Interstitial pneumonia in adult-onset Still's disease

Sirs,

Adult onset Still's disease (AOSD) is a febrile disorder of unknown etiology. It is characterized by a spiking high fever with salmon-pink evanescent rash, inflammatory arthritis, lymphoadenopathy and involvement of various organs such as the liver, kidney and bone marrow (1, 2). Lung complications in AOSD consist of pleural effusion or transient pulmonary infiltrates (3, 4)

A 53-year-old woman was referred to Ushikuaiwa hospital because of spiking fever and eruption in June 2005. Starting eight days before admission, she developed high-grade fever, arthralgia, sore throat and exanthema. At admission, maculopapular nonpruritic salmon-pink rash was observed on both the lower and upper extremities and soft lymph nodes were palpable at the armpit. The patient also complained of arthralgia in both wrists. Laboratory data showed an erythrocyte sedimentation rate (ESR) 42 mm/h, total white blood cell count (WBC) 8500/μL (neutrophils 88%, lymphocytes 6%, monocytes 3% and basophils 3%), haemoglobin (Hb) 12.6 g/dl, platelets (plt) 28.7 $\times 10^4$/μL. Urinalysis demonstrated 1+ protein on dipstick test and numerous white blood cells and bacteria in the urine sediment. Aspartate aminotransferase (AST) 69 IU/L, alanine aminotransferase (ALT) 55 IU/L, lactate dehydrogenase (LDH) 761 IU/L, alkaline phosphatase (ALP) 291 IU/L, γ-glutamyltranspeptidase (γ-GTP) 48 IU/L, creatine kinase 94 IU/L, Serum total protein and serum γ-globulin were 6.8 g/dl and 20.3%, respectively. C-reactive protein 6.70 mg/dL, renal function was normal. On chest radiograph, there were no abnormal shadows. X-ray of the hand did not demonstrate erosive change. The patient was diagnosed as having cystitis and cefotiam hydrochloride (CTM) (1g/day intravenously) was initiated. Four days later, cefazopran hydrochloride (CZOP) (1g/day intravenously) was initiated, but clinical features were not improved. Fever showed persistent spiking, but chest and abdominal x-ray findings were normal. Laboratory data on day 6 included ESR 90 mm/h, WBC 12800/μL (neutrophils 89%), Hb 10.7 g/dl, plt 43.7×10^4/μL. Urinalysis did not demonstrate any protein. AST 54 IU/L, ALT 55 IU/L, LDH 456 IU/L, ALP 377 IU/L, ferritin 5170 ng/ml, C-reactive protein 9.51 mg/dL. On immunological test, both antinuclear antibody, RAPA and MPO-ANCA were negative. EBV-VCAIgG 40×, EBV-VCAIgM <10×, CH_{50} 51.7. Chest computed tomography (CT) (Fig.1a) scan demonstrated mild interstitial shadow and abdominal CT demonstrated splenomegaly. Infection and malignancy were excluded by various examinations. Finally, the patient was diagnosed with AOSD according to the diagnostic criteria for classification of AOSD developed by Yamaguchi *et al*. (5). Loxoprofen sodium was prescribed, although her condition did not improve. On day 16, predonisolone administration (20 mg/day) was started. The level of ferritin and C-reactive protein soon decreased. Interstitial shadow on chest CT worsened on day 18 (Fig 1b), and serum KL-6 (normal range < 500 U/ml), and SP-D (normal range < 110 ng/ml), elevated to 651 U/ml and 228.7 ng/ml, respectively. There were no respiratory symptoms and chest physical examination showed normal findings. Bronchoalveolar lavage was not done. The dosage of predonisolone was increased by 40 mg per day. Soon there after, symptoms and laboratory data gradually improved and abnormal shadow on chest CT regressed (Fig 1c). The patient has remained well for three months on tapering doses of predonisolone.

Between 1993 and 2004, forty-nine cases of AOSD were diagnosed and treated at

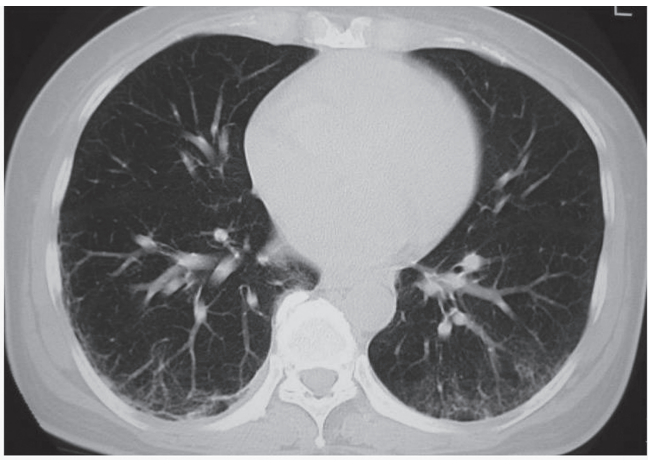

Fig. 1a. Chest CT on July 5, 2005. Interstitial pneumonia at both lung bases.

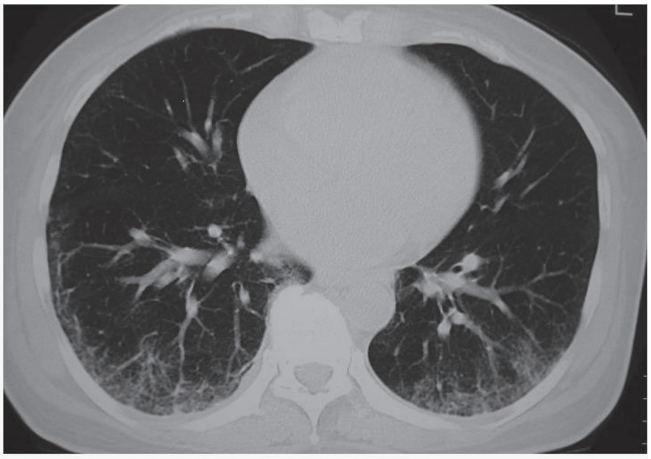

Fig. 1b. Chest CT on July 16, 2005. Interstitial pneumonia worsened.

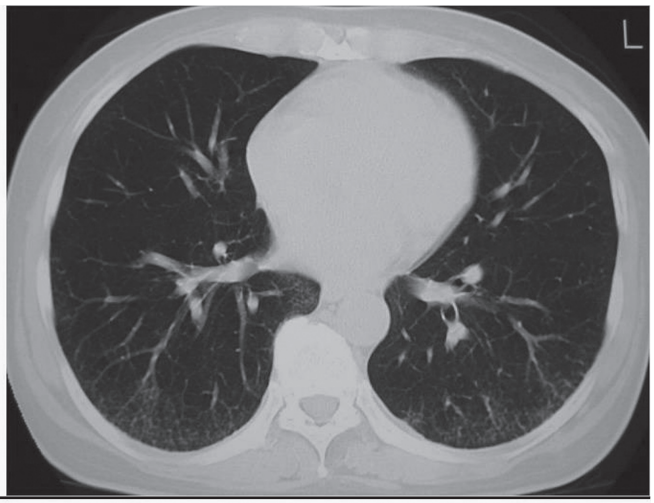

Fig. 1c. Chest CT on September 26, 2005. Interstitial pneumonia improved.

our institute. Five cases developed pulmonary complications. Four of five cases involved pleuritis and one was eosinophilic pneumonia. All cases were treated with predonisolone with or without immunosuppressive drugs. There were no previous cases of interstitial pneumonia.

Corbett *et al*. (6) reported a case of chronic persistant interstitial pneumonia in 1983. Van Hoeyweghen *et al*. (7) described a case showing basal lobe infiltrates. Lung biopsy showed patchy interstitial fibrosis and chronic inflammation. Pouchot *et al*. (8) reported one patient who developed a pleural effusion, pericarditis, and interstitial pneumonia, which into an acute respiratory distress syndrome and required mechanical ventilation. Stoica *et al*. (9) also reported a case of ASOD that was associated with severe respiratory failure.

KL-6 is a high-molecular-weight glycoprotein and is classified as "Cluster 9 (MUC1)" (10). KL-6 is a chemotactic factor for most fibroblasts and the increased level of KL-6 in epithelial lining fluid in small airways may cause intra-alveolar fibrosis in fibrosing lung diseases. Circulating KL-6 has been shown to be a sensitive marker indicating disease activity of interstitial pneumonia. In this case, even though ferritin and C-reactive protein were decreased after predonisolone therapy, interstitial pneumonia worsened. KL-6 reflects lung involvement more sensitively. Lung involvement of AOSD may progress to severe respiratory failure (10). Thus, monitoring KL-6 may be useful for a better estimation of prognosis.

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Maternal and fetal outcome of pamidronate treatment before conception: a case report

Sirs,

Idiopathic hyperphosphatasia is a genetic bone disorder and is accompanied by very high bone turnover and progressive bone deformity (1).

Pamidronate therapy appears to be promising for patients with idiopathic hyperphosphatasia. Bisphosphonates have been shown to cross the placenta in humans (2). Animal studies have shown that this drug during pregnancy can result in shortening of diaphyseal bone, increased diaphyseal trabecular volume, and a reduction in bone marrow volume in the fetus (2). In view of these observations, the use of bisphosphonates during pregnancy is not recommended.

We present a case of a woman with hereditary hyperphosphatasia who had received pamidronate before conception. A 30-year-old woman with idiopathic hyperphosphatasia had been treated with cyclical intravenous pamidronate for 42 months in order to prevent the development of skeletal deformity and disability. Pamidronate was given at a dose of 1 mg/kg on three consecutive days every four months, total cumulative pamidronate dose of 9 mg/kg/year.

The woman conceived one month after the last cycle. No further pamidronate was given during pregnancy. The patient received daily doses of 1000 mg elemental calcium and no vitamin D. All prenatal exams were normal. After 36 weeks of gestation, premature membrane rupture occurred and a female infant was born, with Apgar scores 8/9 and birth weight was 3130 g. The maternal serum ionized calcium, phosphate, alkaline phosphatase, and parathyroid hormone (PTH) concentrations were within reference limits during pregnancy (1.20 mM, 1.42 mM, 102 U/L, and 5.4 pM, respectively), as well as 24 h after delivery (1.16 mM, 1.12 mM, 118 U/L, and 3.1 pM, respectively).

No neonatal dysmorphic features, fractures, or long bone deformities were noted at birth. At 6 and 24 h of age, the child had normal serum ionized calcium, phosphate and PTH concentrations (1.08 mM, 1.39 mM, and 4.6 pM, respectively, at 24 h). She was asymptomatic at that time and there were no signs or symptoms suggesting hypocalcemia as indicated by normal breast-feeding and the lack of irritability, jitteriness, tremors and muscle twitching. There was no clinical evidence of cardiac rhythm disturbances. The mother and her child were discharged from the hospital 60 h after delivery.

Breast-feeding was maintained and the newborn had an uneventful postnatal period. Both mother and child were examined 14 days after delivery and the cardiovascular, respiratory, gastrointestinal, and neurological systems were found to be normal upon clinical examination. Serum biochemical analysis was also normal.

During the third trimester of pregnancy, fetal calcium requirements may exceed maternal intestinal absorption, a fact resulting in the resorption of calcium from the maternal skeleton (3). Previous maternal pamidronate administration might therefore reduce the amount of skeletal-derived calcium that is available for fetal bone mineral accumulation.

The pamidronate administration during pregnancy in animals showed that toxicity, embryo lethality or severe underdevelopment and a marked skeletal retardation of the fetuses were only observed at doses about ten times higher than the human therapeutic dose (2, 4).

Two case reports have been published on pregnant women who received bisphosphonates for malignant hypercalcemia (5, 6) and the infants developed hypocalcemia. Munns et al. published the first report on maternal and fetal outcomes after pamidronate therapy before conception. Two mothers had osteogenesis imperfecta and the pregnancies were uneventful (7).

Bisphosphonates are known to persist in mineralized bone for many years and the fetus may still be exposed to bisphosphonates (2). It is also conceivable that the suppressed bone turnover might result in maternal complications during pregnancy or lactation.

In conclusion, the present case does not provide evidence that maternal health is affected during pregnancy by pamidronate treatment administered before conception. However, the occurrence of adverse events (hypocalcemia, hypercalcemia) during pregnancy or after delivery cannot be ruled out; mother, fetus and newborn should be followed up carefully throughout these periods.

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