Case Report

Efficacy of Probenecid for a Patient with Juvenile Dermatomyositis Complicated with Calcinosis

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ABSTRACT. Calcinosis of juvenile dermatomyositis (JDM) is a crucial problem because it is refractory to various therapies. An 11-year-old boy who had been treated for JDM with interstitial pneumonia developed calcinosis of both legs despite treatment with corticosteroid and cyclosporin A. Images of his knees showed massive calcinosis with restricted range of motion. Probenecid was used to reduce calcinosis, resulting in remarkable improvement of calcinosis accompanied by normalization of serum phosphorus level and disability after 17 months of administration. We suggest that probenecid is useful for the treatment of calcinosis of JDM. (J Rheumatol 2006;33:1691–3)

Key Indexing Terms:
PROBENECID JUVENILE DERMATOMYOSITIS CALCINOSIS PHOSPHORUS

Juvenile dermatomyositis (JDM) is a diffuse connective tissue disease characterized by chronic lymphocytic inflammation of the skeletal muscle and vasculitis and may be followed by calcinosis[1]. Longterm consequences of JDM are influenced by calcinosis, leading to subsequent functional impairment. The incidence of calcinosis has been reported between 30% and 70%[2-5]. There are reports that stepwise, aggressive treatment, directed at achieving rapid control of muscle inflammation, is highly successful in minimizing severe clinical manifestations of JDM, including calcinosis[2]. Surgical resection of calcification was limited to special cases because of a high recurrence rate[6].

We report the efficacy of probenecid for refractory calcinosis in a patient with JDM.

CASE REPORT

An 11-year-old Japanese boy presented at our hospital with low-grade fever and heliotrope rash in January 2001. He was diagnosed with dermatomyositis due to characteristic skin lesions and elevation of muscle enzymes including aspartate aminotransferase (AST), alanine aminotransferase (ALT), and lactate dehydrogenase (LDH). Despite taking 15 mg of oral prednisolone daily, he presented a continuous cough. Because his computed tomography (CT) scan of the chest showed interstitial pneumonia with elevation of KL-6 (1780 U/ml), a mucinous high-molecular weight glycoprotein, expressed on type 2 pneumonocytes and elevated in serum and bronchoalveolar lavage fluid of patients with interstitial pneumonia, methylprednisolone pulse therapy was administrated, followed by oral prednisolone (1 mg/kg) and oral cyclosporin A (3.3 mg/kg) with trough level of 70 ng/ml. Although improvement of muscle weakness, muscle enzymes, and interstitial pneumonia was achieved, the restricted range of motion (ROM) of his knee joints became obvious in January 2003. In July 2003, radiographs of the knees showed subcutaneous calcification. However, bone mineral density of lumbar spine 1-4 was remarkably decreased to 0.570 g/cm^2.

Alendronate was initially administered but could not be continued because of liver dysfunction, although the patient showed no muscle weakness or elevated creatine phosphokinase (CPK). We next administered cimetidine at a dose of 400 mg/day, but it failed to reduce calcification after 6 months of administration. Finally, probenecid was started at an initial dose of 500 mg daily in January 2004. A summary of laboratory findings at the start of probenecid is presented in Table 1. Blood chemistry showed elevated LDH (338 IU/l) AST (35 IU/l), CPK (13 IU/l), and aldolase (11.7 IU/l). The serum phosphorus level was slightly elevated at 5.1 mg/dl, although serum calcium calibrated by albumin, intact parathyroid hormone (PTH), and osteocalcin were within normal ranges. Serologically, antinuclear antibody and anti-Jo1 antibody were negative.

Chest radiograph showed a slight interstitial shadow on bilateral lung fields. However, 5 months later, a radiograph of the patient's right knee showed massive subcutaneous calcification (Figure 1A). We increased the probenecid to 1,000 mg daily. Over the next 12 months the ROM of his knee joints improved gradually, and he could stand up by himself. Calcification of the knee joint on radiograph (Figures 1B and C) as well as clinical symptoms were dramatically improved with reduction of serum phosphorus; in addition to probenecid he was taking 12.5 mg of oral prednisolone and 75 mg of cyclosporin A daily.

DISCUSSION

Ectopic calcinosis in patients with JDM is considered serious because it causes disability with joint contracture and cutaneous infection. Although some medications have been used to reduce calcinosis, effective medical treatment has not been

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Table 1. Summary of laboratory findings at initiation of probenecid treatment (January, 2004) and 17 months later (June, 2005).

Variable (normal range)	January, 2004	June, 2005
AST (13–33 IU/l)	37	25
ALT (8–42 IU/l)	29	10
LDH (119–229 IU/l)	338	166
CPK (57–197 IU/l)	13	35
Aldolase (2–7 IU/l)	11.7	3.1
Creatinine (0.4–1.1 mg/dl)	0.3	0.3
Uric acid (2.3–8.0 mg/dl)	4.9	4.9
Phosphorus (2.5–4.7 mg/dl)	5.1	4.4
Calcium (9.0–10.6 mg/dl)	9.3	9.5
TmP/GFR* (4.3–5.6 mg/dl)	5.80	5.20
Bone-specific ALP (13–33.9 U/l)	35.8	41.7
PTH-intact (10–65 pg/ml)	14.0	20.0
Osteocalcin (2.5–13 ng/ml)	13.0	12.0
KL-6 (< 500 U/ml)	1140	176

* TmP/GFR: the threshold of reabsorption of phosphate was calculated by nomogram determined by Walton, et al[11] using serum phosphorus level and tubular reabsorption of phosphate (TRP) as follows: TRP = 1.0–[urine phosphorus (mg/dl) × serum creatinine (mg/dl)]/[serum phosphorus (mg/dl) × urine creatinine (mg/dl)]. AST: aspartate aminotransferase; ALT: alanine aminotransferase; LDH: lactate dehydrogenase; CPK: creatine phosphokinase; PTH: parathyroid hormone; ALP: alkaline phosphatase.

established. Aggressive therapy including pulse intravenous methylprednisolone or methotrexate is considered efficient in reducing the incidence of calcinosis[2]. However, these therapeutic agents showed no evidence of effectively reducing deposited calcinosis. In addition, we were apprehensive about repeated administration of high-dose glucocorticoid because disease activity of this patient including muscle enzymes or interstitial pneumonia was in remission when probenecid was administered.

Mukamel, *et al*[7] reported that alendronate improved calcinosis, suggesting that calcinosis of JDM might be mediated by activated macrophages and that alendronate may be an effective treatment for this condition. However, in our case, alendronate therapy could not be continued because of liver dysfunction. Regarding other therapeutic regimes, there have been several reports that probenecid improved calcinosis in patients with JDM[8-10]. Eddy, *et al*[9] and Harel, *et al*[10] reported that a case of severe calcinosis was successfully treated with 250-1500 mg of probenecid daily. A common point of these 2 reports was that an elevated level of phosphorus was closely related to the development of calcinosis in patients with JDM. Since the slight elevation of phosphorus in our case was decreased during 17 months of therapy with probenecid, it is likely that the effect of probenecid is related to the excretory process of phosphorus.

We observed a decreased concentration of renal threshold phosphate (TmP/GFR, for definition see Table 1), which correlated with the decrement of serum phosphorus. These data may imply that inhibition of phosphate reabsorption is an important mechanism in treatment with probenecid. In previous reports, duration of treatment with probenecid has varied from weeks to years. Although the TmP/GFR varied in different reports, we predicted in our case that susceptibility to probenecid might be, in part, regulated by TmP/GFR.

Our findings regarding PTH were unlike reports from Eddy[9] and Harel[10]. In the former, subnormal serum level of intact PTH was restored during treatment with probenecid. In

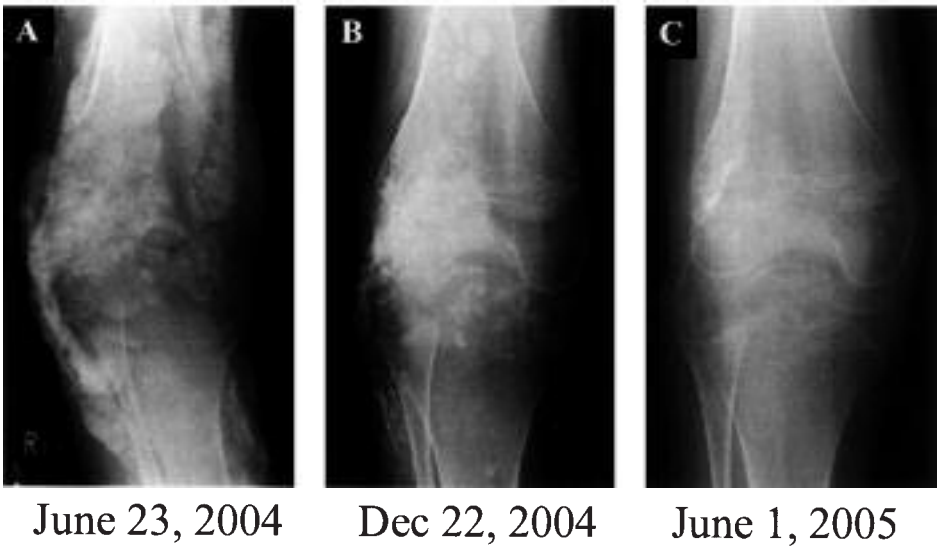

Figure 1. Marked reduction of calcium deposition after administration of probenecid, starting at 500 mg/day in January 2004. Five months later, we still detected massive subcutaneous calcium deposition around the patient's knee joint (Figure 1A). Six months later, in response to 1,000 mg/day of probenecid, calcium deposition began to diminish (Figure 1B). Another 6 months later, in June 2005, calcium deposition was markedly reduced with the same amount of probenecid (Figure 1C).

contrast, the latter found intact PTH was suppressed during therapy. Probably, the increment of serum ionic calcium derived from calcified tissue suppressed PTH secretion in the latter case. In our case, the serum intact PTH level remained within normal limits, and bone-specific alkaline phosphatase and osteocalcin also remained unchanged during therapy. These findings imply that decrease in serum phosphorus in relation to urinary reabsorption may have occurred independent of bone metabolism in our patient.

In summary, we observed the efficacy of probenecid for the treatment of calcinosis in a Japanese patient with JDM. Considering the efficacy and safety of alternative agents, probenecid may be a practical selection for the reduction of calcinosis complicated with JDM. Accordingly, various immunosuppressive therapeutic regimes should be considered to avoid the initiation of calcium deposition.

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