Abstract
Diabetes mellitus is a common disorder and presents in different ways. Shoulder pain is a common musculoskeletal complaint, especially in middle-aged or older-aged men. While it is widely accepted that diabetics have an increased propensity to develop infections, a diagnosis of osteomyelitis of the humerus as the etiology of constant shoulder pain might be delayed, as occurred in this case study, until patients’ develop clear signs of infection. Here, we describe a case of subacute osteomyelitis as the first physical symptom of diabetes; the possibility of osteomyelitis should therefore be investigated in all patients with diabetes mellitus who develop joint or bone-related pain.

Keywords: Diabetes mellitus, Humerus, Osteomyelitis

INTRODUCTION
Pain caused by pathology in the shoulder joint is often experienced in the mid-humerus at the level of insertion of the deltoid[1]. This may be explained by the fact that all shoulder structures, except the acromioclavicular joint, arise from the C5 sclerotome, and pain is distributed from this nerve root[2]. Most patients with painful, limited shoulder movement and maximal levels of pain at the level of insertion of the...
deltoid have a shoulder lesion, such as capsulitis[1].

While a bony lesion of the humeral shaft may in fact exist, diagnosis of this lesion might be delayed, especially when a patient has subacute osteomyelitis (OM) but no clear signs of infection in the upper limb, as an occurrence is rare in this site without prosthetic insertion or penetrating injury in adults. However, in systemically compromised patients, including diabetic patients, as in our case, it is important to investigate an infectious cause[3]. Herein, we report primary subacute OM in the humerus as the etiology of constant shoulder pain and as the first physical symptom of diabetes.

**CASE REPORT**

An otherwise healthy 56-year-old Korean male visited our hospital with a 4-week history of throbbing pain in the left shoulder and upper arm. Pain was observable through examination with maximum tenderness at the level of insertion of the deltoid, and the patient experienced mild pain-restricted movement with shoulder abduction. The patient was a ginseng farmer. He had no history of direct trauma and no history of recent travel abroad or involvement in recreational activities or contact sports. The patient had a smoking history of 30 pack-years and a heavy episodic drinking history (above 60 g/day of alcohol twice per week). Two weeks before visiting our hospital, he visited another pain clinic with the same complaint. According to a copy of his medical records, his simple shoulder radiography results were normal except for a small bone spur at the glenoid of the scapula (Fig. 1A). His erythrocyte sedimentation rate (ESR) and total leukocyte count were normal and upon physical examination of this pain site, no erythema, swelling, warmth, or neurologic compromise were evident. However, the patient had a high blood sugar level (glucose 311 mg/dL) without symptoms of hyperglycemia. Under suspicion of adhesive capsulitis or osteoarthritis, he was treated with physiotherapy, non-steroid anti-inflammatory drugs, and empirical injections at the subacromial space three times over a period of two weeks. He was then

![Image](A)

![Image](B)

![Image](C)

**Fig. 1.** (A) Simple x-ray of the shoulder showed near normal findings except for a small bone spur at the glenoid of the scapula and an incidental mid-humeral osteolytic lesion that was missed upon first examination (arrow). (B) The bone scan showed significantly increased uptake in the mid-shaft of the left humerus. (C) Fat-saturated contrast-enhanced T1 weighted magnetic resonance imaging (sagittal view) revealed Brodie’s abscess formation in the proximal 1/3 and mid-shaft of the left humerus accompanied by diffuse bone marrow signal change and adjacent soft tissue swelling with juxtacortical abscess formation.
admitted to our hospital with poorly controlled diabetes mellitus (glycated hemoglobin [HbA1c] 11.1%) and persistent shoulder and upper arm pain, despite our supportive treatment.

Upon admission to our hospital, a physical examination revealed the following: height, 168 cm; weight, 78 kg; body mass index 27.7 kg/m²; body temperature, 36.6℃; blood pressure, 120/70 mmHg; heart rate, 78 beats/min and regular. The patient’s neck was normal and his lungs were clear of fluid. The abdomen was normal. No lymphadenopathy was found. The spine and pelvis were non-tender. No mass or tenderness was detected along the other long bones. All general laboratory findings were normal except for a mildly elevated C-reactive protein (CRP) level of 0.73 mg/dL (reference range: 0~0.3 mg/dL), and blood was negative for ketones. The patient was treated with intravenous fluids and subcutaneous insulin injections into the abdomen and right arm. Oral hypoglycemic agents were also administered (glimepiride 4 mg and metformin 1,500 mg daily) and the patient chose to take acetaminophen/tramadol to control his shoulder pain. Despite supportive treatment, his shoulder pain worsened, the left shoulder girdle muscles began to atrophy, and a mild fever (up to 37.6℃) was recorded on hospitalization day 4. He also complained of indolent swelling on the lateral side of his left upper arm. Simple radiography of the shoulder revealed normal findings for the shoulder area; however, an osteolytic lesion with sclerotic margins in the mid-humerus was detected. This was consistent with clinical findings, as this area was extremely tender to palpation without any overlying erythema. The bone scan showed significantly increased uptake in the mid-shaft of the left humerus, but not in the shoulder joint (Fig. 1B). An magnetic resonance imaging revealed subacute OM with Brodie’s abscess formation in the proximal 1/3 and mid-shaft of the left humerus, accompanied by a diffuse bone marrow signal change and adjacent soft tissue swelling with juxtacortical abscess formation (Fig. 1C). On hospitalization day 4, laboratory findings revealed obvious increased levels of inflammatory markers, such as white blood cells 16,500/μL (neutrophils 78.5%), ESR 47 mm/hr (reference range: 0~15 mm/hr), and CRP 11.93 mg/dL (reference range: 0~0.3 mg/dL). Other laboratory findings, including liver function, creatinine level, and lipid profiles were within the normal range.

Due to the clinical diagnosis of OM, two blood and aspirated pus samples of the juxtacortical abscess were obtained for culture, in order to guide treatment decisions. The patient was started on 2 g of intravenous ceftriaxone once daily. Because of the presence of intramedullary and juxtacortical abscesses in the mid-shaft of the humerus, emergent surgery was performed. After adequate debridement and lavage of necrotic tissues and bony sequestrations, vancomycin mixed cement beads were inserted (three beads in the dead space of the bone and seven beads alongside the bone) and fixed internally with cerclage wiring.

On the fourth day after surgery, a blood culture revealed no bacteria growth, but methicillin-resistant Staphylococcus aureus (MRSA), only resistant to oxacillin (minimum inhibitory concentration [MIC] ≥ 4 μg/mL), was isolated from pus culture. Therefore, daily therapy with 400 mg intravenous teicoplanin was initiated.

To find the probable source of S. aureus entry into the humerus, we investigated the patient’s medical history in greater depth. No exposure to healthcare settings or any hospital interventions were recorded.
within the previous year except for a recent injection to the shoulder at the subacromial space. The patient had no history of childhood illness, recurrent infections, or recent skin or soft tissue lesions. He had no history of intravenous drug abuse. No members of his household had skin or soft tissue lesions. Laboratory analyses for the source of infection, including echocardiogram, blood, urine, and sputum bacterial culture, were unfruitful. Screens for infections that cause immunodeficiency (human immunodeficiency virus, Hepatitis B and C virus, Epstein-Barr virus, cytomegalovirus) were all negative.

On the fifth day after surgery, a methicillin- and oxacillin-sensitive (MIC = 0.5 μg/mL) *Staphylococcus aureus* (methicillin-sensitive *Staphylococcus aureus* [MSSA]) was isolated from bone cultures taken at debridement. However, intravenous teicoplanin treatment was not discontinued because we could not exclude the possibility of co-infection with both MRSA and MSSA based on the previous culture results. Acid-fast *Bacillus* culture and a polymerase chain reaction assay of bone were carried out to detect *Mycobacterium tuberculosis*, but results were negative. Fungal cultures were also negative.

Two weeks after initiation of intravenous antibiotics, the patient developed a fever (up to 38.7°C) again but felt well without chills while febrile. He complained of mild diarrhea but was negative for *Clostridium difficile* toxin and sigmoidoscopy findings of pseudomembranous colitis. His leukocyte count, ESR, and CRP level all decreased with no signs of infection or relapse at the site of operation. We suspected the possibility of drug fever without skin rash or eosinophilia so we discontinued ceftriaxone first, followed sequentially by teicoplanin to reduce the persistent fever. Resolution of fever occurred within 48 hours of discontinuing all antibiotics. Intravenous cefazidime (1st generation of cephalosporin) at 1 g every 12 hours for a total of 6 weeks was restarted, and the patient was discharged with oral cefpodoxime 100 mg twice daily. It took approximately 4 weeks for ESR and CRP levels to normalize. At the 2-week post-discharge follow-up, the patient’s leukocyte count, ESR, and CRP concentrations were 8,400/μL, 4 mm/hour, and 0.07 mg/dL, respectively, and oral antibiotics were then discontinued.

At the one-year follow-up, the subject had full use of his left upper limb and there was no evidence of relapse. His glucose level was within normal range (HbA1c, 5.2%) controlled by a daily dose of 1,000 mg metformin and 100 mg sitagliptin.

**DISCUSSION**

Our patient arrived at the hospital with pain and restricted movement in the shoulder area. Most patients with painful, limited shoulder movement and pain focused in the mid-humerus (at the level of insertion of the deltoid) have a shoulder lesion such as capsulitis(1). Diabetes mellitus significantly increases the risk of developing adhesive capsulitis(4). However, the etiology of the pain and lost movement in this specific case was not capsulitis, but a lesion at the mid-shaft of the humerus. Loss of range of movement was presumably secondary to the humeral lesion, and the shoulder was entirely normal.

The possibility of OM was not considered initially for a number of reasons. First, we missed the abnormality of the upper humerus on the simple shoulder radiography exam performed two weeks before admission and on
admission day, as we were focused on the shoulder pathology, even though radiographs of the shoulder were cropped at the mid-humerus. Second, although the patient had experienced shoulder pain for 1 month, he did not have a fever or local signs or symptoms of acute inflammation for at least four weeks. Third, the patient did not suffer from any other infective conditions that could have been a source of the OM. Lastly, the patient was a healthy, middle-aged man in excellent physical condition, except for uncomplicated newly-onset diabetes, and he had no problems performing his work as a ginseng farmer, which is a physically demanding occupation.

Subacute OM, whether primary or modified by inadequate or partial treatment with antibiotics, is a distinct entity and different from other forms of OM. Subacute OM is a hematogenous infection of bone characterized by an insidious course (longer than two weeks), and a paucity of systemic symptoms with local tenderness or swelling are the only clinical signs\[^5\]. Because differential diagnosis of other conditions, such as tuberculosis, fungal infection, and bone tumors is difficult, an incorrect diagnosis is often made before operation. The indolent course of subacute OM is thought to be the result of an altered host-pathogen relationship, in which host resistance is relatively increased, and bacterial virulence is decreased\[^5\]. Owing to its insidious onset, mild symptoms, and inconsistent support of laboratory data, diagnosis and treatment are usually delayed, as occurred in this case study. At five weeks post pain onset, our patient was diagnosed with subacute OM, which transformed into an acute component due to a juxtacortical abscess around the affected bone accompanied by fever and soft-tissue swelling with warmth.

In some cases, trauma has been implicated as a predisposing factor to subacute OM (especially Brodie’s abscess), which may account for why the tibia, which is subcutaneous in its anteromedial parts and consequently prone to trauma, is commonly involved\[^6\]. The pathogenesis of the reported patient’s infection was undetermined based on history and clinical findings. However, we assumed that the initial event was probably trauma to his left shoulder. This trauma may have been caused by repetitive physical actions or a single episode of strain, which may or may not have been related to the nature of the patient’s job, and occurred without being noticed by the patient. The trauma may have slightly injured the bone or muscle that then became seeded by \textit{S. aureus} present in the blood.

Hyperglycemia itself may have predisposed the patient to infection, even though he had no obvious evidence of sensory peripheral or autonomic neuropathy or vascular insufficiency, which are generally thought to be the reason for diabetic patients’ predisposition to infection. Studies have demonstrated that neutrophil chemotaxis, adherence to vascular endothelium, phagocytosis, intracellular bactericidal activity, opsonization, and cell-mediated immunity are all depressed in diabetics with hyperglycemia\[^7,8\]. Furthermore, patients with diabetes often have asymptomatic nasal and skin colonization with \textit{S. aureus}\[^9\]. Colonization may be predisposed to cutaneous or incisional staphylococcal infections as well as transient bacteremia, which may then result in infection at distant sites. The role of subacromial space injection in pathogenesis is likely to have been minimal, because our patient received such treatment after appearance of abnormal radiologic findings of the humerus, and the lesion was located
at the diaphysis without signs of shoulder infection in images.

In subacute OM case series, metaphyseal lesions are most common and occur mainly in the tibia of children, while the vertebral form is usually seen in adults[10,11]. Fewer cases of diaphyseal OM have been reported in the literature, and most of these involve adults[12]. Cole[13] described the epiphyseal and metaphyseal types as ‘cavities’ while he described the diaphyseal subtype as ‘aggressive lesions’. Recommended treatment for a culture-positive subacute OM is curettage or excision of the lesion with six weeks of postoperative antibiotic treatment [14]. Clinical signs of subperiosteal pus indicate that the subacute infection has transformed into an acute component, which then must be drained surgically, as occurred in this case.

After cultures have been obtained, if treating empirically, experts recommend use of a broad-spectrum antibiotic effective against *S. aureus*, which is regarded as the most common causative organism of OM. We initially administered intravenous ceftriaxone treatment. However, we maintained a high suspicion of skeletal tuberculosis presenting as bony and soft-tissue infective lesions, particularly because of the history of insidious onset, until negative results for *M. tuberculosis* culture were obtained. Ultimately, only *S. aureus* was identified as the causative pathogen. The patient recovered successfully in response to intravenous and subsequent oral antibiotics after active debridement and abscess drainage. MSSA was more likely to be the true pathogen, rather than both MRSA and MSSA, considering the patient’s positive clinical progress despite administration of teicoplanin for only 2 weeks.

In conclusion, OM should be suspected in all patients with diabetes mellitus who develop pain related to joints and bones despite a paucity of systemic infection signs and no recent injury. Furthermore, in patients with OM, diabetes should be evaluated as a risk factor. In addition, humeral lesions might be the cause of pain in patients whose shoulder symptoms fail to respond to standard therapies, especially if pain is maximal at the insertion of the deltoid.

**CONFLICTS OF INTEREST**

No potential conflict of interest relevant to this article was reported.

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