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REVERSIBLE METHOTREXATE-INDUCED NEPHROTIC SYNDROME IN A DERMATOMYOSITIS PATIENT

Claudia Cobilinschi[1,2], Cristian Cobilinschi[2,3], Constantin-Ioan Busuioc[4], Ruxandra Ionescu[1,2]

[1] Department of Rheumatology and Internal Medicine, "Sf. Maria" Clinical Hospital, Bucharest, Romania
[2] "Carol Davila" University of Medicine and Pharmacy, Bucharest, Romania
[3] Intensive Care Unit, Clinical Emergency Hospital, Bucharest, Romania
[4] Histopathology Laboratory, "Sf. Maria" Clinical Hospital, Bucharest, Romania

Abstract

Adult-onset dermatomyositis (DM) is a rare disease, characterized by muscle weakness, increased serum enzymes, evocative electromyogram and typical histological pattern. We present the case of a 63-year old female patient who was recently diagnosed with DM. The administration of a single low-dose methotrexate (15 mg subcutaneous) induced pancytopenia and nephrotic syndrome. Drug toxicity was reversible with adjunctive therapies and supportive measures. Further immunosuppression was switched to mycophenolate mofetil with good response. Despite worldwide frequent use, physicians should be aware of MTX remaining toxicity and prevent side effects occurrence.

Keywords: idiopathic dermatomyositis, methotrexate, nephrotic syndrome, immunosuppression

INTRODUCTION

Dermatomyositis (DM) is a rare inflammatory condition that affects the striated muscles and skin with potential multisystemic involvement (1). It is defined by significant proximal motor weakness, elevated muscle serum enzymes, abnormal electromyogram and biopsy accompanied by myositis-specific antibodies. Adult females have a 2-3 fold risk than men and more than 20% have an associated underlying malignant disease (2). Once the latter is temporarily ruled out, corticosteroid therapy is recommended together with immunosuppression to rapidly lower the steroid dose. Methotrexate and azathioprine are often used as first-line agents despite their long interval to achieve efficacy (3). However, methotrexate-induced toxicity should be an essential decision factor in choosing an optimal therapeutic approach.

CASE REPORT

We present the case of a 63-year old female patient who was admitted in our Rheumatology Department with severe proximal limb muscle weakness with impaired ambulation with progressive onset in the last three weeks. Patient was transferred from the Clinical Emergency Hospital where clinical and biological setting indicated a rhabdomyolysis syndrome (CK 22 000 UI/l, CK-MB 600 U/l, ASAT and ALAT 400 U/l, potassium levels 6.3 mmol/l). Firstly, a lumbar MRI was performed in order to find a cause for patient's limb weakness. Images showed a high T2 signaling on lumbar paraspinal muscles, piriformis and iliopsoas muscles, indicating a strong inflammation of muscle structures.

Muscle enzyme values were slightly improved with proper hydration, diuretics and Dexamethasone but no immunological investigations were performed at the time.

She had a history of arterial hypertension, type-2 diabetes and alcohol consumption with subjective cessation of over three months.

When admitted in the Rheumatology Department, patient had severe muscle weakness of the limbs and neck muscles (testing 1/5), together with a cutaneous rash over the anterior chest and face with pruritic areas. Patient recounts noticing first cutaneous rash after cosmetic hair dying. Despite the evocative cutaneous signs, patient had no Raynaud's, no cuticular overgrowth and nailfold capillaroscopy had a relatively normal pattern.

Corresponding author:
Claudia Cobilinschi
E-mail: claudia.cobilinschi@umfcd.ro

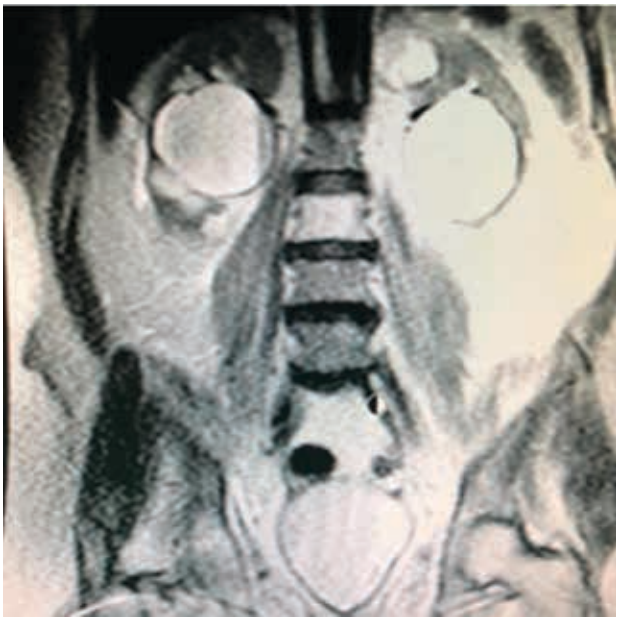

FIGURE 1. *Lumbar MRI showing muscle T2 signaling*

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She had markedly elevated muscle enzymes (serum CK over 100 times the normal range). A priorly performed electromyography detected signs of chronic sensitive polyneuropathy.

A muscle biopsy was performed showing perivascular lymphocytic infiltrate and atrophic areas of the fascia, suggesting an inflammatory myopathy.

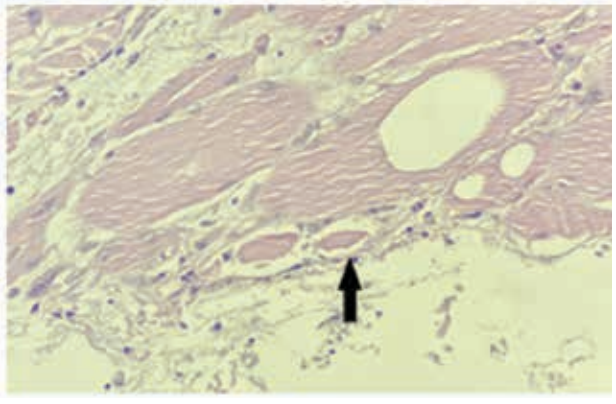

FIGURE 3. *Muscle biopsy showed perifascicular atrophy (arrow) and fat infiltration within the muscle fibers, 40x magnification*

The autoantibody panel showed high titer anti-Mi2, indicating the diagnosis of idiopathic dermatomyositis according to Bohan and Peter criteria in 1975 (4).

No pulmonary, cardiac or gastrointestinal tract complications were identified in this patient.

Knowing the tight link between this type of myopathy and neoplasia, an age-appropriate screening was undergone, including computed tomography, gynecological exam and ultrasound, tumor markers with no abnormal findings.

Once the muscle biopsy was completed, high dose methylprednisolone was administered for three

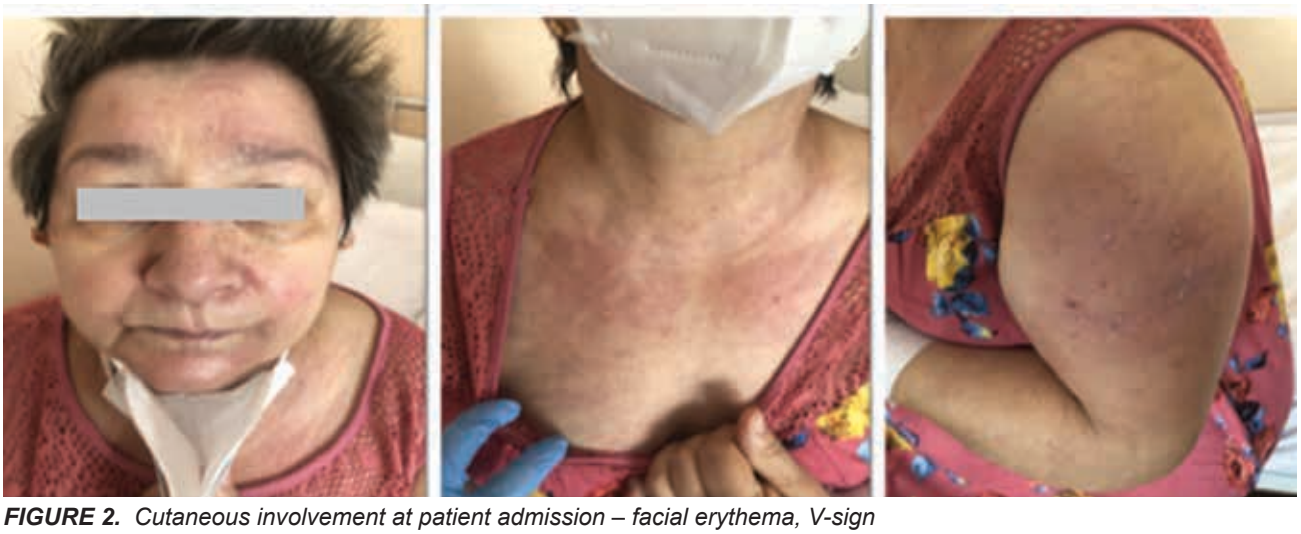

FIGURE 2. *Cutaneous involvement at patient admission – facial erythema, V-sign*

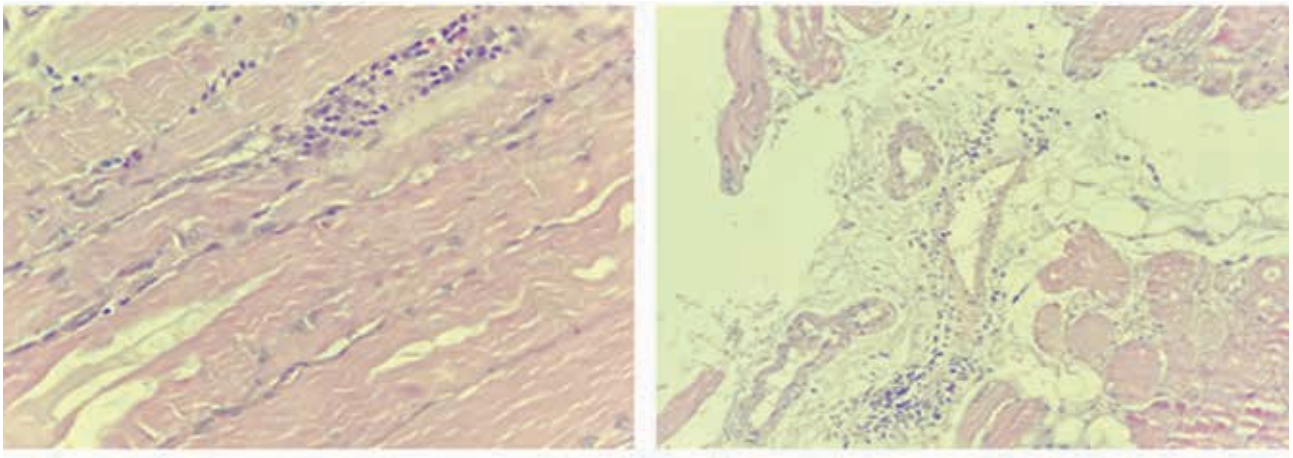

FIGURE 4. *Mixed inflammatory infiltrate inside the myofibers and around the intramuscular blood vessels. The inflammation consisted of plasma cells, lymphocytes and eosinophils, 40x magnification*

days with close monitoring of blood pressure values and serum glucose. No signs of infection was identified. For further corticosteroid sparing effect, subcutaneous methotrexate (15 mg) was elected, followed by folic acid supplementation. Five days after administration, patient develops significant bilateral edema of limbs and altered state. Blood tests showed severe pancytopenia, raised inflammatory markers, high muscle enzymes and low serum proteins. Renal function was stable, with a creatinine clearance of 68 ml/min/1.73 m2, however nephrotic range proteinuria was identified (5 grams in 24-hour collected urine). Repeated urine samples ruled out evidence of infection as did the renal ultrasound. Despite being a relevant indicator, serum MTX concentration measurement was not feasible on site. An important mention is that the patient was on intravenous proton pump inhibitor (PPI, pantoprazole) due to high-dose corticosteroid regimen.

Taking into account the timely relation to administration, both pancytopenia and nephrotic syndrome were attributed to MTX toxicity. Folic acid therapy was initiated, one unit of blood transfusion and filgrastim, a human granulocyte colony-stimulating factor were added. Blood pressure was controlled with angiotensin receptor blockers and other renal toxic drugs were avoided. She was further placed on anticoagulants and received diuretics, statin therapy with complete resolution of the proteinuria a week later (284 mg/24 h). Since the disease was still highly active, but high muscle enzyme values and persistent muscle weakness, patient was switched to mycophenolate mofetil (MMF) with good tolerance and disease control. Dose was slowly escalated in order to assess patient's tolerance and monitor side effect occurrence. When reached to 2.5 grams per day, patient experienced intense muscle cramps and diarrhea and quickly developed symptomatic hyponatremia (118 mmol/l). MMF was again deescalated and initiated crystalloid solutions with symptom remission. Patient was left on MMF 2 grams and 1mg/kg Prednisone equivalent together with PPI, high-dose vitamin D and potassium supplement. Patient was frequently monitored and underwent a strict schedule of corticoid dose reduction. At present she is under MMF 2g and 8mg of methylprednisolone with normal value muscle enzymes, no inflammatory syndrome and no proteinuria. During this time patient intensified daily exercise program with a physical therapist and is currently independent regarding household chores using a cane.

DISCUSSIONS

Glucocorticoids are the initial treatment recommended in both poly- and dermatomyositis with progressive tapering in the following 9 to 12 months, depending on the severity of disease and risk of relapse. Glucocorticoid-sparing agents like methotrexate or azathioprine should be initiated from the diagnoses and later discontinuation once remission is achieved. Intravenous immunoglobulin are held for refractory, resistant myopathies.

Methotrexate (MTX) acts as a folic acid antagonist and is associated with various side effects that can occur with low-dose regimens as used in rheumatic diseases (5). Despite having the kidneys as main excretion route, renal toxicity is relatively rare at up to 25 mg weekly and can manifest as an increase in serum creatinine levels or tubular injury (6). Hence, the nephrotoxicity is either a direct effect

of MTX or due to the cristallisation of metabolite hydroxy-MTX (7-OH-MTX) molecules in the renal tubuli at acidic urinary pH followed by a reduction in the glomerular filtration rate (GFR) (7). Patients' genetic polymorphisms regarding MTX metabolism plays a role in properly eliminating the drug (8).

Adverse events usually occur in patients with previously impaired renal function or with insufficient hydration when administering higher doses (9).

Published in 2008, the MATRIX (Methotrexate and renal insufficiency) study aimed to assess the prevalence of kidney disease, including signs of proteinuria, haematuria and leucocyturia according to drugs prescribed in rheumatoid arthritis patients. In the MTX study group, almost half of the patients with glomerular filtration rate (GFR) less than 60 ml/min/1.73 m2 had no dose adjustment in accordance to their kidney disease, leading to increased toxicity (10).

High-dose MTX therapy used in oncology, higher than 500 mg/m2, can lead to proteinuria due to suboptimal hydration, as stated in an older study published in 1993 (11). Researchers investigated renal parameters in children with malignancies before and after high dose methotrexate administration and found frequent de novo or worsening proteinuria rates and a decrease in the GFR after therapy. Intensive hydration and urinary alkalinisation might prevent proteinuria in most of the patients receiving this immunosuppressant agent (12).

Apart from hyperhydration, urine alkalization and dose-adjustment in renal impaired patients (13), leucovorin is used as a rescue agent, as it neutralizes MTX toxicity, especially myelosupression, gastric or neurological adverse effects (14).

Beside additional protective measures, physicians should investigate potential drug-interactions. Co-administration of PPIs might reduce MTX clearance and increase its toxic effects, as seen in high-dose MTX strategies. The mechanism behind this is that PPIs can inhibit renal elimination of hydrogen ions and block the active tubular secretion of MTX. Since MTX is secreted in the distal tubules using the hydrogen/potassium adenosine triphosphatase pump, the elimination half-life of MTX increases, which results in potentially toxic concentrations of MTX (15).

However, a research evaluating the co-administration of lansoprazole and naproxen in patients with rheumatoid arthritis receiving MTX did not confirm alterations of the pharmacological profile of MTX (16). Thus, dose-dependent drug interactions should be assessed when choosing optimal therapy.

The case presentation is a MTX-fail due to adverse events occurrence but a good responder when switching to MMF which is known to successfully replace MTX especially if lung involvement (interstitial lung disease) is present. However, drug should be closely monitored for tolerance and opportunistic infections.

CONCLUSIONS

Idiopathic inflammatory myopathies are a heterogeneous group of conditions that manifest through slowly progressive muscle weakness and fatigue, inflammatory infiltrate and the presence of specific autoantibodies. Corticosteroid therapy is the cornerstone in treating disease symptoms together with other agents that can further help taper the corticoid dose. Methotrexate is elected as one of the first-line choice agents. However, MTX-related toxicity remains an important issue at present, including nephrotoxicity, hepatotoxicity, gastrointestinal, bone marrow suppression, and neurotoxicity, despite its relatively decreased frequency in low-dose regimens. Rheumatologists should be vigilant and search for signs of drug-related toxicity that are to be promptly managed.

REFERENCES

1. Messer G, Meurer M. Dermatomyositis. Aktuelle Derm. 2000;26(8-9):260-5.
2. Chang L, Zhang L, Jia H, Nie Z, Zhang L. Malignancy in dermatomyositis. Medicine (Baltimore). 2020;99(34):e21733.
3. Fendler C, Braun J. Use of methotrexate in inflammatory myopathies. *Clin Exp Rheumatol.* 2010;28(5 Suppl 61):S164-7.
4. Dalakas MC, Hohlfeld R.. Diagnostic criteria for polymyositis and dermatomyositis. *Lancet*. 2003;362:1762-3.
5. Kinder AJ, Hassell AB, Brand J, Brownfield A, Grove M, Shadforth MF. The treatment of inflammatory arthritis with methotrexate in clinical practice: Treatment duration and incidence of adverse drug reactions. *Rheumatology.* 2005;44(1):61-6.
6. Robey RB, Block CA. Adverse Effects of Low-Dose Methotrexate. *Annals of internal Medicine.* 2020;173:166-7.
7. 7Slørdal L, Sager G, Aarbakke J. Pharmacokinetic interactions with methotrexate: is 7-hydroxy-methotrexate the culprit? *Lancet*. 1988;1(8585):591-2.
8. Yang SL, Zhao FY, Song H, Shen DY, Xu XJ. Methotrexate associated renal impairment is related to delayed elimination of high-dose methotrexate. *Sci World J.* 2015;2015.

9. Fermiano M, Bergsbaken J, Kolesar JM. Glucarpidase for the management of elevated methotrexate levels in patients with impaired renal function. *American Journal of Health-System Pharmacy.* 2014;71:793-8.
10. Karie S, Gandjbakhch F, Janus N, Launay-Vacher V, Rozenberg S, Mai Ba CU, et al. Kidney disease in RA patients: Prevalence and implication on RA-related drugs management: *The MATRIX study. Rheumatology.* 2008;47(3):350-4.
11. Kovács GT, Paál C, Somló P, Koós R, Schuler D, Borsi JD. Proteinuria due to suboptimal hydration with high-dose methotrexate therapy. *Cancer Chemother Pharmacol.* 1993;33(3):262-3.
12. HW, SG. Pre-hydration in high dose methotrexate chemotherapy. J *Oncol Pharm Pract.* 2017;23(8):1-2.
13. Mir O, Ropert S, Babinet A, Alexandre J, Larousserie F, Durand JP, et al. Hyper-alkalinization without hyper-hydration for the prevention of high-dose methotrexate acute nephrotoxicity in patients with osteosarcoma. *Cancer Chemother Pharmacol.* 2010;66(6):1059-63.
14. Howard SC, McCormick J, Pui C, Buddington RK, Harvey RD. Πρεωεντινγ ανδ Μαναγινγ Τοξιχιτιεσ οφ Ηιγη–Δοσε Μετηοτρεξατε. Oncologist. 2016;21(12):1471-82.
15. Beorlegui B, Aldaz A, Ortega A, Aquerreta I, Sierrasesúmega L, Giráldez J. Potential interaction between methotrexate and omeprazole. *Ann Pharmacother.* 2000;34(9):1024-7.
16. Vakily M, Amer F, Kukulka MJ, Andhivarothai N. Coadministration of lansoprazole and naproxen does not affect the pharmacokinetic profile of methotrexate in adult patients with rheumatoid arthritis. *J Clin Pharmacol.* 2005;45(10):1179-86.