

Clinical Case of a Patient with Multiple Sclerosis, Polymyositis and Melanoma. Is There a Connection Between Them?

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Abstract

Background: We present a case of a patient with the sequential development of clinical symptoms characteristic of multiple sclerosis, polymyositis, and malignant melanoma. **Case presentation:** Polymyositis occurred two years after the onset of multiple sclerosis. Clinical signs of melanoma were identified following the development of polymyositis. Treatment with corticosteroids and immunosuppressants positively affected the patient's clinical manifestations of multiple sclerosis. It remains unclear whether there was an insidious progression of melanoma without clinical manifestations and whether the myositis developed in parallel with this melanoma. It is possible that polymyositis developed independently or preceded the onset of melanoma with lymph node metastases. **Conclusion:** The patient's clinical history demonstrates an overlap of demyelinating, systemic, and malignant diseases. Integrated treatment is essential for achieving clinical improvement in these patients.

Keywords: multiple sclerosis, polymyositis, melanoma

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1. Introduction

Multiple sclerosis (MS), polymyositis (PM), and melanoma are interconnected primarily through the complex interplay between autoimmunity, immunosuppressive therapies, and oncological risk. While dermatomyositis exhibits a stronger association with cancer, polymyositis is recognized as a potential paraneoplastic syndrome that can manifest in conjunction with various malignancies, including melanoma. Studies have reported a higher standardized incidence ratio (SIR) for cancer in patients with PM; however, melanoma incidence is relatively rare compared to other types of malignancy, such as adenocarcinoma. While both conditions possess an autoimmune etiology and have been linked to melanoma, the simultaneous occurrence of all three pathologies is exceedingly rare and likely related to the immunomodulatory effects of the prescribed treatments.

2. Case presentation

We present the clinical case of a 54-year-old man presenting with neurological deficits characteristic of multiple sclerosis, polymyositis, and melanoma. The initial clinical symptoms began in October 2017, manifesting as acute paresthesia, stiffness, and fatigue in the right arm, alongside rapid fatigue during exertion and urinary dysfunction. Magnetic resonance imaging (MRI) of the brain and cervical spine confirmed a diagnosis of multiple sclerosis, specifically the cerebrospinal form with a relapsing-remitting disease course.

On January 4, 2018, the patient developed pain and stiffness in the cervical spine, accompanied by paresthesia of the left arm, as well as tingling, stiffness, and fatigue of the right arm, and gait-related fatigue. By October 1, 2018, he reported tingling, stiffness, and fatigue in all extremities. Between 2017 and 2019, the patient underwent annual neurological evaluations. Clinical examinations revealed that the cranial nerves were intact. Motor assessment confirmed a quadripyramidal syndrome with monoparesis of the right arm (resulting in a "useless hand"). Neurological examination revealed proprioceptive hyperreflexia and pathological reflexes in the extremities. Coordination testing showed dynamic ataxia during the finger-to-nose test, while the Romberg test remained stable. Sensory examination revealed impaired two-dimensional spatial localization and joint-muscular sense in the right hand.

Magnetic resonance imaging (MRI) of the brain and cervical spine revealed supratentorial frontal white matter hyperintensities consistent with

vascular leukoencephalopathy, alongside zones of altered signal intensity. Within the cervical spinal cord from C2 to C5, areas of ill-defined signal changes were identified. The patient received a single pulse of 500 mg methylprednisolone, resulting in a favorable clinical response. This was followed by the chronic administration of dimethyl fumarate (240 mg, two tablets daily) to manage the relapsing-remitting course of multiple sclerosis.

Three months later, a follow-up neurological examination showed no significant changes in the patient's status. Motor assessment revealed a quadripyramidal syndrome with latent paraparesis in the lower extremities. Sensory evaluation demonstrated paresthesia in the upper extremities, tactile hypesthesia, and impaired two-dimensional spatial sense in the right hand. Coordination was characterized by static, dynamic, and locomotor ataxia, as well as altered two-dimensional spatial perception in the lower extremities. Follow-up MRI of the brain and cervical spine showed persistent T2-hyperintense lesions situated within the juxtacortical white matter (Figure 1).

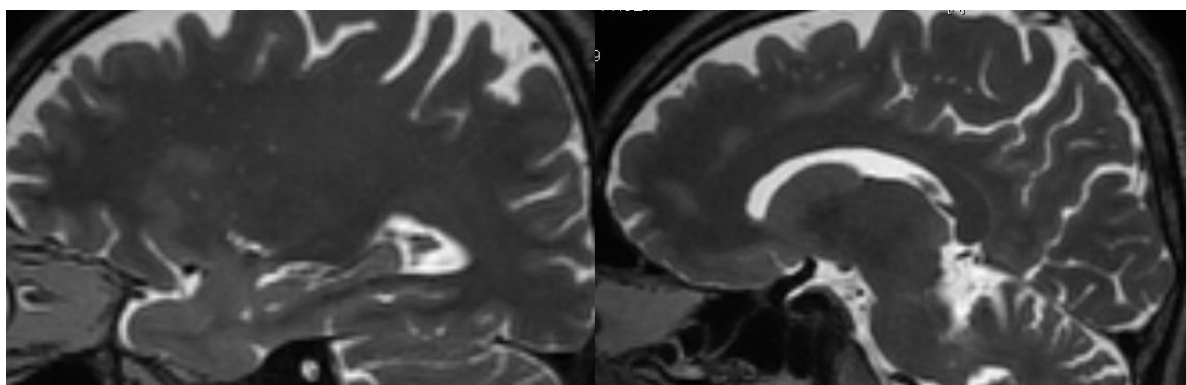


Figure 1. Magnetic resonance imaging (MRI) of brain and cervical spine from January 4, 2018.

This was followed by pulse therapy with 500 mg of methylprednisolone, which had a positive effect on the clinical symptoms. Differential diagnoses considered at this stage included other neurological disorders, such as neuropathies, polyneuritis, and multiple small ischemic zones; however, diagnostic criteria were insufficient to confirm these alternative diagnoses. Subsequent treatment with teriflunomide (14 mg daily) showed no effect on the neurological findings. On October 1, 2018, the patient underwent a third neurological examination, which revealed no significant changes in his neurological status. Motor assessment continued to show a quadripyramidal syndrome with latent paraparesis in the lower extremities. Sensory examination revealed persistent paresthesia in the

upper extremities, tactile hypesthesia, impaired two-dimensional spatial sense in the right hand, and neuropathic pain in the lower extremities. Coordination was characterized by dyscoordination with static, dynamic, and locomotor ataxia. Follow-up brain and cervical spine MRI demonstrated persistent T2 hyperintensities located juxtacortically within the white matter. The MRI also revealed a new subcortical lesion in the right hemisphere. Within the cervical spinal cord (C2–C5), areas of ill-defined signal intensity changes remained present, with the lesion at the C3–C4–C5 level increasing in longitudinal extent from 24 to 30 mm. These MRI findings indicated a progression of cerebrospinal multiple sclerosis (Figure 2).

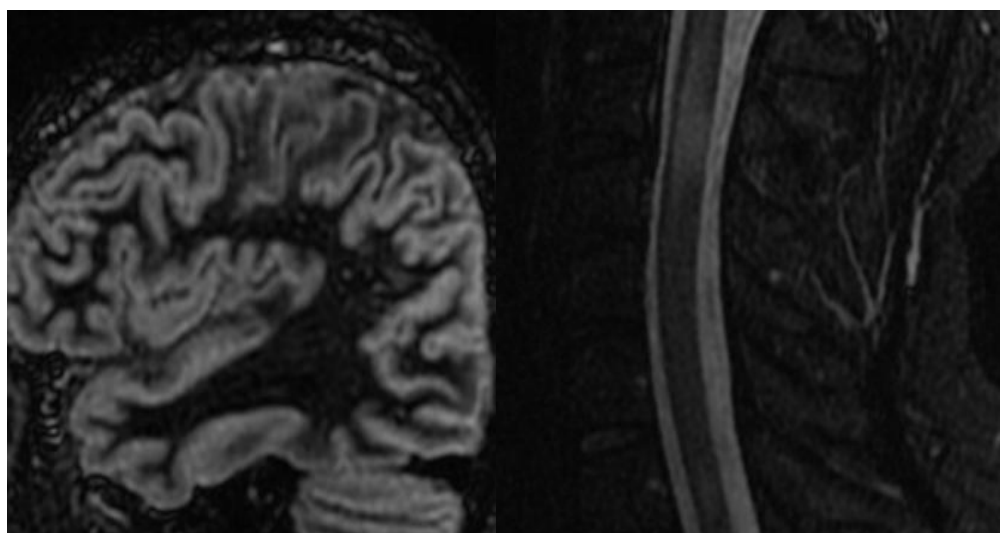


Figure 2. MRI of brain and cervical spine from October 1, 2018.

This was followed by a pulse of 1,000 mg methylprednisolone, which resulted in significant clinical improvement. Following neurological and laboratory investigations, the patient was found to have severely elevated creatine kinase (CK) levels (10,126 U/L). He reported significant proximal muscle weakness in the limbs, difficulty climbing stairs, myalgias, and malaise. Electromyography (EMG) of the upper and lower extremities showed an absence of spontaneous activity, while motor unit action potentials demonstrated decreased duration and an increased number of phases. These findings were consistent with myositis. Immunological testing revealed elevated antinuclear antibody (ANA) titers of 1:1280 (normal < 1:80), as well as myositis-specific antibodies: Anti-PM-Scl100 (8 U/mL) and Anti-TIF1- γ (11 U/mL; normal < 5 U/mL). Based on these results, a diagnosis of polymyositis was confirmed. Initial treatment consisted of 32 mg methylprednisolone (subsequently tapered to 8 mg) and 150 mg azathioprine daily, which led to a reduction in CK levels to 5,509

U/L, then 2,440 U/L, eventually reaching normal values. Dimethyl fumarate was discontinued. From September 25, 2019, to the present, the patient has not experienced any new neurological deficits, and the initial symptoms from 2017 have diminished. A follow-up neurological consultation did not confirm the previous diagnosis of multiple sclerosis. On May 20, 2022, the patient was diagnosed with a high-risk malignant melanoma of the right thigh (T3a) with inguinal lymph node metastases, for which he underwent surgical intervention.

Histological examination of a lymph node demonstrated sinus histiocytosis and a small subcapsular focus containing a cluster of cells with moderate atypia. Technetium-99m nanocolloid lymphoscintigraphy was performed, which revealed rapid lymphatic drainage from the tumor region to the left inguinal region, marked by an intense focus of radiotracer uptake. In August 2024, the patient underwent surgical dissection of the affected lymph node, confirming metastasis from malignant melanoma; this was followed by the initiation of immunotherapy using anti-PD-L1 immune checkpoint inhibitors.

3. Discussion

A review of the scientific literature reveals only sporadic reports of similar clinical cases. Integrated management of systemic, neurological, and malignant conditions is essential for achieving clinical improvement in these complex patients. Several key aspects of this case warrant further discussion. First, it is important to consider whether the combined administration of methylprednisolone and azathioprine contributed to the sustained reduction in clinical symptoms and the stabilization of MRI findings observed from September 2019 to the present. Furthermore, the potential role of dimethyl fumarate in the induction of polymyositis should be evaluated as a possible secondary complication. Finally, the presence of anti-TIF1- γ antibodies - which possess a reported 70% sensitivity and 89% specificity as paraneoplastic markers - may have served as a critical predictive factor for the underlying melanoma, potentially acting as a serological precursor to the oncological diagnosis.

MS is the most prevalent demyelinating disease, characterized by damage to the myelin sheaths of neurons within the central nervous system. Although the exact etiology remains elusive, the underlying pathophysiology is thought to involve either immune-mediated destruction or the failure of myelin-producing cells [1].

Etiological factors include genetic predisposition and environmental triggers, such as viral infections. During symptomatic exacerbations, the administration of high-dose intravenous corticosteroids, such as methylprednisolone, is the standard therapy; however, oral corticosteroids and azathioprine appear to demonstrate comparable efficacy and safety profiles [2]. A review of the literature reveals no existing publications established a connection between treatment with Tecfidera and the development of polymyositis. It remains possible that polymyositis developed independently or as a paraneoplastic phenomenon preceding the progression of melanoma with metastases. It is hypothesized that Anti-TIF1- γ antibodies may serve as a predictive marker for the onset of melanoma.

Analysis of four cohort studies involving 4,239 patients with polymyositis was conducted to assess the risk of malignancy. A total of 19 cases of melanoma were identified, although specific demographic data regarding the age and gender of these patients were not provided [3].

Targeting cancer screening protocols based on idiopathic inflammatory myositis (IIM) subtype, autoantibody profile, and age may help to maximize cancer detection while limiting false positives. In their study, Mecoli et al. analyzed 1,086 patients enrolled in the center's Myositis Research Registry from 2003 through 2020. The analysis included patients with diagnoses of dermatomyositis (DM), polymyositis (PM), immune-mediated necrotizing myopathy (IMNM), and antisynthetase syndrome (ASyS). The researchers also investigated myositis-specific autoantibodies (MSAs), including anti-TIF1 γ , anti-Jo1, and anti-HMGCR. Patients were excluded from the analysis if they had a cancer diagnosis prior to the onset of their myositis. The findings demonstrated that computed tomography (CT) of the chest, abdomen, and pelvis had the highest diagnostic yield in patients with DM and those with DM-specific MSAs (anti-TIF1 γ , anti-NXP-2, anti-SAE, and anti-Mi-2), while showing the lowest diagnostic yield in patients with ASyS and those with PM. These data provide evidence that may inform clinical decision-making to maximize cancer detection while minimizing the risks and costs of over-screening in this patient population [4].

Polymyositis is a systemic autoimmune disorder characterized by proximal muscle weakness, primarily involving the limbs, neck, and trunk. Interferon-alpha is an antiviral cytokine with well-established immunomodulatory and antiproliferative effects; however, its administration is frequently associated with various side effects, particularly autoimmune phenomena. Authors have reported cases of

polymyositis occurring during interferon-alpha therapy in patients diagnosed with malignant melanoma. Indirect evidence suggested that, in these instances, the myositis was not paraneoplastic, as the melanoma was confirmed to be in remission both at the initial diagnosis of the muscle disease and during a one-year follow-up period [5].

Originally utilized for the treatment of psoriasis, dimethyl fumarate (DMF) was approved for the management of multiple sclerosis in 2013. Although the exact mechanism of action of DMF in multiple sclerosis is not yet fully elucidated, it is considered an immunomodulatory therapy that reduces inflammatory T-cell activity by activating nuclear factor erythroid 2-related factor 2 (Nrf2) and modulating glutathione (GSH). These key cellular regulators of the antioxidant response exert potent anti-inflammatory and antioxidant effects. DMF was associated with a low incidence of malignancies in the DEFINE and CONFIRM clinical trials, accounting for less than 1% of all reported adverse events [6].

The primary role of the immune system is to protect the host from pathogenic pathogens and malignancies while maintaining tolerance to self-antigens. Malignant and autoimmune diseases, such as rheumatic disorders and multiple sclerosis, result from immune dysregulation. In multiple sclerosis, an aberrant immune response leads to the demyelination of the central nervous system. Malignant cells adapt to either evade standard immune surveillance mechanisms or directly influence an immune phenotype favorable to malignant proliferation, such as by recruiting and differentiating regulatory T cells (Tregs), regulatory B cells (Bregs), and CD5+ and CD19+ B cells within the tumor microenvironment [6].

A primary objective in the successful management of patients with multiple sclerosis is determining how to optimize the therapeutic manipulation of the immune system without increasing the risk of malignancy, as well as establishing protocols for patients with multiple sclerosis who develop a concomitant malignancy.

In the context of the presented case, it remains possible that polymyositis developed independently or as a paraneoplastic phenomenon preceding the progression of melanoma with lymph node metastases.

The patient's clinical history demonstrates an overlap between demyelinating, systemic, and malignant diseases. A multidisciplinary treatment approach is essential for achieving clinical improvement in these complex patients.

5. Conclusions

The management of central and peripheral nervous system symptoms, initially diagnosed as multiple sclerosis, was successfully stabilized through treatment with methylprednisolone and azathioprine. In our clinical case, the melanoma was detected three years after the diagnosis of polymyositis. This suggests that Anti-TIF1- γ antibodies may serve as a predictive paraneoplastic marker for melanoma.

Declarations

Author Contributions

Conceptualization: V.R.; Methodology: V.R.; Formal analysis: V.R.; Investigation: V.R.; Writing—original draft: V.R.; Writing—review & editing: V.R.

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Informed Consent Statement

Informed consent was obtained by the patient.

Data Availability Statement

The data presented in this study are available on reasonable request from the corresponding author.

Conflicts of Interest

The authors declare no conflict of interest.

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Клиничен случай на пациент с множествена склероза, полимиозит и меланом. Съществува ли връзка между тях?

Резюме

Въведение: Представяме случай на пациент с последователно развитие на клинична симптоматика за множествена склероза, полимиозит и малигнен меланом. **Представяне на случая:** Полимиозитът се проявява две години след началото на множествената склероза. Клиничните признаци на меланом са установени след развитието на полимиозита. Лечението с кортикостероиди и имunosупресори оказва благоприятно въздействие върху клиничните прояви на множествената склероза при пациента. Не е изяснено дали е налице латентно развитие на меланома без клинична изява и дали миозитът се развива паралелно с неопластичния процес. Възможно е полимиозитът да се развие напълно независимо или да предхожда появата на меланом с метастази в лимфните възли. **Заклучение:** Анамнезата на пациента съчетава клиничните характеристики на демиелинизиращо, системно и малигнено заболяване. Прилагането на комбинирано лечение е от решаващо значение за клиничното подобрение при такива пациенти.

Ключови думи: множествена склероза, полимиозит, меланом