Mixed connective tissue disease with severe axonal polyneuropathy
A case report

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Abstract

Mixed Connective Tissue Disease (MCTD) is a unique disorder characterized by the presence of high titer of anti-U1 Ribonucloprotein (RNP) antibody with overlapping features of various connective tissue disorders including Systemic lupus Erythematosus (SLE), scleroderma and Myositis. Severe renal or neurological involvement is unusual with this disorder. In this report we describe a case of biopsy confirmed severe sensorimotor axonal polyneuropathy in a middle aged gentleman as his first presentation for MCTD.

Keywords: Mixed Connective Tissue Disease, Polyneuropathies, Pulmonary Arterial Hypertension.

Introduction

Multi system involvement is the hallmark of syndrome described and named after Gordon Sharp and his colleagues[1]. It is a inflammatory disease characterized by abnormal B- and T-cell response to apoptotically modified nuclear antigens in the messenger RNA , most commonly the U1-ribonucleoprotein. It commonly affects women between the ages of 15-30 years. Not only is neurological involvement rare, generally speaking in autoimmune disorders, it is exceptionally rare in mixed connective tissue disease. The manifestations are variable making the diagnosis and management challenging. These challenges are highlighted in our case report that presented with mixed polyneuropathy.

Case Report

A 36-years-old Omani gentleman presented to the emergency department at the Sultan Qaboos University Hospital with a 6- month history of gradual lower leg weakness and swelling with inability to walk. In the preceding year, he was hospitalized on multiple occasions, both locally and aboard, for polyarthralgia, low back pain and paresthesia involving both of his feet. His other comorbidities included difficult to control hypertension, for which he was on three separate classes of anti-hypertensive medications. The patient was admitted prior to this time with hypertensive encephalopathy requiring high dependency care, from which he made an uneventful recovery. In addition, he had lumbar spine degenerative disc disease. There was no significant family history of connective tissue disorders. He was unfortunately unable to continue his job in construction due to his symptoms. He was also a heavy smoker and previously consumed alcohol of undisclosed duration and quantity.

On examination in the emergency department, he looked unwell, with a Glasgow Coma Scale (GCS) score of 15/15. He was afebrile with a regular pulse at a rate of 82 beats per minute, a transcutaneous O_2 saturation of 98% on room air and blood pressure of 140/88 mmHg. His peripheries were cold but well perfused with no Raynaud's related changes. He had no joint synovitis, skin rash or muco-cutaneous ulcers. His cardio- respiratory examination was unremarkable apart from loud pulmonic component of the second heart sound on auscultation. The

neurological examination was remarkable for bilateral distal muscle weakness in a symmetrical distribution with severe bilateral foot drop. There was absent ankle dorsiflexion, plantarflexion, inversion and eversion. Extension and flexion at the knee joint were estimated at 3/5 power. More proximally, at the hip joint, he was able to perform hip flexion, extension, abduction and adduction with grade 4/5 power. Furthermore, when testing pinprick sensation and temperature, both modalities were absent bilaterally in a symmetrical distribution extending up the knees. These modalities were also tested and noted to be symmetrically diminished to a milder extent in both hands (gloves-and-stockings distribution of sensory deficits). He had marked lower extremity pitting edema extending up to his knees. Bed side urine dipstick was positive 2+ for protein.

His blood investigations during hospital stay are summarized in (table 1). The Radiological workup included, a brain MRI ,which showed diffuse brain atrophy but no focal pathology and a CT chest scan revealing areas of septal and centrilobar emphysema of upper lobes with prominent pulmonary trunk and both main pulmonary arteries. His transthoracic echocardiography demonstrated moderate concentric left ventricle hypertrophy (LVH) with normal systolic function and severe pulmonary hypertension (estimated pulmonary artery systolic pressure of 62 mmHg). Nerve condition study (NCS) revealed absent motor and sensory signals in both lower limbs and mild reduction of sensory amplitude from upper limbs. Electromyography (EMG) of sampled muscles in lower extremities showed denervation and neurogenic action potentials. In summary, the physiological data was suggestive of sensori-motor axonal neuropathy affecting predominantly the lower extremities.

Table 1: summary of pertinent lab investigations.

Investigation	Results	Reference
Haemoglobin	**10.5**	11-14.5 gm/dL
Erythrocyte sedimentation rate (ESR)	**115**	0-30 mml/hr
Direct Antiglobulin Test (Coomb's Test)	**Positive**	
C - Reactive Protein	**24**	0-5 mg/L

Creatinine	**108**	45-84 umol/L
Complement C_3	**0.94**	0.90-1.80 g/L
Complement C_4	**0.27**	0.10-0.40 g/L
Red Blood Cell Folate	**25.9**	7- 46.4 nmol/L
Vitamin B_{12}	**1476**	138-652 pmol/L
Creatine Kinase	**31**	39-308 U/L
Anti-Nuclear Antibody	**1:640 speckled**	
Extractable Nuclear antigens	**Strongly positive anti RNP**	
Myositis screening	**Negative**	
Anti Double Standarded DNA Antibodies	**Negative**	
Anti phospholipid Antibodies	**Negative**	
HIV/hepatitis screening	**Negative**	

In view of the strongly positive ANA and anti U1-RNP, high inflammatory markers and multi systemic involvement, the patient was diagnosed with MTCD and was accordingly pulsed with IV methylprednisolone. A kidney biopsy was suggested for further evaluation given nephrotic range proteinuria. Unfortunately, he refused a kidney biopsy, but consented to a sural nerve biopsy. After careful evaluation of histopathological slides, there were extensive degenerative changes including myelin-ovoid formation and axonal fragmentation (figure 1). More importantly, there was prominent peri-vascular and transmural lymphocytic inflammation and occlusion consistent with vasculitis. (Figure 2).

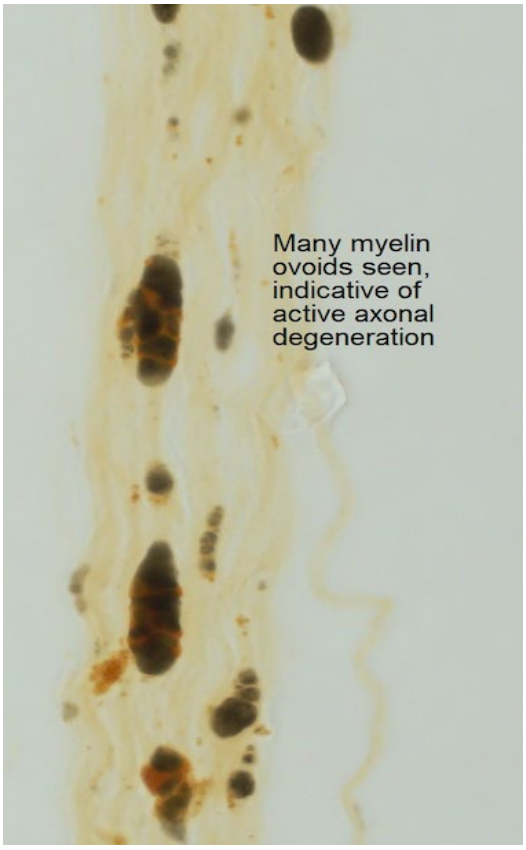

Figure 1: Histopathological section from the sural nerve biopsy specimen showing extensive degenerative changes including myelin-ovoid formation and axonal fragmentation.

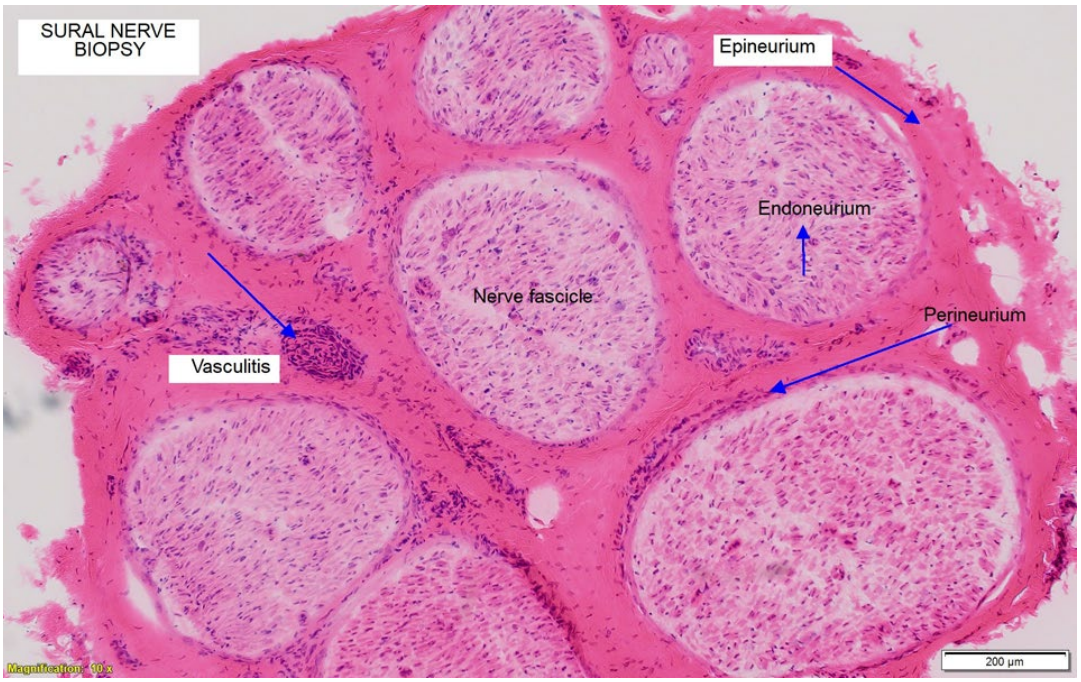

Figure 2: Histopathological section from the sural nerve biopsy specimen showing perivascular and transmural lymphocytic inflammatory infiltrate and vessel occlusion, consistent with vasculitis.

After pulse therapy, he was placed with tapering course of prednisolone in addition to steroid sparking agents including Hydroxychloroquine and Mycophenolate mofetil. He also received nutritional support and physiotherapy in the form of foot drop splints with tone and power restoring exercises. Right heart catheterization was performed and revealed moderate pulmonary hypertension (mean pulmonary artery pressure of 38 mmHg and mean pulmonary capillary wedge pressure of 7 mmHg) with negative vasoreactivity and accordingly was treated with sildenafil.

Discussion

The neurological involvement tends to be mild in patients with MCTD[2]. Trigeminal neuralgia is the most common neurological manifestation[3] but there are published reports of more severe presentations such as Central Nervous System Vasculitis[4] or aseptic meningitis[2] . The pathogenesis of polyneuropathy remains unclear but it is likely related to peripheral neuritis with regional vasculitis as shown on nerve biopsy[5]. There is no standard regimen to manage MCTD related polyneuropathy[6] . Therapy follows standard guidelines on the management of SLE and other connective tissue diseases [6,7].

At first glance, the biopsy showed wide spread degenerative changes, which would have been consistent with a severe nutritional deficiency especially in a chronic alcoholic. However, the fact that our patient had a normal hemoglobin, Red blood cell folate and vitamin B_{12} levels with no evidence of megaloblastosis , made nutritional deficiency less likely a cause for the severe sensory-motor deficit.

On a more careful evaluation, there was clear evidence of vasculitis with vessel wall inflammation , inflammatory cell infiltrates and occlusion. This highlights the importance of meticulous evaluation of biopsy specimens within the clinical context. In addition,it is conceivable that such difficult to spot changes maybe missed on an inadequate biopsy specimen.

The natural history of MCTD related polyneuropathy is unclear, it appears our patient made a near complete recovery with immunosuppressive therapy . Further studies on the outcome of such patients are much needed, but likely to be quite challenging given the rarity of the disease.

Conclusion

Despite being unusual, severe polyneuropathy could be an initial neurological presentation of mixed connective tissue diseases. The diagnosis can be challenging and requires extensive and careful work up including neurophysiology and nerve biopsy. Immunosuppressive therapy along with extensive rehabilitation are integral components of management.

References

1. Sharp GC, Irvin WS, Tan EM, Gould RG, Homan HR. Mixed connective tissue disease – an apparently distinct rheumatic disease syndrome associated with a specific antibody to an extractable nuclear antigen (ENA). Am J Med 1972; 52(2): 148-159. DOI: https://doi.org/10.1016/0002-9343(72)90064-2
2. Nowicka-Sauer K, Czuszynska Z, Majkowicz M, et al. Neuropsychological assessment in mixed connective tissue disease: comparison with systemic lupus erythematosus. Lupus 2012; 21: 927e33. DOI: 10.1177/0961203312441511
3. Nimelstein SH, Brody S, McShane D, Holman HR. Mixed connective tissue disease: a subsequent evaluation of the original 25 patients. Medicine (Baltimore) 1980; 59: 239e48. DOI: 10.1136/ard.50.suppl_4.887
4. Narváez J, Pascual M, Albert Espi G, Millan M, López de Recalde M, Alegre JJ, Castellví I, Gomez Vaquero C, Nolla JM. Prevalence of Organ Involvement in Mixed Connective Tissue Disease. Arthritis Rheumatol. 2017; 69 (suppl 10).
5. Hui M, Meena AK, Rajasekhar L, et al. Vasculitic Neuropathy: A Retrospective Analysis of Nerve Biopsies and Clinical Features from a Single Tertiary Care Center. Ann Indian Acad Neurol. 2019; 22(2): 180-186. DIO: 10.4103/aian.AIAN_47_18
6. Gunnarsson, R., Hetlevik, S. O., Lilleby, V., & Molberg. (2016). Mixed connective tissue disease. Best Practice & Research Clinical Rheumatology, 30(1), 95–111. DIO: 10.1016/j.berh.2016.03.002
7. Ciang NCO, Pereira N, Isenberg DA. Mixed connective tissue disease—enigma variations? Rheumatology 2017; 56(3): 326-333 DOI: 10.1093/rheumatology/kew265