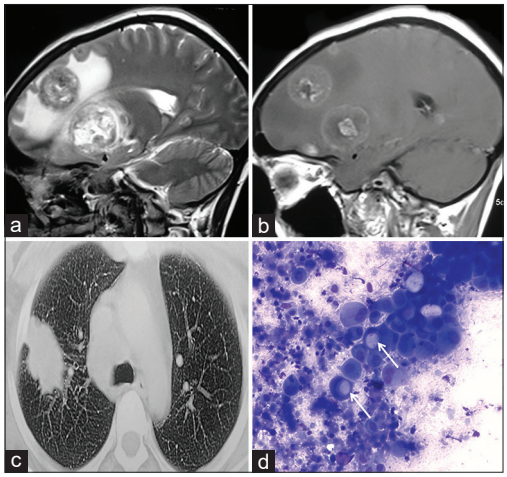

Figure 1: Parasagittal T2W sequence of MRI of the brain (a) shows mixed intensity space occupying lesions involving the right frontoparietal and subcortical areas with moderate to severe perilesional edema, with relatively homogeneous GAD enhancement (b). Axial contrast-enhanced CT of the thorax (c) depicts an ill-defined heterogeneously enhancing soft tissue in the posterior segment of the right upper lobe with spiculated margins suggestive of a neoplastic etiology. Smear of CT-guided aspirated material (d) shows a papillaroid cluster and singly lying cells with moderate sized, round to oval hyperchromatic nuclei, and moderate amount of amphophilic cytoplasm with few mucin vacuoles (arrows), suggestive of a non-small cell lung carcinoma. (May Grunwald Giemsa, x200)

histopathological diagnosis were not possible. Presumptive diagnoses made after imaging were revised if a biopsy was possible and histopathological confirmation was obtained.

Referrals

Based on the final diagnosis, patients were referred to the team of neurosurgery, radiation oncology and surgical oncology for further management.

Statistical analysis

The statistical analysis was performed using the Statistical Package for Social Sciences, Version 16.0 for Windows (SPSS, Chicago, IL). Statistical significance was defined at a *P* value of <0.05 and wherever analysis was done it was a 2-tailed analysis. Categorical variables were expressed as percentages while continuous variables were expressed as mean ± SD. Chi-square test was used to compare proportions; independent sample *t*-test/ANOVA was used to compare means.

Results

There were a total of 4893 admissions to the department of neurology, of which 155 patients were enrolled.

The mean age of the patients was 47.19 ± 17.08 years with 87 (56%) male patients. The mean duration of the presentation was 134.17 ± 24.90 days. Headache (47.7%) was the most common symptom followed by back pain (29.7%). The most common motor symptom was paraparesis (27.7%) followed by hemiparesis (21.1%). Sensory loss in one form or the other was noticed in 40.6% of the patients. Patients were graded on their disability based on the Modified Barthel Index (MBI) with a score of ≤12 (severe) in 39 patients (25.2%) and >12 in 116 patients (74.8%). The baseline characteristics of the cohort have been detailed in Table 1.

The most common site involving the neuraxis was the brain (49.7%) followed by the spinal cord (29.0%). Nearly 24% of the patients had multiple sites of involvement along the neuraxis as well as multiple lesions within the same site. Primary malignancies were seen in 78 cases (50.7%) while secondary malignancies were noted in 77 cases (49.3%). MRI revealed intra-axial involvement in 92 (59.4%) cases and extra-axial involvement in 59 (38.1%) cases with 5 cases having both intra- as well as extra-axial involvement. Histopathological confirmation following biopsy could be obtained in 59 patients (38.1%) [Table 2].

Brain

The mean age was 46.94 ± 17.09 years with 55.8% of patients being male and the rest female. The primary malignancy group constituted 45.5% of these patients while 54.5% fell into the secondary malignancies group. Fifty (64.9%) of these lesions were intra-axial and 24 patients (31.2%) had extra-axial lesion; 3 patients (3.9%) had both type of lesions. Histopathological confirmation could be achieved in 26 patients (33.7%) with the most common malignancy being adenocarcinoma lung.

Table 1: Baseline characteristics of the cohort

Variables	Values
Age in years (Mean±SD)	47.19±17.08
Sex	
Male	87 (56.1%)
Female	68 (43.9%)
Mean duration of presentation (days)	134.17±24.90
Clinical Features	
Pain	
Headache	74 (47.7%)
Back pain	46 (29.7%)
Neck pain	13 (8.4%)
Pain in a limb	33 (21.3%)
Weakness	
Hemiparesis	33 (21.1%)
Paraparesis	43 (27.7%)
Quadriparesis	16 (10.3%)
Monoparesis	03 (1.9%)
Vomiting	42 (27.1%)
Sensory loss	63 (40.6%)
Gait abnormality	79 (51.0%)
Altered sensorium	40 (25.8%)
Seizures	30 (19.4%)
Speech abnormality	24 (15.5%)
Visual disturbances	15 (9.7%)
Cranial nerve involvement	33 (21.3%)
Movement disorders	0 (0.0%)
Sphincter involvement	54 (34.8%)
Disability on admission	MBI >12=116 (74.8%) MBI ≤12=39 (25.2%)
Site of involvement	
Brain	77 (49.7%)
Spinal cord	45 (29.0%)
Plexus/Radicles	23 (14.8%)
Nerve	06 (3.9%)
Neuromuscular junction	04 (2.6%)
Skeletal	39 (25.2%)
Multiple sites	37 (23.9%)
Origin	
Primary	75 (48.4%)
Secondary	80 (51.6%)
MRI Characteristics	
Intra-axial	92 (59.4%)
Extra-axial	59 (38.1%)
Both	05 (2.5%)
Biopsy proven	59 (38.1%)

Spinal cord

The mean age was similar to the 'brain' group (46.96 ± 17.81 years) with 60% males and 40% females. Twenty (44.4%) patients had a primary malignancy and 25 (55.6%) patients were classified in the secondary malignancies group. In contrast to the 'brain' group, extra-axial lesions were found to be in a higher proportion (73.3%) as compared to intra-axial lesions (20.0%). However, in 16 patients (35.6%), the diagnosis could be confirmed histopathologically.

Plexus/nerve root

Two patients had brachial plexus involvement while the rest (21 patients) had involvement of the lumbosacral plexus. The mean age was higher as compared to the brain and spinal

Table 2: Characteristics of lesions based on site of involvement

Variable	Brain (*n*=77)	Spinal cord (*n*=45)	Plexus*/Root (*n*=23)	Nerve (*n*=6)	NMJ
Age	46.94±17.09	46.96±17.81	51.87±14.93	44.67±15.89	36.25±3.15
Sex					
Males	43 (55.8%)	27 (60.0%)	09 (39.1%)	05 (83.3%)	03 (75.0%)
Females	34 (44.2%)	18 (40.0%)	14 (60.9%)	01 (16.7%)	01 (25.0%)
Origin					
Primary	35 (45.5%)	20 (44.4%)	09 (39.1%)	02 (33.3%)	00 (0.0%)
Secondary	42 (54.5%)	25 (55.6%)	14 (60.9%)	04 (66.6%)	04 (100.0%)
MRI Characteristics					
Intra-axial	50 (64.9%)	09 (20.0%)	00 (0.0%)	00 (0.0%)	00 (0.0%)
Extra-axial	24 (31.2%)	33 (73.3%)	23 (100%)	06 (100%)	04 (100.0%)
Both	03 (3.9%)	03 (6.7%)			
Biopsy proven	26 (33.7%)	16 (35.6%)	12 (52.2%)	05 (83.3%)	02 (50.0%)
Pathological diagnosis	Adenocarcinoma lung (7) SCC (3) Bronchoalveolar carcinoma (2) Infiltrating ductal papilloma (2) breast Adenocarcinoma prostate (1) Anaplastic ependymoma (1) Chordoma (1) Follicular ca thyroid (2) NSCLC (2) PDC (2) GBM (2) Craniopharyngioma (1)	Multiple Myeloma (7) Unknown (4) Schwannoma (2) Meningothelial meningioma (1) NSCLC (1) Undifferentiated carcinoma (1)	Adenocarcinoma lung (2) Adenocarcinoma breast (2) Transitional cell carcinoma (2) Adenocarcinoma prostate (1) Adenocarcinoma Colon (1) Renal cell carcinoma (1) (Chromophobe) Squamous cell ca cervix (1) Leiomyosarcoma (1) Multiple myeloma (1)	Multiple myeloma (3) Neurofibroma (1) Adenoid cystic carcinoma (1)	Thymoma (2)
Imaging diagnosis	GBM (14) Schwannoma (4) Cavernous angioma (2) Chordoma (1) DNET (1) Epidermoid (1) Lymphoma (1) Medulloblastoma (2) Meningioma (4) Macroadenoma (4) SEGCA (2) Intracranial metastases (single) (8) Intracranial metastases (multiple) (27)	Schwannoma (3) Meningioma (9)	-	-	Thymoma (4)

*Brachial plexus (2), Lumbosacral plexus (21)

cord lesions (51.87 ± 14.93 years) with 60.9% females and 39.1% males. Secondary malignancies were also higher in this group (60.9%) as compared to the primary ones (39.1%). Twelve of these lesions were proven by histopathology.

Nerve

Five patients were males (83.3%) and one female (16.7%). Histopathology revealed two of these having a primary involvement (neurofibroma and adenoid cystic carcinoma) and the rest of them having multiple myeloma with chronic inflammatory demyelinating polyneuropathy (CIDP).

Primary versus Secondary malignancies

The mean age of patients with secondary malignancies (55.05 ± 13.05 years) was significantly higher (*P*-value <0.001, 95% CI: - 20.644 -10.991) than those with primary involvement (39.23 ± 17.06 years). Severe disability (MBI ≤12) at the time of admission was seen in 32 patients (41.0%) with secondary malignancies, as against 7 patients (9.1%) with a primary malignancy.

On MRI scanning the primary group had 44% intra-axial and 56% extra-axial lesions, whereas in the secondary group extra-axial involvement was proportionally higher (62.5% extra-axial and 32.5% intra-axial). Moreover, 5% of patients in the secondary group had both intra-axial and extra-axial involvement.

The most common imaging diagnosis in the primary group was glioma/glioblastoma multiforme (16), followed closely by meningioma (13). In the secondary group, the most common imaging diagnosis was multiple intracranial metastases (27) followed by multiple vertebral metastases (26). A single intracranial metastatic lesion was seen in eight patients. Histopathological confirmation rate was higher in the secondary group (i.e. 57.7% versus 18.2% in the primary group).

In patients with primary brain tumours, a total of 12 definite histopathologically confirmed diagnoses were obtained. Two patients who presented with myasthenia gravis had a thymoma on chest CT and another two who had a solitary plasmacytoma in the cervical vertebral lamina and spinous process were also included in this list.

The most common histopathological diagnosis in the secondary malignancies group was adenocarcinoma lung and multiple myeloma (ten patients each). Overall, the lung was the most common tissue of primary origin of metastases (15; 10 adenocarcinomas, 3 NSCLC, 2 bronchoalveolar) followed by plasma cells and the prostate. Other prominent diagnoses included adenocarcinoma breast, adenocarcinoma prostate and poorly/undifferentiated carcinoma. The details of diagnoses are listed in Table 3. Ten (6.45%) patients remained undiagnosed [Table 4].

Headache, hemiparesis, seizures, speech abnormality, altered sensorium and vomiting ($P < 0.001$) were seen in a considerably higher proportion in the intra-axial group whereas back pain, pain radiating to a limb, paraparesis and sensory loss ($P < 0.001$) were seen more frequently in the extra-axial group.

Discussion

Out of a total of 4893 patients admitted, 155 patients were enrolled and evaluated during the study period of 2 years. The mean duration of symptoms prior to diagnosis in our study was around 4 months; patients with spinal cord compression showed a shorter duration at a median of 2 months (range 5 days to 2 years).[12] Headache, back pain, and paraparesis were the most common presenting features. The brain was the most common site of involvement. Primary malignancies accounted for nearly 51% of cases with the remaining cases being secondary malignancies. The age of patients with secondary malignancies was significantly higher than of those belonging to the primary group. About 60% of cases were found to be intra-axial on MRI scanning, the rest being extra-axial. The most common imaging diagnosis was glioblastoma multiforme (primary malignancies group) and multiple intracranial metastases (secondary malignancies group). Histopathological confirmation was obtained in almost one-third of cases with the most common diagnoses being adenocarcinoma lung and multiple myeloma. The most common primary tissue of origin of metastases was the lung.

Clouston *et al.* in their study found headache, back pain and altered sensorium to be the most common symptoms in cancer patients having neurological complications. In addition to these, we found weakness (paraparesis, hemiparesis, quadriparesis and monoparesis) to be one of the leading initial manifestations of systemic malignancy. They also reported that 33% of patients with cancer, presenting with undiagnosed back pain, harbour an epidural metastasis.[3] Rodichok *et al.* and Ruff and Lanska, however, reported a higher incidence of epidural metastases in cancer patients with back pain (57% and 43%, respectively).[13,14] In our study, 43.5% of patients presenting with back pain were diagnosed having extra-axial lesions. Le chevalier *et al.* reported 58% of their patients presenting with motor deficits.[15] The high incidence of motor weakness in patients with a malignancy suggests that most primary care physicians tend to treat pain as a trivial symptom and patients are referred late to a specialised centre.

In our study, we noted that a high number of patients with malignancy presented with seizures (19.4%). This result was far more than reported by Gilbert and Grossman (4%) and Clouston *et al.* (4.5%). A higher incidence of seizure in our patient population may be due to the fact that patients with seizures were more likely to be referred to a neurology facility for further management *vis-à-vis* to a non-neurological setting.[1,3,6] We also found sphincter disturbances (bowel or bladder) in a higher proportion of patients (34.8%) as opposed to 2.1% (Clouston *et al.*); a disproportionately high incidence of sphincter involvement (96%) has also been reported from Pakistan.[3,16]

The most common site of malignancies overall was the brain (49.7%; primary and secondary included). A large proportion of patients had involvements of multiple sites, either vertebral or intracranial or both (23.9%), indicating the advanced stage at which first manifestations of malignancy were presented to us. Gilbert *et al.* reported epidural spinal compression in a marginally higher number of patients than the brain (primary and metastases) followed by plexus involvement.[1] Kori *et al.* reported 0.43% of patients with malignancies having brachial plexopathy.[17] Jaeckel reported nearly 15% of patients with malignancies initially presented with lumbosacral plexopathy.[18] A peripheral nervous system including peripheral nerves may be involved in 1.6%–17% of patients with malignancies.[19,20] Clouston *et al.* reported 18.6% of patients with brain metastasis (including skull base metastases).[3] This demonstrates the glaring difference between the presentation of malignancies in neurology versus oncology settings.

Even though our cohort was younger, those with secondary malignancies were in the higher age group (55 versus 40 years). Based on the age at the presentation, the geriatric group (≥65 years) is more likely to present with delirium, neurocognitive deficits, stroke and movement disorders while the non-geriatric group (<65 years) more often presents with headache, seizures and cranial nerve involvement (especially visual disturbances).[21] One must always be aware of hypoactive delirium that may mask as depression in this vulnerable geriatric population.[22] Non-thyroid, urologic, skin and gastrointestinal malignancies have been reported to be significantly higher in the geriatric group while ovarian and haematological malignancies are common in the non-geriatric age group. These findings can help in planning the battery of investigations, prioritizing one over the other, as appropriate.[11]

Imaging revealed a higher number of intra-axial lesions (59.4%) as compared to extra-axial (38.1%) with the most common imaging diagnosis in the intra-axial group being intracranial metastases and glioblastoma multiforme amongst primary tumours. Vertebral metastases among secondary malignancies and meningioma among primary tumours were the most common imaging diagnosis in the extra-axial group. Le Chevalier *et al.* noted multiple metastases in the brain in two-thirds of patients in their series. Approximately 10–15% of autopsies reveal intracranial

Table 3: Comparison between primary and secondary lesions

Variables	Primary	Secondary	*P*
Age (in years)	39.23±17.06	55.05±13.05	<0.001
Sex			
Male	38 (50.7%)	49 (61.3%)	1.866
Female	37 (49.3%)	31 (38.7%)	
Mean duration of illness (days)	169.10±426.51	99.69±101.53	0.168
Clinical features			
Pain			
Headache	39 (50.6%)	35 (44.9%)	0.518
Backache	10 (13.0%)	36 (46.2%)	20.424
Neck pain	06 (7.8%)	07 (9.0%)	0.070
Pain in a limb	09 (11.7%)	24 (30.8%)	8.419
Weakness			
Hemiparesis	15 (19.5%)	18 (23.1%)	5.334
Paraparesis	17 (22.1%)	26 (33.3%)	
Quadriparesis	11 (14.3%)	05 (6.4%)	
Monoparesis	01 (1.3%)	02 (2.6%)	
Vomiting	21 (27.3%)	21 (26.9%)	0.002
Sensory loss	33 (42.9%)	30 (38.5%)	0.310
Gait abnormality	37 (48.1%)	42 (53.8%)	0.521
Altered sensorium	18 (23.4%)	22 (28.2%)	0.472
Seizures	12 (15.6%)	18 (23.1%)	1.394
Speech abnormality	13 (16.9%)	11 (14.1%)	0.229
Visual disturbances	13 (16.9%)	02 (2.6%)	9.089
Cranial nerve involvement	26 (33.8%)	07 (9.0%)	14.212
Movement disorders	00 (0.0%)	00 (0.0%)	-
Sphincter involvement	26 (33.8%)	28 (35.9%)	0.078
Disability on admission			
MBI (0-12)	07 (9.1%)	32 (41.0%)	20.99
MBI (13-20)	70 (90.9%)	46 (59.0%)	
Site of involvement			
Brain	42 (56.0%)	35 (43.8%)	1.450
Spinal cord	20 (26.7%)	25 (31.2%)	0.695
Plexus	07 (9.3%)	16 (20.0%)	1.202
Nerve/Radicles	02 (2.7%)	04 (5.0%)	0.667
Neuromuscular junction	03 (3.9%)	01 (1.2%)	1.053
Skeletal	02 (2.7%)	37 (46.3%)	41.371
Multiple sites	05 (6.7%)	32 (40.0%)	25.426
MRI Characteristics			
Intra-axial	33 (44.0%)	26 (32.5%)	4.998
Extra-axial	42 (56.0%)	50 (62.5%)	
Both	00 (0.0%)	04 (5.0%)	
Biopsy proven	12 (16.0%)	47 (58.7%)	25.628
Pathological diagnosis	Glioblastoma multiformae (2) Thymoma (2)* Plasmacytoma (2)# Anaplastic ependymoma (1) Craniopharyngioma (1) Chordoma (1) Leiomyosarcoma (1) Meningothelial meningioma (1) Low grade glioma (1) Adenoid cystic carcinoma (1)	Adenocarcinoma lung (10) Multiple myeloma (10) Adenocarcinoma prostate (5) Adenocarcinoma breast (4) Squamous cell carcinoma (3) Poorly/undifferentiated carcinoma (3) Non-small cell lung carcinoma (3) Bronchoalveolar ca (2) Transitional cell ca (2) Follicular ca thyroid (2) Insular ca thyroid (1) Adenoca colon (1) Renal cell carcinoma (Chromophobe cell type) (1)	
Imaging diagnosis	GBM (16) Meningioma (13) Schwannoma (7) Ependymoma (6) Neurofibroma (4) Macroadenoma (4) Thymoma (3)	Vertebral metastases (26) Intracranial metastases (single) (8) Intracranial metastases (multiple) (27)	

Contd...

Table 3: Contd...

Variables	Primary	Secondary	*P*
	Cavernous angioma (2) Plasmacytoma (2) SEGCA (2) Craniopharyngioma (1) Chordoma (1) DNET (1) Epidermoid (1) Ewings sarcoma (1) Lymphoma (1) Medulloblastoma (1)		

*Patients with Myasthenia Gravis, #Solitary cervical vertebral lesion

Table 4: Comparison between intra-axial and extra-axial lesions

Variables	Intra-axial	Extra-axial	Both	*P*
Age in years (mean +/- SD)	45.22±17.79	47.98±16.81	58.25±4.71	0.266
Sex				
Male	34	50	03	0.751
Female	25	42	01	
Clinical features				
Pain				
Headache	49 (83.1%)	21 (22.8%)	04 (100%)	56.753
Backache	02 (3.4%)	40 (43.5%)	04 (100%)	37.410
Neck pain	03 (5.1%)	10 (10.9%)	04 (100%)	1.941
Pain in a limb	01 (1.7%)	29 (31.5%)	03 (75%)	26.152
Weakness				
Hemiparesis	25 (42.7%)	07 (7.6%)	01 (25%)	42.031
Paraparesis	03 (5.1%)	37 (40.2%)	03 (75%)	35.455
Quadriparesis	07 (11.9%)	09 (9.8%)	00 (00%)	17.650
Monoparesis	01 (1.7%)	02 (2.2%)	00 (00%)	4.560
Vomiting	30 (50.8%)	09 (9.8%)	03 (75%)	44.952
Sensory loss	13 (22.0%)	46 (50.0%)	04 (100%)	33.383
Gait abnormality	24 (40.7%)	52 (56.5%)	03 (75%)	34.622
Altered sensorium	31 (52.5%)	06 (6.5%)	03 (75%)	0.853
Seizures	25 (42.4%)	04 (4.3%)	01 (25%)	1.314
Speech abnormality	22 (37.3%)	02 (2.2%)	00 (00%)	-
Visual disturbances	07 (11.9%)	08 (8.7%)	00 (0.0%)	3.023
Cranial nerve involvement	14 (23.7%)	19 (20.7%)	00 (0.0%)	
Movement disorders	00 (0.0%)	00 (0.0%)	00 (0.0%)	
Sphincter involvement	19 (32.2%)	32 (34.8%)	03 (75%)	
Disability on admission				
MBI (0-12)	17 (28.8%)	20 (21.7%)	02 (50%)	2.301
MBI (13-20)	42 (71.2%)	72 (78.3%)	02 (50%)	
Site of involvement				
Brain	50 (84.7%)	24 (26.1%)	03 (75%)	50.531
Spinal cord	09 (15.3%)	33 (35.9%)	03 (75%)	11.626
Plexus	00 (0.0%)	06 (6.5%)	00 (00%)	4.274
Nerve/Radicles	00 (0.0%)	04 (4.3%)	00 (100%)	2.812
Neuromuscular junction	00 (0.0%)	35 (38.0%)	04 (100%)	39.842
Skeletal	07 (11.9%)	26 (28.3%)	04 (100%)	18.413
Multiple sites				
Origin				
Primary	33 (55.9%)	44 (47.8%)	00 (00%)	4.998
Secondary	26 (44.1%)	48 (52.2%)	04 (100%)	
Biopsy proven	18 (30.5%)	40 (43.5%)	01 (25%)	2.862
Pathological diagnosis	Adenocarcinoma lung (4) Adenocarcinoma prostate (4) Adenocarcinoma breast (2) Squamous cell carcinoma (1) Transitional cell carcinoma (1) Anaplastic ependymoma (1)	Adenocarcinoma lung (4) Multiple myeloma (4) Undifferentiated carcinoma (2) Non-small cell lung carcinoma (2) Bronchoalveolar carcinoma (2) Follicular ca thyroid (2) Adenocarcinoma prostate (1) Chordoma (1)	Adenocarcinoma lung (2) Transitional cell carcinoma (1) Unknown (1)	

Contd...

Table 4: Contd...

Variables	Intra-axial	Extra-axial	Both	*P*
		Craniopharyngioma (1) Chromophobe cell RCC (1) Leiomyosarcoma (1) Infiltrating ductal papilloma (1) Meningothelial meningioma (1) Ductal carcinoma breast (1) Thymoma (1) PDC (1) SCC invasive large cell keratinizing type (1) Adenocarcinoma colon (1) Adenoid cystic carcinoma (1)		
Imaging diagnosis	Intracranial metastases (single) (4) Intracranial metastases (multiple) (21) GBM (16) Ependymoma (7) Cavernous angioma (2) DNET (2) SEGCA (2) Medulloblastoma (2) Radiation myelitis (1)	Vertebral metastases (26) Meningioma (13) Schwannoma 1) Brachial plexus schwannoma (1) 2) Acoustic schwannoma (6) Paravertebral mass (5) Pituitary macroadenoma (4) Neurofibroma (4) Thymoma (3) Plasmacytoma (2) Epidermoid (1) Ewings sarcoma (1) Cavernous sinus lymphoma (1)	Intracranial and vertebral metastases (4)	

metastatic lesions signifying their asymptomatic seeding in brain parenchyma.[15] Kohler *et al.*, however, reported glioblastoma as the most common malignant and meningioma as the most common non-malignant tumour in adults.[7] A Chinese study also noted that multiple metastases account for nearly three-fourths of the total brain metastases.[23] A study from Pakistan, in an oncology setting reported 59.3% of patients having brain metastases with nearly 60% of them having multiple metastases.[16] The reason for the higher proportion of multiple intracranial metastases (84%) in our and other studies seems to be the better detection rate as a result of MRI and increased survival with better management modalities.

It has been reported that 15–50% of patients with metastases end up with an undiagnosed primary despite an extensive work-up.[15,24] We could not find primary site of malignancy in 1 in 10 cases (6.4%) which were labelled carcinoma with unknown primary [Table 5]. Ante-mortem histopathological confirmation could be achieved in 38.1% of our patients. A higher histopathological confirmation rate; 60% and 44.2% have been reported by Merchut and Le Chevalier *et al.*, respectively.[15,25] With recent advances in imaging, different groups have studied the predictive value of whole body CT, positron-emission CT (PET-CT), and PET-MRI in their respective settings; they recommend initial use of these techniques to increase the yield of cancer detection.[26-28] Overall, PET-CT appears to be a reasonable choice depending on the availability and cost constraints, especially in patients presenting with solitary lesions.[29]

The neuro-oncology register in the Netherlands reported lung, breast and prostate as the most common sites of primary cancer (in that order) causing metastases. Merchut reported lung as the most common primary followed by gastrointestinal tumours.[25] Le Chevalier *et al.* found melanoma to be the second after lung cancer.[14] Jin *et al.* reported an unknown primary followed by gastrointestinal tumours as the second and third most common tumours after lung.[16] Van de Pol *et al.* reported an unknown primary and breast as the second and third most common sites, respectively.[30] Barnholtz *et al.* reported melanoma and renal carcinoma as the next common sources of metastases in that order after lung.[31] Our finding falls in line with the reported literature.

Surprisingly, in our study, plasma cell dyscrasias (22%; 10: multiple myeloma, 2: solitary plasmacytoma) was the second most common diagnosis followed by adenocarcinoma prostate in the third place (9%). This is a novel finding as earlier series have reported a minuscule proportion (approximately 1%) of their patients having myeloma (9 out of 855; 77 out of 7004).[3,32] A higher index of suspicion for plasma cell dyscrasias must be kept while evaluating patients with suspected metastases. Nerve conduction studies in these patients, might unmask the underlying radiculo-neuropathy, especially in the elderly age group.

We did not find a high number of carcinoma breast patients (four patients), being a neurology referral facility, as compared to those reported in the literature. Hovestadt *et al.* reported that patients with breast cancer have a high referral index, almost twice as that of lung cancer for complications.[32] If we compare the age-standardized incidence rates of breast cancer per 100,000 population, India (25.8) has a significantly lower incidence when compared with the world average (43.1) and other parts of the world such as Europe (69.9), Canada (79.8), European Union (80.3) and Northern America (91.6).[33]

Table 5: Primary origin of metastases

A) Definite (histopathologically confirmed)

Primary tissue of origin	Number
Lung	15
Plasma cell	12
Prostate	5
Breast	4
Genitourinary	5
Thyroid	3
Gastrointestinal	1
Head and neck	1
Unknown	10

B) Probable (as defined in the text)

Primary tissue of origin	Number
Lung	12
Plasma cell	3
Gastrointestinal	2
Genitourinary	1
Head and neck	1

There were a few limitations to our study. Based on the evaluation protocol, only admitted patients were considered for inclusion in this study; owing to the low socio-economic profile of a majority of patients the complete battery of investigations planned as per protocol could not be completed. Post-mortem analysis is not done at our centre whereby patients with an undiagnosed primary could not be evaluated further.

Conclusion

Regarding neurological consultations with an unknown primary, organ-specific targeted efforts based on clinical evaluation for systemic localisation must be directed at diagnosing the primary. PET-CT may come handy in such situations. Besides providing an overview of malignancies primarily presenting with a neurological symptom, our study calls for a concerted effort in making a neuro-oncology register to aid early detection and timely initiation of therapy.

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Conflicts of interest

The authors declare that there are no financial and personal relationships with other people or organizations that could inappropriately influence (bias) their work.

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