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Concurrent herpetic hypertensive anterior uveitis and cytomegalovirus retinitis in a non-HIV patient with melanoma differentiation-associated gene-5 dermatomyositis: intravenous immunoglobulin comes to the rescue

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Abstract

Melanoma differentiation-associated gene 5 dermatomyositis (MDA-5 DM) is a rare subtype of dermatomyositis. Cytomegalovirus (CMV) retinitis is an opportunistic ocular infection that has historically been linked to HIV infection. Herpes simplex virus (HSV) uveitis is caused by the reactivation of the varicella-zoster virus. We present the case of a 69-year-old woman diagnosed with aggressive MDA-5 DM associated with interstitial lung disease, who received multiple immunosuppressive therapies and subsequently developed left eye CMV retinitis and right eye acute herpetic, hypertensive, anterior uveitis with dendritic keratitis. After the diagnosis of MDA-5 DM, she was treated with glucocorticoids (GC), followed by rituximab and triple therapy (cyclosporine, cyclophosphamide, and GC); however, she did not improve and multiple adverse effects occurred. The patient then started tofacitinib (TOF) and improved. While being on TOF, she developed right eye acute herpetic, hypertensive, anterior uveitis, followed by left eye CMV retinitis. TOF was stopped, and the patient started oral acyclovir and intravenous and intravitreal ganciclovir, which was later changed to maintenance therapy with oral valganciclovir. Cyclical intravenous immunoglobulin (IVIG) administration was started, resulting in an overall improvement in disease activity associated with MDA-5 DM. This case underscores the uncommon link between CMV retinitis in a non-HIV patient and HSV anterior uveitis in a patient undergoing immunosuppressive therapy and the challenge of treating MDA-5 DM with IVIG, which led to favorable results.

Key words: melanoma differentiation-associated gene 5 dermatomyositis, non-HIV cytomegalovirus retinitis, HSV anterior uveitis, immunosuppressive therapy, intravenous immunoglobulin.

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Introduction

Melanoma differentiation-associated gene 5 dermatomyositis (MDA-5 DM) may present with rapidly progressive interstitial lung disease (RP-ILD), inflammatory arthritis, vasculopathy, and unique cutaneous manifestations, and was first discovered in 2005 (1-4). Currently, there are no established treatment guidelines for MDA-5 DM; however, initiating an early and robust immunosuppressive combination therapy may lead to a sustained remission. Consensus recommendations suggest high-dose glucocorticoid (GC) and calcineurin inhibitors (CNIs), with or without the addition of cyclophosphamide, as the preferred initial treatment option over step-up therapy (5). Alternatively, intravenous rituximab also showed efficacy in 73% of patients with MDA-5 DM associated with RP-ILD. In addition, Janus kinase (JAK) inhibitors, specifically tofacitinib (TOF), are effective in association with GC for ILD linked to anti-MDA-5 antibody positivity. Plasma exchange, polymyxin B hemoperfusion, or intravenous immunoglobulin (IVIG) are employed in patients refractory to standard treatment, but their effectiveness can vary significantly (3-7).

Cytomegalovirus (CMV) retinitis is a severe and vision-threatening opportunistic ocular infection most commonly observed in

patients infected with HIV (8). Non-HIV-related CMV retinitis occurs less frequently and has been seen among patients receiving immunosuppressive treatments even when CD4 T cell counts are within the normal range (9). These include oral GC along with azathioprine or mycophenolate mofetil (MMF) for the treatment of autoimmune disease (10). TOF is a synthetic, second-generation, small molecule that selectively inhibits the JAK1 enzyme and can induce the reactivation of the varicella-zoster virus (VZV) and of tuberculosis. A few clinical trials demonstrated an overall increased risk of CMV infection (11, 12). There are, in fact, only 3 cases reported of TOF-associated CMV retinitis (13-15). Herein, we are reporting a case of CMV retinitis in a non-HIV with HSV anterior uveitis, in a patient undergoing immunosuppressive therapy for MDA-5 DM.

Case Report

A 69-year-old woman with a medical history of well-controlled diabetes mellitus and hypertension presented with bilateral upper and lower limbs weakness, rash over the upper limbs, difficulties in swallowing, and prolonged non-productive cough for 3 months, which were progressively worsening. General physical

examination showed stable vital signs, maculopapular rashes on both upper limbs, and proximal girdles muscle weakness, assessed at a grade 4 of Medical Research Council muscle power grading. On lung examination, generalized fine crepitations were present.

Blood investigations showed a total leukocyte count $14,900 \text{ cells/mm}^3$ ($4000\text{--}11,000 \text{ cells/mm}^3$), lymphocyte count $0.42 \times 10^3 \text{ cells/mm}^3$ ($1.0\text{--}4.0 \times 10^3 \text{ cells/mm}^3$), hemoglobin 10.9 g/dL ($12\text{--}15 \text{ g/dL}$), platelet count $205,000 \text{ cells/mm}^3$ ($150,000\text{--}400,000 \text{ cells/mm}^3$), alanine aminotransferase 139 U/L ($7\text{--}56 \text{ U/L}$), aspartate aminotransferase 237 U/L ($10\text{--}40 \text{ U/L}$), creatine kinase 215 U/L ($30\text{--}200 \text{ U/L}$), lactate dehydrogenase (LDH) 329 U/L ($140\text{--}280 \text{ U/L}$), serum albumin 24 g/L ($35\text{--}50 \text{ g/L}$), creatinine $48 \mu\text{mol/L}$ ($53\text{--}106 \mu\text{mol/L}$), ferritin $1530 \mu\text{g/L}$ ($13\text{--}150 \mu\text{g/L}$) and normal thyroid function tests. Erythrocyte sedimentation rate was 60 mm/hr , and C-reactive protein was 21 mg/L . Positive antinuclear antibodies (1:80) and a strongly positive result for the anti-MDA5 and anti-Ro52 antibodies were present. High-resolution computed tomography (HRCT) reported mild lung fibrosis, mainly at the posterior lower lobes, associated with mild traction bronchiectasis and subsegmental plate atelectasis at the medial lobe bilaterally (Figure 1). Anti-synthetase antibodies such as anti-JO1, anti-threonyl-tRNA synthetase, anti-alanyl-tRNA synthetase, anti-glycyl-tRNA, and anti-isoleucyl-tRNA synthetase were negative.

The patient was given pulse intravenous methylprednisolone, followed by oral prednisolone 1 mg/kg/day , and two infusions of 1000 mg rituximab. Her cutaneous lesions and dyspnea gradually improved. However, after 2 months, dyspnea recurred and worsened. Laboratory examinations revealed elevated ferritin ($3356 \mu\text{g/L}$), $0.2 \times 10^3 \text{ cells/mm}^3$ ($1.0\text{--}4.0 \times 10^3 \text{ cells/mm}^3$), and LDH 261 U/L ($140\text{--}280 \text{ U/L}$). Repeated HRCT showed evidence of RP-ILD. She was given oral prednisolone 0.8 mg/kg/day , intravenous cyclophosphamide 0.6 g/m^2 every 4 weeks, and oral cyclosporin 50 mg twice daily. Bronchoscopy with bronchoalveolar lavage was scheduled but not performed because the patient was unstable and on high-flow oxygen. The sputum culture was negative, and the chest physician diagnosed the condition as acute interstitial pneumonitis, initiating pulse methylprednisolone treatment. After 3 cycles of intravenous cyclophosphamide, she had severe hair loss and worsening of swallowing, requiring a percutaneous endoscopic gastrostomy (PEG) tube for feeding. Subsequently, the patient was initiated on oral TOF 5 mg twice daily. Her respiratory and swallowing improved with a decrease in ferritin concentration ($2421 \mu\text{g/L}$). Unfortunately, after 6 weeks of TOF, the patient developed right eye blurring of vision and was diagnosed with acute, herpetic, hypertensive, anterior uveitis with dendritic keratitis (Figures 2 and 3), which was treated with oral acyclovir 800 mg 5 times per day for 2 weeks, and a maintenance dose of 400 mg BD. Serum immunoglobulin level showed normal levels of IgA 1.28 U/L , IgG 8.58 U/L , and IgM 0.45 U/L . HRCT showed stable ILD. After 4 weeks from the improvement of the right eye, she complained of blurred vision in her left eye. On examination, right eye vision was 6/9, while left eye vision scored only 6/36. Fundoscopy showed a horizontal streak lesion suggestive of retinitis running across the central macula and encroaching into the fovea, and patches of retinitis in the retinal periphery at the 3 o'clock and 7 o'clock regions (Figures 4 and 5). A few blot hemorrhages were also present. Anterior chamber tap was performed, and intravitreal ganciclovir was administered. Later, the anterior chamber fluid tested positive for CMV DNA at PCR. Intravenous ganciclovir was started, and later changed to maintenance therapy with oral valganciclovir.

In view of residual respiratory symptoms, proximal myopathy, and swallowing difficulty, the patient started IVIG 0.4 g/kg/day for

5 days and continued a tapering dose of oral prednisolone. Following 3 cycles of IVIG, a notable improvement in her swallowing difficulties was seen, allowing the patient to resume oral intake, which subsequently led to the removal of the PEG tube. Significant improvement in muscle power, to grade 4 in the girdles and to grade 5 for the distal limbs, was also seen. Ferritin decreased to $616 \mu\text{g/L}$, creatinine kinase to 46 U/L , and absolute lymphocyte count normalized at $2.36 \times 10^3 \text{ cells/mm}^3$. A new HRCT demonstrated mild lung fibrosis with no worsening. Her vision was 6/36 in both eyes with disappearance of dendritic lesions. Serum immunoglobulin levels showed normal levels of IgA 1.59 g/L , IgG 17.61 g/L , and IgM 0.58 g/L .

Discussion

MDA-5 DM is a distinct subtype of dermatomyositis, with often delayed diagnosis and possibly detrimental consequences. Research conducted in the United States has shown that this condition predominantly affects women, with a prevalence rate

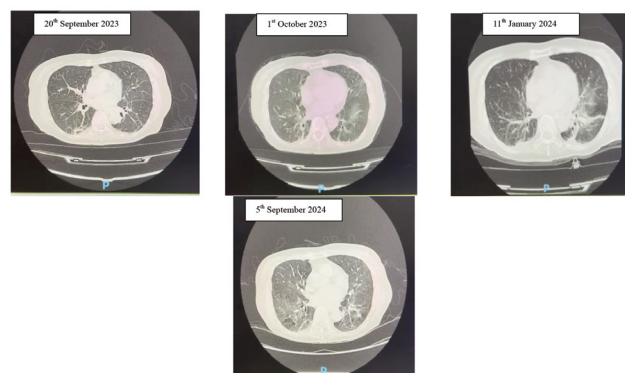


Figure 1. Serial high-resolution computed tomography showing a slight increase in bilateral lung fibrosis in the lungs, mainly at the posterior lower lobes, associated with mild traction bronchiectasis and subsegmental plate atelectasis at the medial lobes bilaterally.

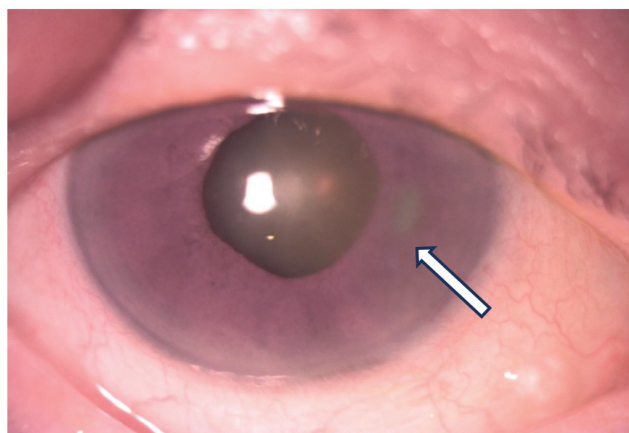


Figure 2. Right eye semi-dilated pupil with patchy iris atrophy. Dendrite medial to pupil in the 3 o'clock region.

between 56% and 73% and an average age at diagnosis between 43 and 47 years, and has a higher prevalence in Caucasians, with rates varying from 48% to 87.5% (16, 17).

In 2020, Allenbach *et al.* classified the manifestations of MDA-5 DM into distinct clusters. Cluster 1, identified as the MDA-5 RP-ILD type, is characterized primarily by pulmonary involvement and the presence of mechanic's hands and is associated with a poor prognosis. Cluster 2, referred to as MDA-5 rheumatic DM type, is characterized by inflammatory arthralgias and arthritis, exhibiting a favorable prognosis with reduced occurrence of skin lesions, myositis, and RP-ILD. Lastly, Cluster 3, known as the MDA-5 vasculopathy DM type, presents an intermediate prognosis and is linked to cutaneous vasculopathy symptoms such as Raynaud's phenomenon, digital necrosis, and calcinosis, along with a higher incidence of myositis (18). Given that our patient exhibited proximal muscle weakness and pulmonary involvement, she falls into cluster 1, which necessitates aggressive immunosuppressive therapy.

Evidence-based management of MDA-5 DM ILD is still lacking. The general agreement among experts is to initiate a combination of immunosuppressive therapies composed of high-dose GC, CNi, and/or cyclophosphamide (alternative: rituximab and plasma exchange) early in the course of the disease due to the potential risk of RP-ILD, which significantly impacts morbidity and mortality rates within the initial 3 months following diagnosis (3, 5, 19). It is recommended to maintain treatment with CNi and MMF. For early-stage disease, the use of JAK inhibitors is suggested. Additionally, pirfenidone is recommended for managing subacute MDA-5 DM associated ILD (19).

Our patient was started on oral TOF after being unable to tolerate other immunosuppressants (rituximab, cyclosporin, and cyclophosphamide). Survival rate 6 months following the onset of ILD was markedly higher in patients with MDA-5 DM-related ILD who were treated with TOF (18 out of 18, 100%) compared to those in the control group who did not receive the treatment (25 out of 32, 78%) ($p=0.04$). Moreover, research indicates improvements in HRCT and pulmonary function test results among patients with MDA-5 DM-related ILD receiving TOF (7).

Unfortunately, our patient has contracted left eye CMV retinitis and right eye acute herpetic hypertensive anterior uveitis with dendritic keratitis while being on TOF. The existing literature indicates that patients undergoing treatment with systemic GC, as well as those receiving a combination of GC and traditional disease-modifying antirheumatic drugs, face an elevated risk of herpesvirus infections, including VZV and CMV (20). Tsuji *et al.* mentioned that preventative strategies for CMV infection should be adopted in MDA-5 DM patients, as they have a higher risk of CMV infection compared to other types of inflammatory myopathies (21).

Our patient had previously received systemic GC therapy and intravenous rituximab, followed by cyclosporin and cyclophosphamide, prior to the initiation of TOF. Consequently, the risk of developing opportunistic infections like CMV retinitis was further increased with the use of TOF, as our patient was not given primary CMV prophylaxis. A study reported improved 1-year survival in MDA-5 DM patients on TOF with valganciclovir prophylaxis compared to those without (22).

When the patient developed CMV retinitis and HSV anterior uveitis, all the immunosuppressants were stopped, and IVIG was started. Plasma exchange would be considered if the IVIG failed, since MMF was contraindicated in view of recurrent and ongoing infections. The role of IVIG in MDA-5 DM is not completely

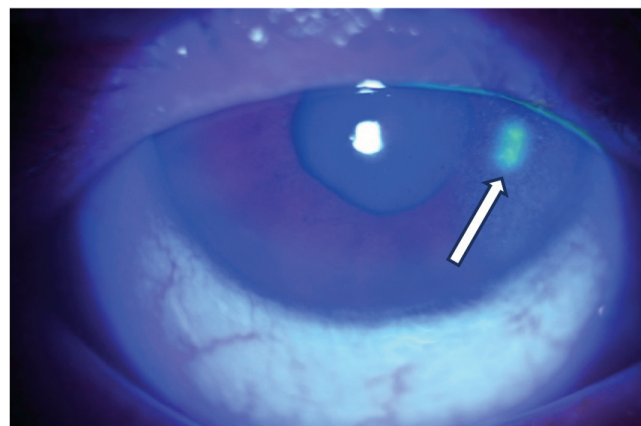


Figure 3. Right eye cornea dendritic keratitis with fluorescein stain.

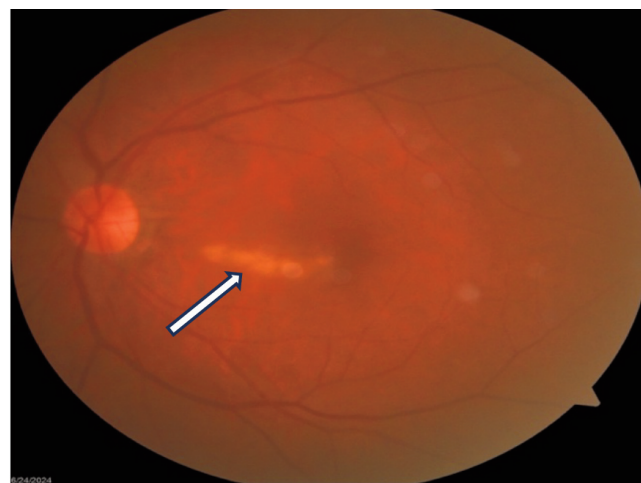


Figure 4. Left eye funduscopy showing a horizontal streak of retinitis across the central macular region.

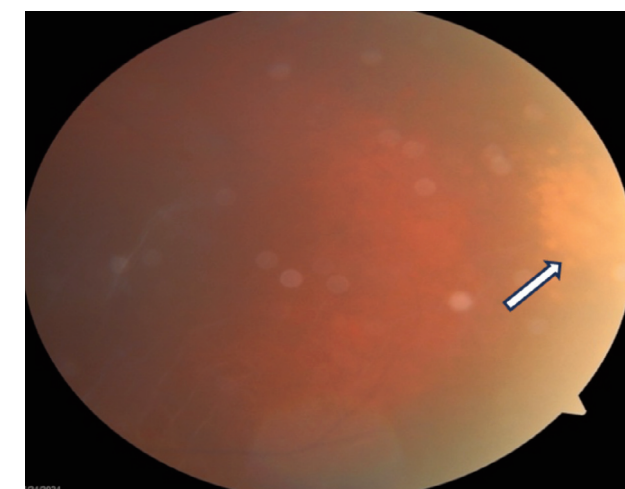


Figure 5. Left eye funduscopy with peripheral retinitis.

clear; Wang *et al.* reported that IVIG, as an adjunct therapy, is highly effective for patients suffering from MDA-5 DM related RP-ILD. IVIG enhances survival and remission rates, reduces ferritin levels and anti-MDA5 antibody titers, and ground-glass opacity scores (23). We observed significant improvement in our patient after she was started on cyclical IVIG, with improvement of swallowing and muscle weakness, and stabilization of ILD.

CMV retinitis has long been linked to HIV infection. However, in 2017, a study reported 170 cases of CMV retinitis in HIV-negative patients. Among them, 142 had systemic immune dysfunction (24). Standard treatment protocols for CMV retinitis in non-HIV patients resemble those used for HIV: valganciclovir is administered at a dosage of 900 mg twice daily for a duration of 3 weeks, followed by a maintenance phase. In individuals with HIV, the maintenance phase persists until immune reconstitution is accomplished. Conversely, in the non-HIV population, there is no defined endpoint (10). Our patient is still on a maintenance dose of oral valganciclovir, showing good response, while disease activity is well controlled on cyclical IVIG.

Another important aspect is the cumulative risk of therapy interactions between different immunosuppressive therapies (rituximab, cyclophosphamide, TOF, GC) and the risk of opportunistic infections. In view of the increasing risk of mortality in a patient with MDA-5 DM with RP-ILD and positive anti-Ro52 antibody, an aggressive immunosuppressive therapy was initiated in this patient (25). She had received triple therapy of intravenous GC and CNI together with cyclophosphamide, following an insufficient response to intravenous rituximab. The patient was unable to tolerate both CNI and cyclophosphamide due to their adverse effect, thus she was initiated on TOF. One study mentioned that the risk of opportunistic infection, especially pneumonitis and CMV infection, was highest in patients receiving cyclophosphamide and CNI (tacrolimus) (25). Therefore, in the event of recurrent and active opportunistic infection, IVIG would be the safer choice to control disease activity without aggravating the infection. Plasma exchange should be considered in refractory cases.

Conclusions

This case highlights the need for prompt diagnosis and aggressive immunosuppressive treatment to combat the rapid progression of MDA-5 DM associated with RP-ILD. The presence of an opportunistic infection, such as HSV anterior uveitis and CMV retinitis, significantly complicated the situation. The timely initiation of alternative treatments, such as IVIG, is crucial in the management of this condition. MDA-5 DM poses significant challenges in both diagnosis and management due to its diverse manifestations requiring a multidisciplinary approach; early treatment may contribute to improved outcomes.

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