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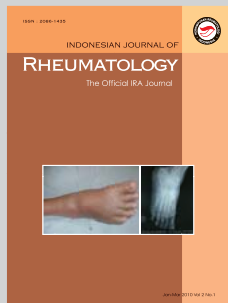


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The Official IRA Journal





Swelling of the right foot and the right ankle joint (left). X-ray of right foot with osteoarticular tuberculosis (right). See page 27-28.

AIMS AND SCOPE: *Indonesian Journal of Rheumatology* is self-focused on rheumatic diseases and connective tissue disorders in forms of original articles (extended or concise reports), review articles, editorial, letters, leaders, lesson from a memorable cases, book review, and matters arising. Both clinical and laboratory including animal studies are welcome.

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Editor's note

YI Kasjmir

In this issue of Indonesian Journal of Rheumatology (IJR), Akil et al (see page 27), by reporting a case about delayed diagnosis of osteoarticular Tuberculosis (TB) of the right foot remind us that diagnosis of infective arthritis is still become a problem for our clinician.¹ An increase incidence of osteoarticular TB has recently been reported. Diagnosis presents clinicians with a number of difficulties and failure to recognize the disease at an early point in the course of illness occurs frequently.² Non specific articular symptoms without any evidence of the disease in other organs and lack of familiarity make differential diagnosis of Tuberculous arthritis is often overlooked during clinical examination hence diagnostic evaluations are often not undertaken until the disease has progressed.^{2,3} If osteoarticular TB is diagnosed and treated at an early stage, approximately 90% to 95% of patients would achieve healing with near normal function.⁴

Hambali et al (see page 30) in this issue also reports a case of septic arthritis caused by *Salmonella* sp., a quite uncommon case.⁵ Septic arthritis is a rheumatologic emergency that could lead to morbidity and mortality if not properly treated. Bacterial infection of joints remains one of the most rapidly destructive joint structure and potentially fatal forms of arthritis. Early diagnosis and prompt treatment are a must to prevent irreversible joint destruction and subsequent disability.⁶ The yearly incidence of septic arthritis varies from 2 to 10 per 100,000 in general population to 30-70 per 100,000 in patients with rheumatoid arthritis and in patients with joint prostheses.⁷ The data from Rheumatology Clinic

of Cipto Mangunkusumo General Hospital, Jakarta in 2007 showed that septic arthritis and arthritis TB cases were found in 8 of 844 (0.9%) outpatients.⁸ We haven't found any epidemiologic data of septic arthritis in Indonesia. It is assumed that the disease has an iceberg phenomenon that challenge the clinicians to be able to diagnose early and treat promptly in order to prevent the morbidity and mortality.

In order to get the epidemiologic data of septic arthritis in Indonesia, we conducted a survey to Puskesmas (Community Health Center) in all over Indonesia from 2008 to 2009 using a questionnaire and we found that incidence of the disease is relatively low. The complete data will be provided in next issue of IJR.

There has not been any practical guideline of septic arthritis that widely accepted or standardized. The treatment of septic arthritis consists of drainage, parenteral antibiotics, and initial joint immobilization. The ongoing controversy surrounding medical versus surgical drainage remains unresolved. Yet a retrospective analysis by Broy et al showed that medical drainage gave a better joint outcome than surgical drainage (66% versus 57%; $p < 0.05$), it still does not permit generation of firm therapeutic guidelines.³

This issue of IJR also contains the first study in Indonesia that attempts to describe the profile of osteophyte in knee osteoarthritis (OA) patients conducted by Mesanti et al (see page 18). From this descriptive study we know the location, size, and direction of osteophyte along with OA grade and functional impairment in knee OA patients.⁹ Further study is needed to verify the correlation among those variables more distinctively.

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Vitamin D and inflammation

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ABSTRACT

The discovery that most body cells and tissues have vitamin D receptors and that some of them have the enzymatic machinery to convert the circulating form of vitamin D (25-hydroxyvitamin D) into the active form (1,25-dihydroxyvitamin D/1,25(OH)₂D₃) gave a new insight about the function of this vitamin. In the course of time, more and more evidences showed that a low vitamin D level leads to the occurrence or recurrence of cardiovascular diseases, type II diabetes mellitus (DM), cell dedifferentiation (oncogenesis), and immune derangement (autoimmune diseases such as lupus, type I DM, rheumatoid arthritis, and multiple sclerosis). Most researchers have agreed that a minimum 25(OH)D₃ serum level of about 30 ng/ml or more is necessary for favorable calcium absorption and good health. Until proven otherwise, the balance of the research clearly indicates that oral supplementation in the range of 1,000 IU/day for infants, 2,000 IU/day for children, and 4,000 IU/day for adults is safe and reasonable to meet physiologic requirements, to promote optimal health, and to reduce the risk of several serious diseases.

Most people assume that once food is already enriched with vitamin D and rickets is already managed, the main health problems resulting from vitamin D deficiency is solved. However, rickets can be considered the tip of the iceberg for vitamin D deficiency. The discovery that most body cells and tissues have vitamin D receptors (VDR) and that some of them have the enzymatic machinery to convert the circulating form of vitamin D (25-hydroxyvitamin D) into the active form (1,25-dihydroxyvitamin D/1,25(OH)₂D₃) gave a new insight about the function of this vitamin. What is most interesting is the role it can play in reducing the risk of many chronic illnesses such as cancer, autoimmune diseases, infectious diseases, and cardiovascular diseases.¹

Vitamin D deficiency can cause metabolic disorder of the bones (osteoporosis and osteomalacia) and muscle weakness (resulting in increased risk of falling).^{1,2} Prevention against the two above is known as the traditional function of vitamin D. In the course of time, more and more evidences showed that a low vitamin D level leads to the occurrence or recurrence of cardiovascular diseases, type II diabetes mellitus (DM), cell dedifferentiation (oncogenesis), and immune

derangement (autoimmune diseases such as lupus, type I DM, rheumatoid arthritis (RA), and multiple sclerosis (MS)).^{1,3,4} Many studies have revealed the non-traditional function of vitamin D. The significance of this non-traditional function was revealed when it was known that besides kidney cells, other cells can produce the active form of vitamin D for their own needs. In these cells, the active form of vitamin D acts as gene expression regulator.² The most convincing evidence of the many vitamin D actions came from reports that correlate vitamin D deficiency with higher risk of death - from any cause - through unknown mechanism.⁵

The study of the association of vitamin D status with various diseases requires the measurement of 25(OH)D₃ status because it is the most accurate measurement of vitamin D status.^{1,3,6} One of the studies showed that the 25(OH)D₃ status was inversely related to TNF α level in healthy women so that it explains part of the role of this vitamin in the prevention and treatment of inflammatory diseases.²

PHYSIOLOGY OF VITAMIN D

Vitamin D is naturally obtained from two sources: sunlight and dietary consumption.^{1,2,7-9} Vitamin D₃ (cholecalciferol) is a form of vitamin D that is synthesized in the skin and is also found in the diet. Vitamin D₂ (ergocalciferol) that is derived by irradiation of fungi is much less efficient as a precursor of active vitamin D (calcitriol).⁷

Vitamin D has two metabolic pathways: endocrine and autocrine (intracellular) and possibly paracrine (around the cell).⁷ This view that has been recently reviewed by Heany is very important because it can expand our understanding about the concept of vitamin D from "bone nutrient that is important only for preventing rickets and osteomalacia" to "an amazing molecule that has a broad effect on various cells and tissues". Furthermore, Heany's differentiation between "short-latency deficiency diseases" such as rickets and "long-latency deficiency diseases" such as cancer can be used as a basis to understand the difference between acute manifestation of severe nutritional deficiency and slow manifestation of chronic subclinical nutritional deficiency.¹⁰

Vitamin D₃ is synthesized in the skin from the precursor (7-dehydrocholesterol) after exposure to sunlight. Dark skin and elderly skin are not that effective in synthesizing vitamin D. Also,

that are known to contain 1-OHase and hence can produce their own calcitriol are cells of the breast, prostate, lung, skin, lymph nodes, colon, pancreas, medulla of the adrenal and brain.^{7,13} As there are a lot of cells and tissues being able to metabolize vitamin D, it is not surprising that vitamin D is also involved in the functions of the above cells and we can understand the biological potential of vitamin D in affecting the function and pathophysiology of various metabolic processes and diseases. Calcitriol is known to modulate the transcription of several genes, modulate neurotransmitter/ neurological function as can be seen from the effect of antidepressants⁷ and anticonvulsants.¹⁴

Vitamin D has evidently an immunoregulating property as seen from its ability to reduce inflammation,^{6,7} suppress and/or prevent certain autoimmune diseases, reduce cancer risk, and possibly reduce the severity and frequency of infectious diseases such as acute pneumonia in children.⁷ Researchers in Belgium have shown that vitamin D lowers CRP and IL-6 levels in critically ill patients. Another researcher showed that vitamin D deficiency is associated with increased risk of inflammation in otherwise healthy people. Furthermore, increased inflammation will increase the risk of chronic inflammatory conditions such as coronary heart disease and DM.⁶

Generally, vitamins play a role in the immune system either in innate or adaptive immunity. Although some vitamins such as vitamin C and E and some vitamins of the vitamin B complex play a role in the immune system non-specifically (for example, as antioxidant), some other vitamins such as vitamin A and D can affect the immune response in highly specific ways. Vitamin D is obviously different from other vitamins (except for vitamin A) in which its bioactive metabolite has hormone-like properties. The active metabolite of vitamin D – $1,25(\text{OH})_2\text{D}_3$ – is synthesized from its precursor by various cells and tissues of the body and stimulate its effect on distant target cells by binding to the nuclear-hormone receptors.⁸

Most autoimmune diseases are found in people who have a genetic predisposition to such disease if exposed to unfavourable conditions such as virus or altered nutritional factors. A classical example is the increase in autoimmune thyroiditis incidence after consumption of iodine supplements in an iodine deficient population. Recently, vitamin D deficiency has been implicated as a trigger factor in autoimmune diseases such type I DM, inflammatory bowel disease (IBD), and MS. Vitamin D modulates the differentiation of T cells towards Th2 phenotype, inhibits the development of Th1 and could result in predisposition to various autoimmune diseases. Epidemiology studies support the association between vitamin D deficiency and the seasonal pattern in the onset of type I DM, IBD, and MS.¹⁵

Calcitriol may possibly mediate the immune effect by attaching to the nuclear VDR of almost all immune cells and thereafter increase the defensive gene expression.² Vitamin D insufficiency may also disturb the development of T cell regulator and increase the risk of autoimmune disease such as MS and type I DM. The evidence of this effect is that the further the region is from the equator, the higher is the prevalence of MS suggesting that the population with lower vitamin D

uses of sunscreen inhibit the UV light needed for vitamin D₃ synthesis.⁹ The synthesized vitamin D₃ is then carried by the blood circulation to the liver where vitamin D is converted to $25(\text{OH})\text{D}_3$ (calcidiol) by vitamin D-25-hydroxylase enzyme.⁷ Next, $25(\text{OH})\text{D}_3$ will travel through the blood circulation to enter the kidney and undergo its final transformation to become $1,25(\text{OH})_2\text{D}_3$ (calcitriol) by 25-hydroxy vitamin D₃-1-alpha-hydroxylase (1-OHase)/(CYP27B¹). Calcitriol is the active form of vitamin D that increases the absorption of calcium and phosphate in the intestine, induces osteoclast maturation for bone remodelling, promotes calcium deposition in bone and a reduction in parathyroid hormone level (PTH).⁷

Calcitriol is a prohormone. Calcitriol is bound to a cytoplasmic receptor. Then the calcitriol/receptor complex is transported to and into the nucleus of the cell. Next, this hormone complex acts as a transcription factor by binding to the specific control elements of the genes and controlling gene expression. Hence, the amount of calcitriol/receptor complex determines the presence of calcium transporter proteins on the surface of the kidney or intestinal epithelial cells and the amount of calcium loaded into the serum. Because calcitriol is synthesized in the kidney, calcium reuptake by the kidney is directly correlated with calcitriol production. If the level of serum calcium is not adequate, the level of calcium in the kidney cells that synthesize calcitriol will also be lower and this will increase the activity of calcitriol/receptor complex. This must be adequate to produce sufficient calcitriol in the serum to increase the calcium uptake in the intestine. If the calcium level is still not adequate, the parathyroid gland will secrete PTH that stimulates both more calcitriol production and release calcium from the bones. Prolonged calcium release from the bones will result in osteoporosis.¹¹ In other words, calcitriol regulates the distribution of calcium supplied from the diet, serum, and bones. The level of calcium must remain constant so that the basic cell processes such as signalling and secretion are not disturbed. A decrease in serum calcium level will decrease nerve and muscle functions.¹¹

Without vitamin D, only 10 to 15% of dietary calcium and about 60% of phosphorus is absorbed. The interaction of $1,25(\text{OH})_2\text{D}_3$ with the vitamin D receptor increases the efficiency of intestinal calcium absorption to 30 to 40% and phosphorus absorption to approximately 80%.¹

While increased calcium absorption is clearly important from the nutritional aspect, suppression of PTH by vitamin D is also important from the clinical aspect because a relatively low PTH level appear to promote and protect health. A higher PTH level is correlated with increased risk of myocardial infarction, stroke, and hypertension.⁷ In line with the above, Fujita proposed “calcium paradox” in which calcium or vitamin D deficiency will result in an increase in PTH level that will increase intracellular calcium so that it will facilitate a cascade of cellular dysfunction that play a role in the development of DM, neurological diseases, malignancy, and degenerative joint diseases.¹²

In the autocrine pathway, $25(\text{OH})\text{D}_3$ is taken up by various cells that contain both 1-OHase and nuclear VDR. Therefore, these cells can produce their own calcitriol without being dependent on the hematogenous supply. Cells and tissues

levels has a higher risk of suffering from this disease. Recent studies also showed that higher blood vitamin D levels can reduce the risk of MS.¹⁶

The discovery of vitamin D receptor in tissues other than in the intestinal and bone tissues - mainly in the brain, breast, prostate, and lymphocyte- and the latest research suggesting that higher level of vitamin D protects a person from diseases such as DM, osteoporosis, osteoarthritis, hypertension, cardiovascular disease, metabolic syndrome, depression, some autoimmune diseases and breast cancer, prostate, and colon enable us today to use vitamin D for a wider range of preventive and curative measures to maintain and improve the health of our patients.⁷

The immune system has evolved to protect us from micro organisms that cause diseases. To do this, the immune system must be able to distinguish between the self tissue and that of non-self. Sometimes the process of distinguishing is disturbed, so that an autoimmune disease occurs in which the immune system attacks the self tissue. In autoimmune diseases, the peripheral T cells attack the target tissue such as the central nervous system (MS), intestine (IBD), joint (arthritis), and pancreas (type I DM). The similarity among these diseases is that the T cells-mainly Th1-control the pathology of disease. The Th1 cell mediated autoimmune disease is characterized by T cells that express TNF- α and IF- γ that are located in the self tissue and induce inflammation in that particular location (intestine, CNS, etc). Generally, if treatment of Th1-mediated autoimmune disease succeeds, it is because of suppression of the number of Th1 cells and/or cytokine (especially TNF- α) produced. In addition, successful treatment of a Th1 driven disease may also be successful in treatment of other Th1 driven autoimmune diseases.⁹

The cause of autoimmune disease is not known. The complex interactions between genes and the environment determine which individual will suffer certain autoimmune disease. Vitamin D may possibly be one of environmental factors that play a role in the development of autoimmune diseases. Autoimmune diseases such as MS and IBD occur because of attacks on the self tissue. Gene analysis of identical twins showed that besides genetic factors, the environment is also an important factor in the occurrence of MS and IBD. The supply of vitamin D from sunlight exposure or diet may play a role in the occurrence of MS and IBD. Convincing data of laboratory animals showed that vitamin D and signalling by VDR determine the results of the experimental MS and IBD. Furthermore, the evidences showed that vitamin D regulates either directly or indirectly the development and function of T cells. Because of the absence of both vitamin D and signal carried by VDR, the autoreactive T cell will develop. With the presence of 1,25(OH)₂D₃ and functional VDR, the balance of T cell response returns to normal and autoimmunity is avoided.⁹

CLINICAL IMPORTANCE OF VITAMIN D

Although there is no consensus on optimal levels of 25(OH)D₃ as measured in serum, vitamin D deficiency is defined by most experts as a 25(OH)D₃ level of less than 20 ng/ml (50 nmol/l). A level of 25(OH)D₃ of 21 to 29 ng/ml (52 to 72 nmol/l) can

be considered to indicate a relative insufficiency of vitamin D, and a level of 30 ng/ml or greater can be considered to indicate sufficient vitamin D.¹ While a universal consensus is lacking, most researchers have agreed that a minimum 25(OH)D₃ serum level of about 30 ng/ml or more is necessary for favorable calcium absorption and good health.¹⁷ Vitamin D intoxication is observed when serum levels of 25(OH)D₃ are greater than 150 ng/ml (374 nmol/l).¹

Risk factors for vitamin D deficiency in otherwise healthy persons include darker-skinned individuals, the obese, the elderly, and those living in northern or southern latitudes greater than 42 degrees. Numerous factors in modern society also may contribute to the problem, including the popularity of non-dairy beverage consumption, diets devoid of the relatively few foods rich in vitamin D, lifestyles of work or leisure spent predominantly indoors, and concerns about sun exposure with the attendant use of lotions that completely block UVB radiation.¹⁷

The council of vitamin D makes the statement that current research has demonstrated that vitamin D deficiency is a major factor in the pathology of at least 17 types of cancer besides other diseases such as coronary disease, stroke, hypertension, autoimmune disease, DM, depression, chronic pain, osteoarthritis, osteoporosis, muscle weakness, muscle wasting, congenital defect, periodontal disease, etc.¹¹

Vasquez et al in their paper stated that although the data is yet to be perfected, administration of vitamin D is seen to give significant benefits in many human diseases such as cardiovascular diseases, hypertension, type II DM, osteoarthritis, MS, type I DM prevention, depression, epilepsy, migraine, polycystic ovarian syndrome, musculoskeletal pain, critical illness, autoimmune/ inflammatory condition and cancer prevention/ treatment.⁷

Autoimmune diseases

Living at higher latitudes increases the risk of type 1 DM, MS, and Crohn's disease. Among white men and women, the risk of MS decreased by 41% for every increase of 20 ng/ml in 25(OH)D₃ above approximately 24 ng/ml (60 nmol/l) (odds ratio, 0.59; 95% CI, 0.36 to 0.97; P = 0.04). Women who ingested more than 400 IU of vitamin D per day had a 42% reduced risk of developing MS. Several studies suggest that vitamin D supplementation in children reduces the risk of type 1 DM. Increasing vitamin D intake during pregnancy reduces the development of islet autoantibodies in offspring.¹

In another study, vitamin D deficiency increased insulin resistance, decreased insulin production, and was associated with the metabolic syndrome. Another study showed that a combined daily intake of 1200 mg of calcium and 800 IU of vitamin D lowered the risk of type 2 DM by 33% (relative risk, 0.67; 95% CI, 0.49 to 0.90) as compared with a daily intake of less than 600 mg of calcium and less than 400 IU of vitamin D.¹

Osteoporosis and fracture

Approximately 33% of women 60 to 70 years of age and 66% of those 80 years of age or older have osteoporosis. It is estimated that 47% of women and 22% of men 50 years of age

or older will sustain an osteoporotic fracture in their remaining lifetime. One study reported that among 3270 elderly French women given 1200 mg of calcium and 800 IU of vitamin D₃ daily for 3 years, the risk of hip fracture was reduced by 43%, and the risk of nonvertebral fracture by 32%.¹⁸ A 58% reduction in nonvertebral fractures was observed in 389 men and women over the age of 65 years who were receiving 700 IU of vitamin D₃ and 500 mg of calcium per day. In studies using doses of 700 to 800 IU of vitamin D₃ per day, the relative risk of hip fracture was reduced by 26% (pooled relative risk, 0.74; 95% CI, 0.61 to 0.88), and the relative risk of nonvertebral fracture by 23% (pooled relative risk, 0.77; 95% CI, 0.68 to 0.87) with vitamin D₃ as compared with calcium or placebo.¹

Muscle strength and falls

Vitamin D deficiency causes muscle weakness.^{1,2,7,17,19} Skeletal muscles have a VDR and may require vitamin D for maximum function. Performance speed and proximal muscle strength were markedly improved when 25(OH)D₃ levels increased from 4 to 16 ng/ml (10 to 40 nmol/l) and continued to improve as the levels increased to more than 40 ng/ml (100 nmol/l). A metaanalysis of five randomized clinical trials (with a total of 1237 subjects) revealed that increased vitamin D intake reduced the risk of falls by 22% (pooled corrected odds ratio, 0.78; 95% CI, 0.64 to 0.92) as compared with only calcium or placebo.¹

Cancer

Brain, prostate, breast, and colon tissues, among others, as well as immune cells have a VDR and respond to 1,25(OH)₂D₃, the active form of vitamin D. In addition, some of these tissues and cells express the enzyme 25-hydroxyvitamin D-1 α -hydroxylase. Directly or indirectly, 1,25(OH)₂D₃ controls more than 200 genes, including genes responsible for the regulation of cellular proliferation, differentiation, apoptosis, and angiogenesis. It decreases cellular proliferation of both normal cells and cancer cells and induces their terminal differentiation. One practical application is the use of 1,25(OH)₂D₃ and its active analogues for the treatment of psoriasis. 1,25(OH)₂D₃ is also a potent immunomodulator.^{1,6,7}

People living at higher latitudes are at increased risk for Hodgkin's lymphoma as well as colon, pancreatic, prostate, ovarian, breast, and other cancers and are more likely to die from these cancers, as compared with people living at lower latitudes. Both prospective and retrospective epidemiologic studies indicate that levels of 25(OH)D₃ below 20 ng/ml are associated with a 30 to 50% increased risk of incident colon, prostate, and breast cancer, along with higher mortality from these cancers. An analysis from the Nurses' Health Study cohort (32,826 subjects) showed that the odds ratios for colorectal cancer were inversely associated with median serum levels of 25(OH)D₃ (the odds ratio at 16.2 ng/ml [40.4 nmol/l] was 1.0, and the odds ratio at 39.9 ng/ml [99.6 nmol/l] was 0.53; P \leq 0.01). Serum 1,25(OH)₂D₃ levels were not associated with colorectal cancer.¹

Osteoarthritis

Vitamin C and D have been hypothesized to be beneficial for osteoarthritis patients. Patients with hip and knee osteoarthritis

show low vitamin D levels.²⁰ Hypovitaminosis D is already an established risk factor for fracture in OA patients. It has been proven that higher intake of vitamin D is associated with a lower risk of osteoarthritis in elder women (55-69 years old).²¹

Cardiovascular Disease

Living at higher latitudes increases the risk of hypertension and cardiovascular disease. In a study of patients with hypertension who were exposed to ultraviolet B radiation three times a week for 3 months, 25(OH)D levels increased by approximately 180%, and blood pressure became normal (both systolic and diastolic blood pressure reduced by 6 mmHg). Vitamin D deficiency is associated with congestive heart failure and blood levels of inflammatory factors, including C-reactive protein and interleukin-10.¹

A prospective study involving 3258 individuals found that the low levels of 25(OH)D₃ and 1,25(OH)₂D₃ were independently associated with cardiovascular mortality and all-cause mortality. In spite of that, an interventional study with vitamin D is needed to determine whether or not there is a causal association between the two.⁵

Schizophrenia, depression, and cognitive performance

Vitamin D deficiency has been linked to an increased incidence of schizophrenia and depression. Maintaining vitamin D sufficiency in utero and during early life, to satisfy the VDR transcriptional activity in the brain, may be important for brain development as well as for maintenance of mental function later in life.¹ Cross-sectional studies in older adults show vitamin D deficiency is associated with low mood and worsened cognitive performance, as well as greater severity of dementia.²

VITAMIN D AND INFLAMMATION

As reported above, the classical function of vitamin D is to regulate the homeostasis of calcium and thereby the formation and absorption of bones.⁹ The discovery of VDR in the peripheral blood mononuclear cell has raised the interest in the study of vitamin D as an immune system regulator.^{22,23} This vitamin D receptor is expressed in the peripheral blood monocytes, macrophages, dendritic cells, leukocytes, and activated CD4⁺ and CD8⁺ T cells so that vitamin D deficiency can have a very broad effect on the immune response.¹⁵ A further study did show that the active form of vitamin D evidently affected the immune response.^{9,24}

This immunomodulation activity occurs through nuclear VDR that is expressed in the APC and the activated T cell. This regulation is mediated through interference with nuclear transcription factors such as NF-AT and NF- κ B or through direct interaction with vitamin D responsive elements in the promoter regions of cytokine genes. The dendritic cells are the main target of 1,25(OH)₂D₃ immunomodulator activity that can be seen from the inhibition in the differentiation and maturation of dendritic cells leading to down regulated expression of MHC-II, costimulatory molecules and IL-12. Moreover, 1,25(OH)₂D₃ increases IL-10 production and promotes apoptosis of dendritic cells. Together, these effects

of $1,25(\text{OH})_2\text{D}_3$ inhibit DC-dependent T cell activation. Immunomodulation by $1,25(\text{OH})_2\text{D}_3$ and its analog in vivo have been demonstrated in various models of autoimmune disease and transplantations. In addition, the combination of analog and other immunosuppressants results in synergism in models of autoimmune and transplantation. The availability of $1,25(\text{OH})_2\text{D}_3$ analog with immunomodulator activity in non-hypercalcemic dose makes it possible to take advantage of this immunomodulator effect in a clinical setting of treatment of autoimmune diseases and prevention of allograft rejection.²⁴ $1,25(\text{OH})_2\text{D}_3$ that mediates its action through vitamin D receptor has been reported to inhibit the Th1 helper cells proliferation and cytokine secretion such as IL-2 and gamma interferon ($\text{IF-}\gamma$). Vitamin D enhances IL-4 response because of its stimulatory effect on Th2 cells.¹⁵

The antiinflammatory properties of vitamin D has been proven in laboratory animals.¹⁷ Recent clinical studies showed that vitamin D supplement modulates or lowers proinflammatory cytokines (for example: CRP, IL-6, IL-12, and $\text{TNF-}\alpha$) while increasing antiinflammatory cytokines (for example, IL-10). Furthermore, researchers suggest that vitamin D can be used as an adjuvant therapy in moderate painful chronic inflammatory autoimmune conditions caused by excessive cytokine activity

such as IBD and Crohn's disease. As a result, vitamin D might reduce musculoskeletal pain caused by or associated with the inflammatory process, but this needs further study.¹⁷ Another researcher showed that vitamin D can reduce the susceptibility to gingival inflammation through its anti-inflammatory effect.²⁵

Obesity becomes a problem because of the property of vitamin D that dissolves in fat. Vitamin D is transported to the fat cell the way it is transported to the liver. Therefore, there is a balance between vitamin D stored in the fat droplet in the fat cell and vitamin D stored in the liver. Unfortunately the capacity of the fat cell is quite larger than that in the liver. Hence, large amounts of vitamin D are needed to saturate the fat storage in the obese person although there is always vitamin D deficiency in each meal. This is one of the reasons why most degenerative and autoimmune diseases increase in prevalence in obese people.¹¹ Sun et al found that calcium diet can decrease inflammatory stress or oxidative stress associated with obesity in mice. They also showed that calcitriol regulates local inflammation by modulating the interaction between adipocytes and macrophages as well as regulating the inflammatory cytokine production in each type of cell through the calcium-dependent and mitochondrial uncoupling dependent mechanisms.²⁶

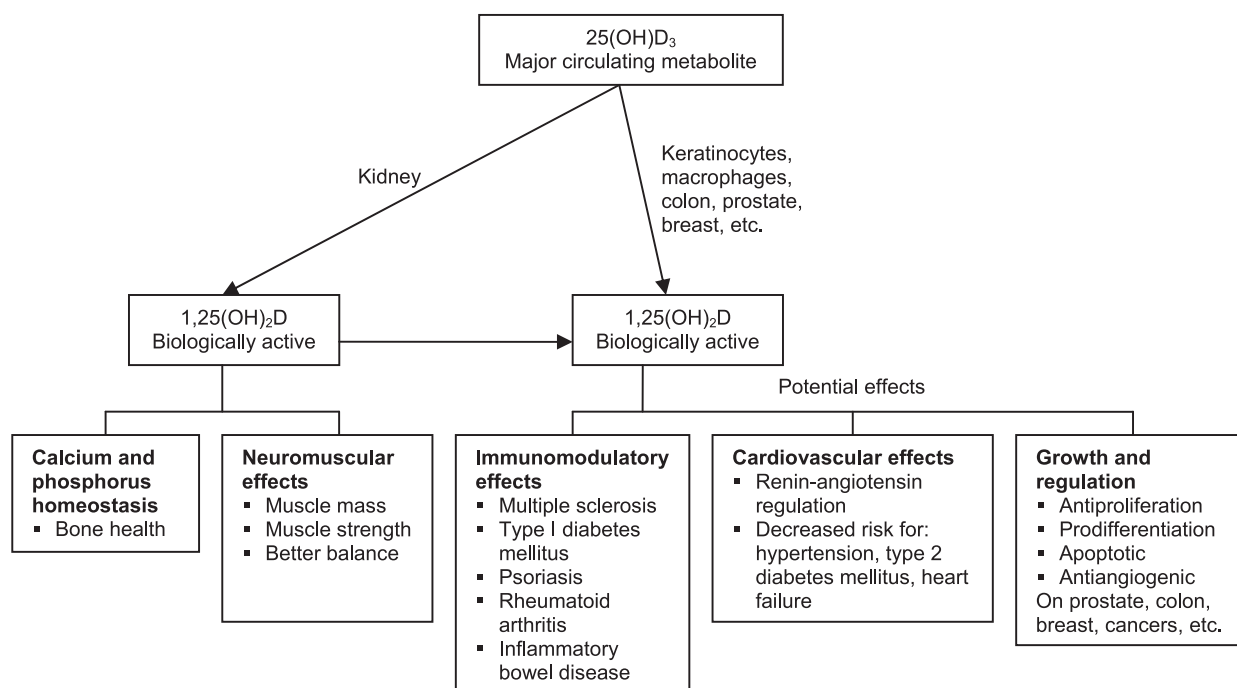


Figure 1 Potential effects of vitamin D (adapted from Rothenberg R, 2008)²⁷

VITAMIN D THERAPY

It is clear that before starting vitamin D therapy we have to make sure that there is vitamin D deficiency (this term is preferred to hypovitaminosis D). Researchers have stressed that the “gold standard” for a presumptive diagnosis of inadequate vitamin D is a review of patient history, lifestyle, and dietary habits that might pose risks for deficiency, along with the recognition of signs/symptoms that could indicate defects in bone metabolism.²⁸ This clinical examination would occur prior to laboratory assessments of serum 25(OH)D₃ or measurements of other biochemical markers.¹⁷

Clinical suspicion based upon history and an awareness of risk factors should remain the gold standard for requesting serum vitamin D measurements. Inadequate sunlight exposure (through veiling and poor outdoor exposure) and poor dietary intake are highly prevalent features of vitamin D deficiency in severely affected patients. Routine measurements of calcium, phosphate, and alkaline phosphatase are not reliable predictors of vitamin D deficiency, even when vitamin D insufficiency has been sufficient to produce a PTH response.²⁸ Diagnosis can also be suspected based on symptoms and signs of rickets, osteomalacia, or neonatal tetany and characteristic bone changes seen on X-ray.²⁹ The diagnosis is then verified by measuring the 25(OH)D₃ status because it is the most accurate measurement of vitamin D status.^{1,3,6}

Adequate sunlight exposure remains the simplest effective way to maintain levels of vitamin D. Exposure of around 15% of body surface (that is, the hands, face and arms or legs) to around one-third of a minimal erythemal dose of sunlight (the amount that causes faint redness), most days, is recommended for adequate endogenous vitamin D synthesis. Although sun exposure can be used to treat vitamin D deficiency, this has to be balanced against the risk of skin damage.^{8-11,19} A 20 minutes of sun exposure can produce 20,000 IU of vitamin D.¹¹

The present Recommended Daily Allowance (RDA) for vitamin D intake is insufficient.^{6,7,11} The old RDA of 400 units was only put forward to prevent rickets. It was established long before the appreciation of sun exposure and optimized vitamin D levels. The requirements for vitamin D are far closer to 10 times the current RDA, or 4,000 units.⁶ However, the optimal daily intake of vitamin D for health is still being debated, and there are differences of opinion based on available evidence. In 1997, the US Institute of Medicine determined that there was insufficient data to specify a RDA. Instead, the organization developed very conservative Adequate Intake (AI) values of 200 IU to 600 IU per day of vitamin D, based on an assumption as people age they would need extra vitamin D supplementation. According to available evidence, at least 1000 IU/day of vitamin D₃ is necessary to maintain adequate serum 25(OH)D₃ levels at or above 30 ng/ml in healthy person.¹⁷

The most recent 2005 Dietary Guidelines for Americans from the US government and recommendations from researchers at the Harvard School of Public Health conclude that healthy children and adults of any age should consume no less than 1000 IU/day of vitamin D₃ to reach and maintain minimum serum 25(OH)D₃ levels of at least 30 to 32 ng/ml. There are some concerns about this guidance. The US Agency for Healthcare Research and Quality (AHRQ 2007) concluded:

“Given the limitations in the measurement of 25(OH)D₃ concentrations and the lack of standardization and calibration, it is difficult to suggest precise recommendations for adequate intakes, especially since optimal levels of serum 25(OH)D₃ have not been defined.” Many experts stress that 1,000 IU/day of vitamin D may be inadequate for maintaining health.¹⁷

Vieth and colleagues (2001) had found that 1,000 IU/day of vitamin D₃ was ineffective for achieving optimal 25(OH)D₃ concentrations. Whereas, 4,000 IU/day of D₃ in their study assured more adequate levels >30 ng/ml. In 2004 they demonstrated that 4,000 IU of D₃ per day was well tolerated during 15 months of therapy. Concentrations of 25(OH)D₃ were increased to more optimal levels and parathyroid hormone was reduced, while calcium levels remained normal.¹⁷ Vitamin D supplementation with doses of 4,000 IU/day for adults is clinically safe and physiologically reasonable since such doses are consistent with physiologic requirements. The physiologic requirement for vitamin D in adults may be as high as 5,000 IU/day, which is less than half of the >10,000 IU that can be produced endogenously with full-body sun exposure.³⁰ Higher doses up to 10,000 IU/day appear safe and produce blood levels of vitamin D that are common in sun-exposed equatorial populations. Periodic assessment of serum 25(OH)D₃ and serum calcium will help to ensure that vitamin D levels are sufficient and safe for health maintenance and disease prevention. Until proven otherwise, the balance of the research clearly indicates that oral supplementation in the range of 1,000 IU/day for infants, 2,000 IU/day for children, and 4,000 IU/day for adults is safe and reasonable to meet physiologic requirements, to promote optimal health, and to reduce the risk of several serious diseases. Safety and effectiveness of supplementation are assured by periodic monitoring of serum 25(OH)D₃ and serum calcium.⁷

Oral cholecalciferol may be the most appropriate agent to treat vitamin D deficiency. To be most effective, vitamin D supplements should be administered with adequate amounts of calcium supplements because of a likely combined deficiency. Calcitriol is not considered ideal for treating patients with simple vitamin D deficiency, in part because of the potential risk of hypercalcaemia. A larger dose is probably required for cancer prevention, aiming to maintain levels of serum 25(OH)D₃ above 75 nmol/l. In patients with a mild to moderate vitamin D deficiency, supplementation with 3,000 to 5,000 IU (75 to 125 µg) per day oral cholecalciferol is recommended (three to five capsules of oral cholecalciferol 1,000 IU per day). At least six weeks of therapy is required to achieve levels of serum 25(OH)D₃ above 75 nmol/l. In patients with a moderate to severe vitamin D deficiency, higher dosages of vitamin D supplementation (above 5,000 IU per day) are usually required. Higher oral dose formulations (10,000 to 25,000 IU capsules) can be used and are available through local compounding chemists. Cholecalciferol can be administered by intramuscular injection to facilitate compliance in elderly patients.¹⁹ Vitamin D intoxication is extremely rare but can be caused by inadvertent or intentional ingestion of excessively high doses. Doses of more than 50,000 IU per day raise levels of 25(OH)D₃ to more than 150 ng/ml (374 nmol/l) and are associated with hypercalcemia and hyperphosphatemia.³¹

CONCLUSION

With the discovery of vitamin D receptor in various cells and tissues of the body, we can conclude that vitamin D plays a role in the function of those cells. Therefore, besides the traditional function of its effect on calcium metabolism and muscle function, vitamin D also has other functions that have

been demonstrated in many studies. One of the non traditional functions is the role as immunomodulator through the regulation of gene expression that in turn determines its role in the inflammatory process. Adequate sun exposure remains the simplest effective way to maintain levels of vitamin D.

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Hyperuricemia and Pro Inflammatory Cytokine (IL-1 β , IL-6, and TNF- α)

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ABSTRACT

Background. Rugerio et al 2006 reported that there were a positive correlation between the level of hyperuricemia and the level of IL-1 β , IL-6, and TNF- α pro inflammatory cytokines value. On the other hand, Choi et al reported a negative correlation between hyperuricemia and the level of pro inflammatory cytokine in the late phase of hyperuricemia.

Methods. Venous blood samples were collected and stored at a temperature of - 80oC from in- and out-patients with hyperuricemia with age of more than 17 years old at Dr. Kariadi Hospital, Semarang. The level of uric acids (mg/dl) were examined with enzymatic colorimetric technique (Roche Diagnostics) whereas the levels of IL-1 β , IL-6, and TNF- α pro inflammatory cytokines (pg/ml) were examined with enzyme linked immunosorbent assay (ELISA) technique using ultra sensitive commercial kit (Human ultra sensitive, Biosource International Inc Europe), and ELX 800, 2002 machine. The normality of the data was tested with One-Sample Kolmogorov-Smirnov technique and the correlation was tested with Spearman correlation (data with abnormal distribution) or Pearson correlation (data with normal distribution).

Results. There was a weak positive correlation between the level of hyperuricemia and the level of IL-1 β cytokine in Spearman correlation test with r value = 0.246 and p value > 0.05 in Spearman correlation test. On the other hand, there was a weak negative correlation between the level of hyperuricemia and the level of TNF- α cytokine with r value = - 0.096 and p value > 0.05. There was also weak negative correlation between the level of hyperuricemia and the level of IL-6 cytokine with r value = - 0.072 and p value > 0.05 in Pearson correlation test.

Conclusion. There was a weak positive correlation but not significant between the level of hyperuricemia and the level of IL-1 β .

Uric acid is produced from protein (purin) metabolism in the liver by urate oxidase enzyme (uricase) in the liver, and then metabolized (oxidative degradation) into allantoin which is more soluble and easier to excrete through the renal. The function of uric acid (monohydrate uric monosodium) in the body is not clear. It is assumed that uric acid acts as primary antioxidant, binding radical oxygen effectively just like vitamin C does.¹ Hyperuricemia occurs when 1) there is an excess production resulted from high purin diet, alcohol consumption, certain conditions with high level of cells degradation, or enzymatic defect in

purin metabolism; 2) there is a disorder in uric acid excretion through the renal. The complications of hyperuricemia include 1) gout, 2) renal stone and renal damage, and 3) an elevated risk factor of ischemic heart disease caused by atherosclerosis and atherothrombosis in blood vessels.^{1,2} In animal study, hyperuricemia in joint or structures around will stimulate monocytes/leucocytes (mast cells in early phase, neutrophils in later phase) to produce various chemoattractant protein and Interleukine-1beta (IL-1 β), IL-6, and Tumor Necrosis Factor alpha (TNF- α) pro inflammatory cytokines. The role of hyperuricemia in the pathogenesis of atherosclerosis and atherothrombosis in blood vessels is still widely debated. Early phase of vascular inflammation begun by a vascular endothelial injury, and then chemoattractant protein will be produced to attract various inflammatory leucocyte, many adhesion molecules (E selectin, intracellular adhesion molecule-1/ICAM-1, vascular cell adhesion molecule-1/VCAM-1), mast cells, and monocytes with all their cytokine products to the injured area.^{2,3} In a study of 967 subjects, Rugerio et al 2006 (USA) reported a positive correlation between the level of hyperuricemia (quintile) with the levels of IL-1 β , IL-6, and TNF- α cytokines value, causing an increase in the level and activation of the three pro inflammatory cytokines. It is supposed that the cytokines were activated through specific receptors such as the toll like receptor on the leucocyte system aided by a protein called My 88 protein (produced in cytokine stimulated tissues).⁵

METHODS

The subjects were in- and out-patients with hyperuricemia, from both sexes with age of more than 17 years old, at Dr. Kariadi Hospital, Semarang. They agreed to participate in the study and signed the informed consent. The study had the permit from the Ethics Committee of Dr. Kariadi Hospital, Faculty of Medicine, Diponegoro University. Peripheral blood samples were collected from the subjects, serum plasmas were collected and stored at a freezer with temperature of - 80°C. The level of uric acid (mg/dl) was examined by enzymatic colorimetric technique (Roche Diagnostics). Hyperuricemia is

a state when the level of uric acid in the serum exceeds 7 mg/dl in men or 6 mg/dl in women.² The levels of IL-1 β , IL-6, and TNF- α pro inflammatory cytokines (pg/ml) were examined with enzyme linked immunosorbent assay (ELISA) technique using ultra sensitive commercial kit (Human ultra sensitive, Biosource International Inc Europe). The result of the ELISA reader was an absorbency value (Optical Density/OD) which was converted to pg/ml using an ELX 800,2002 machine. The normality of the data distribution was tested with One-Sample Kolmogorov-Smirnov test. The correlation was tested with Spearman correlation (data with abnormal distribution) or Pearson correlation (data with normal distribution).^{6,7}

OBJECTIVE

The objective of the study is to identify the correlation between the level of hyperuricemia value and the levels of IL-1 β , IL-6, and TNF- α pro inflammatory cytokines.

RESULTS

There were 44 cases of hyperuricemia (35 men : 9 women) in in- and out-patients at Dr. Kariadi Hospital, Semarang. The mean age was 62.57 ± 9.73 years old, body mass index was 24.81 ± 2.89 . The mean level of hyperuricemia was 8.94 ± 1.46 mg/dl whereas the mean level of IL-1 β was 36.8 ± 69.3 pg/ml, the mean level of IL-6 was 219.17 ± 130.8 pg/ml, and the mean level of TNF- α was 34.9 ± 24.2 pg/ml (table 1).

Table 1 Raw data of the study, the levels of hyperuricemia, IL-1 β , IL-6, and TNF- α

Hyperuricemia (mg/dl)	IL-1 β (pg/ml)	IL-6 (pg/ml)	TNF- α (pg/ml)
Mean/SD	Mean/SD	Mean/SD	Mean/SD
8.94 ± 1.46	36.8 ± 69.3	219.17 ± 130.8	34.9 ± 24.2

One-Sample Kolmogorov-Smirnov test showed that the distribution of the IL-1 β (pg/ml), IL-6 (pg/ml) and TNF- α (pg/ml) were abnormal, thus the correlation between IL-1 β and uric acid were tested with Spearman correlation test.

Spearman* correlation test showed that there was a weak positive correlation but not significant between the level of IL-1 β (pg/ml) and the level of uric acid (mg/dl) ($r = 0.246$ and $p = 0.107$). The correlation test of the level of TNF- α cytokine value (pg/ml) and the level of uric acid (mg/dl) also showed that there was a negative weak correlation but not significant between them ($r = -0.096$ and $p = 0.445$). Finally the correlation between the level of IL-6 value (pg/dl) and the level of uric acid (mg/dl) also showed that there was a negative weak correlation but not significant between them ($r = -0.072$ and $p = 0.445$) (table 2).

Table 2 The correlation between the level of hyperuricemia and the levels of IL-1 β , IL-6, and TNF- α

	Hyperuricemia (mg/dl)	r value	p value
Mean / SD	Mean/SD		
IL-1 β (pg/ml)	36.8 ± 69.3	8.94 ± 1.46 mg/dl	0.24 > 0.05*
IL-6 (pg/ml)	219.17 ± 130.8	8.94 ± 1.46 mg/dl	-0.096 > 0.05**
TNF- α (pg/ml)	34.9 ± 24.2	8.94 ± 1.46 mg/dl	-0.072 > 0.05**

DISCUSSION

The correlation between the level of hyperuricemia and the level of IL-1 β , TNF- α , and IL-6

In this study there was a weak positive correlation (not significant) between the level of hyperuricemia and the level of IL-1 β (figure 1, ROC graph with $r = 0.246$ and $p > 0.05$ in Spearman correlation test). Moreover, there was a weak negative correlation (not significant) between the level of hyperuricemia (mg/dl) and the level of TNF- α (pg/ml) (figure 2, ROC graph with r value = -0.096 and p value > 0.05). Finally, there was also a weak negative correlation (not significant) between the level of hyperuricemia (mg/dl) and the level of IL-6 (pg/ml) (figure 3, ROC graph with r value = -0.072 and p value > 0.05). These results were a contrast to the study done by Rugerio et al 2006 (USA). In the study of 967 hyperuricemic patients, Rugerio reported that there were positive correlations between the high level of hyperuricemia (quintile) and the levels of IL-1 β , IL-6, and TNF- α cytokines. It meant that an increase of the level of hyperuricemia would be followed by the increase and activation of the three pro inflammatory cytokines.² Kim et al (US, 2007) in a five-year cohort study reported that hyperuricemia > 7 mg/dl in a woman was a risk factor of coronary heart disease with an odds ratio of 1.356 in women and 1.121 in men. However, Neogi et al (USA, 2007) in a multicenter analysis reported that hyperuricemia was not related to coronary artery calcification in men and women through helical computed tomography examination technique.⁸ Neogi's finding was supported by Choi et al's hypothesis. Choi stated that monocytes and mast cells were responsible for the early phase of acute inflammation by secreting various inflammatory chemicals (chemoattractant, prostaglandin, etc) and also IL-1 β , IL-6, and TNF- α inflammatory cytokines. Nevertheless, if the inflammation had continued, the stimulated and differentiated monocytes/macrophages would fail to produce and secrete various inflammatory cytokines including IL-1 β , IL-6, and TNF- α .¹ This phenomenon was proven with in vitro culture of well differentiated human macrophage for seven days where it would then failed to secrete cytokine.¹ Macrophage in chronic phase of gout will produce IL-10 and TGF- β cytokines which are able to force down the inflammatory response or reduce the production of IL-1 β , IL-6, and TNF- α .⁷

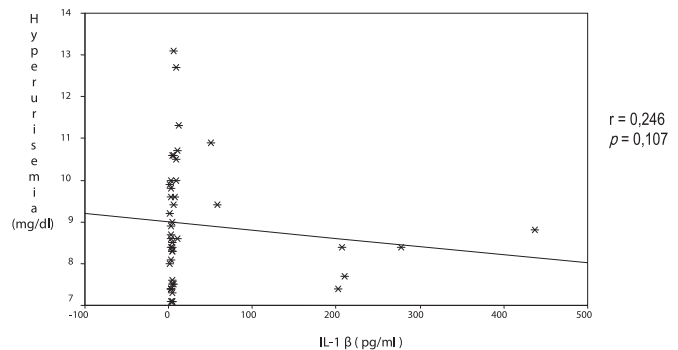


Figure 1 ROC graph of the correlation between the level of hyperuricemia (mg/dl) and the level of IL-1 β cytokine (pg/ml) ($n=44$). There was a weak positive correlation between them with r value = 0.246 and p value > 0.05 in Spearman correlation test.

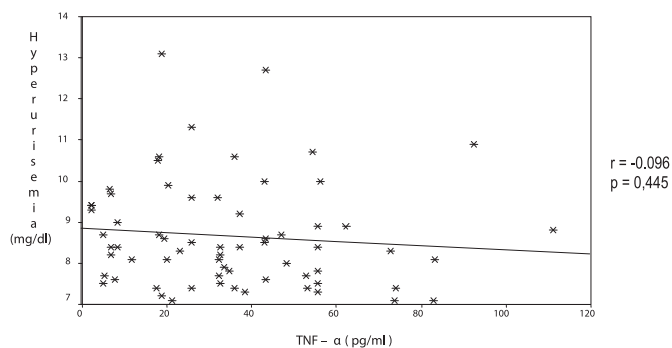


Figure 2 ROC graph of the correlation between the level of hyperuricemia (mg/dl) and the level of TNF- α cytokine (pg/ml) (n=44). It showed a negative correlation between them with r value = -0.096 and p value > 0.05 in Spearman correlation test.

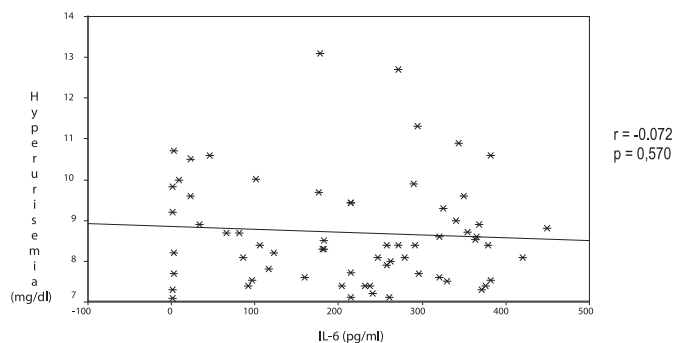


Figure 3 ROC graph of the correlation between the level of hyperuricemia (mg/dl) and the level of IL-6 cytokine (pg/ml) (n=44). It showed a weak negative correlation between them with r value = -0.072 and p value > 0.05 in Spearman correlation test.

CONCLUSION

In this study, there was a weak positive correlation but not significant between the level of hyperuricemia and the levels of IL-1 β .

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Correlation between anti-cyclic citrullinated peptide antibodies and the severity of clinical manifestation, laboratory manifestation, and radiological joint destruction in rheumatoid arthritis patients

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ABSTRACT

Background. The second generation anti-cyclic citrullinated peptide test (CCP2) displays sensitivity comparable to that of rheumatoid factor (RF) (approximately 80%) but with superior specificity (98%). Several observations have indicated that early rheumatoid arthritis (RA) patients with positive anti-CCP may develop a more erosive disease than those without anti-CCP.

Objective. The purpose of this cross-sectional study was to investigate the correlation between anti-CCP antibodies and clinical and laboratory parameters and radiological joint destruction in RA patients.

Methods. We studied 31 patients with RA fulfilling the 1987 revised criteria of American College of Rheumatology in Rheumatology Clinic of Saiful Anwar General Hospital, Malang, Indonesia. Clinical parameters were collected such as age, sex, visual analog scale, disease duration and diseases activity score (DAS28-3(CRP)). Laboratory parameters were WBC, hemoglobin, platelet count, erythrocyte sedimentation rate, and C-reactive protein. Analyzed autoantibody profiles were RF and anti-CCP (ELISA metode). Radiological joint destruction was evaluated from bilateral postero-anterior manus x ray (Sharp score).

Results. Anti-CCP antibodies were detected in 48.4% of RA patients with mean antibody concentration was 291.24 ± 143.67 (range 16-523.8) units. Anti CCP level was significantly correlated with duration of RA (month) ($p=0.04$, $r=0.371$), RF level ($p=0.002$, $r=0.542$) and Sharp score ($p=0.048$, $r=0.358$), but was not significantly correlated with other clinical and laboratory parameters.
Conclusion. Anti-CCP level was correlated with duration of disease, RF, and Sharp score.

with mild disease. To identify the right patient for the right treatment, good predictor is needed.⁵⁻¹⁰

Antibodies against cyclic citrullinated peptide (anti-CCP) are a new and highly specific marker for RA.²⁻⁴ Anti-CCP antibodies are now considered as an important serological marker for the diagnosis of RA and as a possible prognostic marker for the development of erosive disease.^{8,9}

We investigated the correlation between anti-CCP antibodies and the severity of clinical manifestation, laboratory manifestation, and radiological joint destruction in RA patients in a cross sectional study.

METHODS

We included 31 patients with RA fulfilling the ACR criteria for diagnosis.¹¹ All of the patients are the outpatients of Rheumatology Clinic of Dr. Saiful Anwar General Hospital between April 2007 and Desember 2008 who had given their written informed consent.

Clinical evaluation of disease was based on sex, age, duration of disease, duration of DMARD (methotexrate) therapy, BMI, tender joint count, swollen joint count, visual analog scale. Disease activity was assessed by the 28 joint disease activity score (DAS28-3(CRP)).¹²

The patients had venous blood taken for full blood counts, erythrocyte sedimentation rates (ESR), renal and liver function, and C-reactive protein (CRP). Serum antibodies against cyclic citrullinated peptide were analysed using enzyme linked immunoadsorbent assay (ELISA). The result was expressed in units. The samples were considered positive if the antibody titer was greater than 20 U/ml. The Ig-M RF was examined with ELISA and the result greater than 8 IU/ml was regarded as RF positive.

Standardized postero-anterior radiographs of right and left hands were performed and radiographic damage was scored by one rheumatologist who had no information about the clinical and laboratory data of each patient using Sharp modified score.¹³ In each case, 14 joints were scored for joint erosion and 13 joints were

Rheumatoid Arthritis (RA) is a systemic autoimmune disease affecting about 0.5 - 1% of the adult population. The disease is characterized by joint inflammation that can lead to progressive joint damage and affect the quality of life.¹⁻⁴

The course of RA is varied, ranging from mild to progressive forms. Availability of better prognostic markers would make it possible to select predictably severe cases for aggressive therapy at an early stage, while at the same time avoiding unnecessary exposure to the patients

scored for joint space narrowing. Each joint was scored from 0 to 3 for joint erosion and from 0-4 for joint space narrowing. The evaluated joints for joint erosion were interphalangeal (IP) I, proximal interphalangeal (PIP) II, PIP III, PIP IV, PIP V, metacarpophalangeal (MCP) I, MCP II, MCP III, MCP IV, MCP V, proximal of metacarpal I, distal of radius, distal of ulna, and multangulum, naviculare, lunatum, triquetrum as one joint evaluation. The evaluated joints for joint space narrowing were IP I, PIP II, PIP III, PIP IV, PIP V, MCP I, MCP II, MCP III, MCP IV, MCP V, proximal of metacarpal III/IV/V, multangulum/naviculare, lunatum-triquetrum, capitatum-naviculare-lunatum, and radiocarpal. Sharp score is the total sum of grading from joint erosion and joint space narrowing.

Spearman's correlation coefficient expressed the correlations between the assessed variables. Statistical significant was defined as p value of less than 0.05. All analyses were performed using SPSS program version 17 for windows.

RESULT

Patients characteristic

Rheumatoid arthritis patients in this study as many as 90.32% were female. Female to male ratio was 9:1 and the mean age was 51.2 years. The mean disease activity of RA base on disease activity score (DAS28-3(CRP)) was 3.18. Rheumatoid arthritis patients showing high disease activity was less than ones showing low disease activity (table 1).

Table 1 Patients characteristic

Patients characteristic	n=31
Female (%)	90,32
Age (year) (mean±SD)	51,19±12,03(20-70)
Duration of disease (month) (mean±SD)	56,35±102,64(1-444)
Duration of DMARD therapy (month) (mean±SD)	20,58±16,03(0-60)
BMI (kg/m ²) (mean±SD)	21,99±4,02(14,7-32,9)
Tender joint count (TJC) (mean±SD)	7,84±9,64(0-28)
Swollen joint count (SJC) (mean±SD)	4,87±5,65(0-24)
High disease activity (DAS>3,2) (%)	41,90
Low disease activity (DAS≤3,2) (%)	58,10
Ethnic Java (%)	

Hand joint arthritis, symmetric joint involvement, and morning stiffness were the main signs and symptoms of RA that had made patients looked for treatment (table 2).

Table 2 Clinical signs and symptoms in accordance with the 1987 revised criteria of American College of Rheumatology

Classification criteria	n	Proportion
Morning stiffness	27	87.10%
Hand joint arthritis	29	93.50%
Symmetric joint involvement	28	90.30%
Arthritis ≥ joints simultaneously	13	41.90%
Rheumatoid nodule	0	0%
Rheumatoid factor	18	58.10%
Radiographic changes consistent with rheumatoid arthritis	29	93.50%

Correlation between anti-cyclic citrullinated peptide antibody level and clinical manifestation, laboratory manifestation, and radiological joint destruction in rheumatoid arthritis patients

Using spearman's correlation test, Anti CCP level was significantly correlated with duration of RA (month), RF level, the number of joint erosion, and Sharp score (table 3, figure 1).

Table 3 Correlation between anti-CCP level and clinical, laboratory, and radiological damage

Variables	Correlation*	
	p	r
Age	0.848	0.036
BMI (kg/m ²)	0.582	0.103
Duration of RA (month)	0.04	0.371
Duration of therapy	0.268	0.205
Morning stiffnes	0.871	0.031
VAS (mean)	0.906	0.022
DAS (mean)	0.818	0.043
ESR(mm/1 st hour)	0.190	0.242
CRP (mg/L)	0.861	0.033
RF (Unit)	0.002	0.542
JSE (0-78)	0.006	0.481
JSN (0-112)	0.236	0.219
Sharp score(0-190)	0.048	0.358

*Spearman's correlation test; TJC: tender joint count; SJC: swollen joint count; VAS: visual analogue scale; DAS: disease activity score; JE: joint erosion; JSN: joint space narrowing.

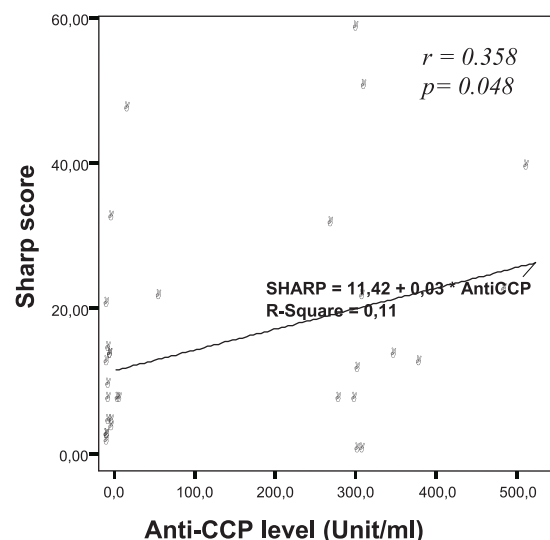


Figure 1 Correlation between serum anti-CCP level and Sharp score in rheumatoid arthritis patient

DISCUSSION

Female to male ratio in this study is higher than the known sex ratio (3:1).¹⁴ Studies in Indonesia (6:1),¹⁵ Malaysia (8:1),¹⁶ Japan (12:1)¹⁷ showed a similar sex ratio. The studies in population of established RA patients may involved in the high sex ratio as showed in these study.

The mean age of patients in this study was 51.2 years with the mean age of onset was 46.6 years. This is consistent that the most RA often occurs in the fourth and fifth decade, 80% of patients got RA at the age of 35-50 years.¹⁴

In this study, anti-CCP antibodies and inflammation (CRP) were correlated with the degree of joint damage assessed by Sharp score, but anti-CCP antibodies were not correlated with the degree of inflammation and clinical manifestations. These finding led to assumption that anti-CCP causes joint damage not through the mechanism of inflammation. A prospective study by Lindqvist et al in 183 early-stage of RA patients, showed the role of anti-CCP, IgA, RF, anti-IL1, ESR, CRP, and cartilage oligomeric matrix protein in predicting damage to the hand and foot joints.⁹ However, Serdaroglu et al showed that there was no significant difference or correlation in DAS, VAS, ESR, CRP, duration of disease, radiological damage of hands between the anti-CCP positive and anti-CCP negative RA groups.¹⁸

The important strategy to prevent joint damage in RA is to start therapy early in the disease course.¹⁹⁻²¹ However, disease severity varies widely, and it is difficult to predict the course of the disease in each RA patient. Rheumatoid arthritis can be stable for a long time in some patients. The ability for early diagnosis and to predict a severe disease outcomes in patients with RA becomes very important. Therefore, sensitive and specific serological tests are needed to predict the development of erosive damage.²²⁻²⁴

Most of the study proved that a positive RF is an important predictor for joint damage over the years of disease. For the long term, RF positivity is associated with an unfavourable prognosis.²⁰ It appears that anti-CCP antibodies have prognostic relevance similar to RF.^{2,8,25-30} Vencovsky et al found that anti-CCP positivity was better than RF at predicting progression of Larsen score over two years.³¹ Also, in a prospective cohort study of 242 patients with early RA followed up for three years, the anti-CCP antibody results correlated with RF, but were better than RF as predictor of a more aggressive disease

course. Kroot et al in a study of patients with early rheumatoid arthritis, found that anti-CCP positive patients at follow up had developed more significant radiological damage than patients without this antibody.³²

We found in this study, the duration of DMARD therapy was not correlated with levels of anti-CCP antibodies. Some studies evaluate the correlation of anti-CCP positivity and anti-CCP levels with therapeutic response. They were generally performed on patients who have been diagnosed with RA who received DMARD therapy, particularly methotrexate and anti-TNF drugs, and showed a low correlation between the therapies and anti-CCP level and some indicators of disease activity as well.^{33,34} In the largest study of this type, Ronnelid and colleagues followed 379 patients with RA under treatment for a total of 5 years. Anti-CCP positivity was reversed in only 3.9% of patients. There was a small but significant decrease in the mean anti-CCP level during the first year of treatment, and this decrease correlated with sulfasalazine treatment but not with other treatment agents. During the subsequent years of follow-up there was no significant change in anti-CCP levels, and no correlation between treatment response, disease activity, and anti-CCP levels.³⁵

Our study limitation were using cross sectional study, uncontrolled duration of disease as confounding variable and less number of samples. Further investigations using cohort study, controlling duration of disease as confounding variable and involving more number of samples are necessary to show the prognostic value of anti-CCP.

CONCLUSION

Anti-CCP level was correlated with duration of disease, RF and Sharp score.

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Profile of osteophyte location in different grades of functional status in patients with knee osteoarthritis

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ABSTRACT

Background. Osteophyte is a reparative response to cartilage breakdown in osteoarthritis (OA) and osteophyte formation is a knee stabilizing factor. Disability could be found in patients with knee OA.

Objective. To identify the profile of osteophyte formation (location, size, and direction) based on knee radiograph and functional status examination in knee OA patients who presented to the Rheumatology Clinic, Cipto Mangunkusumo Central National General Hospital.

Methods. Samples were taken by consecutive approach. Knee radiographs (weight bearing anteroposterior and 30 degrees flexion skyline views) and functional status examinations were performed on 100 patients with knee OA (90 females and 10 males with ages ranging from 51 to 74 years old). A radiologist assessed films for osteophyte profile such as location, size, and direction according to standard atlas. One knee with the severe radiological assessment based on OA grade was selected from one patient to be the profile. Lequesne Algofunctional Index was also taken from the patients. **Results.** The site of osteophyte in patients with knee OA was mostly found at lateral femur (85/100 subjects). Based on specific location, grade 2 osteophyte at lateral femur was the most frequent size (49/100 subjects) and osteophyte extending toward the lower middle at lateral patella (65/100 subjects) was the most frequent direction of osteophyte. The most frequent profile for size and direction of osteophyte at specific location was the grade 2 osteophyte extending toward the lower middle at lateral patella (35/100 subjects). Severe functional status impairment was found in 53% of the patients. The most frequent functional status found according to specific location of osteophyte was severe functional status impairment in patients with osteophyte at lateral femur (46/100 subjects). The most frequent functional status of OA patients based on the size and direction of osteophyte at specific location was the severe functional impairment in the patients with grade 2 osteophyte at lateral femur (27/100 subjects) and the patients with osteophyte extending towards the lower middle at lateral patella (37/100 subjects) respectively.

Conclusions. Osteophyte at lateral femur, osteophyte at lateral tibiofemoral compartment, grade 2 osteophyte at lateral femur, and osteophyte extending toward the lower middle at lateral patella were the profiles of osteophyte which mostly showed severe functional status impairment in patients with knee OA.

were admitted to the Clinic of Rheumatology, Cipto Mangunkusumo Central National General Hospital suffered from one variation of OA in which knee OA is the most frequent variation. According to the degeneration theory of OA, OA will induce various enzymatic reactions producing proteolytic or collagenolytic enzymes by the chondrocyte. These enzymes will destroy cartilage matrix and this injury will induce subchondral bone reparative response through osteophyte formation. Along with this pathogenesis, inflammation process is also involved and the potential damage is caused by the release of destructive cytokines such as interleukin-1 and tumor necrosis factor α . Incompatibility between these destructive cytokines and modulator or anabolic growth factor cytokines further stimulates cartilage breakdown. This destructive inflammatory process will also induce reparative response by circulating bone growth factors, which are transforming growth factor- β and bone morphogenic protein-2, throughout osteophyte configuration.¹

Patients with knee OA usually complain of knee pain and the discovery of osteophyte at the knee joint compartment showing significant correlation between early diagnosis of OA and knee pain. Therefore, finding osteophyte at specific knee compartment could be an important predictor and a reliable sign of knee pain.^{2,3,4,5} Furthermore, limitation of movement or immobilization caused by knee pain would inhibit osteophyte formation whereas osteophyte was needed to stabilize the knee joint. Radiological figures of OA at tibiofemoral joint (TFJ) or patellofemoral joint (PFJ) are associated with osteophytosis at the same compartment.^{5,6} Thus, finding osteophyte could become an efficient indicator to confirm diagnosis of OA at specific compartment.^{7,8} Patients with radiographs of knee OA, even without definite symptoms, proved having lower quadriceps muscle strength. This source of muscle weakness could cause disability in patients with knee OA.⁹ Accordingly, osteophyte could turn out to be an important indicator of determining functional disorder of knee OA.

The knee joint has three major compartments: lateral TFJ, medial TFJ, and PFJ. These compartments are further divided into 8 locations:

Osteoarthritis (OA) is the most prevalent form of synovial arthritis. Around 56.7% of patients who

lateral femur, medial femur, medial tibia, lateral patella, medial patella, lateral femoral trochlea, and medial femoral trochlea. Cartilage breakdown as well as osteophyte development as a reparative response might occur at each of these locations.⁴ Heterogeneity of structural changes, grade of disease, and functional status of patients with knee OA could be assessed by identification of osteophyte formation at specific location. This study is about exploring the profile of osteophyte location through radiograph examination in different grades of functional status by using Lequesne Algofunctional Index assessment in patients with knee OA.

METHODS

Subjects

The population of this study consisted of patients with knee OA who presented to the Clinic of Internal Medicine, Cipto Mangunkusumo Central National General Hospital and samples were taken consecutively from patients who fulfilled the inclusion criteria: had been clinically and radiologically diagnosed with ACR criteria; had not taken any analgesics, nonsteroid anti inflammation drugs, or traditional rheumatic medicines since 1 day before sample collection; had never been injected with intra articular hialuronan or intra articular corticosteroids since 3 months before sample collection; had no history of knee trauma or surgery; had no congenital or acquired knee deformity; had no lower extremity weakness; had no acute inflammation of the knee; and was willing to be involved based on the informed consent.

Data collections

Knee radiographs (weight bearing anteroposterior and 30 degrees flexion skyline views) and functional status examinations were performed on 100 patients with knee OA who fulfilled the inclusion criteria. A radiologist who was assigned by the Department of Radiology assessed films for osteophyte profile such as location, size, and direction according to standard atlas. One knee with the severe radiological assessment based on OA grade was selected from one patient to be the profile. Lequesne Algofunctional Index was also taken from these patients.

Statistics

The design of this study was cross sectional approach. The sample calculation was based on the profile of osteophyte location and functional status which can give the maximum subjects. The location of osteophyte that can give the maximum amount was the medial femur (48.5% rounded to 50%). The functional status that can give the maximum amount was severe functional impairment (47.2% rounded to 50%). Therefore, this study needed 96 subjects, rounded to 100 subjects.

RESULTS

Characteristics of subjects

There were 100 patients with knee OA, 10 males and 90 females. Details are in table 1.

Table 1 Characteristic of the subjects (n=100)

Characteristic	Frequency
Sex	
Male	10
Female	90
Age	
51-62 years old	57
63-74 years old	43
Body mass index	
<23	22
≥23	78
Severity of osteoarthritis based on Kellgren Lawrence Score	
II	50
III	44
IV	6

Profile of osteophyte location

Osteophyte size at specific location

Osteophyte was commonly found at lateral femur (85/100 subjects). Grade 1 osteophyte at lateral femur (34/100 subjects) and grade 1 osteophyte at medial tibia (34/100 subjects), grade 2 osteophyte at lateral femur (49/100 subjects), and grade 3 osteophyte at medial femur (9/100 persons) were the most frequent specific size of osteophyte at specific location. Details are in table 2.

Table 2 Profile of osteophyte size at specific location (n = 100)

Osteophyte location	Grade of osteophyte			Total
	1	2	3	
Lateral femur	34	49	2	85
Medial femur	25	31	9	65
Lateral tibia	38	34	7	79
Medial tibia	34	30	2	66
Lateral patella	28	40	5	73
Medial patella	5	10	2	17
Lateral femoral trochlea	4	5	1	10
Medial femoral trochlea	23	18	6	47

Osteophyte direction at specific location

Osteophyte extending upward was found at lateral tibia or lateral femoral trochlea in only 1/100 subjects. Osteophyte extending toward the upper middle at lateral tibia (35/100 subjects), osteophyte extending outward at lateral femur (51/100 subjects), osteophyte extending toward the lower middle at lateral patella (65/100 subjects), and osteophyte extending downward at lateral patella (8/100 subjects) were the most frequent specific osteophyte direction at specific location. Further data of osteophyte direction is shown in figure 2.

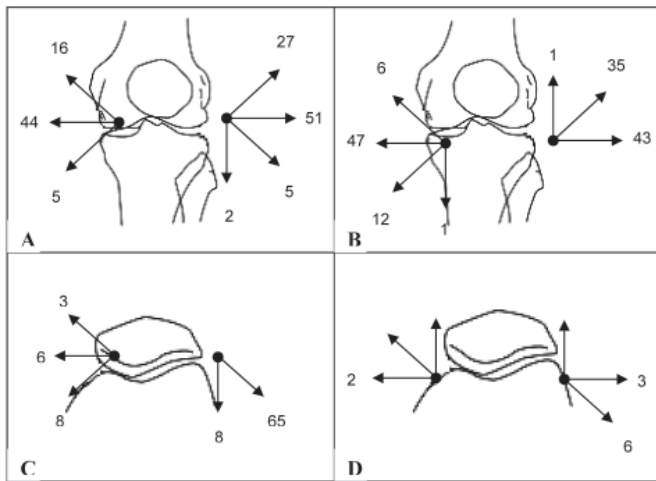


Figure 2 Profile of osteophyte direction among 100 subjects. Size of arrow reflects frequency of direction at each location. A. Femur. B. Tibia. C. Patella. D. Femoral trochlea.

Osteophyte size and direction at specific location

Grade 2 osteophyte extending outward at lateral femur (28/100 subjects) and grade 2 osteophyte extending outward at medial femur (23/100 subjects) are the most frequent osteophyte size and direction found at femur. Grade 1 osteophyte extending outward at lateral tibia (24/100 subjects) and medial tibia (24/100 subjects) are the most frequent osteophyte size and direction found at tibia. Grade 2 osteophyte extending toward the lower middle at lateral patella (35/100 subjects) and grade 2 osteophyte extending outward at medial patella (5/100 subjects) are the most frequent osteophyte size and direction found at patella. Grade 1 and grade 2 osteophytes (3/100 subjects each) extending toward the lower middle at lateral femoral trochlea and and grade 1 osteophyte extending outward at medial femoral trochlea (16/100 subjects) are the most frequent osteophyte size and direction found at femoral trochlea.

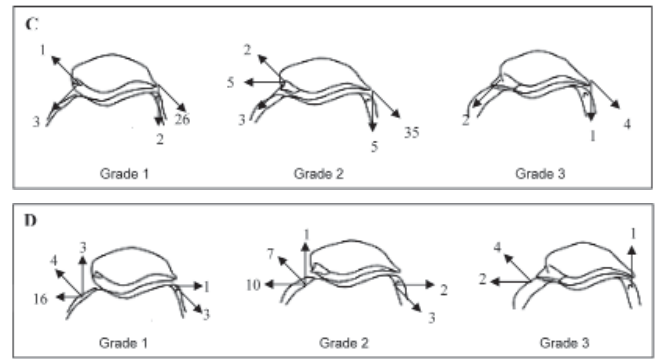
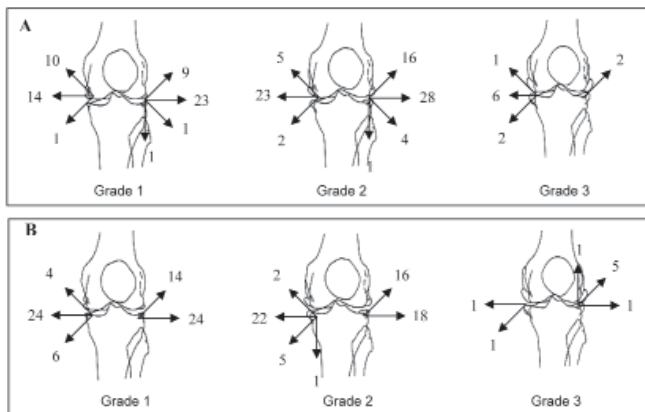


Figure 3 Frequency of osteophyte size and direction. A. Femur. B. Tibia. C. Patella. D. Femoral trochlea.

Profile of functional status

Patients with knee OA commonly suffered from severe functional status impairment (53%). Most male patients had moderate functional status impairment (8/10 subjects) whereas more females suffered from severe impairment (51/90 subjects).

Functional status based on specific osteophyte location

Severe functional status impairment in patients with osteophyte at lateral femur (46/100 subjects) was the most frequent functional status according to specific osteophyte location. Profile of functional status based on specific osteophyte location is shown in table 3.

Table 3 Profile of functional status based on osteophyte location (n = 100)

Osteophyte Location	Functional Status	
	Moderate	Severe
Lateral femur	39	46
Medial femur	30	35
Lateral tibia	35	44
Medial tibia	30	36
Lateral patella	32	41
Medial patella	10	7
Lateral femoral trochlea	4	6
Medial femoral trochlea	20	27

Functional status based on osteophyte size at specific location

Moderate functional status impairment was mostly found in patients with grade 2 osteophyte at lateral femur (22/100 subjects). Severe functional status impairment was mostly found also in patients with grade 2 osteophyte at lateral femur (27/100 subjects). Table 4 shows functional status based on the grade of osteophyte at specific location.

Table 4 Profile of functional status based on osteophyte size at specific location (n = 100)

Osteophyte size at specific location	Functional status	
	Moderate	Severe
Lateral femur		
Grade 1	16	18
2	22	27
3	1	1
Medial femur		
Grade 1	12	13
2	17	14
3	1	8
Lateral tibia		
Grade 1	18	20
2	15	19
3	2	5
Medial tibia		
Grade 1	15	19
2	15	15
3		2
Lateral patella		
Grade 1	15	13
2	15	25
3	2	3
Medial patella		
Grade 1	4	1
2	6	4
3		2
Lateral femoral trochlea		
Grade 1	1	3
2	2	3
3	1	
Medial femoral trochlea		
Grade 1	11	12
2	7	11
3	2	3

Functional status based on osteophyte direction at specific location

As shown in Table 5, moderate functional status impairment was mostly found in patients with osteophyte extending toward the lower middle at lateral patella (28/ 100 subjects), whereas severe functional status impairment was mostly found also in patients with same profile of osteophyte (37/100 subjects).

Table 5. Profile of functional status based on osteophyte direction at specific location (n = 100)

Osteophyte direction at specific location	Functional status	
	Moderate	Severe
Lateral femur		
Upper middle	10	17
Outward	27	24
Lower middle	2	3
Downward		2
Medial femur		
Upper middle	5	11
Outward	22	22
Lower middle	3	2
Lateral tibia		
Upward	1	
Upper middle	18	17
Outward	16	27
Medial tibia		
Upper middle	2	4
Outward	20	27

Lower middle	8	4
Downward		1
Lateral patella		
Lower middle	28	37
Downward	4	4
Medial patella		
Upper middle	3	
Outward	4	2
Lower middle	4	4
Lateral femoral trochlea		
Upward	1	
Outward	1	2
Lower middle	2	4
Medial femoral trochlea		
Upward	3	1
Upper middle	7	8
Outward	10	18

DISCUSSION

Osteophytes are reparative and remodelling response of OA. Osteophytes typically arise as a revitalization or reparative response by the remaining cartilage, but they may also develop from periosteal or synovial tissue. Osteophytes can be formed through the process of endochondral ossification in one or two ways. The first one involves vascular penetration into existing cartilage or also can be formed from the foci of cartilaginous metaplasia at joint margins.^{4,10,11} Osteophyte formation is related to the increase of bone density and the influence of circulating bone growth factor and others such as insulin-like growth factor type-1, platelet-derived growth factor, fibroblast growth factor, transforming growth factor β , colony stimulating factor type-1, and bone morphogenic protein-2. Transforming growth factor β enhances production of extracellular pyrophosphate by chondrocytes through release of ATP whereas chondrocalcinosis in production of calcium pyrophosphate crystals had been confirmed to be associated with osteophyte formation and hypertrophic OA.^{4,7, 12-14}

Joint instability is a biomechanical trigger of osteophyte formation; subsequently, osteophyte and bone remodelling is an effort to stabilize and widen the joint surface thus someone is capable of standing up under biomechanical weight pressure. Osteophytes develop in areas of a degenerating joint with lower stress so that it may be found at peripheral or marginal although they may appear at other articular location as well.^{4,10} Osteophyte is frequently a sign of OA development. Osteoarthritis at specific joint compartment is diagnosed by finding osteophyte while grade of severity and disease progression are identified with assessment of joint space narrowing.^{4,15} Radiological changes of knee OA were caused by the severity of joint damage at specific location as proven by Cicuttini et al. They discovered that there was a significant correlation between volumes of cartilage breakdown at femoral and tibial sites and radiological changes of knee OA at those sites.¹⁶ In their trial on animal model, van Osch et al had concluded that cartilage breakdown would induce osteophyte formation in which the location of the osteophyte and the damage were correlated. This correlation is a compartment revitalization effort of osteoarthritic process.¹⁷ The prevalence of osteophyte at specific compartment increased along with

the narrowing of the joint space.⁴ Neame et al came to the same conclusion regarding the significant association between osteophytosis and joint space narrowing.⁵

According to the theory, medial TFJ is a mechanically unstable knee compartment and gets the largest over pressure during activity so that this compartment dominantly suffers from cartilage breakdown of knee OA. Osteophytosis is more dominant at the contra lateral compartment (lateral TFJ) to stabilize the knee joint.^{10,11} This study found that lateral femur was the most common location of osteophytes in patients with knee OA. Nagaosa et al reported that in over 204 patients with knee OA, lateral tibia was the most common site of osteophyte.⁴ Even though the results were different, Nagaosa et al confirmed the same results that lateral TFJ was the most frequent site of osteophyte.

The location and size of osteophyte are related to joint space narrowing and knee malalignment.^{4,15} Van Osch et al also found that the size of osteophyte was associated with the severity of cartilage damage of knee OA.¹⁷ McCauley et al reported that marginal and central osteophyte were associated with progression of cartilage breakdown of knee OA.¹⁸ Marginal osteophyte seemed to be larger if the joint space was obliterated than if just narrowed.⁴ Kobayashi reported in his prospective study that there was an annual increase in osteophyte length evaluated in a seven-year study and this increase is significantly correlated with femorotibial angle changes that caused deformity of knee OA.¹⁹

Grade 2 osteophyte at lateral femur was the most common size of osteophyte according to specific location found in this study. Nagaosa et al found that grade 1 osteophyte, without specifically informing the location of osteophytes, as the most common size.⁴ Even those results were different, specific size of osteophyte such as grade 1 and 2 at specific location could influence the severity grade of knee OA.

The direction of osteophyte development was influenced by how far at specific direction it should grow to widen the surface of the knee joint, to stabilize the knee joint, to protect against fracture and the restraints of adjacent fibrous structure as well.⁴ This study found that osteophyte extending toward the lower middle at lateral patella was the most common direction of osteophyte among patients with knee OA. Nagaosa et al reported that osteophyte extending outward at medial tibia was the most frequent direction of osteophyte at specific location in his study.⁴

A 6 year prospective study of Miyazaki et al confirmed that dynamic loading of activity of the knee in patients with medial TFJ OA caused more severe progression of the disease at the same compartment. Disease progression is identified by assessing radiological changes such as joint space narrowing, osteophytosis, and the presence of deformity.²⁰ The importance of specifically identified radiological changes of knee OA was also supported by the study of Slemenda et al. They found that there were quadriceps muscle weaknesses in female patients who were radiologically diagnosed with TFJ OA although they had not yet complained of knee pain or suffered from muscle atrophy.²¹ As reported by Hurley et al, cartilage breakdown of knee OA could cause quadriceps sensory- motor function disorder and decreased postural stability which are related to decreased functional performance.²² O' Reilly et al also

had the same conclusion that quadriceps muscle weakness is associated with knee pain and disability of knee OA.²³ Knee joint damage and chronic pain of OA cause muscle atrophy, decreased mobility, and worsened instability that ends in physical disability. Accordingly, OA is responsible of causing disability among the elderly. This disability could be detected by assessing radiological changes caused by cartilage breakdown of knee OA.^{24,25}

Severe functional impairment was the most common functional status found in this study. Kertia et al reported that there was a correlation between inflammation and clinical degree of knee OA. They stated that severe functional impairment was the most common functional status of patients with knee OA so that it could be concluded that the inflammation involved could determine the functional status of patients with knee OA.²⁶

A larger study reported that compared to TFJ angle changes, osteophyte at PFJ was more strongly correlated with knee OA pain. Osteophytes at TFJ was more assumed to be an early sign of OA.² Osteophytes at the unstable joint will be induced by joint movement and inhibited by immobilization. Osteophytes are important to stabilize the knee joint; therefore, removing osteophytes in arthroplasty surgery of knee OA would increase instability.⁴

A study conducted by McAlindon et al discovered that medial TFJ OA was associated with disability of knee OA. Osteophytes are more extensive at the lateral TFJ. However, they did not specifically study the location of osteophytes.²⁷ Severe functional impairment in patients who had osteophytes at lateral femur was the most common functional status in this study. Lateral femur is part of lateral TFJ so that the presence of osteophyte at lateral femur may be an indicator of the severity of functional disorder due to disability of knee OA. This study found that grade 2 osteophyte at lateral femur was the most common profile among patients with knee OA who had severe functional impairment. Larger osteophytes might not influence the more severe functional status but specific osteophyte size at specific location might influence the severity of disease and functional status among patients with knee OA.

Pottenger et al reported that after having gotten osteophyte removal surgeries, 20 patients of knee OA with varus-valgus deformity suffered an even worse knee instability.²⁸ In this case, osteophyte at specific location tended to grow laterally to widen the surface of the knee joint. Osteophytes could go vertically to stabilize the joint in order to reduce excessive valgus motion. Larger osteophytes predominantly extend upwards or downwards whereas the anatomical limitation of small osteophytes to grow laterally will be limited by the restraints of adjacent fibrous structure. The development of osteophytes at specific compartment of the knee joint depends on the need to widen and strengthen the osteophyte base to protect against fracture.⁴

Despite the absence of information about osteophyte direction, McAlindon et al reported that the prevalence of PFJ OA was significantly associated with knee pain and disability.²⁷ Cartilage breakdown at PFJ compartment is usually more frequently found at lateral site whereas osteophytosis is more extensive at the contra lateral site.^{10,11}

This study found that osteophyte extending to lower middle direction at lateral patella was the most common characteristic among patients with knee OA who had severe functional impairment. Here we see that at lateral patella, osteophyte direction (not the size of osteophyte) gave more cases of knee OA with severe functional impairment. Until now there has not yet been a study about the profile of osteophyte direction in different grades of functional status of knee OA patients. Even a study on the association between osteophyte direction and grade of knee OA disease and/or disability causing functional impairment has never been conducted. The direction of osteophyte at this site could become an indicator of severe functional disorder in knee OA patients.

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CONCLUSIONS

Osteophyte at the lateral femur, at the lateral tibiofemoral compartment, grade 2 osteophyte at lateral femur, and osteophyte extending toward the lower middle at lateral patella were the profiles of osteophyte which mostly showed severe functional status impairment in patients with knee OA. This specification of osteophyte location, size, and direction from knee radiograph assessment could inform the severity of knee OA, functional status, and disease progression; therefore, further studies with appropriate design, method, and sample size with the utilisation of other specific diagnosis devices such as MRI and OA biologic marker to detect disease progression are required to verify this association.

Diabetes insipidus in neuropsychiatric-systemic lupus erythematosus patient

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Systemic lupus erythematosus (SLE) is an idiopathic autoimmune chronic inflammatory disease that is unique in its diversity of clinical manifestations, variability of disease's progression, and prognosis. The disease is characterized by the remission and multiple flare-ups in between the chronic phase that may affect many organ systems.¹

The prevalence of SLE in the US population is 1:1000 with a woman to man ratio of about 9-14:1. At Cipto Mangunkusumo Hospital, Jakarta in 2002, there was 1.4% cases of SLE of the total number of patients at the Rheumatology Clinic. Neuropsychiatric manifestations of SLE (NP-SLE) have a high mortality and morbidity rates. The incidence of NP-SLE ranges 18-61%. Diagnosis of NP-SLE is difficult because there is no specific laboratory examination. Accordingly, in all SLE patients with central nervous system (CNS) dysfunction, additional tests will be necessary to confirm an NP-SLE diagnosis and exclude other causes.^{1,2}

Similar to diabetes insipidus, SLE is a systemic disease which affects many organ systems, one being the endocrine system. No data has specified the occurrence rate of diabetes insipidus in SLE patients. This disease arises from a number of factors able to interfere with the mechanism of neurohypophyseal renal reflex resulting in the body's failure to convert water.³ There are three general forms of the disease, a polydipsic-polyuric syndrome caused by partial/complete vasopressin deficiency (central-diabetes-insipidus/CDI), vasopressin resistance of the kidney tubules (nephrogenic-diabetes-insipidus/NDI), and primary polydipsia. CDI occurs in about 1 in 25,000 persons.⁴

CASE ILLUSTRATION

A woman, 25 years old, was admitted to hospital with main complaint being a decline in consciousness one day before hospitalization. For 3 months she has complained of joint pains, hot-flushes and facial rash, especially when exposed to sunlight, the progressive hair loss and aphthae. Since a month ago, she has been diagnosed lupus and was given the prednisone 4 tablets t.i.d. Two days before hospitalization, she had convulsions

for about 2 minutes. Her body was stiff. While having convulsions, she lost consciousness, but came to thereafter. Since yesterday, she has not been able to communicate with people. She had never complained of headache or fever. Her weight has decreased 7 kg in 2 months. No history of previous convulsions, trauma, or abnormality during pregnancy, labor, and childbirth were noted.

Upon physical examination, her general condition indicated severe illness, delirium. Her blood pressure was 100/70 mmHg, pulse rate was 76 times/minutes, respiratory rate was 28 times/minute, and temperature was 36°C. The nutritional status was below average (body mass index was 17.4). Discoid rash was found on the face and all over the body. The conjunctiva was pale. Aphthae on buccal mucosa was found. Upon examination of the lungs, heart, and extremities no abnormality was found. Upon neurological examination: GCS 13, no sign of meningismus or other neurological abnormalities.

Upon laboratory examination, Hb 9.6 g/dL, Ht 29%, MCV 83 fl, MCH 28 fl, MCHC 34 g/dL, leukocyte 6.400/μL, platelet 272,000/μL, diff count -/-/84/14/2, reticulocyte 1.5%, anti-ribosomal P protein antibody (+), anti-dsDNA (-), Lupus-anticoagulant (-), Coomb's test (-). Hemostasis: PT 11" (control 12"), APTT 42" (control 38"), INR 0.93 (control 0.99), Fibrinogen 161 mg/dL (control 279 mg/dL), D-Dimer 1030 Ug/l. ACA IgG (+) (8.395, normal value < 2.418), ACA IgM (-). Upon CT-scanning, the head showed no bleeding, nor infarct/SOL. EEG was suspected to be abnormal in the form of asynchronous bilateral slowdown.

The problems established in this patient were SLE with neuropsychiatric manifestation with vasculitis and anemia. Methylprednisolone of 500 mg b.i.d (iv drip) was administered to this patient for three consecutive days, continued with 500 mg methylprednisolone once daily for two days. Continued with cyclophosphamide 500 mg every 2 weeks (total dose of 3 g) and prednisone 1 mg/kg BW/day. Other therapies given were CaCO₃ 500 mg b.i.d, omeprazole 20 mg, diazepam 10 mg iv (if needed), fenitoin 100 mg t.i.d, folic acid 1 mg, heparin 2 times 5000 IU SC, continued with warfarin 2 mg once daily, aspirin 1 x 80 mg.

After 13 days of the administration of cyclophosphamide, the patient began to gain consciousness. However, in the 6th day after first administration of cyclophosphamide, this patient had hemorrhagic-cystitis. In order to cope with the problem, mesna 400 mg and adequate liquid was administered to the patient.

On the 26th day of hospitalization, the patient had a hypovolemic shock as a result of polyuria. This patient's urine volume ranged between 6000-8500 cc/day with urine gravity was 1.003. It was assumed that polyuria is associated with NP-SLE. The next step was to conduct fluid deprivation test (Martin Goldberg). This test indicated no increase in the urine gravity while the patient was fasting (the urine gravity remained 1.003) (table 1).

Table 1 Water deprivation test

Hour	Blood pressure (mmHg)	Pulse rate (x/min)	Urine Volume (ml)	Urine gravity	Weight (kg)
09:00	100/60	100	(starting)	1.004	43.5
10:00	100/60	104	500	1.003	42.5
11:00	110/60	108	300	1.003	42.5
12:00	100/60	104	300	1.003	42

Serum osmolality, pre-test: 266 (N = 280-300), post-test: 274 (N = 275-295)

Management of the diabetes insipidus in this patient was the administration of Minirin® (desmopressin) spray II puff b.i.d and $\frac{3}{4}$ of the fluid discharged (negative-balance). During observation, the urine-volume was decreased while urine-gravity was increased (table 2).

Table 2 Recapitulation of UMU

Date	6/9	7/9	8/9	9/9	12/9	13/9*	14/9	15/9	16/9	17/9	18/9	19/9	20/9	21/9
Intravenous solution	6250	2250	6000	6000	8000	4000	500	2000	1850	1700	1750	1500	1250	0
Drink	1500	1500	2450	3150	3000	1500	2700	2000	1750	2500	2500	2500	2500	2200
Urine vol.	8400	8400	8100	10600	11600	6500	8000	4000	3950	3600	3100	2350	2850	1800
IWL	500	500	500	500	500	250	500	500	500	500	500	500	500	500
Fluid balance	-1150	-5150	-150	-1950		-1250	-800	-500	-500	100	650	150	450	-100
						(12 hours)								
Urine gravity			1,003		1,003		1,006	1,007	1,009	1,009	1,008	1,008		1,007

* Minirin® starts

During hospitalization, this patient also had depression with psychotic disorder with auditory hallucinations, free association, and interference of reality. Therefore, fluoxetine 20 mg once daily and trihexyphenidil 2 mg b.i.d were administered.

DISCUSSION

The diagnosis of SLE in this patient based on the American College of Rheumatology 1997 criteria, were malar rash, photosensitivity, oral ulcers, neurological dysfunction, and ANA (+) (anti-ribosomal P protein antibody (+)).¹ This was severe and life-threatening cases with seizure and reduced level of consciousness (NP-SLE). Secondary causes of CNS dysfunction such as metabolic disturbance and medicine were excluded. The presence of anti-ribosomal P antibodies

supported the diagnosis of NP-SLE, especially with psychosis/major depression.^{2,4,8}

Seizures of this patient might be caused by hypercoagulability state in which thrombosis (vasoocclusive) occurred and related to antiphospholipid-antibodies (high ACA-IgG titer). Antiphospholipid-antibodies are prothrombotic which can contribute to the development of acute vasoocclusive-thrombosis, endothelial cell proliferation, and intimal fibrosis.² In addition, careful consideration was given to the presence of vasculitis cerebral able to cause vasoocclusion because of vasculitis dermal occurred in this patient. Consideration of the presence of microthrombi and vasculitis in this patient was based on the fact that the occurrence of NP-SLE is rare in SLE patients undergoing therapy. Although the brain CT-scan did not show any irregularity, micro-infarcts had not yet been eliminated. EEG of this patient was abnormal (bilateral asynchrony slowing), but this finding was not specific for NP-SLE.²

The patient was given 500 mg b.i.d methylprednisolone drip for three consecutive days continued with and 500 mg once daily methylprednisolone drip for two days. The treatment was continued with 500 mg cyclophosphamide every 2 weeks (total doses 3 g) and prednisone 1mg/kgBW/day. The treatment of NP-SLE is empiric because there hasn't any controlled clinical-trials done for NP-SLE. Therefore, the treatment was determined on the severity of the presentation and suspected etiology as inflammations or thrombosis.^{1,2,11} Despite cyclophosphamide cannot pass the blood-brain-barrier, it is able to reduce antibody production. Thus, it could be administered to this patient, because basically, the disease arises from antibody. This patient was also treated with 2 times 5000 IU heparin SC, continued with 2 mg warfarin once daily, 80 mg aspirin once daily, and anti epileptic drug.

During medical treatment, the patient experienced hypovolemic shock as a result of polyuria (urine volume exceeded 2.5 liters/24 hours in 2 consecutive days).¹² To establish the polyuria causes, it was necessary to determine whether the diuresis had resulted from water or dissolved substances by measuring the urine specific gravity or osmolality. The urine specific gravity in this patient was 1.003. Accordingly, polyuria in this patient was pure water diuresis (urine specific gravity <1.005 or 200 mOsm.kgBW).⁵ The next step was to determine the disease by conducting fluid deprivation test according to Martin-Goldberg (indirect test) in order to measure the response of osmolality and the rate of urine flow at the time of dehydration and administration of exogenous vasopressin.^{4,5} During the test, the patient was fasting and intravenous fluid was discontinued. Vital signs, body-weight, volume and specific gravity of urine (with urinometer) were measured hourly.⁵ This test was conducted only for 3 hours because the patient's body weight decreased 3-4% (from 43.5 kg down to 42 kg). This test indicated that the urine remained diluted (no increase in the urine specific gravity) while the patient was fasting.

This test showed that the patient had a defect in converting water. To establish diabetes insipidus diagnosis, the next step would be determining the type of diabetes insipidus, whether it

is CDI or NDI by means of DDAVP (1-desamino-8-d-arginine-vasopressin)-Minirin.⁵ During the administration of Minirin, the urine volume decreased although the specific gravity did otherwise. We concluded that this patient had complete-CDI based on the patient's response to the administration of DDAVP.

CDI is a rare hypothalamus-pituitary disease due to the deficiency of arginine-vasopressin (AVP) synthesis from the hypothalamus or secretion from the neurohypophysis. The etiology of CDI is unknown in over one-third of cases classified as idiopathic-CDI. In one study, autoantibodies

to AVP secreting cells (AVPaAb) were found in 23.3% of CDI patients, which is classified as autoimmunity CDI. CDI is rarely reported in association with SLE. A case has been reported on the presence of AVPaAb in CDI patients with SLE. Interestingly, it was characterized by the presence of AVPaAb before the treatment and disappearance after intravenous cyclophosphamide and steroid therapy with restoration of normal postpituitary function.¹⁴ Other literature reported that CDI has been linked with vascular central nervous system damage, with which vascular impairment of the inferior hypophyseal artery system suggests that abnormal blood supply to the posterior pituitary gland is associated.¹⁵

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Osteoarticular tuberculosis of the right foot: a diagnostic delayed

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Extrapulmonary tuberculosis (TB) involving the musculoskeletal system occurs in approximately 1% to 3% of patients with extrapulmonary TB. Concurrent pulmonary or intrathoracic TB is present in less than 50% of cases.¹ Spine is the most frequent site of osseous tuberculous involvement. Other affected sites include the hip, knee, foot, elbow, hand, and bursal sheaths.² Tuberculosis of the foot and ankle remains an uncommon site of the infection, present in 8% to 10% of osteoarticular infection. The diagnosis of osteoarticular tuberculosis is often delayed due to a lack of familiarity with the disease.³ We describe a patient with foot pain and swelling without any respiratory symptom as initial presentation of pulmonary and osteoarticular tuberculosis.

CASE REPORT

A 60-year-old woman was admitted to Cipto Mangunkusumo Hospital with complaint of chest pain for two days. Chest pain was mainly felt when she inhaled. The pain was accompanied by cough and dyspnea. There were decreasing of appetite with 12 kg weight loss in the last 4 months, intermittent fever, and difficulty to fall asleep. The patient denied having night sweats. She had also complained of swelling and tenderness of the right foot since 2 years ago. There was no history of pulmonary tuberculosis previously. She was a smoker, 12 sticks/day, started from the age of 25 and had stopped when she was 40. On physical examination we found that she was alert with poor nutritional status, blood pressure was 120/80 mmHg, pulse rate was 104 times/minute, respiratory rate was 28 times/minute, and body temperature was 38°C. The conjunctiva was pale. On lung examination, the main respiratory sound was bronchovesicular in both of the lungs with rales in the top and basal of the lung. On extremities examination, the right foot and right ankle appeared swollen and painful upon palpation with limitation of the range of motion of ankle joint (figure 1). The clinical examination of the rest of the systems revealed no abnormality.



Figure 1 Swelling of the right foot and the right ankle joint

The results of the blood test were as follows: hemoglobin 9.0 gr/dl, WBC 18,700/ul, platelet 350,000/ul, ESR 27 mm/1st hr, triglyceride 90 mg/dl, total cholesterol 80 mg/dl, HDL 28 mg/dl, LDL 34 mg/dl, uric acid 3.5 mg/dl, creatinine 1.3 mg/dl, SGPT 19 U/L, random blood glucose 106 mg/dl, Na 123 mEq/L, K 4.7 mEq/L, Cl 93 mEq/L, CK 189 mg/dl, CKMB 11 mg/dl. Serial of 3 times electrocardiogram test showed sinus rhythm, normal axis, QRS rate 107 times/minute, and no ST change. Peripheral blood morphological examination revealed normocytic normochromic anemia. Microbiologic examination of her sputum was positive for acid-fast bacilli (AFB). The result of chest X-Ray examination was duplex lung tuberculosis (figure 2). The X-ray examination of the right foot was suggestive for chronic destructive arthritis (figure 3).

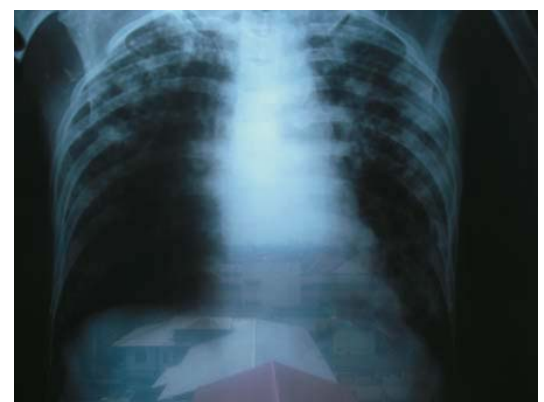


Figure 2 Plain Chest X-ray in posteroanterior view. There were bilateral fibroinfiltrates.



Figure 3 X-ray of right foot. It showed destruction of tarsal bone and proximal third, fourth, and fifth metatarsal bones, the more porous first metatarsal bone, tarsometatarsal joint space narrowing, soft tissue swelling, and calcification.

Surgery was conducted in this case for diagnostic and as well as treatment purposes (figure 4). The result of microscopic examination of pus that was obtained from debridement procedure was positive AFB. The anatomical pathology examination showed non specific chronic osteomyelitis. The patient was given the diagnosis of pulmonary and osteoarticular tuberculosis of the right foot and received the medication of the anti-TB drug of fixed dose combination (INH 300 mg/day, rifampicin 450 mg/day, ethambutol 1,5 g/day, pyrazinamide 1,5 g/day) for two months as the intensive phase. Then the medication will be continued to the maintenance phase for 9 to 12 months based on the clinical and radiographic improvement. After 3 month treatment, the foot swelling and pain are reduced and the range of motion of right ankle joint is improved.



Figure 4 Intraoperative photo showed pus and mass with dimension of 1 x 1 cm.

DISCUSSION

Clinical symptoms of osteoarticular tuberculosis may be nonspecific early in the course of infection: low-grade fever, weight loss, and night sweats being the most common. Patients with more advance disease may exhibit local pain, atrophy of affected limb due to immobilization, muscle spasms, and regional lymphadenopathy.⁴ The diagnosis of osteoarticular TB is made based on clinical and imaging findings, histopathological examinations, culture identification, and polymerase chain reaction.^{5,6,7} The mainstay of the treatment is multidrug antituberculosis chemotherapy and active or assisted non-weight bearing exercises of the involved joint throughout the period of healing. An initial period of rest is to be followed by supervised gradual mobilization. Adequate nutritional support is also essential, as in all forms of TB. Tuberculosis of the foot occurs in various forms. Granulomatous infection adjacent to a joint is the most common form. The second is a central granuloma, especially in the phalanges or the metatarsals. Up to 33% of patients have multiple metatarsals involvement.⁴ In this case report the patient had multiple metatarsals involvement. Based on plain radiography of right foot, there was involvement of tarsal and third, fourth, and fifth metatarsal bones which are destroyed. The patient had swelling and joint pain of the right foot since two years before admission. No history of diagnosed lung TB, but clinical and imaging findings at the admission time revealed active lung TB. It is similar with those reported by Huang et al. In Taiwan's tertiary teaching hospital, they found joint pain (96.1%) and swelling (90.2%) as two major presentations of arthritis TB. Twenty six (51.0%) patients had radiologic evidence of pulmonary TB.³ Plain films of involved extraaxial joints may show a normal, widened (from effusion), or narrowed joint space (in advanced disease). Periarticular osteoporosis may be severe.⁴ Plain photo in this case revealed periarticular osteoporosis where was found destruction of tarsal and proximal metatarsal bone. Diagnosis of the patient was established by the microscopic examination of pus obtained from debridement procedure that showed AFB positive. Response to the treatment of osteoarticular tuberculosis is difficult to assess. Resolution of systemic symptoms, local pain, swelling, or effusion in addition to radiographic improvement are helpful in determining duration of therapy.⁴ Interestingly, there was a delayed diagnosis in this case. Swelling, joint pain, and tenderness of the right foot had been suffered since 2 years before admission. Similar case was reported by Erdem et al, a gonitis TB that was diagnosed after 4 year evaluation with various tests.³

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Septic arthritis caused by *Salmonella* sp.

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Septic arthritis is a rare joint disorder, and can be caused by various pathogenic microorganisms, including bacteria, virus, mycobacterium, and fungus. The incidence of this infection is between 2 to 10 cases per 100,000 populations annually and can reach as high as 30 to 70 cases per 100,000 in immunodeficient population. This disorder is frequently unidentified in early phase of the disease due to its unspecific symptoms and signs.¹ This joint infection can cause numerous problems to the patient ranging from joint damage, bone erosion, osteomyelitis, fibrosis, ankylosis, sepsis, or even death.¹⁻⁵ The case-fatality rate for this disorder can reach up to 11%, comparable to the case fatality rate for other community infections such as pneumonia.^{2,6}

Salmonella sp. is a Gram-negative bacillus bacterium with main invasion predilection in intestinal villi.⁷ This microorganism rarely causes septic arthritis although several cases have been reported before. Ortiz-Neu et al. demonstrated that septic arthritis caused by *Salmonella* sp. has high relapse incidence and a tendency to turn chronic, making the treatment more difficult and challenging.⁸

CASE ILLUSTRATION

A 65 year old male came to emergency room with chief complain of having unilateral knee and ankle joint swelling since 2 days prior to admission. There was continuous pain sensation, fever, and reduced range of movement sensed by the patient. The joints were reddish on inspection and warm on palpation. There was history of nephrotic syndrome documented 2 months before, which was treated with prednisone 15 mg t.i.d. and simvastatin 10 mg q.d. There was no history of local trauma and diabetes mellitus. History of typhoid fever was denied. Laboratory examination revealed marked leucocytosis (15,300/uL), hyponatremia (129 mmol/L), hypoalbuminemia (1.5 mg/dL), while urine analysis showed proteinuria (2+), erythrocyte of 10-15/High Power Field, and no active cast were seen on microscopic examination. Random Blood Glucose was 116 mg/dL, BUN and blood creatinine level were 45 mg/dL and 0.7 mg/dL respectively. Other clinical and laboratory findings were unremarkable. Joint plain radiography showed tissue swelling and no other abnormalities were noted. There was no erosion and osteophyte, whereas narrow space and alignment were within normal limit.

Figure 1
Roentgenographic appearance of right knee and ankle joint, showed unspecific tissue swelling. There was no other abnormalities were noted.



Septic arthritis was suspected and prompt empirical antibiotic treatment using combination of ceftriaxone 2 gr q.d. and ciprofloxacin 500 mg b.i.d. were given. Paracetamol 500 mg q.i.d. was started and the joints were fixated on anatomical position. Joint puncture on knee joint were done on the first day of hospitalization, aspirated 25 cc whitish purulent fluid that indicated active joint infection. On the third day of hospitalization, joint fluid analysis result showed leucocyte level of 68,000/uL, translucent turbidity, low viscosity, poor mucinous test, negative crystal precipitate, and negative fast acid staining. Blood uric acid level was 3.7 mg/dL and leucocyte level was 19,200/uL. Analgetic drug was escalated using tramadol 50 mg t.i.d., and knee joint puncture was performed again, aspirated 45 cc whitish purulent fluid. Antibiotic regimen was still given with the same combination.

On the eighth day of hospitalization, fluid culture showed growth of *Salmonella sp.*, which was sensitive to ampicillin, coamoxiclave, amikacin, gentamicin, tetracycline, cotrimoxazole, ciprofloxacin, levofloxacin, cefazolin, cefuroxime, ceftazidime, cefotaxime, ceftriaxone, cefoperazone, imipenem, and meropenem, besides resistance to chloramphenicol. The highest sensitivity was shown by ceftriaxone, with sensitivity zone of 33 mm. Blood sample analysis for PCR test against *Salmonella* and Tubex Test (IgM anti *Salmonella*) was negative and weak positive respectively. Laboratory result for hsCRP was 108.0 mg/L (N < 10.0 mg/L) indicating active inflammation. Based on these results ceftriaxone dosage was escalated to 3 gram q.d. and ciprofloxacin injection was stopped.

On the twelfth day of hospitalization patient showed considerable clinical improvement and radiographic examination showed neither cartilage destruction nor osteomyelitis. Joint range of movement was good and leucocyte level decreased to 11,200/uL. The antibiotic was continued until the third week, and the patient was discharged using cefixime 100 mg b.i.d. and meloxicam 7.5 mg on p.r.n. basis for another 2 weeks. The result of the treatment was good.

DISCUSSION

Acute oligoarthritis accompanied with sensation of pain, fever, as well as reduced range of movement were the first symptoms complained by the patient. Infection of the joint space should always be suspected in this condition, and prompt empirical antibiotic treatment is justifiable without documented joint fluid analysis and culture results. Joint aspiration to relieve the patient's symptoms and to obtain joint fluid for analysis should be performed immediately. Any delay in carrying out these points can amplify the patient's mortality and morbidity, increasing the risk of joint damage, bone erosion, osteomyelitis, fibrosis, ankylosis, and sepsis.¹⁻⁴

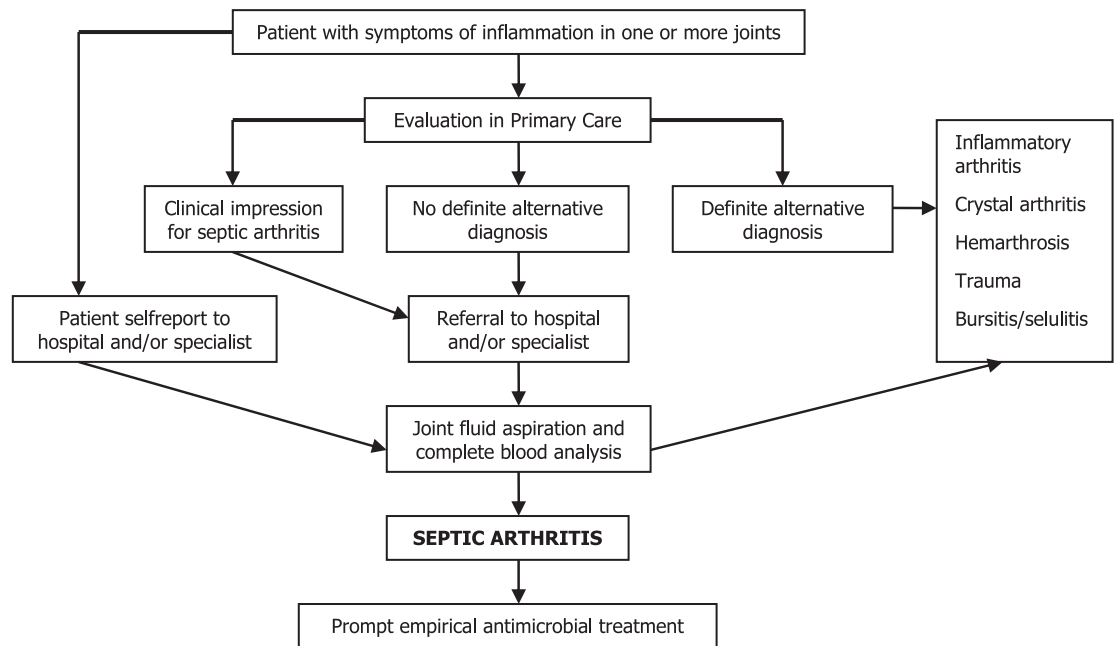
Several conditions are correlated to the increment risk for septic arthritis such as degenerative joint disease, rheumatoid arthritis, diabetes mellitus, leukemia, corticosteroid usage, hepatic cirrhosis, granulomatous disease, malignancy, immunodeficient state, older age, kidney disease, and hypogammaglobulinemia.^{4,5} *Salmonella*-related septic arthritis that was identified in the patient had apparently similar risk factor including older age, use of high dose glucocorticoid, and kidney disease. The symptoms of acute arthritis in knee and ankle joint that had developed in this patient were also comparable to conventional predilection joint for non gonococcal septic arthritis counting knee for 40-50%, hip for 20-25%, and shoulder, wrist, ankle for 10-15% respectively.^{1,4,9}

Salmonella sp. is rarely reported as the causative microorganism for septic arthritis, although several cases have been reported before.⁸ Classic symptoms of joint infection that consist of acute joint swelling and inflammation accompanied with progressive pain and fever are also observed in this *Salmonella*-related septic arthritis. Immediate joint aspiration can relieve acute symptoms of inflammation in this case and proven beneficial in identifying the causative microorganism. The analysis for joint fluid caused by *Salmonella*-related septic arthritis is similar to the results of joint infection caused by another classic microorganisms, that include whitish appearance, low viscosity, poor mucinous test, high level of leucocytes, and translucent turbidity. Leucocytosis and elevation of acute phase reactant (hsCRP) were also observed in this case.

The infection was thought to had originate from systemic transmission that underwent bacteremia and then spread to the joint, although the patient denied any history of typhoid fever before. Negative result for PCR test against *Salmonella sp.* and weak positive for Tubex Test showed previous infection of this microorganism that was presumed subclinical. This finding is parallel to general acceptance, in which majority of joint infection is caused by focal infection in another organ that has spread to the joint space through vascular bed in synovium membrane.^{1,9} Lack of limiting basement membrane in the synovium tissue reduces the ability of the joint to prevent infection spreading.

Recommendation for using broad spectrum of empirical antibiotic treatment, such as third generation cephalosporin, seems reasonable in this case. Prolonged use of intravenous antibiotic followed by oral antibiotic is needed in this case before clinical improvement is seen. This fact is parallel to the study conducted by Gupta et al, in which intravenous and oral antibiotic are given for median 15 days and 21 days respectively before improvement is observed.²

Figure 2 Algorithm for the treatment of patients with suspected joint infection (adapted from Coakley et al., 2006)⁶



CONCLUSION

Septic arthritis is a rare condition and frequently unidentified in the early phase of the disease, due to its unspecific symptoms and signs. This disorder can lead to a number of complaints from the patient, and can cause significant increment in morbidity and mortality rate. *Salmonella sp.*, a Gram-negative bacillus bacterium with its main predilection in the human intestine can cause septic arthritis through systemic bacteremia. Risk factors, clinical symptoms, and laboratory examination in *Salmonella*-related septic arthritis are similar to the findings of septic arthritis caused by other traditional microorganisms.

According to the current recommendation, joint aspiration is mandatory, proven beneficial in relieving symptoms, and used to identify the underlying microorganisms. The resistance patterns that are obtained from microorganism culture could accommodate the use of the appropriate antibiotic. Prompt empirical antimicrobial therapy with broad spectrum antibiotics that are used in most cases is acceptable in this case.

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Chronic polyarthritis mimicking rheumatoid arthritis in a patient with leprosy

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Currently leprosy is now still a global threat in the world even after the introduction of multidrug therapy (MDT), including in Indonesia.¹ World Health Organization (WHO) data revealed that in 2002 there were 597,000 cases worldwide and the prevalence is only less than 1 every 10,000 populations.² Nevertheless, the latest data showed that 83% of leprosy cases concentrated in only 6 countries: Indonesia, India, Brazil, Madagascar, Myanmar, and Nepal.³

The most common manifestations of leprosy are cutaneous and neuritic manifestation. Rheumatologic manifestation is another common manifestation of leprosy.⁴⁻⁷ Prevalence of rheumatologic manifestation of leprosy is range from 1% to 77% of all leprosy patients.⁴⁻¹¹ Study conducted by Mandal et al in India revealed that the prevalence of rheumatologic manifestation was 5.9%, in Brazil,⁶ another study by Pereira revealed the prevalence of 9.1%.⁵ Hadi, in Indonesia, showed the prevalence of arthritic manifestation was 7.5%.⁸ Rheumatologic manifestations that can be found in leprosy are polyarthritis or oligoarthritis, soft tissue rheumatism, non-inflammatory arthritis, and also enthesitis.⁴⁻⁷ We report a patient presenting with polyarthritis as the primary manifestation of leprosy.

CASE REPORT

A 28 years old male patient came to our hospital with chief complaint of joints pain. Patient had suffered joints pain at both knees, shoulders, elbows, wrists, and fingers of both hands since 8 months intermittently. Joints pain usually accompanied by swelling and morning stiffness last for about an hour. In the last 2 weeks prior to admission, joints pain was more severe so the patient had difficulty to walk. The patient also had on and off low grade fever in the last 8 months. He used to take non steroid anti inflammation drugs (NSAIDs) and the pain as well as inflammation was relieved. He also had stiffness of his ring fingers and little fingers on both sides so it was difficult to move those fingers. His father and mother had history of leprosy and already completed the medications about 20 years ago.

On admission, the patient was fully alert, blood pressure 110/70 mmHg, pulse rate 102 times/minute, respiratory rate 18 times/minute,

temperature 37.8°C. There were anemic conjunctiva, madarosis of his eyebrows, and also saddle nose. Another positive findings includes evidence of arthritis on both knees, elbows, shoulders, ankles, wrists, and also proximal interphalangeals I-V of both hands. There were clawed hands, dropped feet, and enlargement of ulnar and posterior tibial nerves of both sides, maculopapular plaques with erythema at the back, hands, and legs, and also dry skin at both palms and soles. There were also pitting edema on both feet. Abdominal examination showed mild splenomegaly (S1). Due to the clinical manifestations (symmetrical polyarthritis, hand arthritis, and morning stiffness more than 6 month) the patient was suspected suffering from rheumatoid arthritis.



Figure 1 A. The patient with madarosis of eyebrows and saddle nose; B. Clawed hand (see ring finger and little finger); C. Arthritis at proximal interphalangeal joints; D. Arthritis of right knee.

Laboratory examinations revealed Hb 8.8 g/dL normochromic normocytic, leucocyte 4,100/uL, thrombocyte count 130,000/uL, ESR 60 mm/h, CRP 1.69 mg/dL, random blood sugar 115 mg/dL, BUN 51.9 mg/dL, serum creatinine 1.26 mg/dL, AST 29 IU/L, ALT 16 IU/L, ANA 7.7 U (negative), negative RA factor, and anti CCP 8 IU/ml. Chest X-Ray was normal. Anteroposterior hands x-ray revealed soft tissue swelling and juxtaarticular osteoporosis. Abdominal ultra sonogram showed splenomegaly.



Figure 2 Anteroposterior view of both hands x-ray revealed soft tissue swelling and juxtaarticular osteoporosis

Because of our highly suspicion of leprosy, we examined patient's ear lobe plasma for the presence of acid-fast bacilli. It revealed positive result and confirmed diagnosis of multibacillary (MB) type of leprosy with type 2 leprosy reaction and we took care the patient together with dermatology department.

The patient was diagnosed with MB type of leprosy with type 2 severe leprosy reaction with chronic polyarthritis manifestation and anemia of chronic disease. He was treated with PRC transfusion, sodium diclofenac 50 mg b.i.d., methylprednisolone 24 mg once daily (with tapering off 4 mg every 2 weeks), omeprazole 20 mg b.i.d., folic acid 500 mcg/day, B1 100 mg bid, B6 200 mg b.i.d., and B12 200 mcg b.i.d. The patient was also treated with MDT consists of rifampicin 600 mg monthly, clofazimin 300 mg monthly, and dapsone 100 mg daily for 12 months. The joint pain and swelling subsided within 3 days after the treatment started, then he was discharged on the following day, with the instruction to continue the MDT treatment. The patient was followed up at outpatient department and showed remarkable improvement. There was no arthritis.

DISCUSSION

Leprosy is still a global health problem especially in Indonesia. World Health Organization classifies leprosy as paucibacillary (PB) and multibacillary (MB). Paucibacillary leprosy has less than 5 anaesthetic plaques, only 1 nerve involvement, and negative acid fast bacilli, while MB leprosy has more than 5 anaesthetic plaques, with more than 1 nerves involvement, and also positive acid fast bacilli. One of leprosy complication is leprosy reaction. The reaction can occur before, during, or after leprosy treatment. There are two types of leprosy reactions: type 1 and type 2. Pathogenesis of type 1 leprosy reaction involves the amelioration of cellular immunity in leprosy patient, while type 2 involves the amelioration of humoral immunity. Type 1 leprosy reaction is characterized by mild fever, worsen skin and neurologic manifestation with rare other organ involvement, and it can be happened both in PB and MB type. Type 2 leprosy reaction is characterized by

fever, generalized weakness, worsen skin manifestation which is sometimes accompanied by erythema nodosum leprosum (ENL). Common other organs involvement are joint, eye, testicle, renal, lymph node, and it can only occur in MB type leprosy.^{2,3,12} Our patient's diagnosis of MB leprosy was based on our findings of long-term contact with leprosy patients (his parents), fever, madarosis, saddle nose, enlargement of more than 2 nerves (ulnar and posterior tibial), clawed hands, and dropped foot that was confirmed by positive findings of acid fast bacilli on ear lobe serum examination. Diagnosis of type 2 leprosy reaction are also established by the presence of fever, weakness, arthritis (extradermal and neural manifestation) and the diagnosis of MB type leprosy.

Rheumatologic manifestation is the most prevalent manifestation of leprosy after dermatologic and neurologic manifestation.^{4,7,10-12} There were some cases reported leprosy without any dermatologic manifestation and preceded with pure rheumatologic or neuritic leprosy.^{9,13-18} Polyarthritis, oligoarthritis, soft tissue rheumatism, non-inflammatory arthritis and enthesitis can be the manifestation of leprosy in earlier stage.^{4,6,7,10,11,19} The common mechanisms of leprosy arthritis is the presence of leprosy reaction in which intra-articular immune-complex depositions and complement activations cause arthritis and also concomitant with activation of cellular immune response by recruitment of inflammatory cells to the joints structure. Several studies also revealed that the most frequent leprosy rheumatologic manifestation is oligo-/polyarthritis with remarkably resemblance with rheumatoid arthritis.^{5,9} Several researches have been conducted to know the association between leprosy and rheumatoid arthritis. It is likely that the resemblance between leprosy arthritis manifestation especially in leprosy reaction and rheumatoid arthritis is caused by the similarity in their pathogenesis, which is immune-complex deposition and complement activation due to the activation of humoral immune response and also activation T-cell (cellular immune response) leading to inflammation process in the joints.^{20,21}

The goal of leprosy reaction treatment is to suppress immune reaction that happened so we can prevent complications and disability and we still continue the leprosy medication.¹ The MDT regiments recommended by WHO can be seen on table 1.

Table 1 WHO-recommended multidrug therapy regiments for leprosy^{2,3,12}

Type of leprosy	Drug treatment		Duration of treatment (months)
	Monthly supervised	Daily, self-administered	
Paucibacillary	Rifampicin 600 mg	Dapsone 100 mg	6
Multibacillary	Rifampicin 600 mg, Clofazimine 300 mg	Clofazimine 50 mg, Dapsone 100 mg	12

Leprosy reaction can be treated with steroids, prednisone or prednisolone 40 mg per day with tapering off 5 mg every 2-4 weeks after demonstration of improvement.^{2,3,12} One randomized controlled trial study concluded that prednisolone

30 mg tapered slowly to zero over 20 weeks was superior to prednisolone 60 mg tapered over 12 weeks.¹² Thalidomide 300–400 mg daily has a dramatic effect in controlling ENL and preventing recurrences. Its use is limited because of teratogenicity (phocomelia) and possible neurotoxicity (although this does not appear to be a problem in leprosy patients).^{3,12} Clofazimine and pentoxifylline have both been used in ENL, but they are less effective than prednisolone or thalidomide.¹² Colchicine and chloroquine have also been used with limited effect.¹² Management of arthritis includes giving of NSAIDs to decrease the inflammation and pain immediately, but the main principle is to overcome the underlying process which is leprosy reaction by giving MDT and steroids.^{2,3,12} Although clinically the patient showed

the manifestation of rheumatoid arthritis, the serology was negative. After treatment with NSAIDs (sodium diclofenac), methylprednisolone, and MDT for leprosy, the arthritis subsided within 3 days and it remained as such for more than a year of follow ups. Based on the result, we concluded that the chronic symmetrical polyarthritis (mimicking rheumatoid arthritis) in the patient was related to leprosy.

SUMMARY

We have reported a 28 years old male patient with leprosy with main manifestation of polyarthritis due to type 2 leprosy reaction. After establishing the diagnosis, with proper treatment consists of steroids, NSAIDs, and MDT according to WHO recommendation, the arthritis manifestation and leprosy reaction was subsided.

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Calcinosis and myocarditis in systemic lupus erythematosus patient

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Systemic lupus erythematosus (SLE) patients have multi-organ involvement related to their chronic inflammatory, autoimmune disease. *Calcinosis* can be clinical manifestations of SLE. Tissue calcinosis is reported in approximately 17% patients and myocarditis in 20-55% patients. Thus, both manifestations are not unusual in SLE. Tachypnea, tachycardia, pericardial effusion, and wheezing are often present and can be misleading in SLE patient.^{1,2}

Calcinosis is less common in SLE, sometimes it is found as an incidental radiological finding. Calcification in SLE maybe periarticular, within joints or muscles, or in the subcutis (calcinosis universalis).¹ Calcinosis is classified into four subsets: dystrophic, metastatic, idiopathic, or calciphylaxis/iatrogenic. When calcinosis cutis is isolated to a small area in extremities and joints, it is called calcinosis circumscripta; whereas its diffuse form, refers to calcinosis universalis, affects subcutaneous and fibrous structures of muscles and tendons. The pathophysiology of this condition is unknown and no effective therapy is currently available.^{3,4,5}

Systemic lupus erythematosus can involve the myocardium, pericardium, cardiac valves, and coronary arteries. Myocarditis in SLE is not likely to produce major regional wall motion abnormalities but may contribute to global left ventricular dysfunction.^{7,8}

We report a young woman with SLE who developed calcinosis and myocarditis.

CASE ILLUSTRATION

CASE REPORT

A 23-year-old female presented with a history of severe fatigue, dyspnea, and dysphagia. Fatigue had developed over the past 3 months and had gotten worse upon exertion. She had dysphagia

from solid meals because of many oral ulcers in her mouth but she could still eat liquids. She also had chest pain associated with breath and dyspnea. She admitted a 20 kg weight loss and the occasional dizziness. She denied chronic cough with hemoptysis or bleeding per rectum. She reported oral ulcer exacerbation for the past 2 months, falling hair with alopecia for the past 10 years, chronic fatigue for the past 3 years, and also intermittent fever and amenorrhea for the past 2 months. She also complained of photosensitivity associated with ultraviolet light.

She was referred from another hospital with diagnoses of suspected pulmonary tuberculosis, anemia and fever, and lymphadenitis axillaries caused by tuberculosis in 1997.

The results of physical examination were as follows. She looked older than her stated age, emaciated and lethargic, mental state was somnolent, blood pressure was 104/60 mmHg, pulse rate was 120 times/minute, respiratory rate was 32-36 times/minute, and body temperature was 38.8°C. She had no lymphadenopathy. On head examination, there were alopecia areata (Lupus hair), pale conjunctiva, malar rash, and oral ulcer. There was no abnormality detected in ears, nose, and throat. On lung examination, the main respiratory sound was vesicular breathing in both lungs. there were rales in right and left thorax, decreased breath sounds, pleural friction rub in left thoracic, and there was no audible murmur or pericardial friction rub. The abdomen was supple on palpation, but we found the chessboard phenomenon and tenderness. The liver and spleen were not palpable and intestinal sound was normal on auscultation. On the extremities, there was vasculitis in palm and sole. There was not any arthritis or oedema.

Figure 1 A. Lupus hair and photosensitivity. B & C. Vasculitis of palm and soles



Laboratory studies disclosed the following values: haemoglobin 8.6 gr/dL, haematocrit 25%, leukocyte count was 13.200-30.300/mm³, platelet count was 170.000/mm³, erythrocyte sedimentation rate 120 / 138, blood glucose levels was 74/104mg/dL, blood urea nitrogen level was 45mg/dL, serum creatinine level was 1.7 mg/dL, Na level was 116 mEq/L, K level was 3.7 mEq/L, SGOT level was 126 U/L, SGPT level was 41 U/L. The urinalysis showed proteinuria (++) , erythrocyte (++++), leucocyte 5-11/high power field.

The first chest x-ray showed calcification but no cardiomegaly. Electrocardiogram showed sinus tachycardia with 120 times/minute. An ultrasonography of the abdomen showed mild hepatomegaly with ascites, there was no enlargement of paraaorta or parailiaca lymph nodes, bilateral pleural effusions, no abnormality in spleen, pancreas, kidney and ureter, and there was a cystitis.

She was admitted to the hospital with working diagnoses of pulmonary tuberculosis and abdominal tuberculosis, suspected SLE, and dehydration caused by low intake.

The patient was getting worst on the third day of hospitalization. The mental state become delirium, loss of consciousness, respiratory distress, arhythmias, bilateral pleural effusions, suspected pericardial effusion, and focal neurological deficit. The working diagnoses were changed into suspected hospital acquired pneumonia, pulmonary and peritonitis tuberculosis, suspected SLE, unconsciousness caused by meningitis tuberculosis with differential diagnoses of hyponatremia and neuropsychiatric lupus. She was subsequently given rehydration with normal saline and intravenous antibiotic. Afterwards the patient was consulted to rheumatologist.

The final diagnoses were established SLE with vasculitis, calcinosis and myocarditis based on the results of blood test of positive antinuclear antibody test with homogenous pattern and positive anti-double-stranded DNA (anti-ds DNA), 936.6 IU/ml (the significance was higher when the anti-ds DNA antibody level was >300 IU/ml) by ELISA method.

The patient was treated with broadspectrum antibiotics (2 gram ceftriaxone, single dose/day) and pulse dose of 1000 mg methyl prednisolone on the last day, but did not give any response. Her condition was deteriorated with infection and complication of the main organ (carditis). The patient had full arrest and was not able to be resuscitated. She died on the fifth day of hospitalization, before get the MRI, CT scan, and serial hemoculture examination, and also an adequate therapy.

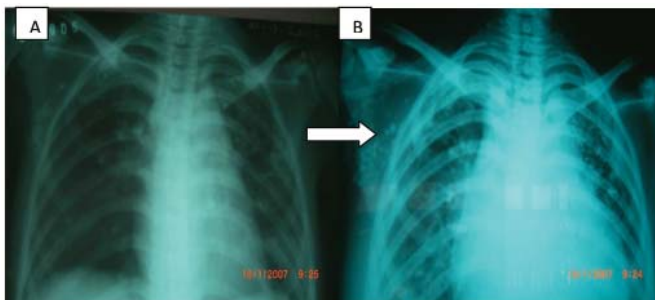


Figure 2 A. X-Ray on the first day of admission. B. X-Ray on the fourth day of admission

DISCUSSION

In this case we discussed about a young woman with SLE who developed calcinosis and myocarditis. Tissue calcinosis is reported in approximately 17% and myocarditis in 20-55% of patients with SLE. Thus, both manifestations are not unusual in SLE. Calciphylaxis and calcinosis can both cause severe morbidity and mortality in patients with SLE.^{1,2} It was hypothesized that in calciphylaxis and calcinosis, ongoing inflammatory activity contributes to the calcium deposition in the media of small arteries, as well as perivascular and periarticular tissues. The neuropsychiatric lupus with wide variety of conditions has been reported in association with SLE. Note that true cerebral vasculitis has been documented in SLE, but it is very uncommon. An example of an uncommon condition associated with SLE is severe cerebral calcinosis. Calcification in the basal ganglia has been reported in SLE at a higher incidence than in the general population, and in fewer cases, the cerebral cortex, cerebral white matter, thalamus, cerebellum, and brain stem are involved.^{3,4,5}

Cardiomegaly can be a result of SLE myocarditis, Libman-Sacks endocarditis, subacute bacterial endocarditis, uremia, pulmonary arterial hypertension with right-sided heart failure, or corticosteroid-related cardiomyopathy.^{6,7,8} Myocarditis may be clinically silent in up to 50% of patients and is an uncommon manifestation of SLE, consisting of myositis with perivascular infiltration by lymphocytes and neutrophils. Intimal proliferation within the smaller intramyocardial arteries with hyalinization has been reported. Transesophageal echocardiography helps define wall motion abnormality. The newer and faster magnetic resonance imaging in cine acquisition mode may allow noninvasive evaluation. In addition, exercise electrocardiography and myocardial scintigraphy may help define reversible ischemia, typically from accelerated atherosclerosis, that is amenable to surgery or intravascular therapy in SLE patients with symptoms of myocardial disease.^{6,7,8}

Exudative pericardial effusions and pericarditis occur in 17-50% of patients with SLE. Unless pericarditis is accompanied by effusion, echocardiography is insensitive for the diagnosis. Clinical symptoms and electrocardiographic findings may be helpful in the diagnosis of SLE pericarditis. Contrast-enhanced chest CT may reveal abnormal thickening and enhancement of the pericardium as well as a pericardial effusion.⁶⁻⁸

Patient with myocarditis may present tachypnea, tachycardia, hyperthermia or hypothermia, and hypotension. Sign of poor perfusion and heart failure such as tachycardia, weak pulses, decreased capillary refill, cool mottled extremities, jugular venous distention, lower extremity edema may also be found. Heart tones may include an S3 gallop and may be muffled if pericarditis is present. An additional sound can be found in lung examination. Although several types of dysrhythmias occur, the most common dysrhythmia is sinus tachycardia. A tachycardia faster than expected for the degree of fever (10 BPM for each degree of temperature elevation) may be indicative of myocarditis. Tamponade may result in hypotension, muffled heart tones, and distended neck vein (present in >50% of patients with tamponade). The ECG

shows tachycardia, low QRS voltages, flattened or inverted T waves with ST-T wave changes, and prolongation of the QT interval. Cardiomegaly may be found on CX-Ray.⁶⁻⁸

Autoimmune myocarditis, a chronic stage of myocardial inflammation, occurs in a small subset of patients after acute cardiotropic viral infection and can lead to dilated cardiomyopathy (DCM). The etiologies of myocarditis are multifactorial and genetically complex. Genetic linkage between susceptibility to myocarditis/DCM and the major histocompatibility complex (MHC) genes has been reported in both humans and experimentally induced mouse models. However, unlike other autoimmune diseases, the non-MHC genes seem to have greater impact than MHC genes on disease susceptibility. In humans, mutations/deletions in immunologically important genes such as CD45, and genes encoding cardiac proteins, have been reported in patients with recurrent myocarditis or DCM. Identification of genetic polymorphisms controlling autoimmune myocarditis will help us understand the mechanisms underlying autoimmune diseases in general, thereby improving potential therapies in patients.⁷

In this case, the patient had clinical characteristic for myocarditis on the last day of her life. The worsening of the disease activities with acute chest syndrome may be associated with myocarditis. The clinical characteristics of acute chest syndrome are fever (80%), cough (62%), chest pain (44%), and radiographic findings which developed in 2-5 days of hospital admission. She should have been treated for acute chest syndrome, including oxygen therapy if the patient is hypoxic, pain control to avoid splinting, fluid therapy at maintenance rates (do not overload), broad spectrum antibiotic such as cefuroxime and macrolide, bronchodilators, furosemide (no digoxin as this may increase cytokines and mortality), dopamin, dobutamine, and nitropruside, pulse dose steroid and cyclosporine, and pericardiocentesis if unstable.⁹

The leukocytosis in this case should be evaluated for many causes, infection or other causes (dehydration, steroid induced, etc). In this case, the blood culture only made on the first

admission, and the result was sterile. We should have made the serial hemocultures to found the microorganism, analysis of the sputum, cultures of the sputum, etc. The result of urinalysis (proteinuria (++) , erythrocyte (++++), leucocyte 5-11/high power field) made the suspicion of kidney involvement came into view, but more information such as measurement of 24-hours was needed. In this case we have no more data, because the patient died before the examination.

There are many limitation in this case: 1) Some laboratory findings are missing: no data for serial hemocultures, 24-hour proteinuria, and other autoantibodies (especially antiphospholipid), 2) The patient developed neurologic manifestations, but MRI or CT was not performed, and 3) We have no any information regarding post-mortem examination, because we did not do the test.

The management of SLE patients depends on the organ involvements, disease activity, and time of establishing the diagnoses. In this case, the diagnoses and the management were missed and delayed. We must be aware for early diagnose of SLE in young woman with the skin abnormalities (lupus hair, vasculitis, calcinosis, etc), and many organ involvement such as lung (pleuritic/pneumonitis), cardiac (myocarditis), kidney (nephritis), and neurologic manifestations, to avoid the delay in the adequate management. In this case, the patient should have been diagnosed earlier and therefore received adequate therapies.⁹

SUMMARY

Systemic lupus erythematosus is a complex autoimmune disease with multisystem involvement. The patients with SLE and calcinosis may increase the severity of disease and can spread to other organs and cause other diseases such as myocarditis. This condition may lead to a life threatening disease and therefore it is crucial to receive an immunosuppressant therapy as soon as possible to save their lives. We can use a set of recommendations for monitoring SLE patients in routine clinical practice. The use of a standardized core set to monitor SLE patients should facilitate clinical practice, as well as the quality control of care for SLE patients.

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