Omeprazole-induced calcium pyrophosphate disease: case report

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Abstract

Calcium pyrophosphate disease is caused by the accumulation of calcium pyrophosphate crystals in cartilage, causing acute intermittent arthritis or chronic arthritis. Risk factors for calcium pyrophosphate disease include old age. Osteoarthritis is the most common comorbidity. Other risk factors include local joint injury, primary hyperparathyroidism, hereditary hemochromatosis, hypomagnesemia (for example, due to intestinal problems), diseases caused by loss of magnesium in the kidneys (especially Gitelman syndrome), familial hypocalcemia, hypophosphatemia, and hereditary calcium pyrophosphate disease. There is evidence that proton pump inhibitors are a clear risk factor for calcium pyrophosphate syndrome. There have been reports of acute tubulointerstitial nephritis, proximal renal tubular cell death and chronic kidney disease. But there has been only one case report of calcium pyrophosphate disease associated with the use of proton pump inhibitor. I therefore report on a case of an 82-year-old Thai woman with pseudogouty arthritis and has hypomagnesemia, kidney impairment, proximal renal tubular cell death and uses omeprazole for more than 10 years. When omeprazole was stopped and hypomagnesemia was corrected, it was found that the kidneys were better. There was no more arthritis after 1 year of follow-up.

Keywords: Calcium pyrophosphate disease, proton pump inhibitors, hypomagnesemia, chronic kidney disease

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Introduction

Calcium pyrophosphate deposition (CPPD) disease results from an immune response to calcium pyrophosphate (CCP) crystals within the joint and cause arthritis. This can cause acute arthritis (formerly called pseudogout) or chronic arthritis. Accumulation of calcium pyrophosphate crystals is strongly associated with cartilage deterioration and osteoarthritis. The pathophysiology of calcium pyrophosphate crystals deposition in the joint is still not completely understood. Clinical presentation varies greatly and CPPD disease is an umbrella term grouping together various phenotypes, ranging from acute and recurrent episodes of inflammatory arthritis to chronic, persistent inflammatory arthritis and CPPD with osteoarthritis. Asymptomatic CPPD is an ambiguous aspect of the disease that is described as the deposition of CPP crystals found on imaging without any apparent symptoms that can be attributed to it.[1-3]Diagnosis requires compatible clinical signs, symptoms and the discovery of calcium pyrophosphate crystals from synovial fluid or radiographic evidence of accumulation of calcium pyrophosphate crystals in cartilage (chondrocalcinosis)[3] According to the guidelines of 2023, The American College of Rheumatology (ACR) and EULAR developed classification criteria for CPPD disease.[4]

The prevalence of CPPD in 2024 in patients with knee pain using ultrasound to detect chondrocalcinosis was found that the overall prevalence was 9.8% in hyaline cartilage and 22.4% in fibrocartilage. The prevalence of CPPD increased to 23.3 % for hyaline cartilage and 46.7% for fibrocartilage in patients older than 80 years.[4] Knees and wrists are the most frequently involved joints.[5]

Risk factors for CPPD include: older age is the most common risk factor, while osteoarthritis is the most common association.[6-9] Other risk factors include local joint injury, such as meniscectomy.[8] Gender and BMI are not risk factors for CPPD.[10] Hereditary and acquired metabolic diseases that cause CPPD include, by order of frequency, primary hyperparathyroidism, hereditary haemochromatosis, hypomagnesaemia (eg, due to short bowel syndrome), diseases of renal magnesium wasting (particularly Gitelman disease), familial hypocalciuric hypocalcaemia, and hypophosphatasia.[11-15] An inherited CPPD caused by mutations in the ANKH (inorganic pyrophosphate transporter) gene and the osteoprotegerin gene. It is a rare cause of disease in families, often with severe symptoms and found in young patients.[16-17]

There is little consistent or robust evidence of any drug being a clear risk factor for CPPD.[18] Proton pump inhibitors (PPIs) are widely available both via prescription and over-the-counter to treat gastrointestinal diseases related to acid. These drugs are generally safe, but there have been reports of drug-induced acute tubulointerstitial nephritis and proximal renal tubular cell death.[19] This causes acute kidney injury and chronic kidney disease, which ultimately leads to tubulointerstitial fibrosis and progressive kidney disease, especially in the elderly.[20-26]

Hypomagnesemia is the newest reported complication caused by PPI, first described in 2006.[27] Numerous case reports and series have confirmed this relationship, which causes a decrease in magnesium reabsorption in the intestines and kidneys.[27-33] In general, PPI-induced hypomagnesemia occurs during long-term PPI treatment (>1 year). Long-term exposure to PPI and hypomagnesemia are seen with all PPIs (class effect)[27-33], and use of PPI has been shown to increase the risk of CPPD.[34-35] This is because magnesium is a co-factor of alkaline phosphatase that helps break down pyrophosphate.[36] However, there was only one case report of CPPD associated with the use of PPI.[39] I therefore report a patient with pseudogouty arthritis who had low serum magnesium and was taking omeprazole (which is a type of proton pump inhibitor) for more than 10 years. For this case study, the patient gave written informed consent.

Case presentation

Chief complaint: A Thai female, 82 years old, had pain and swelling in her both knees, both wrists, and left elbow and unable to walk or move her arm 2 days before coming to the hospital. She denied fever, rash, or previous injuries.

History of the present illness: She had pain in both knees with no swelling for over 30 years. Both her knees had been bent for 10 years. She bought a set of medicines to take led to stomach perforation in 1997. She walked with a 4-legged walker.

Past medical history: essential hypertension, dyslipidemia for 30 years, chronic kidney disease for 10 years, thyrotoxicosis for 3 years. The medicines used include Carvedilol, Methyldopa, CaCO3, folic acid, lercarnidipine, doxazocin, methimazole, simvastatin, vitamin D2 and had been taking omeprazole 1 capsule a day for 12 years to treat gastroesophageal reflux disease.

Systematic review of symptoms: Denies fever, chills, night sweats, weight loss, photosensitive rash, skin rash such as psoriasis or pustules, mucosal ulcers, Raynaud-like symptoms, dry eyes or dry mouth, vision changes, red or painful eyes, recurrent sinusitis, hearing changes, unusual headaches, weakness or numbness, myalgias, unusual bleeding, cough, shortness of breath, chest pain, abdominal pain, urinary or genital symptoms.

Physical examination: somnolence, awake, able to answer questions and follow commands. Temperature 37.3° Celsius, respiratory rate 16 /minute, pulse rate 98 /minute, blood pressure 135/86 mm. Hg. Mild pallor. Arthritis of both knee joints, both wrists and left elbow. Other systematic examinations were within normal limits.

Laboratory results: Hb 10.6 g/dl, Hct 31.8%, WBC 9330 cells/mm^3, PMN 88%, L 7%, platelet 194,000 cells/mm^3, Inflammation value CRP (C- reactive protein) 246.1 mg/L (reference 0-5), BUN 40 mg/dL., Creatinine 2.08 mg/dL., Sodium 129 mmol/L., Potassium 4.5 mmol/L., Chloride 97 mmol/L., CO2 20 mmol/L., Urinalysis revealed protein 1+, red blood cells 1-2/HPF, white blood cells 10-20/HPF, free T3 0.30 ng /dL. (reference 0.23-0.49), free T4 1.36 ng/dL. (reference 0.59-1.54), cloudy yellow synovial fluid, white blood cells 30,220 cells/mm^3, PMN 62%, L 14%, M 21%, rhomboid-shaped crystals (calcium pyrophosphate crystals) were found. Cultures from blood, urine, and synovial fluid did not reveal organism. She was treated with triamcinolone acetate intra-articular injection, Colchicine 1 tablet a day. Arthritis subsided, no pain, no fever.

Seven days later, the patient returned to this hospital again with symptoms of lethargy, pain, swelling, redness, in left wrist, elbow, and knee. No fever. Laboratory results: Hb 10.0 g/dl., Hct 29.6%, WBC 11,940 cells/mm^3, PMN 85%, L 10%, platelet 184,000 cells/mm^3, CRP 164.1 mg/L, BUN 16 mg/dL, Creatinine 1.95 mg/dL, Sodium 128 mmol/L, Potassium 4.0 mmol/L, Chloride 98 mmol/L, CO2 23 mmol/L, Calcium 8. 6 mg/dL, Phosphorus 2.6 mg/dL, Magnesium 0.9 mg/dL (reference 1.7–2.2 mg/dL), Uric acid 4.6 mg/dL, urine magnesium/creatinine ratio 0.027 mg/mg (reference 0.04–0.12 mg/mg), Urine β2 microglobulin 180 µg/L (reference 5.0-154.0 mg/L), Urine examination revealed protein 1+, red blood cells 1-2/HPF, white blood cells 5-10/HPF, free T3 0.23 ng/dL, free T4 1.54 ng/dL.The synovial fluid is cloudy yellow with white blood cells 30,100 cells/mm^3, PMN 65%, L 11%, M 21%, rhomboid shaped crystals were found. Urine and the synovial fluid culture did not find any organism. Radiographs of the wrist and knee showed chondrocalcinosis of the fibrocartilage (Figures 1 and 2).

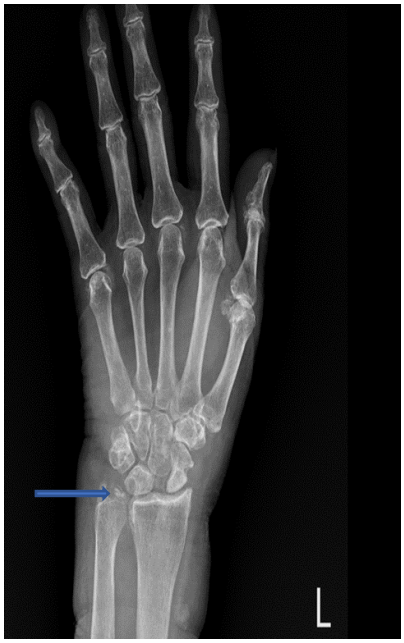

Figure 1 shows calcium deposits in fibrocartilage: Chondrocalcinosis of the wrist

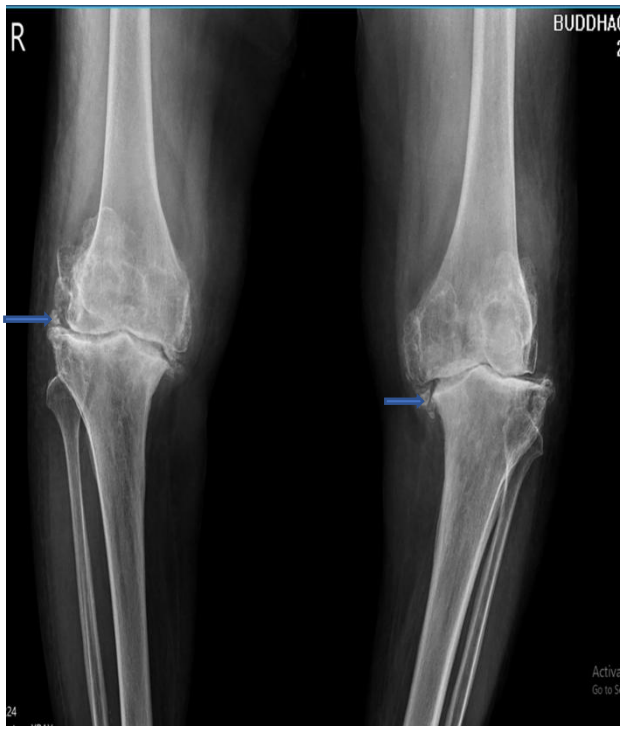

Figure 2 shows calcium deposits in fibrocartilage: Chondrocalcinosis of the degenerated knee joints

She was treated with triamcinolone acetate intra-articular injection and colchicine 1 tablet per day, discontinued omeprazole, changed to sucralfate, administered intravenous magnesium for 3 days, then administered chelated magnesium 3 tablets per day for 3 months. After 6 months of follow-up, BUN was 21 mg/dL, creatinine decreased to 1.30 mg/dL, magnesium 1.6 mg/dL. She had no diarrhea, dyspepsia or reflux symptoms. She had symptoms of joint pain in both knees, but no inflammation. She got physical therapy and treated with colchicine for 6 months, there was no recurrence of arthritis in the knee or wrist. Kidney impairment improved to a stable level, creatinine was at 1.30 mg/dL, and magnesium levels remained within the normal range throughout the 1-year follow-up period after diagnosis.

Discussion

CPPD disease associated with hypomagnesemia that have been described in the literature include Gitelman and Bartter syndrome, short bowel syndrome, liver transplant for chronic liver disease, diseases of renal magnesium wasting, familial hypocalciuric hypocalcaemia, hypophosphatasia, nephrocalcinosis those caused by thiazide diuretics.[11-15]

There is evidence that PPIs are a strong risk factor for CPPD disease.[18,34-35] PPIs are widely available both via prescription and over-the-counter to treat acid-related gastrointestinal diseases. These medicines are generally safe but several side effects have been reported. PPIs are one of the most common causes of interstitial nephritis through mitochondrial injury caused by the generation of oxidative stress. This results in decreased ATP and increased oxidative stress causing proximal tubular cell death and leading to tubulointerstitial fibrosis which ultimately leads to chronic kidney disease, especially in the elderly.[19-26] In a recently published case-control study, to examine the association of acute CCP crystal arthritis and PPIs users. Tedeschi et al. reported risk of CPPD due to PPIs was 1.94 times (OR 1.94 [95% CI 1.61–2.33])[39] Liew et al. found that the use of PPIs did not increase the higher risk of CPPD disease compared to using a histamine receptor antagonist (H2 blocker). Although the use of PPIs and H2 blocker will be a higher risk compared with non-users.[34]

Hypomagnesemia is a recognized complication associated with long-term PPIs use and was first described in 2006.[27] Several case reports and case series have since confirmed this association.[27-33]

Magnesium absorption in the gastrointestinal tract occurs via two mechanisms: passive paracellular transport and active transcellular transport mediated by transient receptor potential melastatin channels (TRPM6 and TRPM7) in enterocytes.

In the kidney, magnesium is freely filtered at the glomerulus. Approximately 15–20% is reabsorbed in the proximal tubule, while the majority (~70%) is reabsorbed passively via the paracellular pathway in the thick ascending limb (TAL) of the loop of Henle. Fine regulation of magnesium reabsorption occurs in the distal convoluted tubule (DCT), primarily through TRPM6 channels.

PPIs are thought to impair intestinal magnesium absorption and renal tubular reabsorption, possibly by affecting TRPM6/7 channel activity, leading to reduced magnesium availability and subsequent hypomagnesemia.[27-33]

Challita et al.[38] reported on a 65-year-old man with a history of 1-year persistent symmetrical bilateral knee and wrist arthritis that was negative for rheumatoid factor and resistant to methotrexate with mild idiopathic hypokalemia. High inflammatory marker and radiographs showed osteoarthritis of the knee. Clear yellow synovial fluid, 35 ml., white blood cell count 1,100 cells/mm^3, of which 47 % were neutrophils, and CCP crystals were found in the white blood cells. Further investigation to evaluate a possible cause of CPPD disease revealed parathyroid hormone (PTH) 18 pg/mL (reference 15–65 pg/mL), phosphorus 3.3 mg/dL. (reference 4–4.5 mg/dL) and 25-hydroxyvitamin D 32 ng/mL (reference 30–50 ng/mL). Magnesium 0.8 mg/dL (reference 1.7–2.2 mg/dL), repeat testing confirmed the result at 0.5 mg/dL, urinary magnesium to creatinine 0.10 mg/mg, which is consistent with our patient's urinary magnesium to creatinine = 0.027 mg/mg (reference 0.04–0.12 mg/mg). This indicates that there is non-renal magnesium loss, such as in the gastrointestinal tract. While the patient does not have chronic diarrhea, malnutrition from malabsorption, and oily diarrhea (steatorrhea), or a history of small intestinal bypass surgery. But there is a history of long-term PPI usage and thus omeprazole was discontinued. Hypomagnesemia was corrected with intravenous replacemence and continue taking magnesium supplements for another period of time. The patient's final diagnosis was CCP arthritis due to PPI cause hypomagnesemia.

This patient has kidney impairment which can be caused by many factors including: essential hypertension, previous use of non-steroidal anti-inflammatory drugs (but stopped using it for more than 20 years) and there is a part that may be caused by omeprazole. Due to high levels of β2 microglobulin detected in the urine, which β2 microglobulin is a sign of persistent proximal tubular dysfunction. PPIs are one of the most common causes of drug-induced acute interstitial nephritis,[21] proximal tubular cell death[19] causing acute kidney injury and chronic kidney disease, which eventually leads to. tubulointerstitial fibrosis and continued kidney impairment, especially in the elderly.[22-29] The dosage and

duration of PPI use, play a role in the severity of hypomagnesemia. It generally occurs in people who have used the drug for many years and is more common in the elderly, especially women.[27] Long-term exposure to PPIs and hypomagnesemia[33-37] found in all PPIs (class effect), the use of PPI increases the risk of CPPD [30-31] because magnesium is a co-factor of alkaline phosphatase that helps break down pyrophosphate.[36] There is currently on treatment strategy to reverse hypomagnesemia in PPI users. Immediate discontinuation of PPI remains standard protocol. It is still controversial whether histamine receptor antagonists cause hypomagnesemia. Kieboom et al. found that use of histamine receptor antagonists increased the risk of hypomagnesemia 2.19 times (OR: 2.19; 95% CI 1.21–3.98)[32] whereas this was not found in another study (OR 1.06; 95% CI 0.54–2.06)[33] High-dose oral magnesium supplement (30–40 mmol/day)[28] often causing diarrhea, nausea and abdominal pain, this treatment option is ineffective and often cannot be tolerated by patients.[29]

Conclusion

Although we have known for a long time that hypomagnesemia and CPPD are related, but this condition may be underdiagnosed. Hypomagnesemia associated with PPIs results from impaired intestinal absorption, proximal renal tubular cells death, and magnesium reabsorption in the distal renal tubules decreases, are the main cause of hypomagnesemia. This increases the risk of CPPD, this is because magnesium is a co-factor of alkaline phosphatase that helps break down of pyrophosphate. PPIs also cause acute tubulointerstitial nephritis, death of proximal renal tubular cells and leads to the formation of tubulointerstitial fibrosis and ultimately chronic kidney disease. Medical personel should check for unexplained hypomagnesemia in all patients with CPPD and asked about the use of PPI to identify potentially treatable causes and reduces the risk of kidney impairment if PPIs are stopped and magnesium levels are corrected.

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