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Case Report

Paraneoplastic Amyotrophic Lateral Sclerosis in a Patient with Pheochromocytoma

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Abstract

ALS is a progressive neurodegenerative disorder involving both upper and lower motor neurons. Paraneoplastic manifestation of ALS has been reported in association with certain cancers such as parathyroid hormone-related peptide-induced hypercalcemia, acromegaly, gynecomastia, gastric cancer. We present a 60-year-old male patient who was hospitalized multiple times for recurrent falls due to bilateral lower extremity weakness and painful muscle cramps. Physical exam findings revealed diffuse fasciculation is, atrophy and cramps suggestive of moto neuron disease. Work up revealed elevated 24 hours urine metanephrines and adrenal mass on abdominopelvic computerized tomography CT scan. He underwent laparoscopic resection of the tumour with histopathology confirming pheochromocytoma. Amyotrophic lateral sclerosis was later confirmed with nerve conduction study and electromyography.

Introduction

Motor neuron diseases have been identified as rare paraneoplastic neurologic syndrome PNS in association with a systemic neoplasm occurring in less than 1% of cancer patients. Paraneoplastic amyotrophic lateral sclerosis (pALS) is even rarer. Compared to pALS, more commonly reported PNS include Lambert Eaton myasthenia, limbic encephalitis, cerebellar degeneration, and peripheral neuropathy. The proposed pathophysiologic mechanism in paraneoplastic neurologic syndrome is an immunologic cross-reaction between tumour and nervous system antigenic epitopes. Anti-Hu, anti-Yo, Anti-Ri are the onconeural antibodies that have been linked to pALS. Pheochromocytoma, a type of neuroendocrine neoplasm, is uncommon, usually benign tumour of chromaffin cells of the adrenal medulla that produce catecholamines. Paraneoplastic syndromes associated with pheochromocytoma have been well established in association with breast cancer and lymphomas. There is paucity of reports regarding PNS in association with pheochromocytoma. Here we present a rare case of paraneoplastic ALS in a patient with pheochromocytoma.

Case Presentation

A 60-year-old male presented with a 2-month history of recurrent falls and generalized weakness worse in the lower extremities. He also reported decreased handgrip, dexterity, diffuse painful muscle cramps and spasms. He had presented to his primary care provider with similar complaints months prior to current presentation and had been treated with gabapentin. At the point of the initial presentation, he had no complaints of dysphagia, focal weakness, and change in speech quality or sensory deficits. Past medical history was significant for essential hypertension, generalized anxiety disorder, bilateral knee osteoarthritis, tobacco, methamphetamine, marijuana, and daily alcohol use. On physical examination, vital signs were within normal limits except for pulse rate of 134 BPM, regular. He appeared dishevelled, but mentally alert and appropriately oriented. Neurological exam revealed normal cranial nerves, with no focal deficits. Musculoskeletal examination revealed atrophy and fasciculation's in both arms in the deltoids, bilateral vast us lateralis and calf muscles, truncal muscles, stiffness of shoulders, elbows, hips, and knees with mild contractures. Muscle strength testing revealed global weakness 3/5 on Medical Research Council grading. 2+ reflexes were elicited in

the upper extremities but absent in the lower extremities. Babinski sign was present bilaterally. Labs were significant for mild anaemia, elevated creatinine phosphokinase and liver enzymes (Table 1). Urine toxicology screening was positive for marijuana and methamphetamines. Other work up including electrolytes were within normal limits. Computerized tomography scan of the head only revealed age related cortical atrophy with small vessel disease. He was admitted for the management of drug-induced rhabdomyolysis, managed with aggressive intravenous isotonic fluids and baclofen for muscle spasms. He made marginal improvement but had persistent, diffuse muscle fasciculation's and physical exam findings as above despite normalization of creatinine kinase level and aggressive management, including physical and occupational therapy up to hospital day five. Neurology was then consulted due to concerns for underlying motor neuron disease. He underwent further work up for rheumatologic disease including erythrocyte sedimentation rate (ESR), rheumatoid factor, anticitrullinated protein antibodies, antinuclear antibodies, anti-double stranded DNA, which were all normal except for elevated ESR. He was discharged to an inpatient rehabilitation hospital to continue physical and occupational therapy. An outpatient nerve conduction study and electromyography were arranged for further evaluation.

Lab	**Value**	**Reference**
Hemoglobin	12.5	13.7-17.0 g/dL
Alanine transaminase	94	16-61 U/L
Aspartate transaminase	384	15-37 U/L
Creatinine phosphokinase	10,508	39-308 U/L
Hypomagnesemia	1.2	1.7-2.4 mg/dL
Erythrocyte sedimentation rate	73	0-20
Rheumatoid factor	<10.0	0.0-15.0 IU/mL

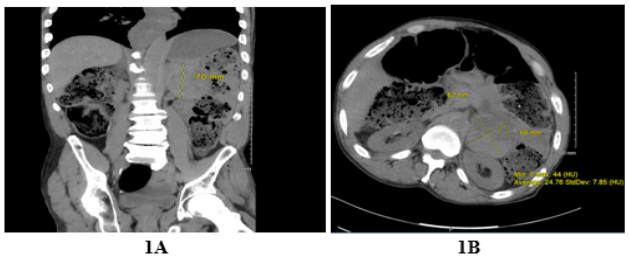
Table 1: Initial laboratory work up.

Nine days after discharge, he was readmitted for management of diffuse abdominal pain with nausea and vomiting. Physical examination again revealed worsening of his motor neuron disease symptoms with diffuse rigidity; diffuse fasciculation's, spasm worse in the lower extremities and inability to ambulate. Labs were unremarkable this time including urine drug screening. He underwent an abdominopelvic CT scan that revealed a 7cm, heterogeneous left adrenal mass with internal areas of calcification or haemorrhage (Figure 1). Work up revealed significantly elevated urine catecholamine's: 24-hr Urine catecholamine's: Epinephrine, Norepinephrine, Dopamine, Vanillylmandelic acid (Table 2). He was started on Terazosin for alpha blockade, with metoprolol initiated for beta blockade 2 days later. These were titrated up to minimize his fluctuations in blood pressure and heart rate. He underwent laparoscopic resection of the mass (measuring 9x6x3 cm). The pathology report confirmed pheochromocytoma with positive synaptophysin and S-100 and negative inhibin immunostaining. Muscle biopsy was normal. Work up for paraneoplastic neurologic syndrome included GAD-65 and Amphiphysin were negative (Table 2). He subsequently underwent outpatient electromyography and nerve conduction study with results consistent with ALS diagnosis.

Lab	Value	Reference
24hr Urine Vanillylmandelic acid	39.9	0.0-7.5 mg/24 hr
24hr Urine Epinephrine	106	0-20 ug/24 hr
24hr Urine Norepinephrine	636	0 -135 ug/24 hr
Urine Dopamine	457	Undefined
GAD-65	< 5.0	0.0-5.0 U/mL
Amphiphysin Antibody, IgG	Negative	

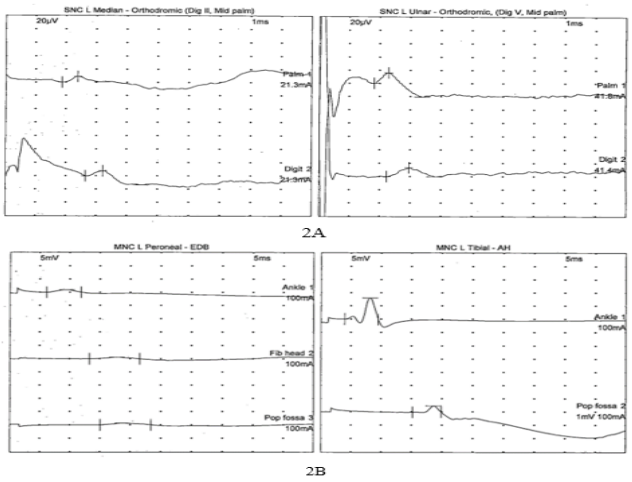
Table 2: Pheochromocytoma laboratory work-up.

Outpatient nerve conduction study of the extremities revealed; latency and decreased amplitude in the bilateral median and right ulnar sensory studies, no response in the bilateral sural sensory nerve action potentials (SNAPs), CMPAs with F waves showed prolonged latency in the bilateral median motor studies with decreased amplitude in the left median motor nerve, prolonged patency in the bilateral ulnar motor studies, with normal amplitudes, prolonged latency with decreased amplitude in the bilateral peroneal motor studies, tibial motor study was normal. (Figures 2A-F and 3) Needle electromyography of the extremities noted diffuse fasciculation's in all muscles, reduced recruitment, acute denervation potentials noted, and chronic changes in the motor units of almost all muscle studied consistent with the diagnosis ALS. The patient declined to further work up with Anti-Hu, Ant-Ri and Anti-Yo. Riluzole was then initiated. His physical examination at one year and then at eighteen months follow up visits were same as at discharge. He had no respiratory insufficiency, bulbar dysfunction, or autonomic dysfunction at the time of the latest follow-up.



1A 1B

Figure 1A: Sagittal view of the adrenal pheochromocytoma, **1B:** Coronal view of the adrenal pheochromocytoma.



2A

2B

Figure 2A: Left ulnar and median sensory nerve conduction (SNC) studies, **2B:** Left Tibial and peroneal sensory nerve conduction (SNC) studies.

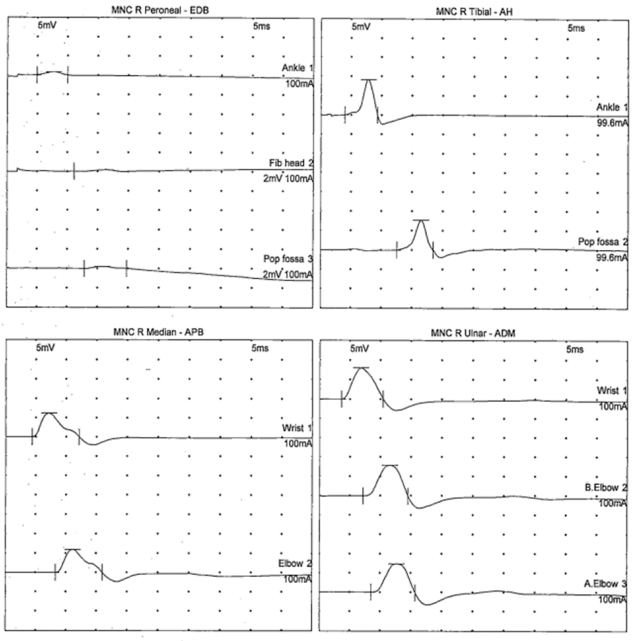


Figure 2C: Right peroneal, tibial, median and ulnar Motor nerve conduction studies.

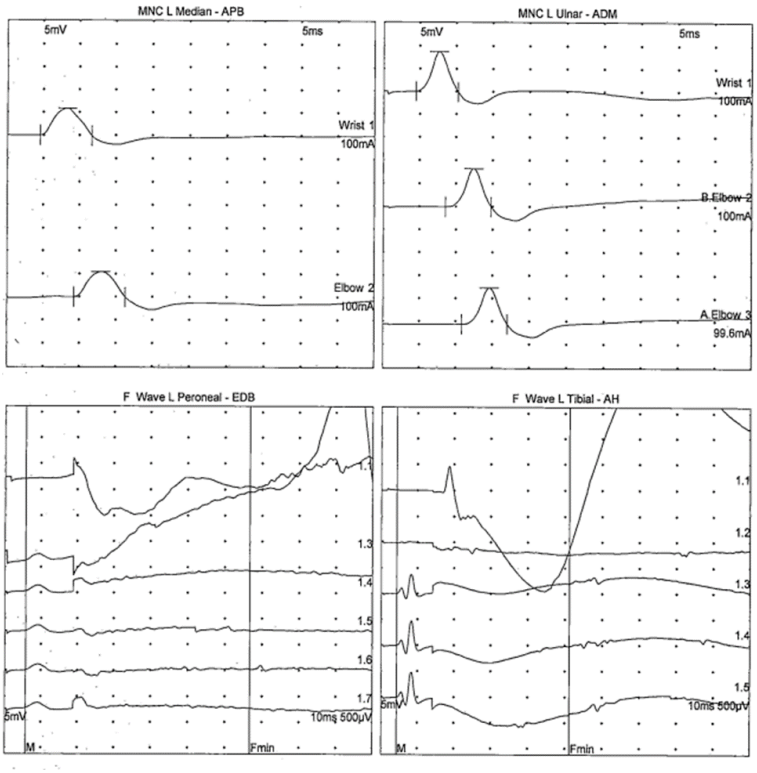


Figure 2D: Top: Left median and ulnar motor nerve conduction studies. Bottom: F waves in Left peroneal and Tibial conduction studies. (MNC: Motor nerve conduction studies, EDB: Extensor Digitorum brevis, AH: Abductor Hallucis)

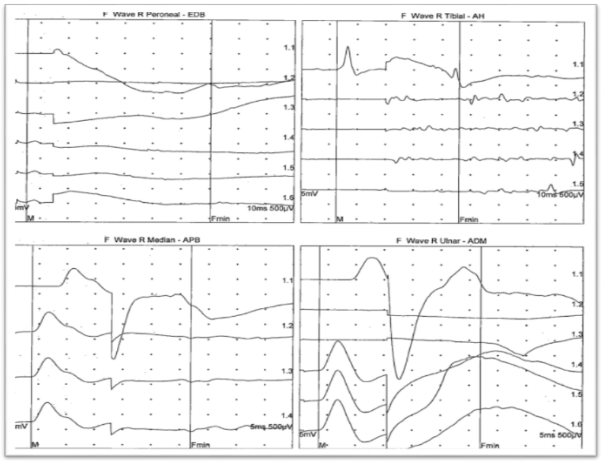


Figure 2E: F waves in Right Peroneal, Tibial, Median and Ulnar nerves. EDB: Extensor Digitorum brevis AH: Abductor Hallucis. APB: Abductor Policis Brevis. ADM: Abductor Digiti Minimi.

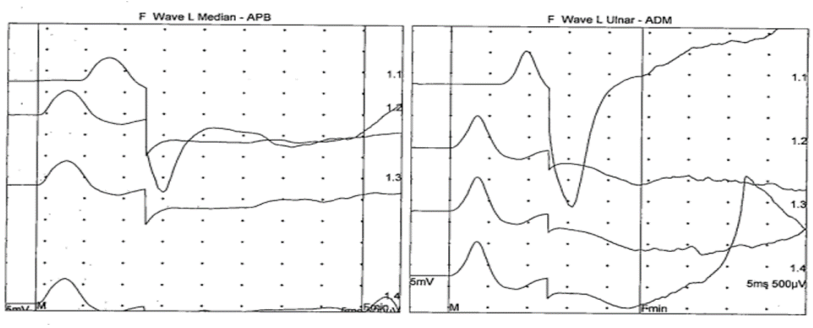


Figure 2F: F waves in Left Median and Ulnar nerves. APB: Abductor Policis Brevis. ADM: Abductor Digiti Minimi.

EMG Summary Table											
			Spontaneous					MUAP			Recruitment
Muscle	Nerve	Roots	IA	Fib	PSW	Fasc	H.F.	Amp	Dur.	PPP	Pattern
L. Abductor pollicis brevis	Median	C8-T1	N	None	None	None	None	1+	1+	1+	Reduced
L. Pronator teres	Median	C6-C7	N	None	None	None	None	N	N	N	N
L. Biceps brachii	Musculocutaneous	C5-C6	N	None	None	1+	None	1+	1+	1+	Discrete
L. Triceps brachii	Radial	C6-C8	N	None	None	1+	None	N	N	N	N
L. Deltoid	Axillary	C5-C6	N	1+	None	1+	None	N	N	N	N
L. Extensor digitorum brevis	Peroneal	L5-S1	N	1+	None	1+	None	1+	1+	1+	Reduced
L. Tibialis anterior	Deep peroneal (Fibular)	L4-L5	N	1+	None	1+	None	1+	1+	1+	Reduced
L. Gastrocnemius (Medial head)	Tibial	S1-S2	N	1+	None	1+	None	N	N	N	Reduced
R. Extensor digitorum brevis	Peroneal	L5-S1	N	None	None	2+ (slow)	None	1+	1+	1+	Reduced
R. Tibialis anterior	Deep peroneal (Fibular)	L4-L5	N	None	1+	1+	None	1+	1+	1+	Reduced
R. Gastrocnemius (Medial head)	Tibial	S1-S2	N	None	None	2+ (slow)	None	N	N	N	Reduced
R. Abductor pollicis brevis	Median	C8-T1	N	None	None	1+	None	N	N	N	Reduced
R. Pronator teres	Median	C6-C7	N	None	None	2+ (slow)	None	N	N	N	Reduced
R. Biceps brachii	Musculocutaneous	C5-C6	N	None	None	2+ (slow)	None	N	N	N	Reduced
R. Triceps brachii	Radial	C6-C8	N	None	None	None	None	N	N	N	N
R. Deltoid	Axillary	C5-C6	N	None	None	None	None	N	N	N	N

Figure 3: Summary of the Electromyographic Study.

Discussion

Case reports or small, uncontrolled case series make up most reports on paraneoplastic manifestation of ALS. Paraneoplastic neurological syndromes (PNS) manifest as heterogeneous neurological disorders in association with cancer. Most reported cases on PNS such as Lambert-Eaton syndrome, peripheral neuropathy, cerebellar degeneration, and motor neuropathy are historically associated with breast cancer, small cell lung cancer and lymphoproliferative disorders. Except for thymoma and small-cell lung cancer, the incidence of PNS in solid tumours is less than 1% [1]. Pheochromocytoma is a neuroendocrine tumour of the adrenal gland. The relatively commoner PNS in the setting of neuroendocrine tumours are Lambert Eaton myasthenia syndrome, autonomic dysfunction, limbic encephalitis, visceral plexopathy and cancer associated retinopathy [2]. Apart from the present case, pALS in association with pheochromocytoma has never been reported. PNS associated with pheochromocytoma tend to be humoral such as, parathyroid hormone-related peptide-induced hypercalcemia, acromegaly, gynecomastia, pyrexia, and marked inflammatory syndrome (related to excessive IL 6 secretion) [2,3]. Remarkably, Mehrpour et al. reported a case of pALS in association with neuroendocrine tumour of the stomach [4]. The pathophysiologic mechanism of PNS is still unclear. It is believed that tumour cells have the potential to produce active antigenic substances capable of cross-reacting with epitopes present on various central and peripheral nervous system cells [3]. There is ongoing research into the role of adaptive cell-mediated immunity in the etiology of PNS, still the mechanism through which onconeural antibodies mediate neuronal dysfunction remains imprecise in most cases. The diagnosis of paraneoplastic ALS is supported by its co-existence with a systemic malignancy with a well-established association. Laboratory evidence of onconeural antibodies such as anti-Hu, anti –Yo, anti-Ri in conjunction with

neurological symptoms among cancer patients lend more confidence to the diagnosis [5,6]. However, absence of these antibodies does not rule out PNS in the right clinical setting [5]. Giometto et al investigated the various types of PNS and onconeural antibodies among patients enrolled in the PNS Euro network database across 20 centres in Europe and reported absence of onconeural antibodies in about 18% of cases [7]. In our patient, initial work up with GAD-65 and amphiphysin for paraneoplastic Stiff man syndrome was negative. Ultimately, factors suggestive of paraneoplastic in this case is the presence of acute, progressive motor neuron symptoms preceding the diagnosis of pheochromocytoma, ALS confirmation by NCS and EMG, and plateauing of his motor neuron symptoms following tumour resection. Manifestation of PNS often precedes the diagnosis of cancer by weeks to months. In our patient, the main clinical symptoms of diffuse muscle cramps, weakness, atrophy and fasciculation's were present several months prior to pheochromocytoma being found incidentally on abdominal pelvic CT scan obtained to investigate abdominal pain. In most cases of paraneoplastic syndrome, the symptoms have been observed to resolve or stunt its progression with removal of the tumour or immune therapy [8-10]. Contrastingly, pALS tend to be indefinite once the deficits are well-manifest and irreversible neurological damage has occurred [8,9,11]. In our patient, the removal of the tumour succeeded in slowing the progression of his neurological deficits with his physical examination remaining same even at eighteen months follow up. Briani et al. investigated the frequency, clinical and immunologic attributes of PNS among lymphoma patients in the PNS Euro-network group database. The authors reported residual neurological symptoms in 24% of patients with PNS and non-Hodgkins' lymphoma [12].

In the end, there is currently no clear guideline or evidence supporting screening for cancer or onconeural antibodies among patients with ALS but should perhaps be considered in patients with ALS who have atypical features like acute or subacute progression, young age of onset, presence of neurologic signs affecting systems other than motor neurons [5,13,14].

Conclusion

Paraneoplastic ALS should be considered among patients presenting with relatively rapidly progressive motor neuron symptoms in the setting of cancer. In the absence of known malignancy, clinical judgment should direct surveillance for an occult neoplasm especially if pathognomonic paraneoplastic neurologic syndrome is present as delay in diagnosis may result in permanent and debilitating neurological dysfunction.

Statement of Ethics: Ethical approval was not required for this study. This case report complies guidelines for human studies and was connected in accordance with the world medical Association declaration of Helsinki. Ethical approval is not required for this study in accordance with national guidelines. No identifying information is revealed in the study. Written informed consent had been obtained from the patient for publication of their medical case and relevant images.

Conflict of Interest: Authors have no Conflict of Interest to disclose

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Data Availability Statement: All data generated or analyzed during this study are included in this article. Further inquiries can be directed to the corresponding author.

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