Case Report

Miller Fisher syndrome associated with polycythemia vera: A rare clinical co-occurrence

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ABSTRACT

Miller Fisher syndrome (MFS) is a rare, acute immune-mediated neuropathy characterized by ophthalmoplegia, ataxia, and areflexia. Polycythemia vera (PV) is a chronic myeloproliferative neoplasm marked by autonomous erythroid overproduction and elevated thromboembolic risk. The clinical co-occurrence of these two distinct conditions is exceptionally rare. We report a case of a 42-year-old male presenting with a 3-day history of walking unsteadiness, bilateral eyelid drooping, and blurred vision following a low-grade fever. Diagnosis of MFS was confirmed through cerebrospinal fluid analysis, showing albumin-cytological dissociation, and a strongly positive serum anti-GQ1b antibody titer. Concurrently, severe erythrocytosis led to a bone marrow diagnosis of PV, notably testing negative for the Janus activated kinase gene but positive for the additional sex combs like 1 mutation. Despite compounded hyperviscosity and thrombotic risks, the patient was successfully treated with standard intravenous immunoglobulin and therapeutic venesection, resulting in full neurological resolution.

Key words: Additional sex combs like 1 mutation, Ataxia, Immunoglobulin, Miller Fisher syndrome, Polycythemia vera

Miller Fisher syndrome (MFS) is a rare, acute immune-mediated neuropathy widely recognized as a distinct clinical variant of Guillain-Barré syndrome (GBS). First comprehensively described by C. Miller Fisher in 1956, the condition is classically characterized by a clinical triad: ophthalmoplegia (paralysis of eye muscles), ataxia (loss of voluntary muscle coordination), and areflexia (absence of deep tendon reflexes) [1]. While it shares underlying peripheral nerve pathology with classic GBS, MFS is uniquely distinguished by its prominent, early involvement of the cranial nerves and descending paralysis, rather than the ascending paralysis typically seen in GBS [2]. The pathogenesis of MFS is strongly associated with molecular mimicry following a prodromal infection, most commonly upper respiratory infections or gastroenteritis caused by pathogens such as *Campylobacter jejuni* or *Haemophilus influenzae*. This triggers an autoimmune response, leading to the production of autoantibodies that target gangliosides highly concentrated in the nodes of Ranvier of ocular motor nerves and large-fiber sensory neurons. Specifically, the presence of serum anti-GQ1b immunoglobulin G (IgG) antibodies serves as a highly specific diagnostic biomarker, found in upwards of 85–90% of cases [2]. Diagnosis relies heavily on matching this clinical presentation with confirmatory serology, cerebrospinal fluid (CSF) analysis demonstrating albuminocytologic dissociation (elevated protein without elevated white blood cells), and electromyography [3]. Although MFS can cause severe temporary disability, its prognosis is generally favorable. Most patients experience a self-limiting course with significant recovery within a few months, often accelerated by immunomodulatory therapies such as intravenous immunoglobulin (IVIG) or plasmapheresis [4].

There are a few reports of an association of MFS with myeloproliferative disorders like polycythemia vera (PV) [5]. The increased thrombotic tendency in PV has been postulated to be the cause in these cases. The rationale behind this case report is the association of two rare clinical entities in the same patient. The patient presented with symptoms suggestive of MFS, with further evaluation detecting an underlying myeloproliferative syndrome. Further studies are needed to explore this association in detail.

CASE REPORT

A 42-year-old male patient with no prior comorbidities presented to the emergency department with a 3-day

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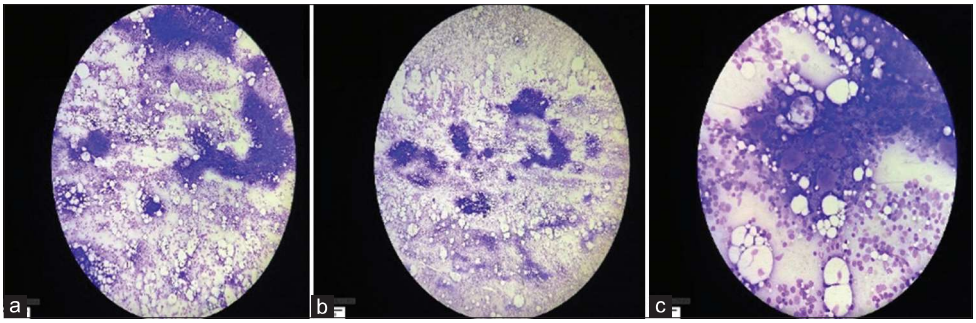

Figure 1: (a) Bone marrow aspirate showing hypercellular aspirate - ×4; (b) Bone marrow aspirate showing increased megakaryocytes-pleomorphic - ×10; (c) Bone marrow aspirate showing increased megakaryocytes and a loose cluster of megakaryocytes - ×40

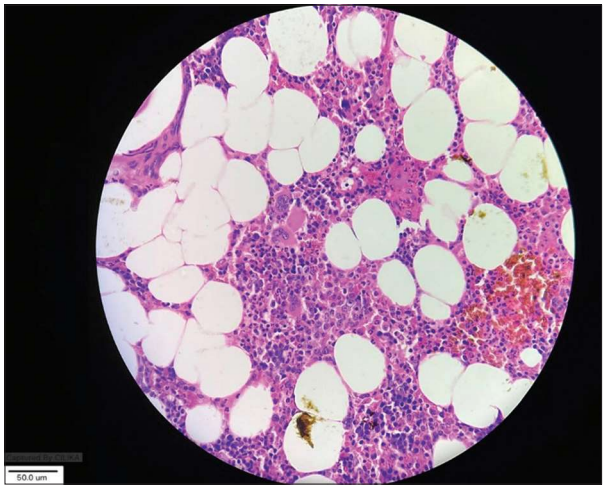

Figure 2: Bone marrow trephine biopsy showing increased megakaryocytes - ×40

history of unsteadiness while walking, along with drooping of both eyelids and blurred vision. There was a preceding history of low-grade fever 1 week before the onset of symptoms. There was no history of headache, vomiting, or seizures. No history of limb weakness or altered behavior. There was no significant past history or family history of similar symptoms. No history of smoking or alcohol intake.

Clinical examination revealed normal vital signs. General examination showed no evidence of anemia, hepatosplenomegaly, or lymphadenopathy. Oxygen saturation levels were normal on room air. Neurological examination revealed bilateral ptosis with dilated and fixed pupils bilaterally. There was restriction of extraocular movements in all directions. Motor power and sensations were normal. Deep tendon reflexes were absent in all four limbs. There was significant gait ataxia with a positive Romberg's sign. There were no meningeal signs. Because of the presence of ophthalmoplegia, gait ataxia, and areflexia with a preceding history of fever, a clinical possibility of MFS was considered. The differentials considered were a posterior circulation stroke, brainstem demyelination, and a neuromuscular junction disorder like myasthenia gravis.

He was investigated for the same. Magnetic resonance imaging (MRI) of the brain and cervical spine showed no abnormalities. He underwent a nerve conduction study with repetitive nerve stimulation (RNS), which was negative for myasthenia. Lumbar puncture done showed evidence of albumin-cytological dissociation in the CSF with 5 cells and 55 mg/dL proteins, which was in keeping with MFS.

In view of disabling symptoms, he was given a course of IVIG at a total dose of 2 g/kg body weight over 5 days. He had a significant improvement in symptoms following the treatment. He was also started on physiotherapy and gait training. Serum for ganglioside antibodies was sent, which came strongly positive for anti-GQ1b antibody. He was able to walk with support at discharge.

During the course of the hospital's stay, he was found to have elevated hemoglobin (19.1 g/dL) and packed cell volume (PCV)-55.1% with normal total count and platelet counts. He was investigated for the same, and a peripheral smear done showed evidence of normocytic normochromic RBCs with neutrophilic leukocytosis. Serum erythropoietin levels were 2 mU/mL, which were below normal levels (2.5–18 mU/mL). Medical oncology opinion was taken, and the possibility of PV was considered likely. He fulfilled the World Health Organization criteria for diagnosis with 2 major and 1 minor criteria [6]. Accordingly, he underwent a bone marrow aspiration and biopsy, which showed evidence of a hypercellular aspirate with increased megakaryocytes (Figs. 1 and 2). There were loose clusters and increased numbers of pleomorphic megakaryocytes. Genetic testing was done for myeloproliferative neoplasm panel, which proved negative for the Janus activated kinase (*JAK*) gene but was positive for the additional sex combs like 1 (*ASXL1*) gene. Since this gene carries a high risk for transformation to myelofibrosis, it was decided to keep him under regular follow-up with blood monitoring. He also underwent venesection for the reduction of hemoglobin and PCVs.

At the last follow-up after 6 months, his hemoglobin was stable at 15 g/dL, and his gait ataxia had reduced to the extent that he was able to walk without support. He was on treatment with hydroxyurea for his underlying PCV. He had no focal neurological deficits and was symptom-free. Repeat antibody testing for GQ1b antibody was negative after 6 months.

DISCUSSION

MFS represents a distinct, acute immune-mediated peripheral neuropathy characterized by the hallmark clinical triad of acute ophthalmoplegia, ataxia, and areflexia. The pathogenesis of MFS centers on molecular mimicry. A prodromal infection, frequently upper respiratory or gastrointestinal, provokes an immune response wherein generated antibodies mistakenly cross-react with gangliosides (predominantly GQ1b) heavily concentrated in the nodes of Ranvier of the oculomotor, trochlear, and abducens nerves, as well as large-fiber sensory neurons [7]. Our 42-year-old male patient presented with this classic triad following a febrile prodromal illness. Given the acute onset of neurological deficits, initial differential diagnoses rightly included acute vascular emergencies such as a posterior circulation stroke, brainstem demyelination, or neuromuscular junction disorders like myasthenia gravis. Brain and cervical spine MRI effectively ruled out structural and ischemic brainstem or cerebellar lesions. Furthermore, a negative RNS study excluded myasthenia gravis. The diagnosis of MFS was definitively substantiated by CSF analysis demonstrating classic albuminocytologic dissociation, and further confirmed by a strongly positive serum anti-GQ1b IgG antibody titer, which serves as a highly specific diagnostic biomarker [8].

The most extraordinary dimension of this case is the concurrent, incidental discovery of PV, a chronic, myeloproliferative neoplasm driven by autonomous erythroid proliferation. During his hospitalization, the patient demonstrated profound erythrocytosis, with a hemoglobin of 19.1 g/dL and a PCV of 55.1%. Coupled with a normal serum erythropoietin level and suggestive peripheral smear findings, the diagnostic pathway for PV was initiated through bone marrow aspiration and biopsy. The co-occurrence of MFS and PV is exceedingly rare in medical literature. This intersection poses several critical pathophysiological and therapeutic insights.

Diagnostic mimicry and vascular risk

PV fundamentally alters blood rheology. It drives hyperviscosity, reduces cerebral blood flow, and drastically accelerates both microvascular sludging and macrovascular thromboembolic events. When a patient with underlying, undiagnosed PV presents with acute unsteadiness and visual disturbances, a transient ischemic attack or a posterior circulation ischemic stroke is the primary clinical assumption. This case highlights that clinicians must maintain a broad diagnostic horizon; neuro-immunological conditions can occur in patients with severe pro-thrombotic risk profiles.

Immunological cross-talk

While PV is classically categorized as a myeloid malignancy, myeloproliferative neoplasms are increasingly understood as states of profound, chronic systemic inflammation. The altered bone marrow microenvironment and persistent cytokine upregulation in PV can lead to broader immune dysregulation. It is plausible that this background of altered immune surveillance lowered the threshold for the aberrant, post-infectious autoimmune cascade that drove the anti-GQ1b antibody production in this patient [9]. Therapeutic Considerations: Standard management for disabling MFS involves immunomodulatory therapy, primarily IVIG or plasmapheresis [10]. This patient received a standard course of IVIG (2 g/kg over 5 days), resulting in excellent clinical improvement. However, administering IVIG to a patient with concurrent, uncontrolled PV requires extreme clinical vigilance. IVIG is known to transiently increase plasma viscosity. In a patient who already possesses a high PCV (55.1%) and sluggish blood flow, the addition of IVIG compounded the theoretical risk of a major thrombotic event [11]. Fortunately, this patient tolerated the therapy without adverse vascular sequelae and showed significant neurological recovery.

In PV, approximately 15% of patients harbor additional non-JAK2 mutations, with ASXL1 being one of the most common. The ASXL1 *gene* plays a critical role in the epigenetic modification and regulation of how blood cells grow and mature [12]. Patients who possess ASXL1 mutations are at a notably higher risk for their PV evolving into post-PV myelofibrosis (where scar tissue builds up in the bone marrow) or transforming into acute myeloid leukemia. Studies have identified ASXL1 as an age-independent risk factor for thrombosis, significantly increasing the likelihood of dangerous blood clots. In PV cohorts, the presence of an ASXL1 mutation is often significantly correlated with inferior overall survival and worse outcomes, especially if the patient eventually requires a stem cell transplant. The presence of this gene in our patient leads us toward closer patient monitoring over his follow-up period.

CONCLUSION

This case outlines an exceptionally rare clinical convergence of MFS and PV. It underscores the vital importance of pursuing a comprehensive, multidisciplinary diagnostic workup when neurological presentations overlap with severe hematological abnormalities. Ultimately, it demonstrates that even when faced with the high thromboembolic risks associated with uncontrolled polycythemia, standard neuro-immunotherapy with IVIG can be safely administered and highly effective, provided there is astute, continuous clinical monitoring.

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