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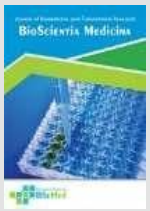

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Genu Sinistra Tuberculosis Arthritis with Drug-Induced Liver Injury Caused by Anti-Tuberculosis Drugs in Patients Confirmed with COVID-19

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A B S T R A C T

Background: Tuberculous arthritis is a form of extrapulmonary tuberculosis and has a significant effect on patient morbidity and mortality. This case report aims to describe clinical signs and symptoms, results of laboratory tests, radiology, and outcome of tuberculosis arthritis cases. **Case presentation:** A 36-year-old woman came to the emergency room with the main complaint of pain, swelling, and warmth when palpating the knee for the past week. The pain felt worse during activities such as walking. The patient also complains of fever, loss of appetite, and unwanted weight loss. Physical examination showed sharp pain and swelling in the knee, limited range of movement (ROM), and a positive balloon sign, while laboratory tests showed increased leukocytes, neutrophils, and C-reactive protein. After the diagnosis of genu tuberculosis arthritis was established, the administration of anti-tuberculosis drugs (OAT) was started. After one week, the patient complained of pain in the left knee and progressive nausea. Liver function tests showed an increase in SGOT and SGPT. The patient then started OAT desensitization. A month later, the patient underwent an open synovectomy with liquefaction necrosis. Although the first desensitization of tuberculosis still causes drug-induced liver injury, the second desensitization involves gradually increasing doses of rifampicin accompanied by close monitoring of liver tests. **Conclusion:** Early administration of anti-tuberculosis drugs in tuberculosis arthritis can improve healing, maintain joint function, and prevent further damage. Anti-tuberculosis drug desensitization is the primary management of drug-induced liver injury.

1. Introduction

Tuberculosis (TB) is still a significant health problem, especially in developing countries. Although pulmonary tuberculosis is the most common form of the disease, extrapulmonary tuberculosis also contributes significantly to patient morbidity and mortality.[1,2] Approximately 10-15% of extrapulmonary TB cases are tuberculous arthritis. Vascular (hematogenous) and percontinuital pathways are common pathogenesis pathways in tuberculous arthritis, while lymphatic pathways are rare in this condition.[3]

The diagnosis of tuberculous arthritis is usually delayed because the possibility of tuberculosis is often overlooked in the differential diagnosis of joint disease.[4] In addition, the classic constitutional symptoms of tuberculosis, such as fever, night sweats, and weight gain, are usually absent in patients with tuberculosis arthritis. This disease involves the large joints, especially the hip, knee, and ankle joints. In

tuberculosis arthritis, the course of the disease is slow, chronic, and usually affects only one joint, and there is a decrease in joint function and other activity. The supporting examinations that can be carried out are imaging, microscopic examination, biopsy, and culture. Microscopic examination is the fastest examination but is not sensitive. Only 10-30% of cases have positive smears. A biopsy is the gold standard examination in tuberculosis arthritis.[3,4] This case report aims to describe clinical signs and symptoms, results of laboratory tests, radiology, and outcome of tuberculosis arthritis cases.

2. Case Presentation

A woman, 36 years old, came with complaints of pain in her left knee, which had been aggravating since 1 week before entering the hospital. Four months before admission, the patient complained of pain in the left knee. The pain felt like being stabbed, intermittent, especially when walking. The patient has not been treated, she only bought painkillers at the pharmacy, and the complaints have lessened a little. One month before admission, the patient complained of knee pain that was getting worse than before. The knee feels enlarged, feels a lump, and the pain is like being stabbed. The knee looks reddish and feels warm. The patient is difficult to move. Fever exists. The temperature is not measured and goes away with a febrifuge. Decreased appetite accompanied by weight loss is present, felt by the patient through slightly loosened clothing. The patient then went to a local clinic and was told he had arthritis. The patient is given painkillers and antibiotics, the patient forgets the name of the medicine, and the complaint is not reduced. 1 week before admission, the patient complained of pain in the knee that was getting worse than before. The knee feels enlarged, the patient cannot bend the leg, and the pain is like being stabbed. The patient is no longer able to do activities at home. The patient was then taken for treatment to the internal medicine rheumatology polyclinic at Dr. Mohammad Hoesin General Hospital, and joint fluid was taken to obtain ± 30 ccs of fluid, yellowish green in color and odorless. The patient was then advised to be hospitalized.

On physical examination, normal vital signs were obtained, with normoweight body mass index (BMI) status, swelling in the genu sinistra region, positive tenderness, limited active, passive range of movement (ROM), and positive balloon sign. The diameter of the genu dextra is 37 cm, while the genu sinistra is 45 cm (Figure 1).

Figure 1. Clinical appearance of the genu sinistra region of the patient upon admission to the hospital.

Laboratory tests showed an increase in leukocytes (13.070/mm^3), increased neutrophils (74%), decreased lymphocytes (17%), and increased quantitative C-reactive protein (CRP) of 97 mg/L. A radiological examination of the lungs showed no abnormalities (Figure 2), whereas an X-ray of the genu sinistra showed apple bites (Figure 3), which indicated septic arthritis and was supported by an effusion on the ultrasound of the genu sinistra. From the drainage procedure, 350 ccs of greenish-yellow liquid/pus was obtained (Figure 4A). Cytology results of the patient's genu sinistra synovial fluid showed acute suppurative inflammation with positive smears (Figure 4B-C) and GeneXpert sputum in the form of *Mycobacterium tuberculosis* (MTB) not detected.

Figure 2. X-ray of the genu sinistra.

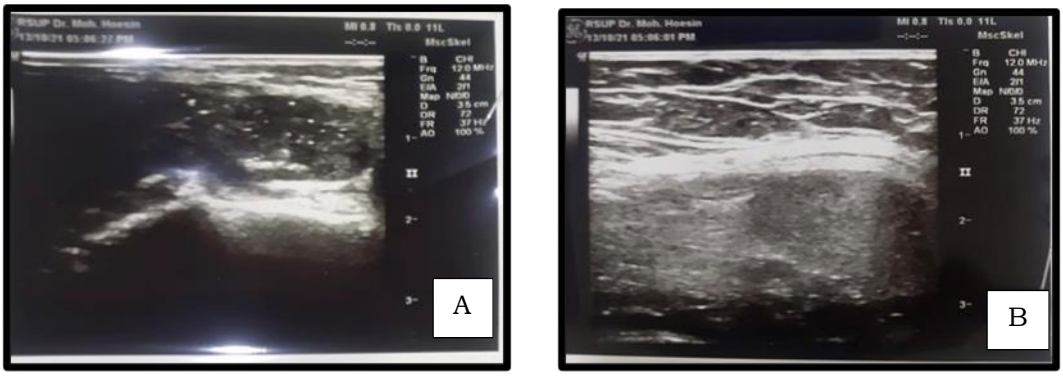

Figure 3 (A-B). Ultrasound imaging of the genu sinistra.

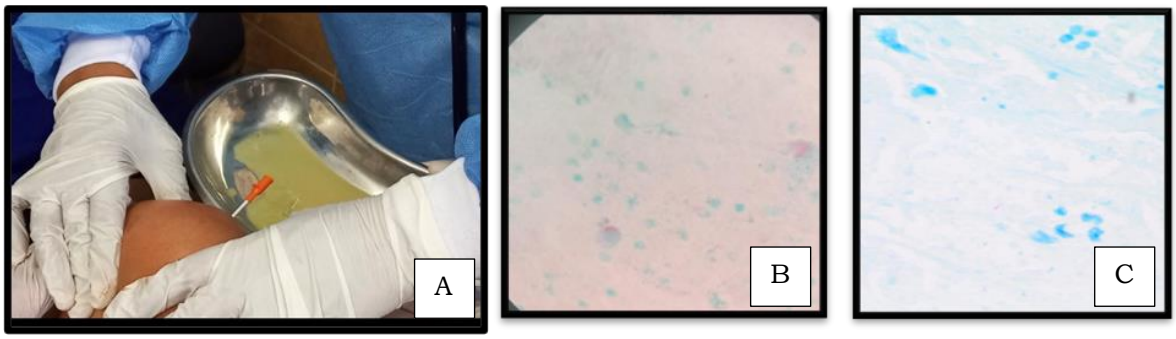

Figure 4. Results of fluid aspiration (A) and examination of acid-fast bacilli (B-C).

The patient received pharmacological therapy in the form of paracetamol, ketoprofen suppository, 4 anti-tuberculosis drugs (OAT) 4 KDT 4 tablets every 24 hours orally, and vitamin B6. Twelve days later, the patient came to the outpatient clinic with complaints of increasing pain and swelling in the left knee accompanied by severe nausea. On physical examination, normal vital signs were found. The genu sinistra region appeared swollen and tender positive, felt warm on palpation, and had limited active, passive ROM with a diameter of 56 cm. Laboratory tests showed a decreased liver function, as indicated by an increase in SGOT 427 units/L and SGPT 385 units/L. In addition, there was an increase in uric acid of 13.8 mg/dL. The results of the history, physical examination, and investigations indicated the presence of drug-induced liver injury due to OAT and pyrazinamide-induced hyperuricemia. This condition caused the temporary suspension of OAT. The patient was hospitalized and given supportive pharmacological therapy in the form of curcuma, allopurinol, domperidone, cefixime, and paracetamol.

After OAT was stopped for 3 days, liver function tests showed a decrease in SGOT levels to 43 units/L and SGPT levels to 99 units/L. Also, during this desensitization period, the patient was found to have confirmed COVID-19 through a PCR examination. The patient was then transferred to the isolation inpatient room and received additional treatment in the form of metronidazole, methylprednisolone, vitamin C, vitamin D, N-acetylcysteine , and $CaCO_3$.

On the 14th day of hospitalization and cessation of anti-TB drugs, desensitization was carried out by giving isoniazid 300 mg/24 hours of anti-tuberculosis drugs, rifampicin 600 mg/24 hours (starting on the 4th day after the start of isoniazid), pyrazinamide 1500 mg/24 hours (5th day after initiation of rifampicin) followed by close quarterly monitoring of liver function. However, two days after giving pyrazinamide, there was an increase in SGPT 187 units/L, SGOT 81 units/L, and a slight decrease in albumin 3.1 g/dL, so pyrazinamide was replaced with ethambutol 800 mg/24 hours. On the 4th day after ethambutol administration, a follow-up examination of liver function was carried out. An increase in SGOT 218 units/L and SGPT 281 units/L was obtained, so the administration of ethambutol was stopped.

In addition to pharmacological therapy, the patient also underwent a surgical procedure in the form of a synovectomy due to the patient's clinical picture experience of genus effusion back after the termination of antibiotic injection. Surgery showed the presence of necrosis of the disease in the genu sinistra region. After surgery, OAT in the form of isoniazid 300 mg/24 hours and rifampicin 600 mg/24 hours is continued. Anatomical pathology (PA) examination of the surgical tissue showed a synovial cyst with non-specific chronic inflammation at the genu sinistra. Synovial fluid GeneXpert examination showed MTB detected low and Rif-resistance not detected.

The results of laboratory tests on the 6th postoperative day showed an increase in SGPT 375 u/L, SGOT 320 u/L, total bilirubin 2.20 mg/dL, and direct bilirubin 1.50 mg/dL. In addition to OAT (rifampicin and INH), patients receive additional therapy in the form of methylprednisolone, gentamicin, ketorolac, and vitamin B6. On the 7th postoperative day, OAT was decided to be temporarily stopped until liver function returned to normal due to aggravation of clinical symptoms in the form of icteric sclerae and nausea. The patient was then discharged and asked to come back for control at the outpatient clinic.

On the 8th day after discharge, the patient came back with complaints of pain and swelling in the left knee. The patient was again hospitalized, and the ultrasound results showed an effusion in the genu sinistra, with the results of liver function tests within normal limits. The patient then received paracetamol, methylprednisolone, tigecycline, OAT in the form of INH 300 mg/24 hours, and rifampicin 1x150 mg on the 5th day after INH was started (re-desensitization). The dose of rifampicin and INH was increased slowly and reached the optimal dose 14 days after the start

of OAT desensitization, with rifampicin 600 mg/24 hours orally and INH 300 mg/24 hours. The results of the follow-up examination of the liver function panel, such as total, direct, indirect, SGPT, and SGOT bilirubin, were within normal limits.

3. Discussion

Septic arthritis is an inflammatory condition of the joints caused by the inoculation of infectious microorganisms in the joints.[5] This disease is an emergency in rheumatology. The risk factors for septic arthritis are old age, history of joint disease, history of joint surgery or injections, skin or soft tissue infections, use of intravenous drugs, use of indwelling catheters, and immunosuppression, including diabetes.[6]

The occurrence of septic arthritis is caused by hematogenous spread or through direct inoculation.[7,8] Synovial joints that have extensive vascularization do not have a basement membrane, so they are susceptible to infection through the hematogenous spread of systemic infection. Septic arthritis can also occur through direct injury, stab wounds, and intra-articular injections. Percontinuital spread from adjacent osteomyelitis may also occur. Vulnerable places for the occurrence of this disease through a percontinuital mechanism are the hip and shoulder joints. Bacterial invasion, followed by an inflammatory process, causes joint damage. Other factors that play an important role are bacterial toxins and pathogenic surface components such as adhesins *Staphylococcus,* which allows the attachment of bacteria to intra-articular proteins.[8]

In this case, there is an infection in the knee that is included in the synovial joint, and there is no history of trauma. Therefore, the possibility of per continuity spread can be eliminated so that the possibility of pathogenesis is deployment hematogenous. The diagnosis of septic arthritis is made on the basis of clinical signs and symptoms. Joint fluid analysis is necessary to make the diagnosis.[9,10] The onset is usually acute, with pain and swelling, and heat in the joints that worsen over time. The knee is a joint that is often involved, and other places are the pelvis, wrist, shoulder, and ankle. Other places that are less often affected are the sternoclavicular or sacroiliac joints, which can be involved in intravenous drug users. Chills and fever are often found but not found in 20% of patients. Infection from the pelvis usually does not cause swelling, but there is groin pain that is aggravated by walking. In this case, according to the theoretical view that has been mentioned, there is an infection in the unilateral patient's back. However, shivering and fever were not found in the patient, which is typical for bacterial causes, so other causes were thought of.

There are many kinds of microbes that can cause septic arthritis. Broadly speaking, the classification of septic arthritis according to microbes is nongonococcal arthritis, gonococcal arthritis, and other infections (fungal arthritis and tuberculosis arthritis). Blood and synovial fluid cultures should be performed to determine the causative microbe as well as acid-fast bacilli to confirm or rule out the diagnosis of tuberculous arthritis. On investigation, no bacteria were found in the culture, while the acid-fast bacilli gave positive results, so the diagnosis of tuberculosis arthritis was established.[10]

Joints that are often affected are large joints such as the hip or knee joints. Other joints that can be affected are the sacroiliac, shoulder, forearm, ankle, carpal, and tarsal joints.[11] On physical examination, a swollen joint can be found with or without warmth. Limited movement due to pain and swelling hypertrophy Synovial and effusions may also be found. In developing countries, the diagnosis of tuberculosis of the bones and joints can be established by clinical and radiological examination. Clinical examination is carried out by looking at the existing signs and symptoms and carrying out laboratory tests (increased ESR, AFB sputum test, tuberculin test).

On radiological evaluation, the process of tuberculous arthritis may start in the synovium or in the bone. In the early stages, atypical signs that appear are thickening of the joint capsule, the joints looking dull, the joints slightly widened due to intra-articular effusion, and osteoporosis in the bones

around the joints due to hyperemia.[11] In this case, clinical support was a complaint about one joint, namely the left knee joint, sub-febrile symptoms, pain, and limitations in the range of motion of the joint, so that the joint was very difficult to move, and the patient could not walk. On touching the skin above the area of pain, it feels warm. On supporting ultrasound examination of the genu sinistra, an intra-articular effusion was found. On staining of acid-fast bacilli also found mycobacterium, and on radiology, there were signs supporting septic arthritis.[2]

In this case, because the main diagnosis of tuberculosis arthritis was initially not established, antibiotics could be given while waiting for the test results because, based on epidemiology, bacterial causes were found to be the highest. Delay in giving antibiotics can cause germs to multiply rapidly and will cause permanent damage to the cartilage, causing hematogenous spread and ultimately raising sepsis which can cause death. Another thing to do is to puncture/aspire the synovial fluid to remove as much pus as possible. If it fails with aspiration, it is necessary to do drainage with surgery.

In administering antibiotics, there are several things that need to be considered, such as the severity of the disease, the age of the patient, the pattern of germs in the hospital concerned, as well as existing risk factors, such as rheumatoid arthritis, SLE, intravenous drug abuse, got drugs immunosuppressive or immunocompromised state. The duration of antibiotic administration varies. In general, on arthritis septic without complications, antibiotics are given 2 to 4 weeks. In severe cases, the use of antibiotics can take up to 6 weeks.[12]

After the diagnosis of TB arthritis has been successfully established by smear examination, anti-tuberculosis drugs (OAT) can be given. Giving OAT earlier can improve healing, maintain joint function, and prevent further damage. Based on the TB treatment guidelines in Indonesia, TB arthritis therapy is 2RHZE/10-16RH and should be given 1 year to 18 months in some cases.[13] Dosage according to the patient's body weight. This patient weighs 60 kg, so she is given 4 tablets for a duration of 1 year. In addition to pharmacological therapy, therapy non-pharmacological such as walking aids and surgery can be performed therefore, this patient is consulted by orthopedics.

This patient has a diagnosis of COVID-19, so she is given supportive treatment in the form of vitamin C and vitamin D because she has no symptoms, so antivirals or antibiotics are not indicated. It is mandatory for COVID-19 patients to be isolated for a maximum of 10 days from the time the specimen is collected for a confirmed diagnosis or, if there are symptoms, a maximum of 10 days isolation plus 3 days free from fever or respiratory symptoms.[14]

Drug-induced liver injury (DILI), or drug-induced hepatotoxicity, is a liver injury caused by exposure to drugs or non-infectious agents.[15] In this patient, there were complaints of nausea that were felt in the solar plexus. The results of laboratory checks showed an increase in transaminase enzymes and hyperuricemia, so the patient was suspected of having DILI due to OAT drugs. Hepatocyte death in DILI can occur through two processes, namely, processes mediated by apoptosis or necrosis.[16] In apoptosis, there is shrinkage and fragmentation of the cell into small pieces with the cell membrane intact. These fragments are cleared by phagocytosis and generally do not stimulate the host's immune response. Conversely, necrosis causes loss of mitochondrial function and ATP depletion, which causes swelling and cell lysis which stimulates local inflammatory processes. The main management of DILI is delaying the drug that might cause it. In most cases, spontaneous recovery occurs without the need for any treatment. In this case, OAT was delayed until liver function returned to normal and clinical symptoms such as nausea and abdominal pain disappeared. Then if DILI has been completed, OAT can be administered one by one.

4. Conclusion

Early administration of anti-tuberculosis drugs in tuberculosis arthritis can improve healing, maintain joint function, and prevent further damage. Anti-tuberculosis drug desensitization is the primary

management of drug-induced liver injury. The management of TB tuberculosis arthritis that must be carried out is the synovial fluid aspiration to remove as much pus as possible.

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