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Case Report

Complete and sustained resolution of calcinosis universalis in a juvenile dermatomyositis case with mycophenolate mofetil

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Juvenile dermatomyositis (JDM) is a rare, multisystemic, idiopathic vasculopathy mainly affecting the muscles and the skin. Gastrointestinal system, lungs, joints and heart may also be involved. Characteristic skin findings are heliotrope rash and Gottron papules but extensive skin involvement as large necrotic lesions are rarely reported. Calcinosis is one of the major issues in the long term. Delay in diagnosis, inadequate therapy at the initial phase, prolonged persistent disease activity are considered as major risk factors for the development of calcinosis. Treatment of calcinosis is also a major issue because no single treatment modality has been found to reproducibly stop or reverse calcification.

A 5-year-old girl was admitted to our clinic with typical signs and symptoms of JDM. She was initially treated with high-dose corticosteroids, methotrexate and intravenous immunoglobulin (IVIG). Soon after, she developed necrotic ulcerative skin lesions and cyclosporine was added to her treatment regimen. By this treatment all muscle and skin manifestations were controlled but on the first year of follow-up she developed superficial calcification plaques on the upper extremities and calcinosis universalis like calcifications on the lower extremities. Calcifications did not respond to bisphosphonate (pamidronate) and IVIG treatment but mycophenolate mofetil resulted in rapid and sustained resolution of all calcification plaques.

Key words: calcinosis, juvenile dermatomyositis, mycophenolate mofetil.

Juvenile dermatomyositis (JDM) is a rare (2-4 cases per million children/year), multisystemic disease primarily affecting the muscles and skin. Typical skin findings are heliotrope rash and Gottron papules but extensive skin involvement as large necrotic lesions are rarely reported. Muscle involvement is manifested as symmetrical proximal muscle weakness.[1,2] Initial treatment of JDM consists of corticosteroids and methotrexate and/or intravenous immunoglobulin (IVIG) with sun protection, adequate calcium/vitamin D intake and physical therapy.[3,4] In patients having severe manifestations at the onset or with resistant disease cyclophosphamide, cyclosporine A, mycophenolate mofetil, or biologics (rituximab, infliximab, adalimumab) are considered as alternatives.[1,3,4] Mortality is reported to be less than 2% and mostly secondary to cardiopulmonary involvement and intervening infections.[1,2] Calcinosis is one of the main problems in the long term follow-up of children with JDM. Delay in diagnosis, inadequate therapy at the initial phase, prolonged persistent disease activity are considered as major risk factors for the development of calcinosis. Treatment of calcinosis in JDM is challenging because no single treatment modality has been found to reproducibly stop or reverse calcification.[1-4]

Case Report

A 5-year-old girl was admitted to our clinic with the complaints of inability to walk and climb stairs properly, rash and swellings around the face, arms and hands that all started 5 months ago. On the initial examination, she had all the signs of JDM namely, heliotrope rash around the eyes, Gottron papules on the dorsum of the hands, symmetric and severe proximal muscle weakness with prominent Gower's sign, edema on the face, hands and arms. She had livedo racemose rash on the extremities and the trunk. On the skin of the left scapular area there was small macular pinkish lesion with small necrotic dots in the center. She had minimal nasal speech but had no difficulty in swallowing and esophago-gastro-duedonography did not show any sign of reflux. She had no sign of respiratory muscle involvement with normal blood gas analysis. Laboratory tests showed mildly elevated muscle enzymes and inflammatory markers [creatinine kinase (CK): 457 U/L (normal: < 155), CK-MB: 38 U/L (normal < 25), AST: 65 U/L, ALT: 30 U/L, LDH: 479 U/L (normal < 314), aldolase: 21 U/L (normal <7.6), C-reactive protein: 15 mg/L (normal <5 mg/L), erythrocyte sedimentation rate: 22 mm/hr]. Anti-nuclear antibody and Anti-Jo1 was negative with normal thyroid function tests, blood chemistry, urinalysis and renal function tests. Electromyographic study was compatible with myopathic changes. Lower extremity magnetic resonance imaging showed extensive myositis and subcutaneous edema in all muscle groups. Capillaroscopy demonstrated prominent dilatation and loss of capillaries with microhemorrhages.

Initial treatment consisted of intravenous high-dose methylprednisolone (30 mg/kg/day, 3 consecutive days) continued with prednisolone (2 mg/kg/day, intravenous), methotrexate (15 mg/m^2/week, subcutaneous) and IVIG (2 gr/kg/month, 6 consecutive months). After the first month, muscle strength and enzymes started to improve but new necrotic skin lesions developed on the back, both arms, hands, shoulders and under the chin. Cyclosporine (5 mg/kg/day, per oral) was added to the regimen. By the third month all necrotic lesions healed with minimal scarring. Cyclosporine was discontinued on the ninth month and continued with prednisolone and methotrexate.

On the first year of the treatment, small calcific nodules were felt by palpation on the distal part of the extremities that were verified on the X-rays. Pamidronate (1 mg/kg/d, 3 consecutive days, every 3 months), IVIG (1 gr/kg/month, 6 consecutive months) and colchicine were added to methotrexate and prednisolone. But soon after, the child developed calcinosis universalis like picture on the lower extremities (Fig. 1a). On the twelfth month of pamidronate treatment, calcific

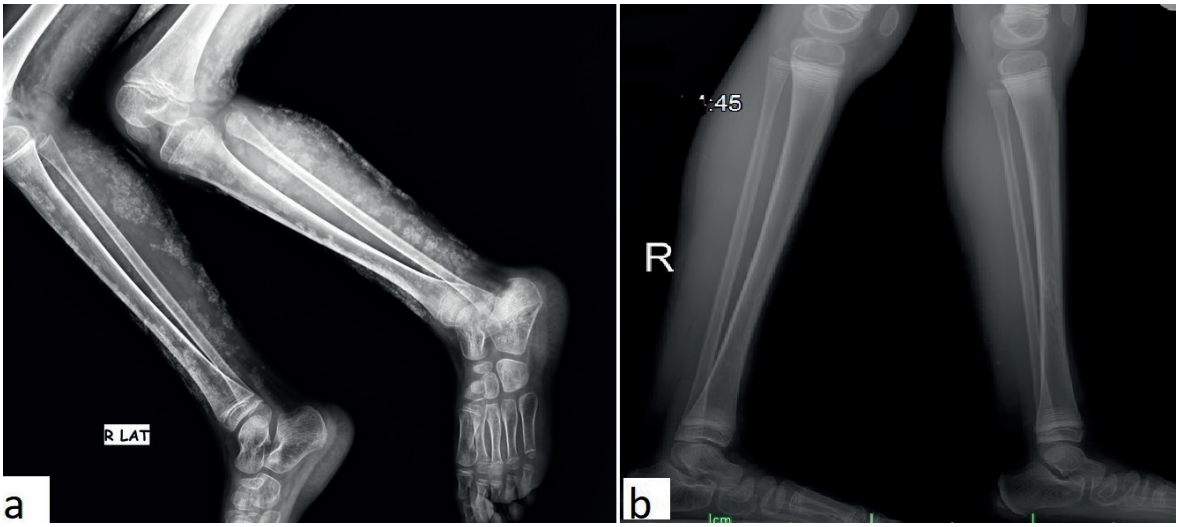

Fig. 1. a) the view of the calcifications as intermuscular fascial deposits (calcinosis universalis) on the lower extremities **b)** total resolution of calcinosis universalis.

lesions did not regress, so methotrexate was switched to mycophenolate mofetil (MMF; 25 mg/kg/day, per oral) and pamidronate was discontinued. On the sixth month of MMF, we have observed dramatic resolution of all calcifications (Fig. 1b). The child is being followed for more than 3 years and currently using prednisolone (0.15 mg/kg/every other day), MMF and colchicine without any sign of calcinosis, with normal muscle enzymes, full muscle strength and normal skin findings. Informed consent was received from the family for this publication.

Discussion

Juvenile dermatomyositis (JDM) is a chronic idiopathic inflammatory myositis characterized by inflammation of striated muscle and skin. Diagnosis is based on combination of typical skin manifestations and demonstration of muscle involvement either by muscle enzymes, muscle biopsy, electromyography (EMG) or imaging modalities.[1-4] Bohan and Peter criteria set that was developed in 1975 for adult dermatomyositis is being used for the diagnosis of JDM. This set includes a typical skin rash and 3 or more of the following items: symmetric muscle weakness, increased serum muscle enzyme levels, EMG abnormalities and muscle biopsy findings consistent with myositis.[5] With the advent of imaging modalities especially of magnetic resonance imaging (MRI), demonstration of muscle edema on MRI is used more commonly in diagnosis of JDM instead of invasive techniques like EMG or muscle biopsy.[1-3] Muscle biopsy is strongly recommended in patients with atypical cutaneous manifestations or in patients that do not respond to treatment.[1,2] Our case had all classic cutaneous manifestations of JDM and fulfilled Bohan and Peter criteria system.

Typical cutaneous manifestations of JDM include heliotrope discoloration of the eyelids, periorbital edema, erythematous papules over the extensor surfaces of hands, elbows, or knees (i.e., Gottron papules). These skin findings are seen in nearly all cases and are highly suggestive of JDM. JDM is also considered as a form of vasculopathy and this may be reflected clinically as skin ulcers or severe gastrointestinal bleeding.[1] Nailfold capillaroscopy is a noninvasive way of demonstrating vasculopathy in JDM. Typical abnormalities seen by capillaroscopy are dilatation of loops, thrombosis and hemorrhage, tortuosity, bushy loop formation, arborization and dropout of vessels.[1,6] Studies have shown that decreased capillary density was associated with more severe chronic disease course, skin ulcerations and development of calcinosis.[1,6,7] Schmeling et al.[7] reported initial and follow-up capillaroscopy manifestations in 28 JDM patients and they concluded that reduced baseline capillary density improved as the disease improved. Our patient had typical capillaroscopy manifestations of JDM like dilatation and loss of capillaries and soon developed extensive necrotic skin ulcers, emphasizing the importance of performing capillaroscopy at the time of diagnosis of JDM. The frequency of skin ulceration is reported to be in 5-30% of JDM cases. The presence of skin ulcerations at the beginning of the disease is accepted as a warning sign for a chronic unremitting course, severe visceral organ involvement and calcinosis.[2] Initial treatment of JDM consists of methylprednisolone pulses (15-30 mg/kg/dose on 3 consecutive days) followed by oral prednisolone and methotrexate and/or monthly IVIG infusions.[3,4] In patients unresponsive to this regimen adding or switching to other medications is recommended.[3,4,8] Cyclosporine A is a calcineurin inhibitor and suppresses T cells. There are reports on beneficial effects of cyclosporine A in JDM cases especially in cutaneous ulcers and interstitial lung involvement.[9] Some authors have suggested that cyclosporine should be considered as first-line therapy particularly in severe onset cases.[2] Our case developed extensive necrotic skin lesions under intensive treatment with corticosteroids, methotrexate and IVIG. Cyclosporine A resulted in complete healing of skin ulcers.

Calcinosis is a major issue in the long term and dystrophic calcification occurs in 12-47% of JDM patients.[10] Calcinosis may rarely develop at the time of diagnosis but most of the times occur a few years after the diagnosis. Dystrophic calcifications may occur as superficial plaques or nodules, deep large tumorous deposits (i.e., calcinosis circumscripta), intermuscular

fascial deposits (i.e., calcinosis universalis), subcutaneous exoskeleton-like deposits and mixed forms.[1,10] The most common form is superficially located small plaques or nodules on the extremities. Dystrophic calcifications may give rise to recurrent skin infections, pain, and flexion contractures.[10] The most important risk factor for calcinosis development is considered as delay in the diagnosis and the duration of untreated active disease.[1,10,11] Other risk factors for calcinosis are male gender, young age at disease onset, accompanying cardiac or pulmonary disease, having anti- MJ (NXP2) autoantibody, TNF-α-308A allele and inadequate treatment.[1,10,11] The study of Tansley et al.[11] looked for risk factors for calcinosis in a large JDM cohort. The study included 285 patients and 33% developed calcinosis during the follow-up period. They concluded that disease onset at a young age had a high risk of calcinosis irrespective of autoantibody positivity and the presence of anti-NXP2 autoantibodies increased the risk of calcinosis in all age groups. Kim et al.[8] reported that early and aggressive treatment lead to complete and sustained remission in JDM. They reported 49 JDM cases and persistent calcinosis were observed only in 4%. Our case was aggressively treated with corticosteroids, IVIG, methotrexate and cyclosporine A, nevertheless developed superficial calcinosis plaques on the upper extremities and calcinosis universalis like calcifications on the lower extremities.

Treatment of calcinosis is challenging because no therapy has proven to be reproducibly efficacious. Therapies used in JDM-associated calcinosis are anti-inflammatory drugs (IVIG, colchicine, thalidomide, rituximab, abatacept, infliximab) and drugs that affect calcium or phosphorus metabolism [bisphosphonates (pamidronate, alendronate, etidronate), sodium thiosulfate, aluminum hydroxide, probenecid].[10] As stated, unfortunately none of these modalities has been consistently effective and no randomized controlled trial has been conducted in JDM.[1,10] MMF inhibits proliferation of T and B lymphocytes by selectively by inhibiting de novo purine metabolism. It has proven to be effective in the treatment of systemic lupus erythematosus nephritis and neuropsychiatric involvement and there are reports that MMF decreases skin and muscle disease activity in resistant JDM cases.[12-14] To the best of our knowledge, this is the first report of MMF in treatment of JDM-associated calcinosis.

In conclusion, early and aggressive treatment may not prevent near future development of necrotic skin involvement and calcinosis. Extensive necrotic skin involvement at the initial phase may be an impending sign of calcinosis. In selected patients, MMF may be a good alternative in JDM-associated calcinosis.

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