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Case Report

Zoledronic Acid in Treatment of Calcinosis in a boy with Juvenile Dermatomyositis – A Case Report

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Abstract

Calcinosis cutis is one of the dermatological manifestations of juvenile dermatomyositis. We present a case of an eight year old boy who presented with proximal myopathy, Gottron papules and heliotrope rash. Raised muscle enzymes and electromyography confirmed the diagnosis of juvenile dermatomyositis; and treatment started with steroids and methotrexate. Patient had poor compliance and three years later, presented with multiple calcinotic lesions over lower abdomen, buttocks and thighs. Due to lack of improvement in calcinosis after six months of treatment with steroids and methotrexate; 3-monthly zoledronic acid and fortnightly etanercept were started. After one year, patient is in remission with improved calcinosis.

Introduction

Juvenile Dermatomyositis (JDM) is a rare multi-system autoimmune disorder primarily affecting cutaneous, muscular and vascular systems.[1] One of the debilitating complications associated with JDM that occurs in up to 20 - 40% of patients throughout their course of illness is calcinosis, causing significant morbidity and disability. JDM-associated calcinosis is characterized by dystrophic calcium and hydroxyapatite mineral deposition. It occurrs often secondary to inflammation or trauma, within skin, muscles and other connective tissue including fasciae and tendons. It occurs typically after one to three years of disease onset and may have concerning complications including muscle atrophy, joint contractures, skin ulcerations, and nerve entrapment.[2]

The treatment of calcinosis can be challenging. In addition to the management and control of primary disease, several drugs have been tried as additional calcinosis-specific therapy with variable results.[1,2] Zoledronic Acid (ZA) is a second-generation bisphosphonate that is easily available and is about 10,000 times more potent than the initial first-generation bisphosphonate, etidronate.[3] We present a rare case of an eight year old boy suffering from JDM who was given intravenous ZA in addition to steroids, methotrexate (MTX) and etanercept as part of his treatment regime; and subsequently had resolved calcinosis. Preceding data regarding use of ZA in JDM-induced calcinosis is scarce.

Case Report

An eight year old boy presented with complaints of low-grade fever, generalized muscle weakness, and difficulty in climbing stairs and getting out of bed for the previous three years. He had no significant past medical or family history. He had been diagnosed as a case of JDM on the basis of presence of Gottron papules and heliotrope rash; increased creatinine phosphokinase (CPK) and lactate

dehydrogenase (LDH). C-reactive protein (CRP) was 190 mg / dL. Electromyography had revealed abnormal motor-unit action potentials especially in proximal muscles having short duration with low amplitude along with full inference with recurrent pattern suggestive of inflammatory myopathy. He was started treatment on oral prednisolone along with MTX. However, patient had poor compliance and was lost to follow-up for three years.

Before the current presentation, he had history of generalized body stiffness and multiple painful swellings mainly over the lower abdomen; buttocks and thighs; which had gradually worsened over the previous one year. He was short with height of 103 cm and weight of 17 kg (BMI = 18.03). Examination revealed proximal muscle weakness and wasting and a positive Gower's sign. There were also Gottron papules on knuckles of fingers and a characteristic heliotrope rash. There were multiple subcutaneous, hard, immobile, non-pruritic nodules predominantly around the joints with ulcerations of the overlying skin and surfacing cheesy material. He had normal blood counts with CRP - 170 mg / dL, CPK - 272 U / L, serum LDH - 464 IU / L and normal serum calcium, phosphate and parathyroid hormone levels. Anti-nuclear antibodies were positive while anti-double-stranded DNA and anti-Jo antibodies were negative. Echocardiography was normal. X-Rays revealed multiple linear and stippled calcifications in the subcutaneous tissue; more marked in lower abdominal and pelvic area (Figure 1-a).

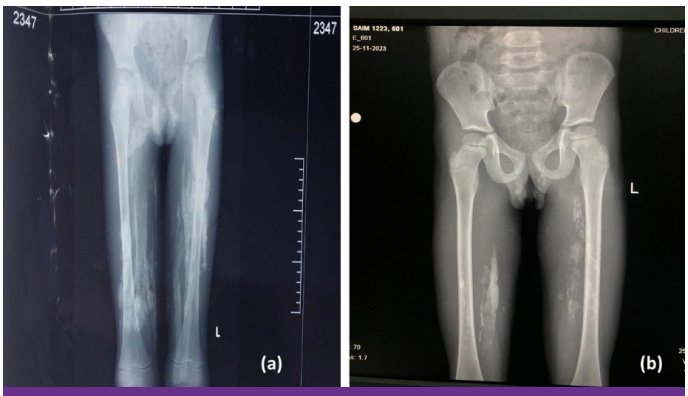

Figure 1: (a) Extensive calcification in abdomen, pelvic area and bilateral thighs (b) Improvement seen after one year of treatment

Patient was given intravenous methylprednisolone pulses therapy for three days and then put on MTX at 20 mg / m^2 / week along with oral prednisolone at 2 mg / kg / day. Six months later, he had improvement of muscle weakness and power but no significant improvement in calcinotic lesions was observed. Injection ZA was added to his treatment regime at 0.05 mg / kg three monthly along with injection Etanercept at 25 mg S / C fortnightly. The patient went into remission after one year and clinically, calcinosis and enzymes levels improved. No new lesions have appeared in the last six months (Figure 2). CRP done at six months and one year follow-up was 12 mg / dL and 6 mg / dL respectively. X-Rays repeated at one year follow-up showed marked improvement (Figure 1-b). Currently, patient is in remission and is taking monthly Etanercept and three monthly ZA, MTX and low-dose steroids. We plan to continue with Etanercept for one year along with ZA and follow-up on three monthly basis.

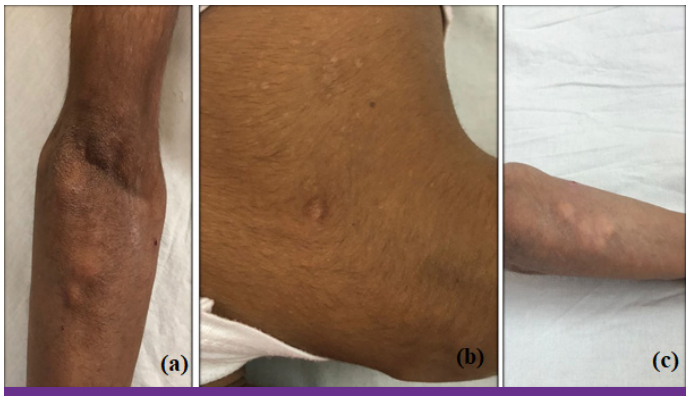

Figure 1: Improved calcinotic lesions after treatment (a) over the left elbow (b) at the back (c) on right leg on ventral aspect

Discussion

Bisphosphonates are inhibitors of bone resorption that are used widely in osteoporosis, osteogenesis imperfecta, myositis ossificans and hypercalcemia. In JDM-associated calcinosis, they are thought to reduce osteoclastic activity by inhibition of new osteoclast formation from monocytes, reduced activation, maturation and activity of already formed osteoclasts and by increasing their apoptosis.[3] They also impede macrophage proliferation, causing reduced levels of pro-inflammatory cytokines.[3,4] These properties can explain their role in prevention of calcinosis in JDM. However, the mechanism by which bisphosphonates are effective in already formed calcinosis remains unclear. The beneficial role of bisphosphonates in JDM-associated calcinosis has been suggested as early as 1971. Etidronate administration to a nine year old girl was reported to improve her symptoms.[5] Marco Puche et al described three cases where intravenous pamidronate therapy resulted in significant improvement or complete resolution of calcinosis.[4] Similarly, the administration of alendronate in a six year old JDM patient with severe calcinosis was described to have led to complete resolution by one year of therapy.[6]

No consensus has yet been developed on bisphosphonate use guidelines in patients with JDM-associated calcinosis. This may be due to the fact that JDM itself is a rare condition.[1] Secondly, the available literature is limited to very small sample-size studies or isolated case reports.[4,6] Moreover, there has been a considerable variation in the overall management of JDM in

these patients, especially in regard to choice and duration of concomitant immunosuppressive therapy.[1,2,4,6] In a study done in Turkey, two out of six patients of JDM-related calcinosis showed no response to oral alendronate administration despite concomitant administration of steroids, MTX, IVIG and immunosuppressive therapy.[7]

The role of etanercept in JDM-associated calcinosis is also not well-established. Tayfur et al reported a case of a girl who initially showed no response to steroids, MTX, IVIG and alendronate. But with the addition of cyclosporin-A, hydroxychloroquine, etanercept and intravenous pamidronate to her treatment regime, her pain and skin disease improved after two years.[7] However, another study involving nine patients of refractory JDM demonstrated etanercept use to cause only mild or no improvement in disease activity score.[8]

Conclusions

The authors conclude that intravenous zoledronic acid can be beneficial in resolution of JDM-associated calcinosis particularly in combination with steroids and immunosuppressive therapy.

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