

Resolution of Calcinosis using Bisphosphonates in Overlap Syndrome – A Case Report

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Case Report

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Abstract

Background Calcinosis cutis is a common complication of pediatric rheumatologic diseases. However, there is currently no consensus on first-line treatment. Bisphosphonates have been described as successful treatment in several case studies, but most of these cases are limited to patients with isolated juvenile dermatomyositis or systemic sclerosis. Specifically, there are limited reports of their usefulness in treating overlap syndromes and mixed connective tissue disorders.

Case Presentation: We describe the case of a 13 year-old girl with overlap syndrome with mostly features of juvenile dermatomyositis and systemic lupus erythematosus. After 22 months of extensive immunosuppressive therapy, including monthly IVIG, she continued to have pain and weakness of the lower extremities. A CT scan was performed which showed significant multifocal soft tissue calcifications of the pelvis. She was started on treatment with oral alendronate with the goal of improving her calcinosis and improving her symptoms. After several months of therapy, our patient reported subjective improvement of her lower extremity pain and weakness, as well as complete resolution of abnormalities previously seen on physical examination. A repeat CT scan of the pelvis was performed after 11 months of therapy and demonstrated complete resolution of the previously seen calcinosis.

Conclusions We report the successful treatment of soft tissue calcinosis with oral bisphosphonates in a patient with juvenile dermatomyositis-systemic lupus erythematosus overlap syndrome. These results provide further evidence that bisphosphonates can be used successfully to treat calcinosis cutis in pediatric rheumatologic disorders. Additionally, the results provide new evidence that they can be used specifically in juvenile dermatomyositis-systemic lupus erythematosus overlap syndrome, which has not been previously reported.

Background:

Pediatric autoimmune connective tissue disorders (ACTD) encompass a wide range of diagnoses, each with their own unique symptoms and complications. One of the most common sources of morbidity amongst these diseases is subcutaneous calcinosis, which has been identified in 20–40% of cases of juvenile dermatomyositis (JDM) [1–3]. Calcinosis is most commonly identified in JDM and systemic sclerosis, but it can be seen in nearly all ACTDs [4]. The calcinosis in these disorders most commonly affects the knee joints, elbow joints, and hip processes [5]. Although it is a well-recognized source of morbidity in these disorders, there are currently no standardized recommendations for its treatment [3]. Of the ACTDs, treatment of calcinosis in JDM and systemic sclerosis has been most frequently reported, although there are currently no large scale, case-controlled studies. Rheumatologists often treat calcinosis with immunomodulating agents such as intravenous immunoglobulin (IVIG) and systemic glucocorticoids, or alternative agents such as bisphosphonates and calcium channel blockers [6]. Of these choices, bisphosphonates have been inconsistently associated with complete resolution of calcinosis in various case reports of patients with JDM [7, 8]. They are also noted to be relatively safe, with short term side effects consisting of bone pain, hypocalcemia, and gastrointestinal symptoms such

as diarrhea and abdominal pain. Longer term use has been infrequently associated with impaired mineralization and nephrocalcinosis [9]. Although demonstrated to be effective and safe in treating calcinosis in JDM and systemic sclerosis, there is very limited data on the use of bisphosphonates in other rheumatologic disorders such as overlap syndromes and mixed connective tissue disorders (MCTD). In this review, we report the case of a 13 year-old girl with JDM-systemic lupus erythematosus (SLE) overlap syndrome who developed large, bulky calcinosis of the pelvis while on immunosuppressive therapy and demonstrated complete resolution after treatment with oral bisphosphonate therapy.

Case Presentation:

We report the case of a 13 year-old, Hispanic girl who was diagnosed with JDM-SLE overlap syndrome at age 10. She initially presented to our hospital with complaints of symmetric upper and lower extremity muscle weakness and a photosensitive rash for one week prior to presentation. Her initial laboratory examination was significant for elevated muscle enzymes with an AST of 611, ALT of 392, alkaline phosphatase of 118, LDH of 1740, and creatine kinase of 16012. She subsequently had a lower extremity MRI performed that showed diffuse, symmetric intramuscular T2 hyper intense signal within the gluteal adductor, extensor, and flexor musculature, consistent with diffuse proximal lower extremity myositis. On further laboratory examination, she was found to have a strongly positive ANA of 1:1280 and a positive dsDNA, with normal complements and negative Smith/RNP antibodies. With her clinical findings, laboratory evaluation, and radiologic findings she was diagnosed with overlap syndrome with mostly features of JDM and SLE. As an inpatient she was treated with IV methylprednisolone and oral hydroxychloroquine, and was discharged one week after admission.

As an outpatient, she was continued on oral hydroxychloroquine and was started on weekly methotrexate injections, per previously recommended protocols in the treatment of JDM. During her first year of treatment, she required two admissions for flares of her dermatomyositis component. The first flare occurred two weeks after her initial admission, and during both admissions she received treatment with methylprednisolone and IVIG. She also underwent two treatments with Rituximab. At approximately one year after diagnosis, due to her continued lack of improvement, her treatment protocol was advanced to include monthly IVIG.

At 22 months after diagnosis, she continued to complain of pain and weakness in her bilateral lower extremities, despite receiving monthly IVIG and intense ongoing physical therapy. On physical examination during a follow up visit at this time, she was very hesitant to sit on the floor, and had to use Gower's maneuver to stand from sitting. There was also decreased passive range of motion of the right hip when compared to the left. Due to her continued symptoms, an x-ray of the pelvis was ordered, which showed a rounded ossification near the right femoral neck, a smaller ossification near the left medial acetabulum, and multiple muscular calcifications in the adductor groups near the hip. A CT scan of the pelvis was ordered to further evaluate these findings, which showed a region of bulky, dense, soft tissue calcification measuring 3.8 × 2.3 cm within the ischiofemoral region on the right (Figs. 1 and 2), as well as scattered coarse linear calcifications within the abductor muscles bilaterally (Fig. 3). It also showed a

5.0 × 1.0 cm ovoid calcification in the left obturator internus muscle near the ischium. It was felt that these calcifications were contributing to her limitations in range of motion and subjective complaints, so additional therapy was pursued. She was started on the bisphosphonate alendronate at 10 mg orally once daily in addition to her immunosuppressive therapy with hydroxychloroquine, weekly methotrexate, and monthly IVIG.

Our patient continued to follow up every three months in our clinic. Three months after starting alendronate she reported some improvement in her pain and strength, but on physical examination still had difficulty with squatting, and still used Gower's maneuver when standing. A repeat x-ray was ordered at seven months on bisphosphonate therapy, which showed complete resolution of previously seen calcified lesions. At her next follow up visit, after being on bisphosphonates for 10 months, she no longer had to use Gower's maneuver with standing, and had equal range of motion in her bilateral lower extremities. A repeat CT scan was performed 11 months after therapy, which, similar to the x-ray, showed complete resolution of the previously seen soft tissue calcifications (Figs. 4 and 5). With complete resolution of the calcinosis, her alendronate was discontinued at her next follow-up visit. Throughout the duration of treatment, she did not report any of the short-term side effects such as GI irritation or new bone pain related to her bisphosphonate therapy.

Discussion And Conclusion

Our case demonstrates the successful use of oral bisphosphonates in resolving soft tissue calcinosis in a patient with JDM-SLE overlap syndrome. In previous case studies, it has been reported that bisphosphonates have been used successfully to treat calcinosis in patients with JDM [7, 8]. In one of the largest studies to date, six patients with JDM and calcinosis were all treated with bisphosphonates, and four of the six patients demonstrated complete resolution [7]. Additionally, in a large survey of pediatric rheumatologists, when asked about treating calcinosis in JDM, 73% said they would use bisphosphonates, and 60% ranked them as the most effective treatment [6]. While bisphosphonates are commonly used to treat calcinosis, the mechanism of action at this time is unclear. Additionally, there are currently no recommended guidelines for the treatment of calcinosis in JDM or other rheumatologic disease. Our case provides further evidence that bisphosphonates can be an effective and safe medication used to treat calcinosis in rheumatologic diseases. Furthermore, while bisphosphonates have been reported as effective use in JDM, its use in other disorders is less widely reported. Our case demonstrates that bisphosphonates can be effective in rheumatologic diseases apart from JDM, in diseases such as overlap syndrome as seen in our patient.

Abbreviations

JDM

Juvenile dermatomyositis; SLE: Systemic lupus erythematosus; MCTD: Mixed connective tissue disorder; ACTD: Autoimmune connective tissue disorder; IVIG: Intravenous immunoglobulin; AST: Aspartate aminotransferase; ALT: Alanine aminotransferase; LDH: Lactate dehydrogenase; MRI: Magnetic resonance

imaging; ANA:Antinuclear antibody; dsDNA:Double stranded DNA; RNP:Ribonucleoprotein; IV:Intravenous; CT:Computed tomography.

Declarations

Ethics Approval and Consent to Participate

Written and verbal consent obtained from patient and parent (legal guardian).

Consent for Publication:

Written and verbal consent obtained from patient and parent (legal guardian).

Availability of Data and Materials:

Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.

Competing Interests:

The authors declare that they have no competing interests.

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Authors' Contributions:

RP - primary rheumatologist for our patient, revised and edited the report. MP - performed the literature review and chart review of our patient, and was the primary author in writing the case report. BP – initially interpreted the images for our patient, and formatted the images and wrote the figure keys for this paper.

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References

1. Mathiesen P, Hegaard H, Herlin T, Zak M, Pedersen FK, Nielsen S. Long-term outcome in patients with juvenile dermatomyositis: a cross-sectional follow-up study. *Scand J Rheumatol*. 2012. doi:10.3109/03009742.2011.608376.
2. Clemente G, Piotto DG, Barbosa C, Peracchi OA, Len CA, Hilario MO, et al. High frequency of calcinosis in juvenile dermatomyositis: a risk factor study. *Rev Bras Rheumatology*. 2012;52(4):549–53.
3. Gara S, Jamil RT, Litaiem N. Juvenile dermatomyositis. In: *StatPearls*. StatPearls Publishing. <https://www.ncbi.nlm.nih.gov/books/NBK534236>.
4. Balin SJ, Wetter DA, Andersen LK, Davis MDP. Calcinosis cutis occurring in association with autoimmune connective tissue disease: The Mayo Clinic experience with 78 patients, 1996–2009. *Arch Dermatol*. 2012. doi:10.1001/archdermatol.2011.2052.
5. Miyamae T, Mori M, Inamo Y, Kohno Y, Takei S, Maeda M, et al. Multi-center analysis of calcinosis in children with juvenile dermatomyositis. *Ryumachi*. 2003;43(3):538–43.
6. Orandi AB, Baszis KW, Dharnidharka VR, Huber AM, Hoeltzel MF. CARRA Juvenile Myositis subgroup. Assessment, classification and treatment of calcinosis as a complication of juvenile dermatomyositis: a survey of pediatric rheumatologists by the childhood arthritis and rheumatology research alliance (CARRA). *Pediatr Rheumatol Online J*. 2017. doi:10.1186/s12969-017-0199-4.
7. Tayfur AC, Topaloglu R, Gulhan B, Bilginer Y. Bisphosphonates in juvenile dermatomyositis with dystrophic calcinosis. *Mod Rheumatol*. 2015. doi:10.3109/14397595.2014.988197.
8. Martillotti J, Moote D, Zemel L. Improvement of calcinosis using pamidronate in a patient with juvenile dermatomyositis. *Pediatr Radiol*. 2014. doi:10.1007/s00247-013-2738-6.
9. Batch JA, Couper JJ, Rodda C, Cowell CT, Zacharin M. Use of bisphosphonate therapy for osteoporosis in childhood and adolescence. *Journal of Pediatrics Child Health*. 2003;39(2):88–92.

Figures



Figure 1

Axial CT image of the pelvis demonstrates a large area of bulky soft tissue calcification in the right ischiofemoral space (white arrow).



Figure 2

Coronal CT image of the pelvis from the same examination as figure 1 again shows the large area of soft tissue calcification in the right ischiofemoral space (white arrow).



Figure 3

Coronal CT image from the same examination as figure 1 shows additional areas of soft tissue calcification in the right and left adductor musculature (white arrows).



Figure 4

Axial CT image of the pelvis from a follow-up examination showed complete resolution of the area of bulky calcification (white circle).



Figure 5

Axial CT image of the pelvis from a follow-up examination showed complete resolution of the area of bulky calcification (white circle).