Spinocerebellar ataxia and necrotizing myositis: two coexisting pathologies in a case of progressive neurologic dysfunction

Michael James Smith MD[1], Mohamed Bilal Haradwala MD[2], Ashir Mehra MD[2], Erik Ensrud MD[2]

[1]Barrow Neurological Institute, 2910 N 3rd Ave, Phoenix, AZ 85013
[2]University of Missouri School of Medicine, 1 Hospital Dr, Columbia, MO 65212

Introduction

Immune-mediated necrotizing myopathy (IMNM) is a group of myopathies distinct from polymyositis.[1] The most common antibodies associated with IMNM are anti-SRP, anti-HMGCR, and antisynthetase autoantibodies, but some cases can be seronegative.[1-2] Clinically, IMNM presents with an acute or subacute onset of symmetric muscle weakness, more pronounced proximally. Some patients may also experience myalgias and dysphagia. IMNM typically causes greater weakness in the legs than in the arms.[1] Spinocerebellar ataxia (SCA) refers to a group of autosomal dominant neurodegenerative disorders, typically caused by a CAG nucleotide repeat expansion.[3] Over 40 types of SCA have been identified, with SCA type 3 being the most common subtype.[3] The most frequent presenting symptoms of SCA include gait ataxia, incoordination, nystagmus, visual problems, and dysarthria.[3] The following case outlines a 53-year-old patient that presented with subacute weakness in all extremities, difficulty swallowing, and significant weight loss. Our patient was diagnosed with both SCA type 2 and IMNM. This case underscores the importance of a systematic diagnostic approach to any patient with new-onset weakness and provides a stepwise method for developing a differential diagnosis. Readers are guided through this approach, ultimately leading to the final diagnosis. Additionally, this case highlights how undiagnosed chronic conditions can complicate the diagnostic process.

Case Presentation

A 53-year-old man presented with a month-long history of progressive weakness, which left him unable to use his wheelchair. He also reported developing difficulty swallowing solids and liquids throughout this time. He denied fevers, chills, nausea, vomiting, recent illnesses, or pain. He also denied any history of alcohol, tobacco, or recreational drug use. Further medical history revealed that around the age of 30, he had begun experiencing gradually progressive incoordination that had resulted in him being wheelchair bound. The exact etiology of his incoordination remained unclear, but family history was significant for similar symptoms affecting his mother and maternal uncle, raising suspicion for a hereditary process though no formal diagnosis was ever made.

On neurologic examination, the patient was cachectic. He had shortness of breath and was using accessory muscles of respiration at rest. Speech was hypophonic, dysarthric, with intermittent gasping. Cranial nerve examination was remarkable for multi-directional nystagmus, decreased smooth pursuit with catch-up saccades, and hypometric saccades. Facial movement was normal. Coordination testing was limited due to weakness. There was no prominent muscle atrophy in the upper and lower extremities. Tone was normal in the upper extremities and the lower extremities. There was weakness of the following muscles (right/left Medical Research Council [MRC] grades): deltoids (2/2), biceps (3/3), triceps (3/3), flexor digitorum indicis/abductor pollicis brevis (4/4), hip flexors (2/2), quadriceps (2/2), hamstrings (2/2), ankle plantar and dorsiflexors (5/5). Tendon reflexes were absent throughout, and sensory examination was normal.

The subacute onset of constant, progressive bilateral symmetric proximal muscle weakness with associated bulbar symptoms in the setting of preserved sensation raised concerns for myopathy. However, this did not explain the patient's history of chronic, progressive incoordination which had led to the patient being wheelchair bound in the first place. These symptoms, especially in the context of a relevant family history, suggested possible spinocerebellar ataxia (SCA). Leading us to the possibility of two co-existent neurological pathologies.

Upon admission, the patient's serum creatinine kinase (CK) level was elevated at 4,357 units/L. Thyroid function tests, erythrocyte sedimentation rate, C-reactive protein, and parathyroid hormone were normal. Commercially available panels for immune mediated myopathies were sent. The panels included evaluation of Anti-3-hydroxy-3-methylglutaryl-CoA reductase (HMGCR) Ab, Anti-signal recognition particle (SRP) Ab, Anti-PL-7 Ab, Anti-PL-12 Ab, Anti-EJ Ab, Anti-OJ Ab, Anti-Mi-2-Ab, Anti-U3 RNP (Fibrillarin), Anti-U2 RNP Ab, and Anti-Ku Ab. Testing for acetylcholine receptor and muscle-specific kinase antibodies was negative. Further testing for serum monoclonal immunoglobulins (IgG, IgA, IgM, kappa, and lambda) and other antibodies including anti-glial neuronal nuclear antibody, amphiphysin antibody, angiotensin-converting enzyme, leucine-rich glioma inactivated protein 1, CASPR2-IgG, GQ1b, GD1b, and GD1a were all negative.

Computed tomography (CT) of the head revealed moderate to severe cerebellar and pontine volume loss, with no other lesions. MRI imaging could not be obtained early in

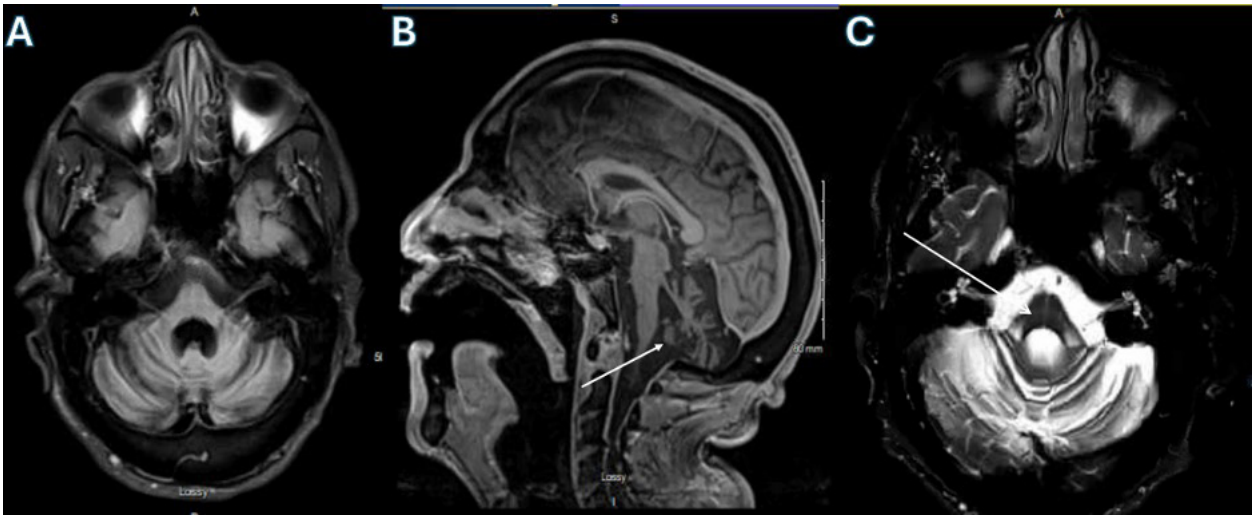

Figure 1: A. MRI FLAIR of the brain in the axial section at the level of the pons showing generalized atrophy of the cerebellum. B. T1 sequence with contrast at the midline level showing severe atrophy of the cerebellum (white arrow) as well as the brainstem structures. C. MRI T2 sequence of the brain shows the hot cross bun sign (white arrow).

the hospitalization due to ongoing respiratory distress. An electromyography/nerve conduction study was considered but ultimately not performed as it was unlikely to change management. A lumbar puncture was performed, revealing protein at 49 mg/dL, glucose at 58 mg/dL, and no cells. The patient was started on a five-day course of intravenous immunoglobulin (IVIG). The patient remained stable after IVIG but showed no strength improvement. His CK levels trended down to 1,779 units/L.

A few days later, the patient's breathing stabilized enough to undergo MRI scans of the brain, arm, and leg with anesthesia assistance. The brain MRI revealed asymmetric volume loss of the brainstem and cerebellum, with a "hot cross bun" sign observed in the pons (Figure 1). MRIs of the humerus and femur with contrast showed diffuse edema, multifocal fascial edema, and global atrophy across multiple muscle groups. At this point his Anti-HMG COA Ab results returned which were positive at 76.1 (normal <20). He also underwent a polymerase chain reaction test (PCR) for SCA which resulted in abnormal repeats for SCA 2, diagnostic for SCA.

Discussion

The patient was diagnosed with IMNM and SCA type 2. Following the MRI, a genetic panel for SCA returned positive for SCA type 2. IMNM is a group of myopathies distinct from polymyositis.[1] The most common antibodies associated with IMNM are anti-SRP, anti-HMGCR, and antisynthetase autoantibodies.[1-2] While these antibodies may be present, approximately 20% of IMNM cases are seronegative.[2] Diagnosis of the specific subtypes of IMNM requires the presence of anti-HMGCR or anti-SRP autoantibodies.[1] A common risk factor for IMNM is cancer, making it crucial to rule out malignancy in patients with seronegative IMNM.[1] The anti-HMGCR or anti-SRP subtypes have either no increased risk of cancer or only a mild increase, in contrast to the seronegative subtype.[1] An important risk factor for the development of anti-HMGCR IMNM is exposure to statin medications. Some reports have shown 63% of patients with anti-HMGCR IMNM had previous statin exposure.[1] However, our patient had no exposure to statins prior to his development of his condition. Clinically, IMNM presents with an acute or subacute onset of symmetric muscle weakness, more pronounced proximally. Some patients may also experience myalgias and dysphagia. IMNM typically causes greater weakness in the legs than in the arms, and CK levels often exceed 6,000 IU/L.[1] Treatment involves IVIG or glucocorticoids. Malignancy and cardiac involvement are common causes of death in these patients.[1]

SCA refers to a group of autosomal dominant neurodegenerative disorders, typically caused by a CAG nucleotide repeat expansion.[3] Over 40 types of SCA have been identified, with SCA type 3 being the most common subtype.[3] The most frequent presenting symptoms of SCA include gait ataxia, incoordination, nystagmus, visual problems, and dysarthria.[3] Depending on the specific type of SCA, other symptoms may include pyramidal and extrapyramidal signs, ophthalmoplegia, and cognitive impairment.[3] SCA type 2 is specifically associated with a CAG repeat expansion in the ATXN2 gene.[4] The hallmark of SCA type 2 is gait ataxia, but patients often experience additional symptoms such as muscle cramping, postural instability, dysarthria, nystagmus, and ocular dysmetria.[4] Other possible findings include slow or absent saccades, dystonia, myoclonus, and spasticity.[4] As with other forms of SCA, there is no known treatment. The "hot cross bun sign" has been reported in rare cases of SCA type 2,

although it is typically pathognomonic for multiple system atrophy (MSA) type C.[5] When this radiologic finding is present, SCA type 2 should be considered in the differential diagnosis. Other potential causes of cerebellar atrophy on imaging include episodic ataxia, excessive alcohol use, olivopontocerebellar atrophy, and Friedreich ataxia.

This case highlights the importance of thorough history-taking and distinguishing between acute and chronic pathologies. The patient presented with subacute weakness predominantly in the proximal muscles of the upper and lower extremities, which should suggest a possible myopathy. The imaging findings of pontine and cerebellar atrophy might initially be confusing without a comprehensive history. The patient's history of progressive coordination difficulties beginning around age 30, along with a family history of a similar condition, should suggest a chronic, genetic disorder as the cause of his imaging findings. Finally, the markedly elevated CK levels strongly support a diagnosis of myopathy. Taken together, these findings lead to the conclusion of an acute on chronic process involving SCA type 2 with superimposed myopathy. After two months of treatment, the patient's CK levels decreased to 56 units/L. His motor recovery is lagging behind, but we expect this to return over the coming months.

Teaching Points

1. SCA type 2 should be considered when the "hot cross bun sign" is seen on imaging.

2. IMNM, especially the seronegative subtype, is commonly associated with cancer. It is vital to screen for cancer in these patients.

3. Treatment of IMNM involves either IVIG or systemic glucocorticoids.

4. Statin medications are an important risk factor for the development of anti-HMGCR subtype of IMNM.

References

1. Allenbach Y, Benveniste O, Stenzel W, Boyer O. Immune-mediated necrotizing myopathy: clinical features and pathogenesis. Nat Rev Rheumatol. 2020 Dec;16(12):689-701. doi: 10.1038/s41584-020-00515-9.
2. Luo YB, Mastaglia FL. Dermatomyositis, polymyositis and immune-mediated necrotising myopathies. Biochim Biophys Acta. 2015;1852(4):622-632. doi:10.1016/j.bbadis.2014.05.034.
3. Sullivan R, Yau WY, O'Connor E, Houlden H. Spinocerebellar ataxia: an update. J Neurol. 2019 Feb;266(2):533-544. doi: 10.1007/s00415-018-9076-4.
4. Scoles DR, Pulst SM. Spinocerebellar Ataxia Type 2. Adv Exp Med Biol. 2018;1049:175-195. doi: 10.1007/978-3-319-71779-1_8. PMID: 29427103.
5. Naidoo AK, Wells CD, Rugbeer Y, Naidoo N. The "Hot Cross Bun Sign" in Spinocerebellar Ataxia Types 2 and 7-Case Reports and Review of Literature. Mov Disord Clin Pract. 2022;9(8):1105-1113. Published 2022 Oct 13. doi:10.1002/mdc3.13550.