Clinical Oncology: Case Reports

Case Report

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Acute Motor Sensory Axonal Neuropathy (AMSAN), a variant of Guillain Barré syndrome in a patient of Non-small cell Lung Carcinoma-A Case Report

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Abstract

Introduction: Guillain Barré Syndrome (GBS), has been commonly seen as a paraneoplastic manifestation in patients of small cell lung cancer. However, few published case reports of GBS are seldom re-ported in non-small cell lung cancer patients worldwide.

Case report: Here, we present the case of a 38 year old male, non-smoker, diagnosed with non- small lung carcinoma, specifically Ana-plastic Lymphoma Kinase (ALK) positive pulmonary adenocarcinoma with brain metastasis, treated with chemotherapy and palliative whole brain radiotherapy, that developed sudden onset weakness of all four limbs, along with bulbar involvement and respiratory compromise. The patient was diagnosed as Acute Motor Sensory Axonal Neuropathy (AMSAN), a variant of GBS, based on the Cerebrospinal Fluid (CSF) analysis and nerve conduction studies. He was treated with Non-In-vasive Ventilation (NIV) and Intravenous Immunoglobulin (IVIG) 2 gm/kg body weight over 5 days, after which he recovered satisfactorily.

Conclusion: To our knowledge, this is the first case report in India where AMSAN variant of GBS, developed in a patient of non-small cell lung carcinoma. We recommend that the oncologists should be cognizant of GBS presenting either as a paraneoplastic neurological syndrome or as a immune related adverse events of Immune Check-point Inhibitor (ICI) drugsused to treat patients of non-small cell lung cancer.

Keywords: Acute Motor Sensory Axonal Neuropathy (AMSAN); Guillain Barré Syndrome (GBS); Non-small cell lung carcinoma; Paraneoplastic Neurological Syndrome (PNS); Case report

Introduction

Paraneoplastic Neurological Syndromes (PNS) comprise a rare group of neurological disorders that can affect any part of the central nervous system, occurring due to the immune response against the antigens shared between the cancer cells and the neural cells [1]. It is caused by mechanisms other than brain metastasis or carcinomatosis meningitis, cancer therapy-related neurotoxicity, infections, coagulopathy, and metabolic or nutritional defects. Previously, few epidemiological studies have shown the incidence of PNS to be 1/100,00 person-years, proving the rarity yet underreporting of these syndromes [2]. PNS is more frequently seen in lung cancer patients, especially small cell lung carcinoma, where the most frequently reported PNS were Lambert-Eaton Myasthenic Syndrome (LEMS), sensory neuropathy, and limbic encephalitis [3]. Guillain Barré Syndrome (GBS) is one such disease of peripheral neuropathy, which rarely occurs as paraneoplastic syndrome in non-small cell lung carcinoma patients. Till date, very few cases of GBS have been recorded worldwide in patients with non-small cell lung carcinoma, especially pulmonary adenocarcinoma [4, 5].

To add further understanding, we are reporting this rare case of a 38-years-old male diagnosed with non-small cell lung carcinoma, specifically ALK-positive pulmonary adenocarcinoma, who presented with the complication of Acute Motor Sensory Axonal Neuropathy (AMSAN) variant of Guillain Barré Syndrome (GBS).

Case Presentation

History

A 38-year-old male patient, nonsmoker, hypertensive patient, was diagnosed with biopsy-proven non-small cell lung carcinoma in 2016. Patient had persistent complaints of right sided chest pain and dyspnea on exertion in 2016, with past history of hypertension since 2006 which was treated with 40/25 mg telmisartan and metoprolol and hypertriglyceridemia treated with 20 mg atorvastatin. Histopathology specimen showed tumor with tubule-papillary growth patterns, tubules and complex papillae lined by cuboidal to columnar cells and Psammoma calcifications (Figure 1). Immunohistochemistry panel was suggestive of pulmonary adenocarcinoma where tumor cells were positive for CK7, TTF-1, and p63 (Figure 2-8). Epidermal Growth Factor Receptor (EGFR) mutation analysis was negative but Anaplastic Lymphoma Kinase (ALK) translocation was positive for ALK D5F3. The whole body PET CECT scan at that time suggested distant metastasis, confirming the diagnosis of stage IV ALK positive non-small cell lung carcinoma.

The patient received three cycles of chemotherapy with pemetrexed 870 mg/m^2 and carboplatin 600 mg/m^2, along with folic acid and vi-tamin B12, and was started on maintenance oral Crizotinib. Howev-er, in August 2022, he experienced headaches and vertigo for 3 to 4 days. MRI brain with contrast showed multiple metastatic deposits, the largest measuring 33.4 mm × 26.5 mm × 33.5 mm in the right cer-ebellar vermis, causing effacement and narrowing of the fourth ventri-cle, for which the patient received palliative whole brain radiotherapy by 2DCRT to a dose of 30 Gy in 10 fractions, 5 fractions per week, following which the brain metastatic lesions reduced in size. He was then switched to palliative chemotherapy, where he received six cycles of paclitaxel and carboplatin until January 2023. The patient later received 7 cycles of 100 mg Lorlatinib, a third-generation ALK tyrosine kinase inhibitor.

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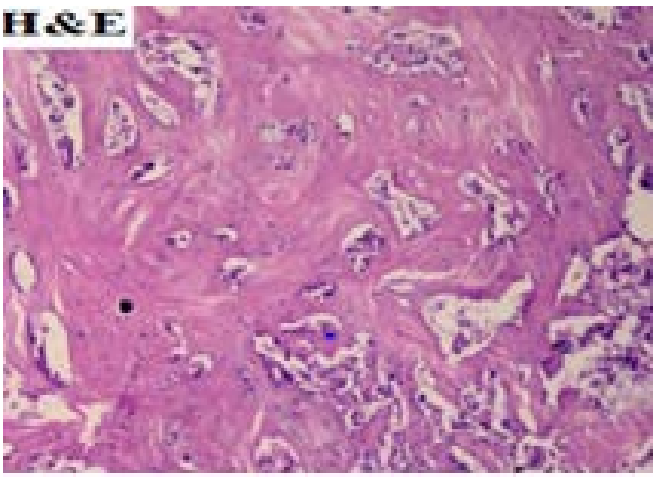

Figure 1: Histopathology showingpsammoma calcifications.

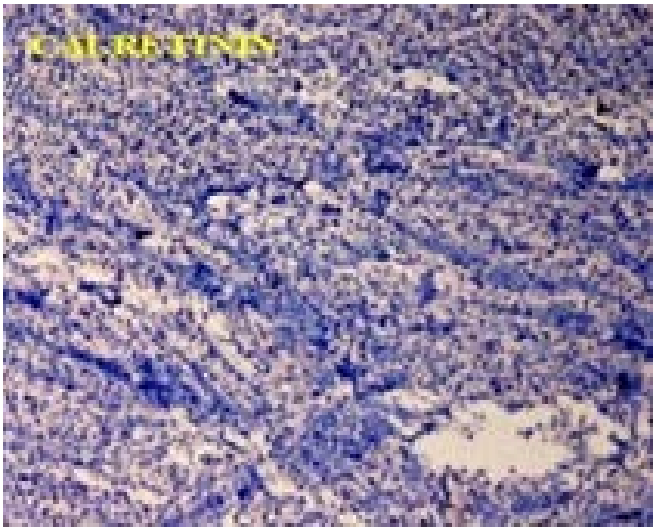

Figure 2: Calretinin (polyclonal) negative.

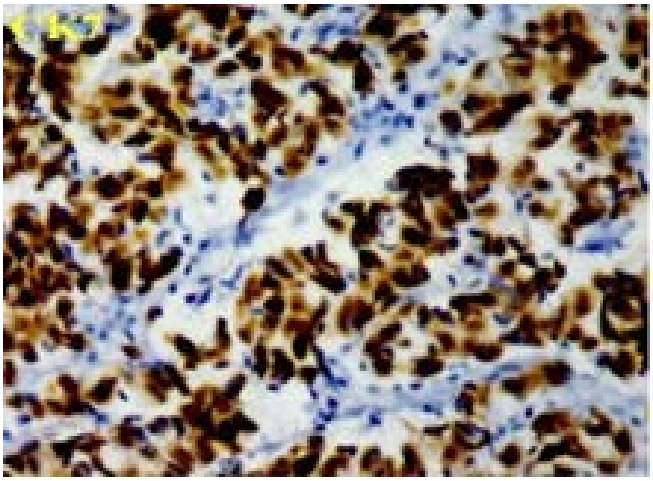

Figure 3: CK7 (OV-TL12/30) positive.

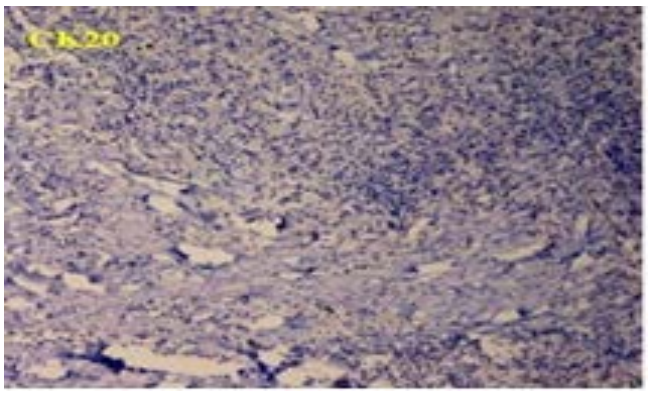

Figure 4: CK20 (L25) negative.

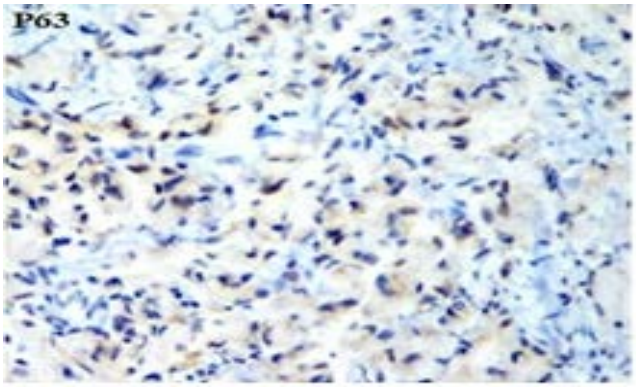

Figure 5: P63 (DAK-p63) positive.

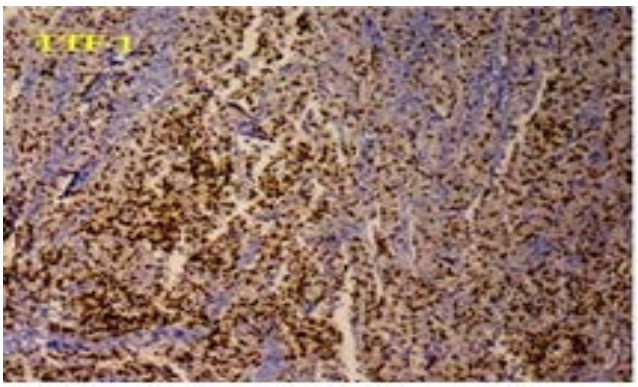

Figure 6: TTF-1 (8G7G3/1) positive.

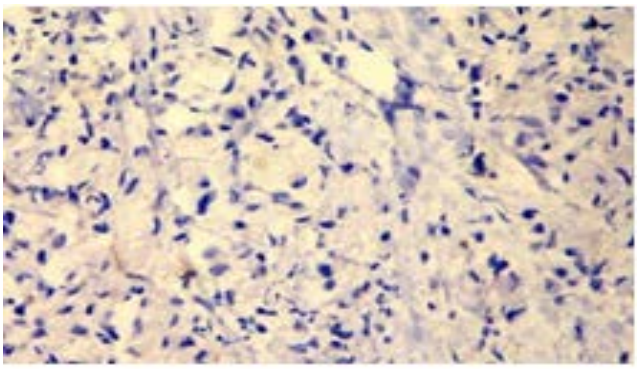

Figure 7: WT-1 (6FS-H2) negative.

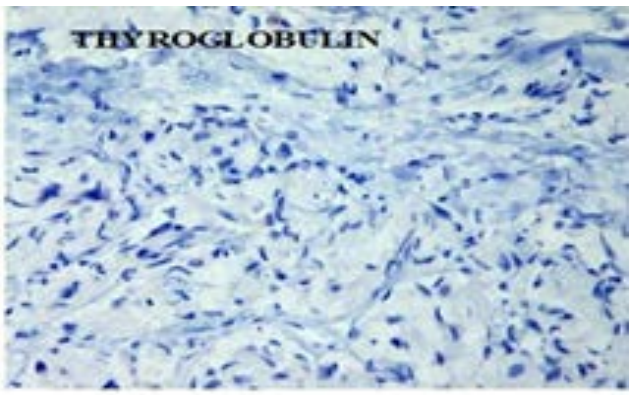

Figure 8: Thyroglobulin (2411) negative.

Recently, in January 2024, he developed a mild fever and cough, for which the patient took common cold medications. Two weeks later, the patient presented to the emergency department with complaints of numbness and pain in the legs since 8 days. He started experiencing acute onset weakness in the lower limbs since 4 days, which gradually progressed to the upper limbs over the next few days. He had difficulty standing up and walking on his own. The patient also had tingling sensation and facial weakness in left side of face and lips, slurred speech, nasal regurgitation, and difficulty swallowing for 4 days, which eventually progressed to shortness of breath after 2 days. He did not report any difficulty in urination or defecation, seizures, or tinnitus. He had no recent history of vaccinations, surgery, or trauma. Informed consent was obtained from the patient for the publication of this case report.

Clinical findings

On physical examination, his pulse was 132/min, blood pressure was 140/110 mmHg. Patient was conscious, oriented to time, place and person with an ECOG performance status of grade III. No pallor, cyanosis, clubbing, icterus or edema were noted. Neurological examination revealed pupils to be bilaterally reactive to light. There was symmetric distal weakness in all four limbs with motor power of 3/5 in lower limbs and power of 4/5 in upper limbs, along with hypotonia and areflexia. The plantar reflex elicited flexion, which ruled out upper motor neuron lesions. He had absent deep tendon reflexes as well as a reduced jaw reflex and gag reflex, suggesting bulbar palsy due to a lower motor neuron lesion. Sensory examination of pinprick, light touch, vibration, and proprioception were normal (Table 1).

Table 1: Timeline of clinical progression and management.

Dates	Clinical Manifestation	Diagnostic Assessments	Therapeutic Interventions
August to October 2016	Patient had persistentright sided chest painand dyspnea on exertion	Immunohistochemist rysuggestive of ALK positive pulmonary adenocarcinoma	He received three cycles of chemotherapy with pemetrexed 870 mg/m^2 and carboplatin 600 mg/m^2 along with oral Crizptinib
August-22	Patient experienced headaches and vertigo	MRI brain with contrast showed multiple metastatic deposits, the largest measuring 33.4 mm × 26.5 mm × 33.5 mm in the right cerebellar vermis	He received palliativewhole brain radiotherapy
August 2023 to january 24	-	-	He received palliative chemotherapy of six cycles of paclitaxel and carboplatin until January 2023 and then7 cycles of 100 mg Lorlatinib till January 2024
January 16th, 2024	Patient experienced fever and cough, followed by acute onset weakness in the lower limbs, gradually progressing to the upper limbs, slurred speech, nasal regurgitation, and difficulty swallowing,which eventually progressed to shortness of breath after 2 days	CNS examination revealed motor powerof 3/5 in lower limbs and power of 4/5 in upper limbs, along with hypotonia and areflexia and absent deep tendon reflexes	Lorlatinib was withheld. He was admitted in MICU and received NIV and IVIG 2 gm/kg body weight over 5 days. He was discharged after 10 days
	-	January 16th 2024: MRI brain revealed metastatic lesion in right cerebellum	-
		January 17th 2024: CSF analysis after lumbar puncture revealed albuminocytologica ldissociation. Nerve conduction studies diagnosed AMSAN variant of GBS	
February 20th, 2024	Follow up visit: power in his upper and lower limbs had increased upto 4/5	-	He was advised to continue limb physiotherapy, exercise continued

Diagnostic assessment

Blood investigations showed normal hemogram, normal liver and renal function tests buthypercholesteremia and hypertriglyceridemia was noted (serum cholesterol=251 mg/ dL, triglyceride=225 mg/dL, HDL=36 mg/dL, LDL=170 mg/dL).

Radiological examination with MRI Brain revealed haemorrhagic metastatic lesion measuring 1.4 cm × 1.3 cm × 1.1 cm in size in anterosuperior portion of right cerebellar hemisphere, which was a consistent finding in the previous scans, with no evidence of ischemic or hemorrhagic lesions or brain herniation (Figure 9). MRI whole spine screening exhibited no evidence of compression of cauda equine or canal stenosis (Figure 10).

Cerebrospinal Fluid (CSF) analysis after lumbar puncture revealed albuminocytological dissociation with elevated CSF proteins (87 mg/dL) and acellular, clear fluid with normal CSF glucose. GeneXpert of CSF for mycobacterium tuberculosis, CSF culture and KOH mount for fungal elements were negative.

Nerve conduction studies recorded prolonged distal latency, reduced Compound Muscle Action Potential (CMAP), reduced Conduction Velocity (CV) and absent F wave, suggestive of sensorymotor polyradiculopathy likely axonal, favoring AMSAN variant of GBS (Figures 11-13).

Based on the linical presentation and CSF findings, the diagnosis of Acute Motor Sensory Axonal Neuropathy (AMSAN), a variant of Guillain Barré syndrome with progressive bulbarpalsy was made.

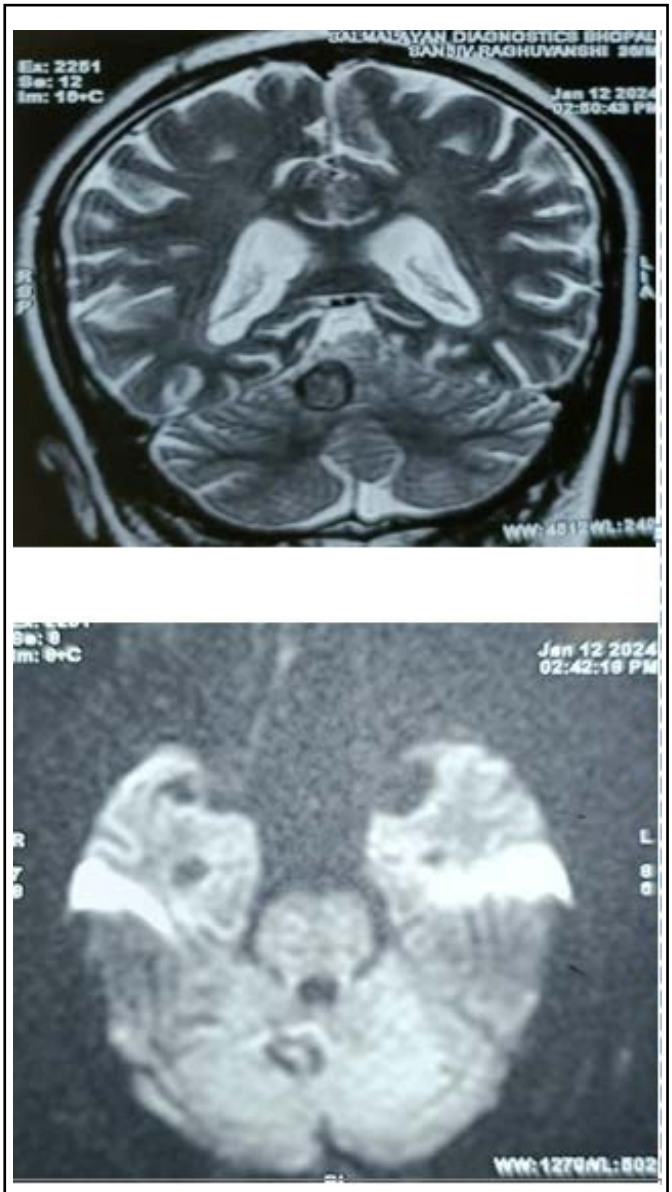

Figure 9: MRI brain plain showing 1.4 cm × 1.3 cm × 1.1 cm hemorrhagic metastatic lesion in right cerebellum.

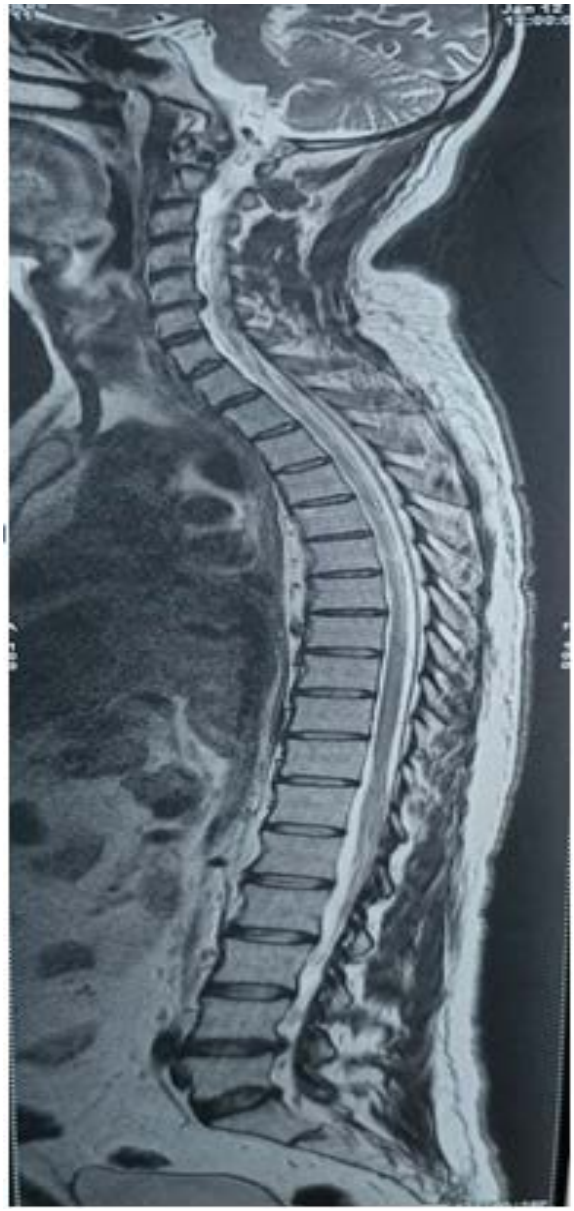

Figure 10: MRI whole spinescreening.

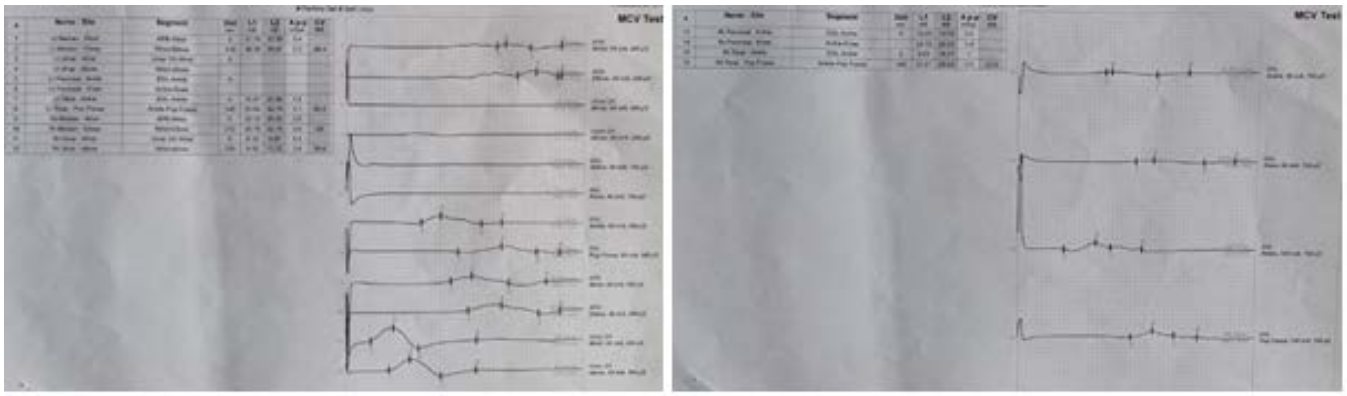

Figure 11: Motor conduction velocity.

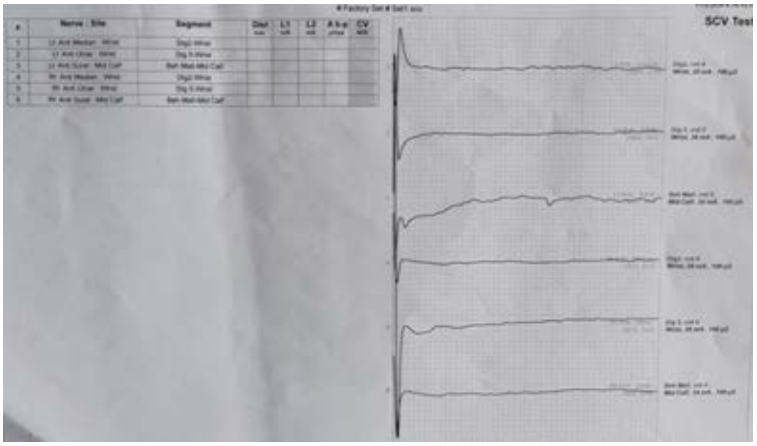

Figure 12: Sensory conduction velocity.

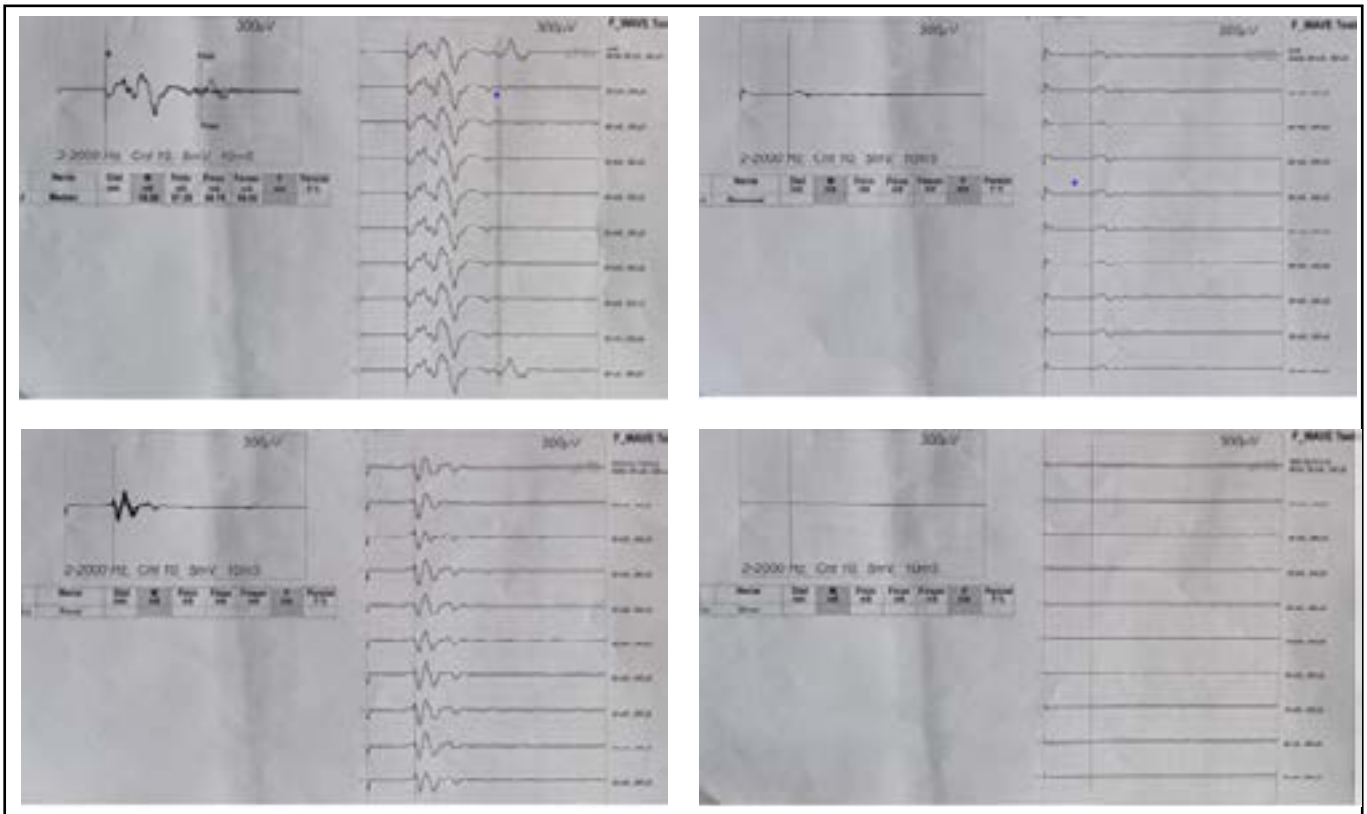

Figure 13: F-wave.

Therapeutic intervention

After onset of the neurological syndromes, Lorlatinib was withheld until further evaluation. Since the patient developed respiratory distress over next 2 days, he was admitted in Medical Intensive Care Unit (MICU) and was on oxygen support through Non-Invasive Ventilation (NIV).The patient was started on empiric IV piperacillin and tazobactam antibiotics and was treated with Intravenous Immunoglobulin (IVIG) 2 gm/kg body weight over 5 days for Guillain Barré syndrome. On treatment with IVIG therapy, physiotherapy and incentive spirometry, the patient was discharged after prolonged course of 10 days.

Follow-up and outcome

In the follow up clinic visit that was performed 1 month after the discharge, the patient had recovered satisfactorily. His power in upper and lower limbs had increased upto 4/5 and was advised to continue limb physiotherapy exercises.

Discussion

Guillain Barré Syndrome (GBS) is an acute immune-mediated polyneuropathy, that is triggered by a previous gastrointestinal or upper respiratory infection, causing demyelination or axonal damage. The demyelinating subtype causes Acute Inflammatory Demyelinating Polyradiculoneuropathy (AIDP), whereas the axonal subtype causes Acute Motor Axonal Neuropathy (AMAN) or acute motor and sensory axonal neuropathy (AMSAN) [6]. The pathogenesis involves a cross reaction of an antecedent infection (Campylobacter jejuni, Mycoplasma pneumoniae, cytomegalovirus, or even recent reports of SARS-Cov-2 infection) with the epitopes on the peripheral nerve, a mechanism known as "molecular mimicry" [7].

AMSAN is a rare but severe variant of GBS that requires prolonged ventilator support and poor functional residue as compared to other subtypes [8]. A recent prospective study in India found that the recov-

ery time was prolonged in the AMSAN subtype as well as those with cranial nerve involvement [9].

There have been numerous published reports of GBS seen in patients with small cell lung carcinoma patients [3-11]. However, only a few cases have been recorded in patients with non-small cell lung carcinoma. Most GBS cases in pulmonary adenocarcinoma are caused either due to paraneoplastic neurological syndrome or immune related adverse events of thenovel Programmed cell Death-1 (PD-1) Immune-Check Point Inhibitor (ICI) drugs [4, 5, 12-14].

With the advent of groundbreaking research in neuroscience and the identification of onconeural antibodies, PNS has intrigued clinicians due to their difficulty in diagnosis and management.

Theguidelines for the diagnosis of PNS were recently updated in 2021, which introduced the PNS- Care Score, requiring the presence of neuronal antibodies to confirm the diagnosis of paraneoplastic neurological syndrome [15]. However, in our case, the patient did not perform therecommended paraneoplastic panel, hence, the causal relationship between the AMSAN variant of GBS and non-small cell lung carcinoma could not be established in our study.

New onset neurological symptoms in lung cancer patients must require evaluation by the neurologists, as delayed diagnosis can lead to grave complications. In this case, symptoms of acute ascending paralysis with respiratory involvement and recent history of upper respiratory tract infection, prompted towards the diagnosis of GBS. The work up should include radiologicalinvestigations such as MRI brain, CSF analysis, and nerve conduction studies, as well as the paraneoplastic panel to rule out the paraneoplastic neurological syndromes. The use of ICIs like pembrolizumab and nivolumab must be noted, as they can cause rare yet underreported neurological immune-related adverse events like GBS in non-small cell lung carcinoma patients.

Conclusion

This is the first case report in India that highlights the rare complication of the AMSAN subtype of GBS in the patients with non-small cell lung carcinoma, which, if missed, can lead to poor clinical outcomes. It is imperative for oncologists to be cognizant of GBS as a paraneoplastic paraneoplastic manifestation, not just in small cell lung carcinoma patients, but also in patients of non-small celllung carcinoma.

Limitations

The patient did not perform the recommended antiganglioside antibodies or paraneoplastic antibodies panel, which could have aided in the definite diagnosis of paraneoplastic neurological syndrome.

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