Pseudogout Attack Associated with Chronic Thyroiditis and Sjögren's Syndrome

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A 66-year-old woman, diagnosed with chronic thyroiditis at age 63, presented with anorexia and fatigue. Therapy for the chronic thyroiditis consisted of levothyroxine sodium (100 µg/day). Her symptoms were attributed to the insufficient supply of levothyroxine sodium. Following a dosage increase to 150 µg/day, she suffered from an acute attack of pseudogout. Clinical features were complicated by Sjögren's syndrome, which appeared after treatment onset. Pseudogout was effectively treated by colchicine after administration of diclofenac sodium failed to alleviate the symptoms. Pseudogout is a recognized complication of thyroid replacement therapy, but association with Sjögren's syndrome has not been previously reported. (Internal Medicine 38: 59–62, 1999)

Key words: calcium pyrophosphate dihydrate (CPPD), chondrocalcinosis, Hashimoto's thyroiditis

Introduction

Pseudogout is a constellation of clinical symptoms and signs that simulate gout but differs in that calcium pyrophosphate dihydrate (CPPD) crystals are present within the synovial fluid (1). Various kinds of disorders (e.g. primary hyperparathyroidism (2), hemochromatosis (3), hypomagnesemia (4), hypophosphatasia (5), gout (6), and hypothyroidism (7)), are reportedly associated with CPPD crystal deposition. Dorwart and Schumacher (7) described 6 patients who developed pseudogout attacks during thyroid replacement therapy in 1975. The misdiagnosis of a pseudogout attack is one of the important points in the treatment for hypothyroidism.

We describe a case of pseudogout attack caused by thyroid replacement therapy, wherein Sjögren's syndrome developed during the course of the treatment. We are unaware of any previous report of pseudogout associated with hypothyroidism and Sjögren's syndrome in the English and Japanese literature.

Case Report

A 66-year-old woman who had three-year history of chronic thyroiditis (Hashimoto's thyroiditis) was admitted to our hospital on May 6, 1997 because of anorexia and fatigue. Her ailment had been diagnosed earlier as hypothyroidism in con-

sequence of chronic thyroiditis, and she was treated with levothyroxine sodium (100 µg/day) for 3 years. Laboratory data in 1994, three months after the thyroid replacement therapy, showed free thyroxine (FT4) 0.2 ng/dl, free triiodothyronine (FT3) 1.1 pg/ml, thyroid-stimulating hormone (TSH) 4.7 U/ml, antithyroglobulin antibody (+), and antithyroid peroxidase antibody (+). There was no history of trauma or arthritis nor any family history of autoimmune diseases or metabolic disorders.

Fatigue was first noted early in April 1997, and was followed by persistent dysphoria. Physical examination revealed anemic conjunctivae, a low body temperature (35.5°C), constipation, an apathetic look with pudgy face, slow speech, slow actions, and emaciation with a body mass index 18.7; pretibial edema was not found. A complete blood count showed normocytic normochromic anemia; red blood cell count $359 \times 10^4/\mu\text{l}$, hemoglobin 10.9 g/dl, mean corpuscular volume 91.4 fl. Endocrinological investigations were consistent with hypothyroidism (TSH 20.00 U/ml, plasma FT3 2.7 pg/ml, and plasma FT4 1.3 ng/dl); serum parathyroid hormone was normal and serum cholesterol level was 225 mg/dl. Plasma glucose, uric acid, creatine kinase, and transferrin saturation were normal. Liver function tests and renal function tests were also within normal limits. Further investigation showed evidence of autoimmunity: rheumatoid factor (RF) 2+; rheumatoid arthritis particle agglutination (RAPA), $\times 40$; antinuclear antibody more

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than $\times 1,280$ (homogenous pattern); anti-ss-A/Ro antibody $\times 16$; anti-ss-DNA immunoglobulin G (IgG) antibody 21 U/ml; antithyroglobulin antibody 2.4 U/ml; positive thyroid test ($\times 100$). Serum magnesium, calcium, inorganic phosphate and iron were normal. Serological tests together with sputum and urine ex-

Figure 1. Microscopic findings of the minor salivary glands showed lymphocytic infiltration and atrophy of the glands (HE stain, $\times 100$).

Figure 2. Radiograph of the knee joint demonstrating a linear deposit of calcium pyrophosphate dihydrate (CPPD) in the menisci and articular cartilage.

aminations for viral and bacterial infection were negative. A 12-lead electrocardiogram, an analysis of an arterial blood gas sample, a chest radiograph, abdominal ultrasonography, and esophagogastroduodenoscopic examination were all normal. Given these data, we considered that her condition was partly due to exacerbation of the persistent hypothyroidism. The dosage of levothyroxine sodium was increased to 150 μg from 100 μg daily on May 8.

TSH returned to normal levels within a week after the dosage increase. However, her left knee and elbow rapidly swelled along with myalgias, arthralgias, and the development of a low grade fever (37.5°C). Her C-reactive protein level increased to 1.7 mg/dl. Also, she complained of difficulty in swallowing dry food and xerostomia. Schirmer's test revealed a decreased level to 0 mm bilaterally and keratitis sicca was diagnosed by an ophthalmologist. Pathological findings of minor salivary glands showed lymphocytic infiltration and atrophy of the glands (Fig. 1). A diagnosis of Sjögren's syndrome was made on the basis of European community criteria (8) for Sjögren's syndrome. We initially thought her sign of myalgias and arthralgias was one of the manifestations of Sjögren's syndrome. However, since oral administration of diclofenac sodium did not alleviate the symptoms, we carried out radiographic evaluations of knees, shoulders and pubic symphysis, which demonstrated linear calcifications in the articular cartilage (Fig. 2). Needle aspiration from the knee joints revealed weakly positive birefringent rhomboid shaped crystals under the polarized microscope (Fig. 3). Diagnosis of pseudogout was made on the basis of roentgenography and synovial fluid analysis. Colchicine therapy at a dose of 0.5 mg/day was initiated on June 5 with gradual resolution of the inflammation after the failure of diclofenac sodium. The articular symptoms and signs also gradually subsided with the treatment. Three months after beginning the colchicine therapy, her articular condition remained in remission, although the xerostomia and the dry eyes were not remarkably improved.

Figure 3. A weakly positive birefringent rhomboid shaped crystal was seen under the polarized microscope (polarized light, $\times 1,000$).

Discussion

We describe a case of pseudogout attack induced in the treatment of hypothyroidism secondary to chronic thyroiditis when the dosage of levothyroxine sodium was increased. Pseudogout is a term that describes intermittent episodes of CPPD-associated acute arthritis that can mimic acute gouty arthropathy, and is different in that CPPD and not monosodium urate crystals are present within the synovial fluid (1). In this case, radiographs of hip joints and the pubic symphysis taken 3 years previously did not illustrate deposition of CPPD crystals; radiographs of knee joints and shoulders had not been taken. Sjögren's syndrome was noted during the course of the thyroid replacement therapy. The precise time of onset of Sjögren's syndrome is unknown, but apparently she had it previously and subclinically before the diagnosis of pseudogout and the symptom became obvious during the treatment against hypothyroidism.

Discussion concerning a possible association between CPPD deposition disease and hypothyroidism has already been reported in the literature. Dorwart and Schumacher (7) and Alexander et al (9) suggested an association between pseudogout and hypothyroidism when 10% of their CPPD study patients were found to have hypothyroidism. However, Job-Deslandre et al (10) examined patients with well-documented symptomatic hypothyroidism and age- and sex-matched controls for evidence of radiographic chondrocalcinosis, and found no significant differences in 17% of the patients and 10% of the controls. The present patient suffered from primary hypothyroidism as a consequence of chronic thyroiditis. The precise mechanism of crystal deposition of CPPD in hypothyroidism is not yet known.

The diagnosis of Sjögren's syndrome that is sometimes associated with hypothyroidism could clearly be dismissed. The most possible cause of hypothyroidism is chronic thyroiditis (11), which coexists with Sjögren's syndrome with some frequency (18.0% to 40.0%) (12, 13). There is no well documented report of a complication of the 3 diseases, pseudogout, chronic thyroiditis and Sjögren's syndrome, but we believe there are other cases such as this that have been overlooked or misdiagnosed.

CPPD crystal deposition disease may be complicated with a variety of heritable and metabolic disorders, although it is most frequently idiopathic and most common in the elderly (1). CPPD crystal deposition disease occurs more often in those who have suffered previous articular trauma and in persons who have undergone meniscectomy (1). Disturbance of metabolic pathways may explain CPPD crystal deposition in primary hyperparathyroidism (2), acromegaly (14), hemochromatosis (3), hypomagnesemia (4), hypophosphatasia (5) gout (6), and hypothyroidism (7, 9). In the present case, as far as we know the patient had no history of trauma, meniscectomy, or any other metabolic disorder.

The misdiagnosis of crystal-induced arthritis as rheumatoid arthritis is fairly common, particularly in the absence of syno-

vial fluid aspiration and in Sjögren's syndrome, which is sometimes complicated with rheumatoid arthritis and other autoimmune disease (1, 14, 15). CPPD associated arthropathy may exist in the absence of the radiographic appearance of calcification within articular cartilaginous structures. The crystal-induced diseases, such as gout and pseudogout, often may be diagnosed on the basis of the clinical picture alone, but definitive diagnosis requires aspiration and examination of synovial fluid with identification of the causative crystals by regular and polarized light microscopy. The crystal composition may be confirmed in some cases by atomic force microscopy, which is thought not to be indispensable in the clinical diagnosis.

Treatment of pseudogout has 2 objectives: 1) to relieve the pain of the acute attack, thus restoring normal function; and 2) to prevent the accumulation of crystals that can lead to degenerative diseases (14). The therapeutic finding is of interest in the present case because colchicine seemed to be effective against the acute attack of pseudogout while diclofenac sodium, a nonsteroidal anti-inflammatory drug (NSAID), had little effect on the symptoms. But it is doubtful that colchicine was really effective against the pseudogout attack, because pseudogout occasionally remits spontaneously without treatment. As Schumacher (14) reported that colchicine is not as effective for acute pseudogout attacks as it is for gout attacks, if it is necessary to carefully consider the administration of colchicine because of its toxicities.

Pseudogout attack should be included in the differential diagnosis of arthritis and myalgia associated with hypothyroidism during thyroid replacement therapy. It is not well known yet what will happen in the articular space when the dosage of levothyroxine sodium is increased. Some reports suggest a relationship between crystal shedding and alteration of the matrix and/or concentration of calcium and inorganic phosphate (16, 17). Although no report has clarified the mechanism of the reaction. TSH might stimulate fibroblasts to synthesize excess hyaluronic acid and adenylate cyclase activities, resulting in a gross alteration of the proteoglycan-collagen ratio and loss of physical properties of the involved connective tissues (18). But the precise mechanism of crystal shedding in thyroid replacement therapy is yet to be determined.

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