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Case Report: Suspicion of Amyloidosis Induced Peripheral Neuropathy

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Abstract

39 years old known case of chronic polymyositis and multiple comorbidities, developed new onset progressive sharp pain, numbness and reduced sensation on feet. Symptoms increased in severity and started ascending over one month duration affecting whole both lower limbs. Initial investigation started with Nerve Conduction Study (NCS)/ Electromyography (EMG) testing which showed sensory axonal neuropathy, then a full spectrum lab workup and lumbar magnetic resonance scans were done which didn't show any acute changes related to the concerning symptoms. Due to amyloidosis query, a buccal biopsy was done and result came back positive for Congo red stain raising the possibility of amyloidosis induced peripheral neuropathy. This case presents the diagnostic path of acute onset peripheral neuropathy in a patient with autoimmune condition, multi-comorbidities and suspicion of amyloidosis.

Keywords: Polymyositis; Amyloidosis; Peripheral neuropathy; Electromyography

Introduction

Peripheral neuropathy is one of the common neurologic problems encountered by neurologists and pain practitioners. The onset can be acute, subacute or chronic. Peripheral nerves consist of sensory, motor and autonomic nerve fibers. Nerve damage can be caused by several different conditions or might be idiopathic (unknown) [1,2]. Damage affecting sensory nerves might present as tingling, sharp, burning pain, extreme sensitivity to touch, lack of coordination and falling. If motor nerves are affected, muscle weakness and paralysis might present. Autonomic nerves damage cause heat intolerance, sweating disturbance, bowel motion and bladder contraction disturbance, drop in blood pressure which might cause dizziness or light-headedness [3]. Common causes of peripheral neuropathy are diabetes, exposure to toxic substances including (chemotherapeutics, alcohol, insecticides, solvents and heavy metals), B12 and folate vitamin deficiencies, connective tissue conditions, immune-mediated conditions, cancers such as lymphoma and multiple myeloma, chronic liver and kidney disease, HIV, lyme and thyroid conditions [1]. Neuropathy cases need comprehensive assessment including; detailed clinical history, complete physical examination, nerve conduction studies, full spectrum blood workup, genetic testing and in some cases nerve biopsies are carried out to identify the cause [4,5].

Case Presentation

Patient is a known case of multiple comorbidities (albinism, morbid, obesity, chronic polymyositis, osteoporosis, vitamin D insufficiency, multiple lumbar spine compression fractures treated with kyphoplasty procedure, steroid induced myopathy, multiple healed rib fractures, primary testicular dysfunction, diverticulitis, anal fistulae, chronic venous disease (stage 4) and hyperuricemia).

Patient presented with progressive sharp pain bouts, numbness and reduced sensation on feet. It has increased in severity over one month duration, ascending and covering lower limbs symmetrically to reach the saddle area. Patient denies any history of (recent major trauma, recent spinal interventions, new onset joint changes/pain, fever, rash, bowel motion changes, urinary symptoms, night sweats, weight loss, IV drug use, new medication/vaccination use, exposure to sick contacts, travel, risky sexual exposure) and sphincter control was not affected.

Physical exam

Albinism, obesity and general muscular atrophy. No (jaundice, pallor, cyanosis, enlarged lymph nodes).

Vital signs

Temperature: 36.8°C.

Blood pressure: 145/70 mmHg (when lying down), 140/70 mmHg (after standing up).

Heart rate: 84/min.

Respiratory rate: 15.

Neuro: PERRLA, intact cranial nerves 2-12, no focal signs, no diadochokinesis, physiologic finger-nose-test.

Lumbar Sacral Spine (LSS): Kyphoplasty procedure scar, no spine tenderness on percussion, evident reduced (flexion, extension, lateral flexion and rotation).

Lower limbs: Low gait velocity, short stride length, muscular atrophy, stage 4 varicose veins with skin hemosiderosis over ankles, soles skin dryness and multiple calluses. Proximal myopathy of both hipslexion grade 3/5 on the MRC scale.

Evident hyperalgesia, reduced perception of fine, sharp, vibration and position sense over lower limbs bilaterally more noticed on his soles and ankles. No foot drop.

Deep tendon reflex status: Patellar tendon 2 /2, Achilles tendon 0/2 bilaterally.

CVS: No facial rash, no increased cardiac dullness, no Jugular Vein Distention (JVD) elevation, normal S1/S2, no pathologic murmurs.

Respiratory: Trachea central, good chest expansion, resonant percussion, good air entry bilaterally, no added sounds.

Abdomen: Soft lax, no distention or fullness, no tenderness of the abdomen, no hepato spleen megaly, no pulsatile motion or masses, bowel sounds are regular.

Investigations

NCS/EMG: Decrease SNAPs of both sural nerves, decrease MAPs of both peroneal nerves **(Tables 1 and 2) (Figures 1-6)**.

Table 1: Sural le t and right comparison.

Site	NR	Peak (ms)	Normal peak (ms)	O-P Amp (μV)	Normal O-P Amp	Site 1	Site 2	Delta-0 (ms)	Distance (cm)	Velocity (m/s)	Normal velocity (m/s)
Left sural anti sensory (Lat mall)											
Calf	-	3.7	<4.0	6.8	>14	Calf	Lat mall	3	13	43	>35
Right sural anti sensory (Lat mall)											
Calf	-	3.7	<4.0	6.9	>14	Calf	Lat mall	3.1	13	42	>35
Note: Reduced anti sensory nerve action potential for both sural nerves.											

Table 2: Motor left and right comparison.

Site	L Lat (ms)	R Lat (ms)	L-R Lat (ms)	L Amp (mV)	R Amp (mV)	L-R Amp (%)	Site 1	Site 2	L Velocity (m/s)	R Velocity (m/s)	L-R Velocity (m/s)
Peroneal motor (Ext Dig Brev)											
Ankle	3.9	2.7	1.2	2.6	2.9	10.3					
Tibila motor (Abd Hall Brev)											
Ankle	5.4	5.5	0.1	4.9	5	2					
Note: Reduced both peroneal motor nerve conduction velocity.											

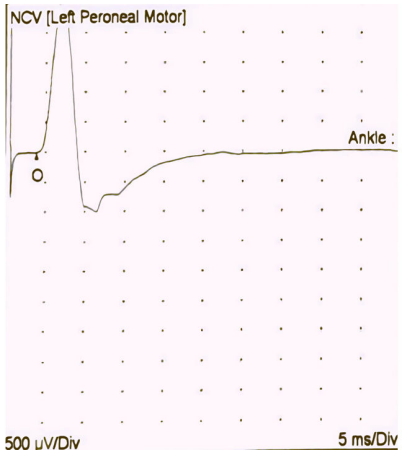

Figure 1: Reduced left peroneal motor nerve conduction velocity at 500 μV/Div.

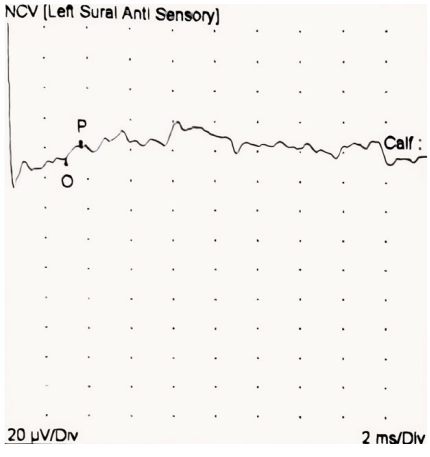

Figure 2: Reduced left anti sensory sural nerve action potential at 20 μV/Div.

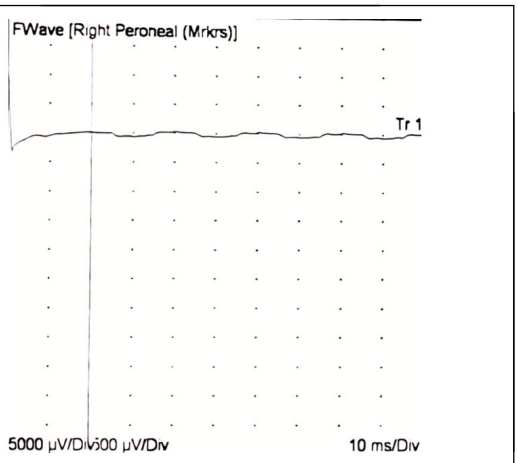

Figure 3: Reduced right peroneal motor nerve conduction velocity at 5000 µV/Div.

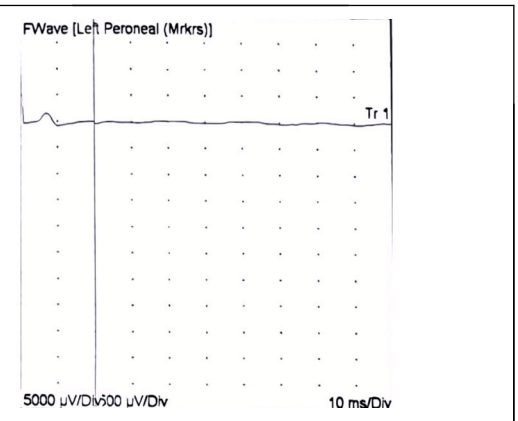

Figure 4: Reduced left peroneal motor nerve conduction velocity at 5000 µV/Div.

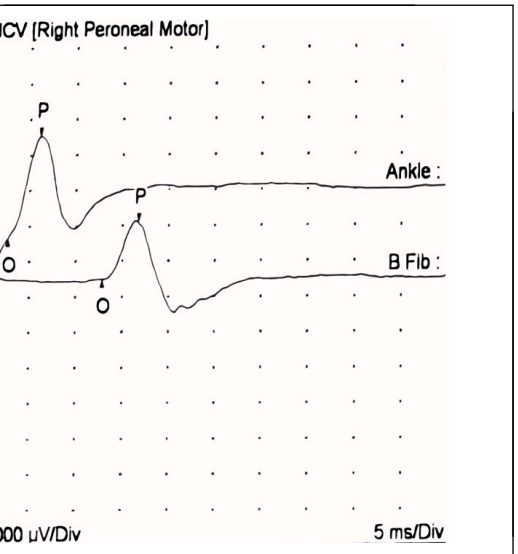

Figure 5: Reduced right peroneal motor nerve conduction velocity at 1000 µV/Div.

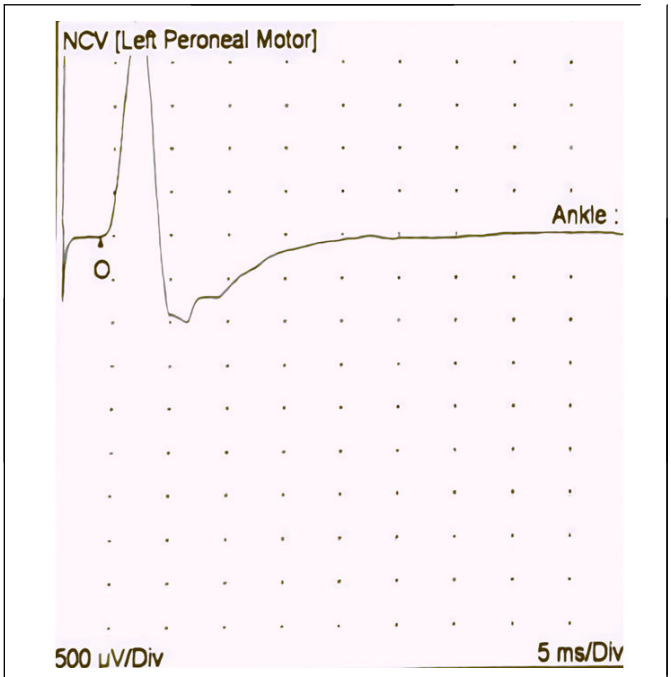

Figure 6: Reduced right peroneal motor nerve conduction velocity at 500 µV/Div.

LSS MR: Mild to moderate degenerative disk disease changes, no (disk protrusion, canal stenosis, foraminal narrowing) at any level, lumbar vertebral heights well restored, no fractures-cement leakage, conus is unremarkable.

Blood workup: HBA1c, random blood sugar, Creatine Phosphokinase (CPK), Aspartate Transaminase (AST), Alanine Aminotransferase (ALT), vitamin B12/B1/E, Complement levels (C3,C4), Erythrocyte Sedimentation Rate (ESR), Anti-Double Stranded DNA (Anti-dsDNA), Myeloperoxidase (MPO), Systemic mastocytosis (Sm), Ribonucleoprotein (RNP), anti-jo-1, Scl-70, cenp-b, Antinuclear Antibodies (ANA), Anti-Neutrophil Cytoplasmic Antibodies (C-ANCA), Perinuclear Anti-Neutrophil Cytoplasmic Antibodies (P-ANCA), ross-a-52, PR3 (proteinase 3), M2 Anti-Mitochondrial Antibodies (AMA-M2), antibodies to Liver Cytosol Antigen Type 1 (LC1), Liver Kidney Microsomal Antibody Type 1 (LKM1), pm-scl100, srp54, sp100, gp100, ku, lass-b, Serum Protein Electrophoresis (SPEP), anti-gliadin Ab., copper test **(Table 3).**

All the blood workup investigations listed above were normal. Due to this presentation, it was worth to look for fewer common conditions as amyloidosis, so a buccal biopsy was done. Biopsy pathology report showed; thickened eroded oral mucosa, severely inflamed granulation tissue with dense plasma cell infiltrate. Congo red stain for amyloid is positive, with no malignancy.

This positive test has raised the possibility of amyloidosis induced peripheral neuropathy. In order to reevaluate the case and confirm the biopsy results, the patient was referred to amyloidosis specialized center. The positive buccal mucosa biopsy done initially was sent to the center for revaluation.

The re-evaluated buccal biopsy pathology report shows: Mixed, dense inflammatory infiltrates with abundant plasma cells in subepithelial connective tissue and few lymphocytes. No certain evidence of atypical birefringence in the Congo red stain. The inflammation is compatible with periodontitis, no positive reaction with antibodies against amyloid P component, AA-amyloid, apolipoprotein A1, lambda light chain (3 antibodies), kappa light chain (2 antibodies) and transthyretin no light chain restriction in the inflammatory infiltrate **(Table 4).**

Table 3: Blood workup investigations.

Test	Result	Test	Result
HbA1c	Normal	Antibodies to Liver Cytosol Antigen Type 1 (LC1)	Normal
Random blood sugar		Liver Kidney Microsomal Antibody Type 1 (LKM1)	
Creatine Phosphokinase (CPK)		pm-scl100	
Aspartate Transaminase (AST)		srp54	
Alanine Aminotransferase (ALT)		sp100	
Vitamin B12		gp100	
Vitamin B1		ku	
Vitamin E		lass-b	
Copper test		Serum Protein Electrophoresis (SPEP)	
Complement Levels (C3,C4)		anti-gliadin Ab.	
Erythrocyte Sedimentation Rate (ESR)		M2 Anti-Mitochondrial Antibodies (AMA-M2)	
Anti-Double Stranded DNA (Anti-ds DNA)		Ribonucleoprotein (smRNP)	
Myeloperoxidase (MPO)		Anti-jo-1	
Systemic Mastocytosis (SM)		Scl-70	
Perinuclear Anti-Neutrophil Cytoplasmic Antibodies (P-ANCA)		Cenp-B Antinuclear Antibodies (ANA)	
ross-a-52		Anti-Neutrophil Cytoplasmic	
pr3		Antibodies (C-ANCA)	

Table 4: Buccal biopsy investigations.

Biopsy	Result
Buccal biopsy pathology report	Congo red stain for amyloid is positive with no malignancy. Thickened eroded oral mucosa severely inflamed granulation tissue with dense plasma cell infiltrate
Re-evaluated buccal biopsy pathology report	Mixed, dense inflammatory infiltrates with abundant plasma cells in subepithelial connective tissue and few lymphocytes. No certain evidence of atypical birefringence in the congo red stain. No positive reaction with antibodies against amyloid P component, AA-amyloid, apolipoprotein A1, lambda light chain (3 antibodies), kappa light chain (2 antibodies) and transthyretin no light chain restriction in the inflammatory infiltrate.

The following investigations were done at the amyloidosis specialized center:

Molecular genetic investigation of the peripheral blood: No disease-causing pathogenic sequence variants in the analyzed regions of the *TTR* gene. We can exclude hereditary amyloidosis due to a pathogenic sequence variant in the coding regions of the *TR* gene in the patient.

Echocardiography: Good systolic function (left ventricular ejection function 60%), no regional contraction disturbances, good longitudinal function, no relevant left-ventricular diastolic dysfunction, LA, RA and RV not enlarged, good RV function. No pericardial effusion. The vena cava is not congested, valves sonography and doppler are regular. Echocardiographic criteria for amyloidosis not fulfilled.

Abdominal fat aspiration: No deposits of amyloid found **(Table 5)**.

Table 5: Amyloidosis specialized center investigations.

Test	Result
Molecular genetics of the peripheral blood	No disease-causing pathogenic sequence variants in the analyzed regions of the *TTR* gene
Echocardiography	Good systolic function (left ventricular ejection function 60%), no regional contraction disturbances, good longitudinal function, no relevant left-ventricular diastolic dysfunction, LA, RA, and RV not enlarged, good RV function. No pericardial effusion. The vena cava is not congested, valves sonography and doppler are regular. Echocardiographic criteria for amyloidosis not fulfilled
Abdominal fat aspiration	No deposits of amyloid found

Results and Discussion

Approaching cases of polyneuropathy needs a thorough systemic path; detailed history, complete physical exam and NCS/EMG are important steps in the path to confirm neuropathy diagnosis. Blood workup, tissue aspiration, genetic testing and skin biopsy are investigations carried to reach solid diagnosis. Sural nerve biopsy is rarely done, it is reserved if the picture is not clear and needs further confirmation. It has its own complications of pain, infection, sensory loss and delayed wound healing [1,4,6,7]. In this case, it is noteworthy that the patient suffered from multiple comorbidities and autoimmune polymyositis condition, which raised the suspicion of autoimmune connective tissue disease as the triggering cause, but the investigations meant for connective tissue disease were normal. As part of the workup, metabolic, celiac, copper, B vitamins and folate levels were done and turned also normal. This acute painful and rapid progressive presentation brought up a query of more rare cause as amyloidosis, so a buccal biopsy was done to check for Congo red stain, which turned positive, raising concerns about amyloidosis condition [6,8]. Patient was assessed at amyloidosis specialized center. The buccal biopsy was retested again for Congo red staining and furtherly for amyloid antibodies. The patient was tested correspondingly for molecular genetics of the peripheral blood, echocardiography and abdominal fat aspiration for deposits of amyloid [6,9,10]. All these tests turned negative for amyloid and the buccal biopsy revaluation was compatible with periodontitis, with no evidence of amyloid deposits.

Patient was started on vitamin D 50,000 IU weekly, daily (oral b complex, oral alpha lipoic acid 1000 mg and pregabalin 75 mg) [11-13].

Patient was directed to follow-up with neurology and pain clinics after two weeks for revaluation of a presumed case of connective tissue versus idiopathic peripheral neuropathy condition.

Conclusion

In order to confirm or exclude amyloidosis suspicion, full spectrum amyloidosis testing should be completed at a

specialized center through revaluating biopsies for amyloid antibodies, undertaking peripheral blood molecular genetics, echocardiography and abdominal fat aspiration.

Data Availability Statement

The original contributions presented in the study are included in the article.

Supplementary Material

Further inquiries can be directed to the corresponding author.

Ethics Statement

The patient and participants provided their written informed consent to participate in this case report.

Author Contributions

The authors listed have made a substantial, direct and intellectual contribution to the work and approved it for publication.

Conflict of Interest

The authors declare that the report was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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