Calcium pyrophosphate deposition disease after total knee arthroplasty: Comparison with periprosthetic joint infection

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1. Introduction

Calcium pyrophosphate deposition (CPPD) disease is an arthritis-related condition that is caused by the deposition of calcium pyrophosphate (CPP) crystals in the joints. Pseudogout is a term coined by McCarty et al. to refer to a syndrome analogous to classic gouty arthritis. The term “pseudogout” originated from an early description of this disease in patients with acute gout-like arthritis whose synovial fluid crystals were resistant to digestion by uricase and who thus did not have gout. Pseudogout is a disease of acute or chronic inflammatory synovitis characterized by CPP crystal deposition in the joints.¹ Until recently, CPPD disease was considered pseudogout. In 2011, a group from the European League against Rheumatism recommended that the term ‘acute CPP crystal arthritis’ be used to refer to acute inflammatory arthritis that was formerly known as pseudogout and that the term ‘chronic CPP crystal arthritis’ be used to signify other types of arthritis associated with CPP crystals. The term ‘chondrocalcinosis’ (CC) refers to the common radiographic correlation of CPPD disease and does not imply clinical arthritis.^{2,3}

Acute CPP crystal arthritis (or pseudogout) is the most commonly recognized form of CPPD disease. Patients with CPPD disease typically present with the acute onset of monoarticular or oligoarticular arthritis. The vigorous inflammatory response to CPP crystals manifests as warmth, erythema and swelling in and around the affected joint, and it is often clinically indistinguishable from acute gouty arthritis or septic arthritis.

In 2007, Hirose and Wright illustrated CPPD disease in the early

period after a total knee arthroplasty (TKA).⁴ However, at present, limited data are available about CPPD disease after TKA. The acute onset of pain and swelling after TKA should prompt an immediate and comprehensive check-up to omit any infection. Unfortunately, to the best of our knowledge, no study to date has compared CPPD disease after TKA with periprosthetic joint infection (PJI). Hence, this study investigated the pathological condition of both diseases.

2. Materials and methods

2.1. Patients

The present retrospective study was approved by the institutional review board. This study conducted at our institution examined 202 TKA cases between 2002 and 2016. We selected cases of CPPD disease and PJI that developed less than 3 months after surgery. We included one case with CPPD disease of the knee after a TKA, two cases with CPPD disease of the contralateral knee after a TKA and one case with PJI after a TKA.

We diagnosed CPPD disease according to the following criteria: (1) sudden onset of severe pain, swelling, redness and warmth of the affected joint; (2) the demonstration of weakly birefringent rhomboid crystals characteristic of CPP in the synovial fluid; (3) elevated synovial white blood cell (WBC) count; (4) negative sterile culture of the synovial fluid; and (5) elevated serum C-reactive protein (CRP) concentration and WBC.^{1,5}

PJI was diagnosed according to the following criteria: (1) sudden

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onset of severe pain, swelling, redness and warmth of the affected joint; (2) elevated serum CRP concentration and WBC; (3) a pathogen isolation by a culture from tissue or fluid samples obtained from the affected prosthetic joint; and (4) elevated synovial WBC count.⁶

2.2. Radiographs

Based on imaging or histological results, CC is the calcification of the cartilage. We evaluated radiographs before and after surgery to ascertain whether such calcification was present. The severity of knee osteoarthritis (OA) was classified using the Kellgren and Lawrence grades.⁷

2.3. Blood and synovial fluid examination

We performed a routine blood examination, including WBC and CRP, 3 days and 1, 2 and 3 weeks after the surgery. The knees were aspirated on the day of onset for the identification of crystals, Gram staining and bacterial cultivation.

2.4. Ethical statement

All procedures performed in studies involving human participants were in accordance with the ethical standards of the Institutional and/or National Research Committee and with the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards.

3. Results

Each patient was diagnosed with OA before TKA. Table 1 summarizes the clinical characteristics of the patients in this study. The period of onset of the same-side CPPD disease was 18 days after TKA. The periods of onset of CPPD disease of the contralateral knee were 2 and 14 days after TKA. The period of onset of PJI was 38 days after TKA. Table 2 summarizes the characteristics of radiographs. Radiographs of both knees of one patient revealed CC.

Shortly after the onset (i.e., knee pain, swelling and redness), we observed increased CRP in 3 patients with CPPD disease (mean: from 6.2 to 12.2 mg/dL), similar to the PJI case. The high CRP levels rapidly decreased after the administration of nonsteroidal anti-inflammatory drugs (NSAIDs) in 3 patients with CPPD disease (mean: from 12.2 to 1.2 mg/dL; Fig. 1). We observed a similar tendency in serum WBC levels (Fig. 2).

3.1. CPPD disease case on the same side as TKA

Eighteen days after TKA, the same side of the knee was erythematous with moderate effusion. The patient reported severe pain with a limited range of motion. The knee was aspirated under sterile conditions, and a thick, yellowish fluid was aspirated, which demonstrated CPP crystals on microscopic evaluation. The WBC count in the joint fluid aspirate of the knee was 5600 cells/mm³; however, the patient did not demonstrate elevated serum WBC (4500 cells/mm³; Table 2). Notably, the CRP was elevated at 6.3 mg/dL. Radiographs demonstrated well-aligned TKA without any sign of loosening or

osteolysis (Fig. 3). We identified no bacteria from the aspirated joint fluid. The symptoms and high CRP levels rapidly declined after the administration of NSAIDs.

3.2. PJI case after TKA

Thirty-eight days after TKA, the same side of the knee was erythematous with moderate effusion. The patient reported severe pain with a limited range of motion. The knee was aspirated under sterile conditions, and a thick, brownish fluid was aspirated, which did not demonstrate CPP crystals on microscopic evaluation. In addition, the WBC count in the joint fluid aspirate of the knee was 37,800 cells/mm³ (Table 2), and the patient also demonstrated elevated serum WBC of 15,900 cells/mm³. The CRP was also elevated at 10.1 mg/dL. Furthermore, methicillin-susceptible *Staphylococcus aureus* was identified from the aspirated joint fluid. As the repeat debridement and antimicrobial regimens failed, the implant was replaced with an antibiotic-loaded cement spacer 3 months after the TKA. A revision TKA was performed 6 months after the cement spacer surgery (Fig. 4).

4. Discussion

In the current literature, there is little information about CPPD disease after TKA. Apparently, CPPD disease of prosthetic joints is rare. Levi et al. reported one patient with bilateral CPPD disease 8 years after bilateral TKA.⁸ Similarly, Yahia et al. reported five cases with CPPD disease among 517 TKA and unicompartmental knee arthroplasty cases.⁹ To the best of our knowledge, no study to date has compared CPPD disease after a TKA with PJI.

When a TKA patient presents with an intensely painful and swollen knee, the workup for infection should be initiated immediately. The joint should be aspirated under sterile conditions, and the joint fluid should be assessed for the cell count, crystals, Gram stain and culture. Unfortunately, the aspirate from both crystal arthropathy and septic arthritis might contain elevated WBC levels. Ultimately, CPPD disease is diagnosed by the presence of positively birefringent CPPD crystals in the synovial fluid, whereas gout involves the presence of negatively birefringent crystals when viewed under polarized light microscopy.¹ In addition, tests for microcrystals should be performed on freshly sampled joint fluid, as CPPD crystals tend to disappear after 12–24 h. If prompt crystal detection is not feasible, the sample should be refrigerated at 4 °C or frozen at –20 °C.^{10,11}

CC has been proposed as the calcification of the cartilage identified by imaging or histological techniques. Although CC is most commonly caused by CPP crystals, it is not exclusive to this disease and could appear as a casual finding or coexist with structural changes that resemble OA.²

Previous studies reported the detection of calcium-containing crystals, including CPPD and basic calcium phosphate crystals, in 60% of osteoarthritic synovial fluids obtained from patients with end-stage OA at the time of TKA. The recognized risk factors are aging, OA, previous joint trauma/injury, metabolic disease and familial predisposition.¹² The prevalence of articular CPPD disease exhibits a direct correlation with age, from 1% to 2% between 60 and 70 years to 6%–8% between 70 and 80 years, 20%–30% after 80 years and more than 30% after 90

Table 1
Clinical characteristics of patients.

Case No.	Diagnosis	Sex	Age	From TKA to onset (days)	Medical history
1	Same-side CPPD disease	Male	84	18	Atrial fibrillation, brain infarction
2	Contralateral CPPD disease-1	Female	92	2	Hypertension
3	Contralateral CPPD disease-2	Male	83	14	Rectal cancer, lumbar fusion operation
4	PJI	Female	84	38	Hypertension, hyperlipidaemia

CPPD: calcium pyrophosphate deposition, TKA: total knee arthroplasty, PJI: periprosthetic joint infection.

Table 2

Radiographic characteristics and the results of joint fluid aspiration.

Case No.	Diagnosis	TKA- side OA grade	Contralateral OA grade	TKA- side CC	Contralateral CC	WBC count (/mm ³)	Glucose (mg/dL)
1	Same-side CPPD disease	3	3	–	–	5600	100
2	Contralateral CPPD disease-1	4	4	+	+	11,000	189
3	Contralateral CPPD disease-2	4	4	–	–	1500	96
4	PJI	4	4	–	–	37,800	None

CPPD: calcium pyrophosphate deposition, TKA: total knee arthroplasty, OA: osteoarthritis, CC: chondrocalcinosis, WBC: white blood cell.

CRP

Fig. 1. CRP levels in all cases.

WBC

Fig. 2. Serum WBC levels in all cases.

Fig. 3. An 84-year-old male (Case 1 in Table 1). A, Radiographs before surgery show OA changes in bilateral knees with no CC. B, Radiograph after left TKA. C, Rhomboid, birefringent CPP crystals observed under polarizing light microscopy in the synovial fluid.

Fig. 4. An 84-year-old female (Case 4 in Table 1). A, Radiograph before surgery shows severe OA change in the right knee with no CC. B, The first TKA. C, Radiograph after surgery of a cement spacer. D, Revision TKA.

years.^{13,14}

At present, the factors underlying CPPD disease arising after TKA are unclear. Reportedly, cartilage produces inorganic pyrophosphate, and almost all cartilage in the knee joint, including the patella, was resurfaced in our case. Sonsale and Philipson suggested that tissue, except for cartilage, could produce CPP crystals.¹⁵ Crawford et al. detected CPP crystals in 13 (1.6%) of 789 loosened hip prostheses.¹⁶ A consistent feature of periprosthetic tissues that contained CPP crystals was histological evidence of cartilaginous metaplasia, confirmed by staining with the metachromatic dye toluidine blue.¹⁷ Although the

mechanism described above can describe the occurrence of late-onset CPPD disease after TKA, it cannot explain the early onset CPPD disease after TKA, including the present case.

It is clinically challenging to distinguish between an inflamed joint due to crystal-induced arthritis, including CPPD disease, and an inflamed joint due to septic (bacterial) arthritis. This distinction is imperative because any delay in the diagnosis and treatment of septic arthritis could cause permanent destruction of the affected joint.¹⁸ Standard blood tests comprise a complete blood count with differential erythrocyte sedimentation rate and CRP; however, these can all be

elevated in both septic and crystal arthritis. The presence of crystals and positive synovial fluid culture confirm the diagnosis of crystal-induced arthritis and septic arthritis, respectively. Although uncommon, these two arthritides can coexist, and the presence of crystals does not always rule out bacterial arthritis. A retrospective study found positive culture in 1.5% of joint aspirates containing crystals.¹⁹ However, at present, the reasons for the simultaneous occurrence of crystalline and septic disease remain unclear. One widely accepted postulate is that an infective process might promote the release of crystal particles from the cartilage and synovial membranes, so-called crystal shedding and mining.²⁰ Another possible explanation is that crystal-induced arthritis, like other inflammatory arthritides, might be a factor predisposing individuals to an intra-articular infection.

There are currently no reliable clinical clues to distinguish between isolated CPPD disease and CPPD disease with concomitant septic arthritis because both can present without fever and have a synovial WBC count of less than 50,000 cells/mm³.^{19,21} Some studies have reported cases of septic arthritis with a similarly low WBC count. Although our data are consistent with some earlier studies, they contradict the common notion that septic arthritis is infrequently diagnosed in patients with WBC less than 50,000 cells/mm³.²²

If CPPD disease is misdiagnosed as PJI, patients might undergo multiple unnecessary surgical procedures. Hence, distinguishing an inflamed joint due to crystal-induced arthritis from an inflamed joint due to septic (bacterial) arthritis is imperative. The present study is considered to contribute to distinguishing CPPD disease after TKA from PJI.

It is not clear why CPPD disease is found in the contralateral knee following TKA. In the present cases, the results of blood examination (WBC and CRP) and joint fluid aspiration test did not differ markedly between the same-side CPPD disease and contralateral CPPD disease.

The main limitation of this study is the small sample size. Because acute CPPD disease of prosthetic joints is rare, further studies on a large number of cases are needed.

5. Conclusions

If CPPD disease is misdiagnosed as PJI, patients might undergo multiple unnecessary surgical procedures. Hence, distinguishing an inflamed joint due to crystal-induced arthritis from an inflamed joint due to septic (bacterial) arthritis is imperative. Overall, the diagnoses of arthritis after TKA should be confirmed by aspiration.

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