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Pulmonary Tuberculosis with Acute Gout Arthritis in East Nusa Tenggara: A Case Report

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Abstract: ***Tuberculosis (TB) is one of the oldest infectious disease known to affect human and caused by bacteria from Mycobacterium group that has the highest mortality rate in the world. The main bacteria ismycobacterium tuberculosis that most ofteninfect lungs. Although pulmonary TB is curable if treated properly, there could be adverse effect from the anti-TB drugs. Hyperuricemia is a common adverse effect from pyrazinamide, while clinical gout requiring a treatment is rare.A 69-years-old man with Pulmonary TB complaint about pain in all of his joints for the last 7 days while taking anti-TB drugs for about 2 month.Physical examination reveal multiple masses with tenderness at right toe, left ankle, knee bilateral and left thumb. Uric acid 4.71mg/dL.Diagnosed as pulmonary TB and acute gout arthritis then treated with analgesic IV and colchicine while still giving Anti-TB drugs. Knowledge of these adverse effects is important especially for clinician in endemic countries. Miss-diagnosed lead to wrong medication that could exacerbationacute gout. While not life-threatening, screening for hyperuricemia could prevent complication from anti-TB drugs.***

Keywords: pulmonary tuberculosis, anti-TB, adverse effect, gout arthritis, pyrazinamide

1. Introduction

Tuberculosis (TB) is one of the oldest infectious diseases known to affect human and caused by bacteria from *Mycobacterium* group that has the highest mortality rate in the world. The main bacteria is*Mycobacterium Tuberculosis* (M.Tb) that commonly infect lungs. This disease is spread from human to humanby airborne.[1,2] Despite being preventable and curable, every year, 10 million people get TB and 1.5 million people die from it. Most of the people live in low to middle-income or developing countries. About one-quarter of the words population is estimated to be infected by M.Tb but only 5-15% of these people will fall ill with active TB disease.[2] Based on Global TB Report 2021, every year, there are 842.000 (319 per 100.000 people) new cases of TB in Indonesia and 116.400 (44 per 100.000 people) death cases. Indonesia is ranked 3 after China and India in new cases of TB each years.[3] Prevalence TB in Indonesia is 0.42% while East Nusa Tenggara is 0.27%. [4]

The first line regiment for pulmonary TB treatment are Isoniazid (H), Rifampicin (R), Pyrazinamide (P) and Ethambutol(E) that divide into 2 phases; intensive for 2 months and continuation for 4 months(2RHZE/4RH)3. [1,2] Treatment for TB could range from 6 up to 12 month depend on location and severity of the TB.[1]Although pulmonary TB is curable if treated properly, there could be adverse effect from anti-TB agents. Isoniazid and Rifampicin are the critical during intensive and continuation phases. Isoniazid (H) is generally well tolerated, but sometimes drug-induced liver injury or peripheral neuropathy could happen.Rifampicin (R) is the most active anti-TB agent that available for now, the adverse effect from it are infrequent and generally mild, hepatotoxicity could happen but uncommon in the absence of preexisting liver disease. Ethambutol (E) and Pyrazinamide (Z)are the cornerstone in intensive phase. Ethambutol is the least potent against M.Tb, with optic neuritis as the most serious adverse effect reported. Ethambutol also reported to increased uric acid serum level < 24 hour after the initiation, but the effect commonly seen in 2 – 4 weeks after therapy.Pyrazinamide is given for the first 2 months of therapy that could shortened the duration of treatment from 9 to 6 months and also decrease the rates of relapse. Pyrazinamide had many benefit that could outweigh the adverse effect, at higher dosage, hepatotoxicity was seen in 15% patients, hyperuricemia is common that usually could be managed conservatively and clinical gout is rare.[1,2,5]

Hyperuricemia is an increased uric acid serum level (> 6.8mg/dL), while arthritis gout is inflammation at the joint because of the deposit of monosodium urate (MSU) in the joint and clinical manifestation because of hyperuricemia.[1] Many people could have hyperuricemia but never get acute manifestation in their life, only up to 36% of the patients who develop gout, and not all gout patients have hyperuricemia.[6] Goutoccurs 4 times more in men than women and usually at the age of 60 years old and older.[1.7] Hyperuricemia observed in 58.3% patient who received anti-TB [8], TB patient who developed gout is rare and usually had a history of gout or hyperuricemia before the anti-TB treatment.[9,10]Many variablescould make hyperuricemia or increase risk of flare, from lifestyle to drugs. Anti-TB is one of the drugs that could make patients hyperuricemia that asymptomatic,the hyperuricemia.[1,5]

2. Case Report

A 69 years old male come with complaint of pain in joints at both feet, knees and hands for about 7 days before and the pain intensified 2 days prior. The patient couldn't walk for long because of the pain.Patient also complain about swelling and red in the joints. 3 days before, patient went to public health center, had uric acids serum level 11mg/dL then get analgesic and allopurinol. Patient had history of gout and hyperuricemia that keep come and go, andalways got treatment at public health center. 2 months before the patient diagnosed as Pulmonary TB. Chest x-ray at that time

showed infiltrates on the left apex and Gene Xpert MTB/RIF test results were MTB detected without rifampicin resistance. The patient already treated with standard Anti-TB regimen(2RHZE/4HR 3) for 1 month. The patient had habit of consuming alcohol and eating seafood daily.

On physical examination, the patient has low body mass index. Vital signs are normal. Thorax, heart and abdomen examinations are normal. Examination of the extremity showmass at right toe, left ankle, knee bilateral and left thumb. The masses are red in color, warm and tenderness at touch. The masses were suggests as tophaceous deposit.

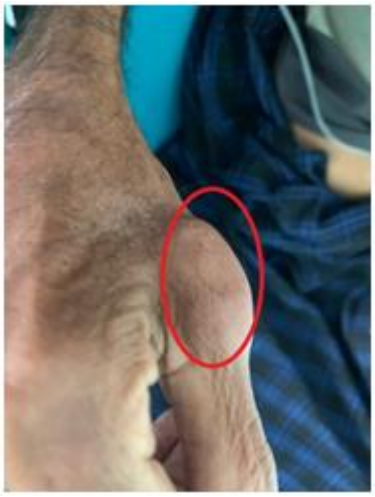

Figure 1 Right Hand Mass

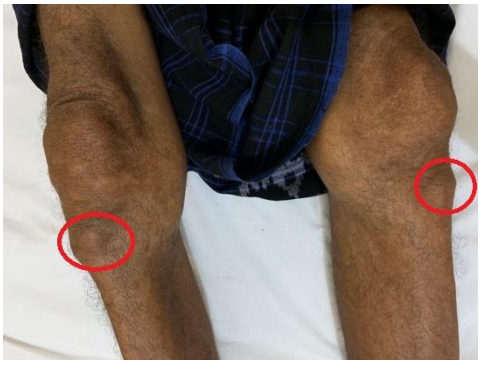

Figure 2 Both Knees Masses

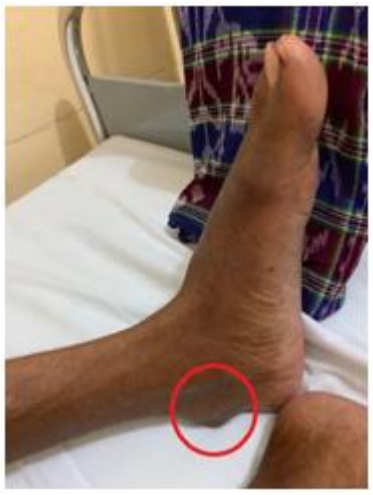

Figure 3 Left Ankle Mass

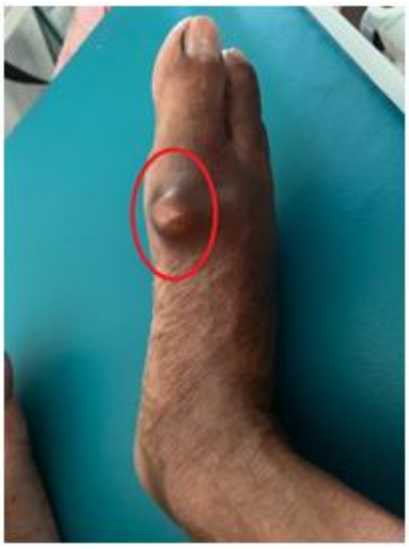

Figure 4: Right Feet Mass

Table 1: Laboratory Examination

Examination	Result
Complete Blood Count	
Hb	12.3 g/dL
Ht	36.5%
Leucocyte	8.000 cell/uL
Thrombocyte	257 cell/uL
Kidney Function	
Ureum	37 mg/dL
Kreatinin	0.71 mg/dL
eGFR	95.7 cc/minute/1.73m^2
Liver Function	
AST	25 U/L
ALT	18 U/L
Blood Chemistry	
Random Blood sugar	126 mg/dL
Uric Acid	4.71 mg/dL

The laboratory examination was within normal range. Uric acid serum level 4.71 mg/dL and before at public health center was 11mg/dL. From these finding, the patient diagnosed as Pulmonary TB with Acute Gout Arthritis.

For Management, the patientcontinue the intensive phase of Fixed Drugs Combination (FDC) of Anti-TB regimen that consisted of Isoniazid (H) 225mg, Rifampicin (R) 450mg, Pyrazinamide (P)1200mg, and Ethambutol (E) 825mg, all thrice a week. We suggest to hospitalized the patient because he can't walk yet, while giving analgesic and colchicine 1mg as initial dose then 0.5 twice daily.

3. Discussion

Acute gout is the most common early clinical manifestation of gout, usually only 1 joint affect, but polyarticular acute gout can occur in subsequent episode. The most common sites are metatarsophalangeal joint of the toe (MTP-1) about 75%, tarsal joints, ankles, and knee.[1,7] In elderly patients, finger joints also a possibility manifestation site.[1] Several event may precipitate acute gout, like dietary excess, trauma, surgery, excessive ethanol, hypouricemic therapy, and serious medical illness.[1,11] Ingestion of pyrazinamide, made a strong urate retention agent, making renal cleareance decrease about 80% at 300mg dose daily. Incidence of

hyperuricemia in patient ingesting pyrazinamide are from 43% - 86.3%.[12] Ethambutol as another anti-TB, may precipitate hyperuricemia although not frequently. Ethambutol suggest to reduce the fractional excretion of uric acid in renal, also in a prospective study, 66% of patient who receive SHE found a significant rise in serum uric acid level.[5]Acute Gout in TB patient is rarely happen, despite Indonesia being an endemic TB. Usually, acute gout in TB patients happened when there are preexisting gout or hyperuricemia before the treatment.[1]In this case,patient had ahistory ofhyperuricemia and gout before, involvement of MTP-1, dietary of alcohol and seafood as a stample food, and ingestion of anti-TB make the suggestion that the diagnose is acute gout.

Alcohol, such as beer and distilled liquors, can increase uric acid level in blood by increasing ATP degredation then metabolisme throung purine salvage pathway. Risk of gout increase by 1.16 times for people drink alcohol < 1 drink per day, 1.58 times for drink 1-3 times per day and 2.64 times for drink >3 times perday.[7,13] Drinking alcohol can be said to be a culture in Sikka, so the patient already had an increase risk of hyperuricemia and gout. Diet high protein like seafood also increase purine level. Some type of seafood such as anchovies, shellfish, sardines and tuna are higher in purines and was associated with increased OR of goutfrom 1.27 to 1.31 [11,13]. East Nusa Tenggara isa gathering ofislands and most of the inhabitants work as fishermen, so seafood become theirs daily meal.

Joint fluid analysis need to be done to confirm the diagnosis, but it can't be done because of limitation in our area. We diagnosed the patient withGout Classification Criteria with entry criterion > 1 episode of swelling, pain or tenderness in peripheral joint/bursa.[14]

Table 2 Gout Classification Criteria

Criteria	Category	Score
Patern of joint/bursa involvement during episodes.	Joint/bursa other than ankle, midfoot or 1st MTP (or involvement in a polyarthritis)	0
	Ankle OR midfoot (as part of monoarticular/ oligoarticular episode without 1st MTP)	1
	1st MTP (as part of monoarticular/ oligoarticular episode)	**2**
How many characteristics during episode(s) Erythema overlying joint, can't bear touch or pressure to joint, great difficulty with walking or inability to use joint.	No Characteristics	0
	One Characteristics	1
	Two Characteristics	2
	Three Characteristics	**3**
How many episodes with the following time-course? >2 time course symptomps	No typical episodes	0
	One typical episode	1
	Recurrent typical episodes	**2**
Evidence of tophus Draining or chalk-like subcutaneous nodule, located in typical locations: joints, ears, olecranon bursae, finger pads, tendons (e.g., achilles)	Absent	0
	Present	**4**
Serum Urate Ideally scored when patient not taking urate-lowering treatment and patient was >4 weeks from episode. If pratical, retest under those conditions. Higher value irrespective of timing should be used.	<4mg/dL (< 0.24mM)	-4
	≥4 or < 6mg/dL (≥ 0.24 or < 0.36mM)	**0**
	≥ 6 or < 8mg/dL (≥ 0.36 or < 0.48mM)	2
	≥ 8 or 10mg/dL (≥ 0.48 or < 0.6mM)	3
	≥ 10mg/dL (≥ 0.6mM)	4
Synovial fluid analysis of a symptomatic (ever) joint or bursa Should be assessed by a trained observer	Negative for MSU	-2
	Not done	**0**
Imaging evidence of urate deposition in symptomatic joint/bursa Ultrasound: double-countour sign OR DECT : Demonstrates urate deposition	**Absent or not done**	**0**
	Present	4
Imaging evidence of gout-related joint damage X-Ray of hands or feet with > 1 eroision	**Absent or not done**	**0**
	Present	4

Score need to be over 7 to determinate positive for gout arthritis without analysis joint fluid as the gold standard.[14,15] In Indonesia or other developing countries, not all places could do analysis joint fluid, so another method is needed.This criteria already validated and can be used when analysis joint fluid couldn't be done.[15] In this case, analysis joint fluid can't be done, so we use the criteria from **table 2** and got 11 points. From this criteria we can already said the patient positive gout arthritis.

In this case, flare happened because of many variables, the patient had a history of repeated gout and hyperuricemia, drinking alcohol, eating seafood daily, ingesting anti-TB and lastly reducing uric acid level too fast by ingestion allopurinol from public health center. Allopurinol could precipitate gout due to urate lowering resulting in urate crystals being shed from articular cartilage into the joint space, resulting in acute inflammation.[1,5] All of these variables contribute to forming MSU and precipitating gout arthritis in the patient.

The fundamental treatment for gout arthritis is to reduce pain in the acute episode, colchicine is the first line treatment for acute gout, with initial dose 1mg and 0.5 mg

an hour later, it can be repeated 3 times daily.Before administrationcolchicine to patient with acute gout, renal functions need to be checked, and the doseneed some adjusted for GFR < 10mL/minute/1.72m^2. Combination withanalgesic such as NSAIDs can also be used to reduce the pain and inflammation that happen in the joint. [16,17,18] The patient has GFR 95.7mL/minute/1.72m^2, so we gave patient colchicine 1mg as initial dose and 2x 0.5mg daily. Because of the severe pain, we also gave NSAIDs (Ketorolac 3 x 30mg) daily. Allopurinol as urate lowering agent is not needed at acute period, and can be given 2 weeks after the acute period finish.[19] Urate lowering agent in acute period need to be avoided because it could cause drastic changes in uric acid serum level and trigger precipitation of uric acid crystal in the joints.It is also associated with the release of uric acid from MSU that already exist in the joints and form nucleus for the formation of new MSU.[16,19] Anti-TB can't be stopped until the treatment is completed, so after the acute period is over, all we had to do are reducing alcohol intake, limiting seafood intake, monitoring uric acid serum level periodically and giving allopurinol 100mg daily as initial dose that can increased step by step to achieve target uric acid serum level.

4. Conclusion

Hyperuricemia often occurs in patients taking anti-TB. Although rarely happened, acute gout arthritis can also occur. Many variables can increase the risk of acute gout such as alcohol, diet, anti-TB regiment and hypouricemic therapy. Gold standard to diagnose gout is analysis joint fluid, but in places where analysis joint fluid can't be done, Gout Classification Criteria can help to determine the diagnosis. There is a need of screening hyperuricemia or preexisting gout before anti-TB treatment, patients with higher risk should be closely monitored while ingesting anti-TB, especially during intensive phase which have pyrazinamide and ethambutol. In acute setting, the fundamental treatment is to reduce pain, sohypouricemic treatment can be given 2 weeks after acute period finish.

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