"Person in the barrel" syndrome: Unusual heralding presentation of squamous cell carcinoma of the lung

Rajesh Verma, Rakesh Lalla, Tushar B Patil, Suresh Babu[1]

Departments of Neurology and [1]Pathology, King George Medical University, Lucknow, Uttar Pradesh, India

Abstract

Paraneoplastic neurological syndromes (PNS) are rare and relatively unusual in day to day clinical practice. Occasionally, PNS may be the heralding manifestation of the malignancy. Paraneoplastic syndromes are most commonly associated with small cell lung carcinoma and are rarely seen with non small cell lung carcinoma. In this case, we report a non-smoker, middle aged lady, who presented with "person in the barrel" syndrome due to myelo radiculoplexopathy as the first clinical manifestation of squamous cell carcinoma of the lung.

Key Words

Myelo-radiculoplexopathy, non small cell carcinoma, onco-antibodies, paraneoplastic neurological syndromes, person in the barrel syndrome

For correspondence:
Prof. Rajesh Verma, Department of Neurology, King George Medical University, Lucknow, Uttar Pradesh, India.
E-mail: drrajeshverma32@yahoo.com

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Introduction

Paraneoplastic neurological syndrome (PNS) is a disorder caused by remote effect of the tumor on the nervous system and not by direct invasion of the tumor cells. These are caused by cross reactivity between the cytokines, peptides or antibodies secreted by tumor cells which leads to damage of normal neural tissue.[1,2] The spectrum of paraneoplastic syndromes due to the lung cancer is diverse and can affect the central nervous system, peripheral nervous system, neuromuscular junction as well as the muscle [Table 1]. PNS is more commonly reported in patients with small cell lung carcinoma whereas non small cell carcinoma (NSCLC) is more commonly associated with hypertrophic osteoarthropathy. NSCLC comprises of adenocarcinoma, squamous cell carcinoma and large cell carcinoma and these variants of the lung cancer are rarely associated with PNS.[3] We hereby report a rare occurrence of paraneoplastic myelo-radiculoplexopathy as an initial presentation of squamous cell carcinoma of the lung.

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Case Report

A 37-years-old female patient presented with complaints of pain in the left arm since three months followed by weakness a month later. The patient had dull boring pain around the left shoulder which radiated on lateral aspect of left arm. The pain progressed over 15 days to involve lateral forearm as well as the thumb and the index finger. This pain did not interfere in her daily activities and would respond partly to analgesics. After about a month, she noticed acute onset weakness in raising her left arm above the shoulder. The weakness progressed over a day to involve the entire left limb and she was unable to flex her elbow or grip objects. The patient also had decreased perception of hot and cold as well as texture of clothes. The patient had noticed that her left shoulder appeared thinner than the right

Table 1: Paraneoplastic syndromes associated with lung cancer

Encephalomyelitis
Limbic encephalitis
Opsoclonus myoclonus
Cerebellar degeneration
Longitudinally extensive transverse myelitis
Retinopathy
Optic neuritis
Mononeuritis multiplex
Polyneuropathy
Autonomic neuropathy
Lambert eaton myesthenic syndrome
Dermatomyositis

and had history of occasional fasciculations in that region. There was no history of weakness or sensory loss in lower limbs or bladder bowel complaints. The patient had no history of fever, cough with expectoration or hemoptysis, trauma, weight loss, diabetes mellitus or hypertension. The patient did not complain of arthralgia, arthritis, rash or oral ulcers. She denied recent vaccination or unsafe sexual practices. With these above complaints, she consulted neurologist and was subjected to nerve conduction studies and electromyography and was diagnosed to have idiopathic left upper trunk brachial plexopathy. The patient was started on oral steroids, pain subsided transiently and the weakness did not respond to treatment. After about a month's therapy, she started noticing similar complaints in the right arm and at that time she was referred to our center for further evaluation and management. When the patient was presented in our outpatient department, she had developed painful weakness in both upper limbs (left > right) along with paraesthesia in both arms.

On examination, she was conscious, oriented and had normal higher mental functions. Cranial nerve examination was normal. Wasting was noted around the left shoulder girdle and left arm. The patient had hypotonia in both upper limbs. The power was grade 2 at shoulder joint, grade 3 at elbow joint, grade 4 at wrist extension and grade 5 at wrist flexion in the right upper limb as per Medical Research Council (MRC) grade. On the left side, power was MRC grade 2/5 at shoulder joint, 2/5 at elbow joint, 3/5 at wrist extension, 4/5 at wrist flexion and hand grip weakness was noted. The patient had normal power in both lower limbs. Deep tendon jerks in bilateral biceps, triceps, supinator were absent, ankle and knee jerk were normally elicitable. Bilateral plantar reflexes were flexor and abdominal reflex were present in all 4 quadrants. Sensory examination revealed about 30% loss in pin prick sensation in left arm in C5-C7 dermatome. Joint position and vibration sensation were impaired in the upper as well as lower limbs. The patient had positive Romberg's sign. There were no cerebellar signs, thickened nerves, stigma of tuberculosis or syphilis. No lymphadenopathy or spine abnormality was noted.

Complete hemogram, fasting blood sugar, renal and liver function tests were within normal range. Erythrocyte sedimentation rate was 24 mm at the end of one hour by Westergren method. C-reactive protein and anti- nuclear antibodies were negative. Anti-neutrophilic antibody (cANCA and pANCA), extractable nuclear antigens (ENA), serum were negative and cerebrospinal fluid (CSF) angiotensin converting enzyme (ACE) level was within normal limits. Microscopy of CSF revealed 10 cells, all of which were lymphocytes. CSF biochemistry showed protein 48 mg/dl and CSF sugar 67 mg/dl (corresponding blood sugar: 98 mg/dl). CSF for oligoclonal bands was positive. The CSF virology assessment for HSV PCR and IgM antibodies against herpes simplex, cytomegalovirus, Japanese encephalitis, varicella zoster virus, dengue and Epstein Barr virus was negative. Enzyme linked immunoassay (ELISA) for human immunodeficiency virus I and II was negative. Hepatitis B surface antigen (HBsAg) and anti- HCV antibody were also negative. Polymerase chain reaction for *M. tuberculosis* was negative. Cancer antigen 125 (CA-125) level was 45.39 U/ml (normal value below 35 U/ml). Onconeural antibodies could not be performed. The repeat nerve conduction studies revealed left sided pan-plexopathy and right upper trunk plexopathy. Electromyography was suggestive of denervation and showed fibrillation, fasciculations and large amplitude motor unit action potentials.

Magnetic resonance imaging (MRI) of cervical spine showed mild swelling of the cord along with hyperintense signals within the spinal cord on T2 weighted images. In addition, hyperintensities of multiple radicles were noted bilaterally on T2 fat suppression images [Figure 1]. Incidentally, MRI revealed an ill defined, heterogeneously enhancing lesion ($4 \times 3 \times 3$ cm^3) in the left upper lung [Figure 1]. Computed tomography (CT) thorax showed well defined heterogeneously enhancing soft tissue attenuation lesion with speculated margin in apico posterior segment of left upper lobe [Figure 2]. Rest of the lung parenchyma was normal and no significant mediastinal lymphadenopathy was noted. CT guided fine needle aspiration cytology revealed malignant epithelial cells lying in clusters in a hemorrhagic background [Figure 3].

The patient received intravenous methylprednisolone 1 gm/day for 5 days followed by oral prednisolone 1 mg/kg/day for one month. After the confirmation of the lung malignancy on follow up imaging, she was referred to oncology and was advised chemotherapy followed by radiotherapy.

MRI cervical spine [Figure 2] done after one month of steroid therapy showed disappearance of the cord hyperintensity but the mass lesion had increased significantly in the size ($6 \times 4 \times 6$ cm^3). The arm pain had responded but weakness persisted. The patient is currently receiving chemotherapy and radiotherapy.

Discussion

The neurological deficits in a patient harboring any malignant tumor can be either due to direct invasion of tumor, metastasis

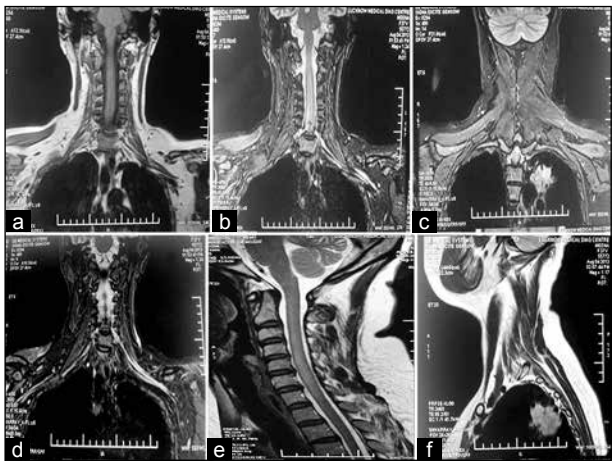

Figure 1: MRI cervical spine (coronal section) shows spinal cord swelling on (a) T1 and (b) T2 short tau inversion recovery (STIR) and (c) T2 STIR shows hyperintense lesion in the left lung apex. Figure d shows enhancement of multiple nerve radicles on T2 STIR coronal MRI. Figure e shows spinal cord swelling on T2 sagittal image extending from C3-C7 and (f) parasagittal T1 fat suppression with contrast image shows contrast enhancing irregular mass in the left lung apex

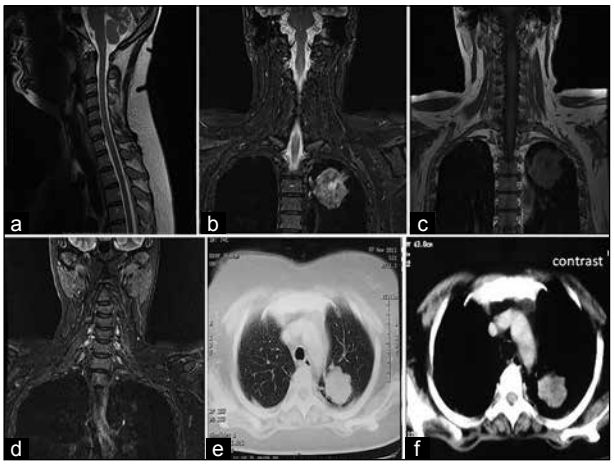

Figure 2: Follow up imaging after 2 months shows (a) resolution of hyperintensity in cervical cord on sagittal T2 weighted MRI. However, the lung mass was clearly evident and increased in size on, (b) coronal T2 short tau inversion recovery (STIR) and (c) T1 fat suppression. (d) STIR coronal view shows resolution of signal changes in the nerve roots. Figures e and f shows contrast enhancing rounded opacity in the apex of left lung on computed tomography of chest

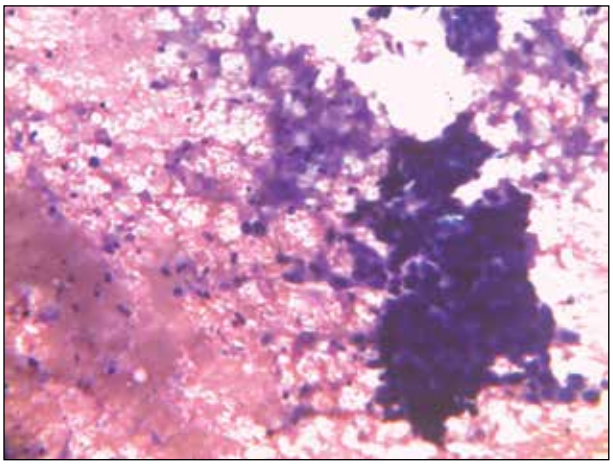

Figure 3: The tumor cells are pleomorphic, round to oval in shape having high nucleo cytoplasmic ratio, hyperchromatic nuclei inconspicuous nucleoli surrounded by moderate to abundant cytoplasm suggestive of squamous cell carcinoma

or as a part of paraneoplastic syndrome. Paraneoplastic neurological syndromes are rare and extremely disabling. Onset of symptoms is often acute to subacute with a progressive course and these symptoms may or may not be responsive to treatment. PNS have been commonly reported with cancers of lung, breast, followed by others like kidney, ovaries, thyroid, colon, etc.[4] PNS is almost exclusively reported with SCLC.[3] NSCLC is rarely associated with neurological paraneoplastic syndromes.[5,6]

In this case, the patient presented with sequential involvement of both upper limbs and normal strength in lower limbs mimicking the "person in the barrel" syndrome. Severe bilateral shoulder girdle weakness clinically defines the "man-in-the barrel" syndrome, rather more appropriately "person in the barrel" syndrome in this case. It was originally reported in the setting of cerebral hypoperfusion.[7] This syndrome has also been described in focal variant of amyotrophic lateral sclerosis (also known as Vulpain Bernhardt variant)[8] in which severe flaccid paralysis limited to upper limbs and it rarely involves lower limbs or bulbar musculature.[9] Anterior horn cell may be infected by viruses like enterovirus, HTLV, Japanese encephalitis virus, West Nile virus.[10-12] Similar syndrome of bi-brachial weakness was observed in human immunodeficiency virus (HIV) patients due to destruction of anterior horn cells, either by direct invasion or by cytokines. This weakness may occasionally respond to anti-retroviral therapy.[12,13] Other causes of bi-brachial weakness are spinal cord infarction, traumatic brain injury, central pontine myelinosis, medullary infarction and brachial plexopathy.[14,15]

Bilateral brachial plexopathy has been previously reported due to Hodgkin's disease or during its therapy, immune mediated nerve damage in diabetes mellitus, polyarteritis nodosa and Henoch Schonlein purpura.[14-17] Brachial plexopathy due to infiltration by tumor cells usually involves the lower trunk whereas immune mediated neuralagic amyotrophy is associated with upper trunk involvement.[18] In our patient, the mass was found in the apex of the left lung, without infiltrating the plexus and hence the etiopathogenesis was probably paraneoplastic.

Most paraneoplastic myelopathies (PNM) have associated encephalitis and have detectable titers of anti-Hu antibodies.[19] Spinal cord edema, a non specific sign of PNM, may be noted with or without changes in the brain MRI.[19,20] In our patient, spinal cord edema was noted [Figure 1] but the brain MRI was normal. Anti-Hu antibodies are not specific for PNM. Various other antibodies have also been detected associated with myelopathy.[19,21] These antibodies may vary as per the primary malignancy. On the other hand, different onconeural antibodies have been detected in the same tumor. On the basis of MRI, longitudinally extensive transverse myelitis (LETM) is defined as spinal cord involvement of more than 3 vertebral segments.[22] LETM is commonly seen in patients with neuromyelitis optica, multiple sclerosis, sarcoidosis, acute demyelinating encephalomyelitis, Sjogren syndrome, infectious diseases, paraneoplastic myelitis, etc.[22-25] LETM is an important differential diagnosis for paraneoplastic myelopathy.[19,26] Recently in a series of paraneoplastic myelopathy, LEM was noted in almost 65% patients. This study also highlighted the fact that it is not uncommon to find elevated CSF protein, pleocytosis and oligoclonal bands even in paraneoplastic myelopathy. Most patients were poorly responsive to steroids as well as definitive therapy.[27] In our patient, though follow-up spinal cord MRI T2 hyperintensity disappeared [Figure 2], the patient did not respond clinically and the weakness persisted. Mori *et al*., has also reported paraparesis with signal changes on spinal cord MRI due to PNS caused by squamous cell carcinoma of the lung.[5] Ezka *et al*., reported mononeuritis multiplex as the first manifestation of the lung adenocarcinoma.[6] Usually, myelopathy and radiculoplexopathy associated with malignancy is compressive in nature due to spinal metastasis or immune mediated as in PNS or due to radiotherapy.[28-30] Recently myeloradiculopathy with similar clinical presentation of bi-brachial weakness was reported in association with testicular malignancy and anti-Ma 2 antibody.[21] In this case, we report a patient who had features of both myelopathy (loss

of joint position sense, Romberg's positive along with spinal cord swelling) as well as plexopathy (weakness and sensory loss in upper limbs). To best of our knowledge bibrachial weakness due to paraneoplastic myeloradiculopathy has not been reported in the literature till now, especially in squamous cell carcinoma of the lung.

In absence of clinical manifestations of primary tumor, PNS is a difficult condition to diagnose and requires high degree of suspicion. It is an important differential diagnosis in cases of LETM, unexplained neuropathy or neuromuscular diseases. One should consider its possibility if symptoms are rapidly progressive and poorly responsive to the therapy. In our patient, PNS aided early diagnosis of the patient before the spread of tumor. Even though the tumor has responded to chemotherapy but the bi-brachial weakness remained unchanged.

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