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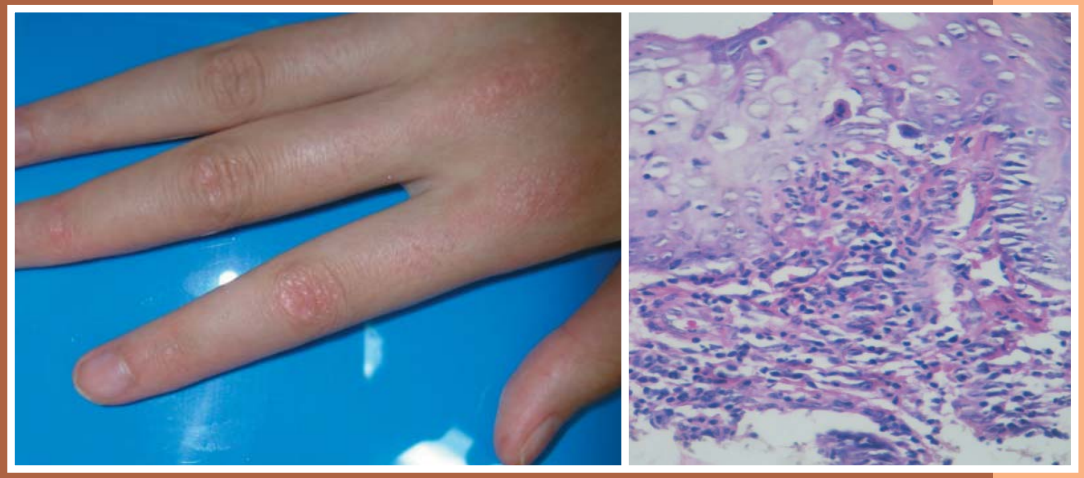

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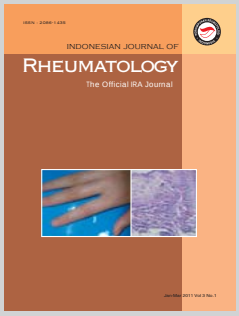

Cover image: Sclerodactyly and Gottron's papules on PIP and DIP surface (left; see page 32) and histopathological skin specimen showing liquefactive degeneration (right; see page 33) of a patient with sclerodermatomyositis.

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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Editorial office
Indonesian Journal of Rheumatology,
Division of Rheumatology, Department of Internal Medicine,
University of Indonesia School of Medicine

Jl. Salemba Raya No. 6
Jakarta Pusat, 10430
INDONESIA
T +62 21 31930166
F +62 21 31936736
E-mail: reumatik@indosat.net.id

Permission
Linda Kurniaty Wijaya, Permissions Excecutive
T +62 21 31930166
F +62 21 31936736
E-mail: permissions@IJR.com

Supplement inquiries
Siti Mahfudzoh, Managing Editor
T +62 21 31930166
F +62 21 31936736
E-mail: sitimfd@IJR.com

Subscription
Rudy Hidayat, Subscription Manager
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IRA
IRA Executive Secretariat
Jl. Salemba Raya No. 6
Jakarta Pusat - INDONESIA
E-mail: reumatik@indosat.net.id

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Editor's note

YI Kasjmir

Rheumatology is characterised by a large variety of diseases, consist of not only inflammatory rheumatic and systemic diseases, but also degenerative joint and spine diseases, soft tissue rheumatism, and metabolic bone diseases.[1] This group disease usually progress towards morphologic and functional deficits causing impairment of physical health.[2] Compared with any other group of disorders, it accounts for more lost working days and contributes most to the burden of disability in the longer term.[3] To achieve the best outcome in management of the disease, the holistic approach is a must, either medical or rehabilitative intervention. Both of them have their own role in improving patient's quality of life. While medical interventions focus on causation and disease processes, rehabilitation—including most elements of physical therapy—is concerned with the consequences of disease. Its goals are to reduce symptoms, improve function, and minimize disability.[4]

Physiotherapeutic strategies are often required for life. Although substantial progress has been achieved in the development of pharmacotherapy, physiotherapeutic strategies are indispensable in rheumatic cases. They are indicated to improve articular and vertebral function under curative, preventive, and rehabilitative aspects, in combination with a sufficient anti-inflammatory and analgesic therapy.[2] Based on a meta-analysis conducted by Roine et al[5] in evaluating cost-effectiveness of exercise-based interventions in treatment of various diseases, exercise interventions in rheumatic disease were deemed to be cost-effective in 75 percent of the cases. Even though the evidence for physical therapy does not achieve the grade of drug therapy, it is needed for a multimodal treatment concept according to expert opinion.[2] Therefore, more research about this topic should be conducted concurrently.

In this issue of Indonesian Journal of Rheumatology (IJR), Widjanantie et al[6] (see page 11) attempted to evaluate knee function measured by timed up-and-go test (TUGT) and stair-climbing test (SCT) as well as muscle strength after isometric exercise of quadriceps femoris muscles in female patients with knee osteoarthritis (OA). From this study, all patients showed significant increase in knee function according to TUGT and SCT and quadriceps muscle strength at week 4 and 6 of isometric exercise. Previously, the similar studies at the same institution—conducted by Tulaar et al, Djuanda, and Shanti—stated that a 6-week program of isometric exercise increased the strength of quadriceps muscles and was safe for knee OA patients with grade 2 and 3 Kellgren-Lawrence scale. This result is also supported by the study conducted by Shakoor et al[7], who suggested that isometric quadriceps muscle strengthening exercise has its beneficial role to reduce symptoms in knee OA by observing 64 patients of knee OA which were given isometric quadriceps muscle strengthening exercise plus non-steroidal anti-inflammatory drugs (NSAIDs) and compared with another 75 patients with NSAIDs only as control. The improvement was gradually increased day by day and finally was highly significant improvement in group with additional treatment of isometric exercise.

The reasonable mechanism why it was effective in relieving clinical symptoms were explained by Miyaguchi et al[8], who observed the biochemical changes in joint fluid after isometric quadriceps exercise for three months in patients with knee OA. Increase of high-molecular-weight hyaluronan (MWHA)—as shown in that study—might be directly responsible for pain relief in knee OA patients through effects on joint lubrication. Furthermore, no adverse effects of the isometric exercise were reported by the patients during this study[6], strenghten this modality to be considered as an additional therapy in knee OA.

We also feature a study by Noviar et al[9] (see page xx) who evaluate the effectiveness of ultrasound therapy compared with local steroid injection for pain relief and movement limitation in rotator cuff tendinitis. By conducting parallel randomized trial for two weeks, one group received 10 sessions of ultrasound therapy, the other received a single dose of local steroid injection. The ultrasound and steroid injection showed comparable effectiveness in alleviating pain and improving ROM limitation in patients with rotator cuff tendinitis. Based on this fact, ultrasound therapy may be used as a safer alternative to steroid injection. Because of less adverse effects, ultrasound therapy may provide a safer alternative to steroid injection, particularly in patients to whom steroid injection was contraindicated. However, because of the limitation of this study such as the limited number of samples, further studies with larger sample size are necessary to verify this result as a standard therapy for rotator cuff tendinitis.

See also other topics in this IJR issue, such as the rare case report of sclerodermatomyositis, an overlap syndrome between scleroderma and

dermatomyositis, written by Febyani et al[10] (see page 32). Another case report by Setiyohadi and Sinto [11] (see page 27) reporting effectiveness of cyclophosphamide in relieving recurrent dermatomyositis, which was failed to get remission using azathioprine and methotrexate. In review article, Utari et al[12] (see page 5) describe a comprehensive review of cardiovascular risks related to patients with rheumatoid arthritis and its management. Other topics are also necessary to know.

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Risk of cardiovascular disease in rheumatoid arthritis patients

AP Utari,[1] R Hidayat,[2] B Setiyohadi[2]

[1] Department of Internal Medicine, University of Indonesia School of Medicine/ Cipto Mangunkusumo General Hospital, Jakarta;
[2] Division of Rheumatology, Department of Internal Medicine, University of Indonesia School of Medicine/Cipto Mangunkusumo General Hospital, Jakarta

ABSTRACT

Despite rheumatoid arthritis (RA) therapy development has been in advance level today, its mortality remains increasing in general population. The mortality is mainly caused by early-manifested atherosclerosis and other cardiovascular complications. Available evidences show this condition appears in early stage of the disease. Thus, early detection and management of cardiovascular risk, followed by control of these factors are necessary to reduce morbidity and mortality of RA patients.

Cardiovascular disease (CVD) is a common cause of death, with higher number than cancer, chronic lower respiratory tract disease, and accident. It is estimated that 81,100,000 adults (more than a third) in US have one or more CVD. Everyday 2,300 patients die because of CVD which means one death in every 38 seconds.[1] Cardiovascular disease is the main cause of death in UK. Every year 191,000 patients die (1 of 3 deaths) because of the disease.[2] In Indonesia, 59.5% deaths caused by non-communicable diseases such as stroke (15.4%), hypertension (6.8%), diabetes mellitus (DM) (5.7%) , and ischemic heart disease (5.1%).[3]

It has been known that traditional risk factors such as hypertension, smoking, and physical inactivity are the main contributors to atherogenesis. Recently, it is proposed that inflammation may have a role in atherogenesis. The importance of inflammation in the pathogenesis of atherosclerotic CVD is supported by findings of higher prevalence of CVD in diseases related to systemic inflammation such as psoriasis, periodontitis, hypertension, DM, and rheumatoid arthritis (RA).[4]

Rheumatoid arthritis is the most common inflammatory arthritis which found in 0.5-1% adult population. Prevalence in female is twice higher than male. Prevalence becomes higher in older population and mostly found in female aged more than 65 years. It is reported that incidence of RA is approximately 5-50 per 100,000 every year.[5,6] An epidemiological study reported RA prevalence of 0.3% in Central Java.[7] Although etiology of RA is yet unknown, many studies suggested that combination of genetic and environmental factor plays role. Genes predisposing to RA are HLA-DRB1, PTPN22, STAT4, TRAF1/C5, and genes from 6q23 region.[8]

Rheumatoid arthritis is related to increase of mortality and decrease of life expectancy. Despite RA therapy development has been in advance level, mortality rate of RA patients remains high compared to general population. Higher mortality of RA patients is mainly caused by early-manifested atherosclerosis of coronary artery and cerebrovascular which is accompanied by other cardiovascular complications such as heart failure.[9] A meta-analysis concluded mortality due to CVD is 50% higher in RA patients compared to general population.[10] The CARRE study reported RA patients have similar risk of CVD to diabetic patients. This study found prevalence of CVD of 5% in non-diabetic and non-RA patients, 12.4% in type 2 DM patients, and 12.9% in RA patients.[11] Lindharsen reported risk of myocardial infarction in RA patients is similar to diabetic patients.[12] Mechanism of increased mortality caused by CVD in RA patients is thought to start very early in pathogenesis of the disease. Thus, it is important for medical doctor to understand the treatment strategy of CVD in RA patients in order to increase treatment quality.

PATHOGENESIS OF CARDIOVASCULAR DISEASE IN RHEUMATOID ARTHRITIS

The exact mechanism lies on the relation of RA and CVD is not yet fully known. Higher prevalence of traditional risk factors can explain some parts of it, but evidence from prospective cohort study found risk of CVD in RA patients remains constant after adjustment of those traditional risk factors.[14]

Inflammation is thought to be another pathophysiologic pathway causing higher cardiovascular risk in RA patients. Inflammatory mediators in circulation can affect arterial wall where these mediators play role in every stage of atherosclerosis, starts from endothelial dysfunction, plaque formation, until plaque rupture. The similarity of inflammatory and immunologic response between RA and atherosclerosis has been revealed in recent years. Earlier atherosclerosis is suggested as a result of interaction between traditional CVD risk factors in RA patients and newly risk factors, mainly systemic inflammation.[15] It is summarized in figure 1 and table 1.

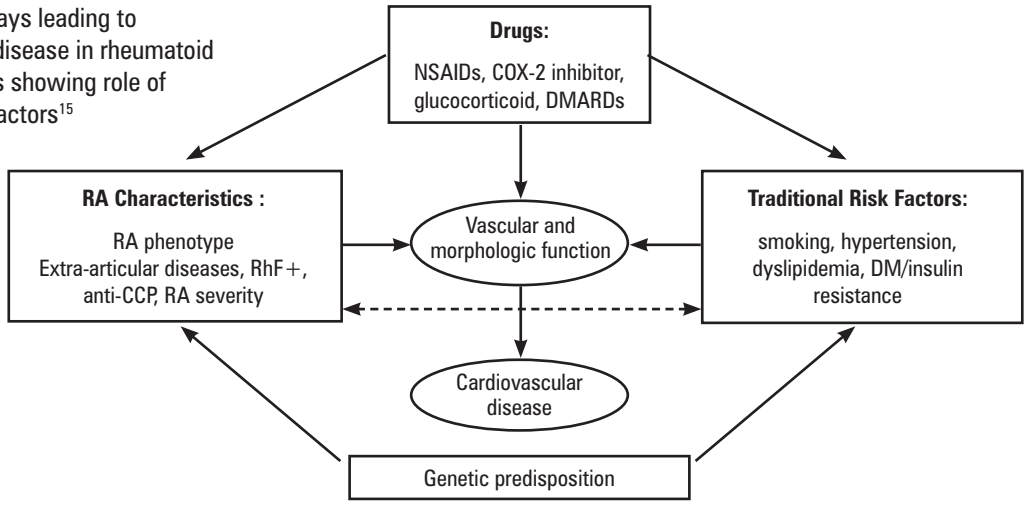

Figure 1 Pathways leading to cardiovascular disease in rheumatoid arthritis patients showing role of traditional risk factors[15]

Table 1 Atherogenesis in rheumatoid arthritis: traditional risk factors and disease-related risk factors[16]

Risk factors	
Traditional	Age, smoking, dyslipidemia, insulin resistance / diabetes mellitus, hypertension, physical inactivity, obesity
Disease related	
Inflammatory	Proatherogenic cytokine, chemokine, increasing expression of adhesion molecule, autoantibody, subset perturbation of T cells, genetic polymorphism, hyperhomocysteinemia, oxidative stress, apoptosis disorder, prothrombotic variable
Non-inflammatory	Immobilization, body weight gain
Iatrogenic	Glucocorticoid, methotrexate, NSAIDs, COX-2 inhibitors

NSAIDs, nonsteroidal anti-inflammatory drugs; COX-2, cyclo-oxygenase-2

RHEUMATOID ARTHRITIS AND TRADITIONAL CARDIOVASCULAR RISK FACTORS

A meta-analysis reported some traditional cardiovascular risk factors such as smoking, DM, and low level of high density of lipoprotein (HDL) are more often found in RA patients.[17]

Smoking

A study stated that prevalence of smoking was increased in RA patiens with OR 1.56. Smoking can increase the risk of RA in seropositive patients who smoke ≥25 cigarettes for more than 20 years. Smoking is also related to RA with more severe manifestation. This condition may be caused by genetic and environmental factors. Combination of smoking and double-copy of allele HLA-DRB1 increases risk of RA and earlier mortality, especially caused by CVD.[17]

Diabetes

Patients with RA have higher risk to have insulin resistance. Disorder in glucose process occurs as a result of peripheral insulin resistance mediated by inflammatory response.[9] Interleukin-6 (IL-6) is suggested to be linked to insulin resistance in human.[18,19] Inhibition of IL-6 is shown to reduce risk of insulin resistance in RA patients.[20] Some studies reported no significant difference in percentage of DM between RA patients and control,[21,22] while other studies reported higher risk of DM in RA population.[17,23]

Use of glucocorticoid may influence glucose metabolism in RA patients. Due to the effects of chronic inflammation and glucocorticoid use to glucose metabolism, it is difficult to consider that increasing prevalence of DM is caused only by RA.[17] However, Hoes reported no difference in risk of insulin resistance between RA patients who consumed and did not consume steroid.[24]

Blood Pressure

Prevalence of hypertension in RA patients varied from 3.8 to 73%.[25] A meta-analysis reported no significant difference in blood pressure betweeen RA patients and general population.[17] A 10 year follow-up cohort study in 325 RA patients concluded that hypertension increases cardiovascular events risk (hazard ratio 3.76; 95% CI 0.99-15.06).[26]

Dyslipidemia

Dyslipidemia is found in 55-65% RA patients.[27] Dyslipidemia in RA is related to activity of inflammatory disease. Higher disease activity is related to lower level of total cholesterol, especially HDL. This condition occurs because proinflammatory cytokines—mainly tumor necrosis factor α (TNF-α)[15]—increase serum triglyceride (TG) level and decrease level of HDL.[28] Level of HDL in RA patients is lower than general population, but prevalence of hypercholesterolemia is not different in both groups.[17] Furthermore, RA patients have HDL dysfunction which causes HDL cannot prevent oxidation of low density lipoprotein (LDL).[29,30] Therapy can improve lipid profile, especially HDL which further can improve atherogenic index.

Proinflammatory cytokines can be mediator for rheumatoid cachexia, a condition where skeletal muscle is wasted and fat mass increases progressively. Consequently, RA patients have higher percentage of body fat compared to control group although body mass index (BMI) are similar. Furthermore, higher body fat mass contributes to CVD.[15] Cachexic patients have higher total cholesterol and LDL level, and also higher frequency of hypertension and metabolic syndrome compared to RA patients without rheumatoid cachexia.[31]

Physical Inactivity

Although it is not included in absolute risk estimation of CVD, this factor has been linked to higher risk of CVD in general population. Physical inactivity in RA patients occurs when disease becomes uncontrolled and/or chronic joint damage leading to disability, pain, and stiffness.

Waist circumference and higher BMI in RA patients may be also related to physical inactivity. However, no consistent findings in literature explaining BMI in RA patients. It is possible that patients with RA are reported having higher, similar, or lower BMI compared to general population. In relation to CVD, available evidences indicate patients with low BMI (<20 kg/m^2) have higher cardiovascular risk. Possibly it is related to severity of RA because systemic inflammation often causes decrease of body weight.[21]

RHEUMATOID ARTHRITIS AND NON-TRADITIONAL RISK FACTORS

Increasing risk of CVD and its mortality in RA patients which cannot be explained by traditional risk factors have been reported in literature.

Inflammation

It is thought that systemic inflammation, like in RA, has important role in premature atherosclerosis. Proinflammatory cytokines are trigger for expression of cellular adhesion molecule in endothelial cells, and also can induce atherogenic changes including dyslipidemia, insulin resistance, oxidative stress, and prothrombotic state.[16] Potential inflammatory mechanisms leading to vascular damage are: (a) endothelial dysfunction via excessive nitric oxide production; (b) activation of coagulation cascade; and (c) induction of secondary dyslipidemia with atherogenic profile.[15] Endothelial dysfunction causes change in its permeability and increases adhesion of leucocytes and thrombocytes. Furthermore, infiltration of T-cell and macrophage to arterial wall and release of inflammatory mediators induce chronic inflammation and progressive atherosclerosis.

Systemic cytokines response activates immune cells and causes phenotypical perturbation and functional subset of T-cell. Increasing level of CD4+CD28null T-cell is common in RA patients, which is autoreactive and can induce cytotoxicity of endothelial cells. Increasing subset of T-cells also can be found in patients with acute coronary syndrome and they can invade unstable atherosclerotic plaque.[16]

Genetic Influence

Cardiovascular disease in RA is suggested to be influenced by genetic factors. Functional polymorphism related to expression of major histocompatibility complex (MHC) is associated with increase of susceptibility to RA, myocardial infarction, and multiple sclerosis.[9] Despite status of autoantibody, allele of shared epitope (genotype HLA-DRB1) is associated with mortality in RA. Combination of shared epitope, smoking habit, and anti-CCP antibody will cause higher increase of premature death risk in RA patients. Shared epitope is also thought to be related to ischemic heart disease in RA with yet unknown mechanism.[9] TRAF1/C5, STAT4, and HLA-DRB1 may involve in regulation of lipid metabolism in RA patients.[32]

Hyperhomocysteinemia

Hyperhomocysteinemia, a condition frequently found in RA patients, has been considered as an independent risk factor in atherosclerotic disease. Hyperhomocysteinemia involves in endothelial dysfunction, lipoprotein oxidation, and has prothrombotic effects.[16]

Thrombotic Marker

Prothrombotic state such as increase of fibrinogen, von Willebrand factor, PAI-1, and thrombocytosis in RA patients may play a role in cardiovascular complications.[33]

RHEUMATOID VASCULITIS

RA patients possibly can suffer from rheumatoid vasculitis. Generally, it is found in small and medium blood vessels, including coronary artery. Although it is less frequently found than endothelial damage caused by systemic inflammation, rheumatoid vasculitis causes 2-3 times higher risk of ischemic heart disease in RA patients.[34]

EFFECTS OF RHEUMATOID ARTHRITIS THERAPY TO RISK OF CARDIOVASCULAR DISEASE

Non-steroidal anti-inflammatory drugs (NSAIDs)

NSAIDs and cyclo-oxygenase-2 (COX-2) inhibitors are commonly used in RA therapy. Both drugs are thought to be related to side effects of hypertension, congestive heart failure, and kidney disorder.[35] Compared to placebo, COX-2 inhibitors group has 42% higher risk of cardiovascular events. In the same study, it is concluded that compared to naproxen, use of COX-2 inhibitors increases risk of vascular events (OR 1.57, 95% CI 1.21-2.03) and myocardial infarction twice higher (OR 2.04, 95% CI 1.41-2.96).[36] Generally, now it is recommended to use NSAIDs or COX-2 inhibitors with the lowest possible dose and the shortest possible duration. If NSAIDs should be used in therapy, naproxen is the drug of choice because cardiovascular risk of this drug seems to be lower than others.[35]

Glucocorticoid

Glucocorticoid can induce hypertension, insulin resistance, blood lipid disorder, obesity, and hypercoagulability.[9] However, it is difficult to estimate its effect to cardiovascular risk in RA patients. Glucocorticoid is thought to be linked to cardiovascular risk, but in the other hand glucocorticoid can decrease disease activity and inflammation. Until further data reported the effect of glucocorticoid, it is recommended to use it with dose as low as possible.[35]

Disease-modifying antirheumatic drugs (DMARDs)

a. Nonbiological DMARDs
   Methotrexate (MTX) is one of the main therapy of RA. It improves clinical signs of disease and slows radiologic progression.[35] A cohort study involving 1,240 RA patients reported hazard ratio of mortality in group taking MTX is

0.4 (95% CI 0.2-0.8).[37] Use of MTX is also related to lower risk of metabolic syndrome.[38] Ongoing Cardiovascular Inflammation Reduction Trial (CIRT) study is purposed to observe effect of very low dose of MTX (10 mg/week) to cardiovascular events in general population. It is expected that result of this study can provide evidence to confirm cardioprotective effect of MTX, as the agent is used widely in RA therapy.[39]

Effect of other nonbiological DMARDs to CVD risk is yet unknown. Azathioprine, cyclosporin, and leflunomide are thought to increase cardiovascular events. One of the reasons possibly because leflunomide and cyclosporin can induce hypertension.[35]

b. Biological DMARDs

In US, biological agents that have been approved today for RA therapy consist of TNF inhibitor (infliximab, etanercept, adalimumab, certolizumab pegol, dan golimumab), anakinra (antagonist of IL-1 receptor), abatacept (CTLA4-Ig protein fusion), rituximab (anti-CD20 antibody), and tocilizumab (antireceptor IL-6 antibody).[42]

Anti TNF-α agent is a potent drug to decrease inflammation and slow radiologic progression in RA patients. Thus, possibly this drug can give cardiovascular benefit. British Society for Rheumatology Biologics Register observed myocardial infarction in 8,670 RA patients administered with anti TNF-α agent compared with 2,170 RA patients treated with traditional DMARDs. This study did not find reduction of myocardial infarction incidence in patients treated with anti TNF-α agent (hazard ratio 1.44; 95% CI 0.56-3.67). However, in group which gave response to therapy in six months, incidence of myocardial infarction was 3.5 per 1,000 patient-year compared to 9.4 per 1,000 patient-year in non-responsive group.[40] Another study reported lower risk of cardiovascular events in group treated with TNF-α antagonist compared to non-biological DMARDs group.[41]

Effect of other biological agents to CVD risk is not known thoroughly. Anakinra, the IL-1 antagonist, was reported to improve vascular and left ventricular function in RA population.[43] Rituximab was reported to have beneficial effect to endothelial function and plasma cholesterol level. A 16 week-research involving five RA patients treated with rituximab found decrease of total cholesterol and increase of HDL level.[44] Use of tocilizumab causes slight increase of TG, LDL, and HDL level, but it could decrease lipoprotein (a).[20] Monotherapy of tocilizumab could reduce arterial sclerosis. Similar effect were found in etanercept and adalimumab.[45] The effect of abatacept to CVD risk is still unknown yet.

TREATMENT

Medical treatment for RA patients including management of joint disease and related comorbidities such as osteoporosis, depression, CVD, and malignancy. These comorbidities have significant impacts to quality of life, work disability, and mortality.[15] Preventive strategy to decrease CVD risk in RA patients should be initiated immediately after diagnosis of RA is made. Cardiovascular evaluation in RA patients is initiated by detecting comorbidities such as hypertension, tobacco use, hyperglycemia, dyslipidemia, increased BMI, central obesity, physical inactivity, and family history of CVD.[9]

In 2010, The European League Against Rheumatism (EULAR) released a recommendation for treatment of cardiovascular risk in RA and other inflammatory arthritis diseases.

Table 3 Ten recommendations for treatment of cardiovascular risk in rheumatoid arthritis[46]

No.	Recommendation	Level of evidence	Strength of recommendation
1.	RA should be considered as a condition related to higher risk of CVD. Increasing risk possibly due to increase of traditional risk factors and inflammatory burden	2b-3	B
2.	Proper control of disease activity is necessary to reduce cardiovascular risk	2b-3	B
3.	Assessment of cardiovascular risk using national recommendation is recommended for all RA patients. Risk assessment should be repeated if antirheumatic therapy changes	3-4	C
4.	Model of risk assessment should be adapted to RA patients by using multiplication factor of 1.5. This multiplication factor should be used in RA patients who fulfill minimally 2 of 3 following criteria: disease duration >10 years, positive RF or anti-CCP, and having extra-articular manifestation	3-4	C
5.	Ratio of total cholesterol/HDL should be used if SCORE model is utilized	3	C
6.	Intervention should be performed based on national guideline	3	C
7.	Statin, ACE-I, and/or AT-II blocker are drugs of choice	2a-3	C-D
8.	Role of COX-2 inhibitor and most NSAIDs in the cardiovascular risk are not yet well-understood and need further investigation. Thus, physician should be thoughtful to prescribe them, especially in patients with CVD or having risk factors	2a-3	C
9.	Use glucocorticoid with the lowest possible dose	3	C
10	Tell the patient to stop smoking	3	C

RA, rheumatoid arthritis; CVD, cardiovascular disease; RF, rheumatoid factor; SCORE, Systematic Coronary Risk Evaluation; ACE-I, angiotensin converting enzyme inhibitor; AT, angiotensin; COX, cyclo-oxygenase; NSAIDs, nonsteroidal anti-inflammatory drugs

Although pathologic mechanism of cardiovascular system in RA has been known widely, the treatment remains unclear. It is not yet known neither at what level of lipid and blood pressure should pharmacological therapy be started, nor the intervention can improve cardiovascular risk. Beside, although DM and RA has similar risk of CVD, it is not clear whether guideline for DM can reduce CVD risk significantly in RA patients.[9] It is also necessary to evaluate whether the drugs usually used for CVD can be used in RA patients. Type of drugs and its risk-benefit is summarized in table 4.

Table 4 Type of drugs and its function for cardiovascular treatment in rheumatoid arthritis patients[35]

Focus to cardiovascular	
Statin	Having statistically significant antiinflammatory activity, but no clinically significant effect was reported
	Its use should follow general recommendation for cardiovascular treatment
Antihypertensive drugs	Its use should be based on general recommendation
	Whether ACE-I or ARB become drug of choice still needs further investigation
Aspirin	In patients with unclear cardiovascular disease, benefit-risk consideration is necessary
	General recommendation may help decide whether indication exists or not. Consider interaction with NSAIDs
Focus to anti-inflammation	
DMARDs	Methotrexate seems to give benefit
	Leflunomide, azathioprine, and cyclosporine may be related to inadequate cardiovascular outcome
TNF-α inhibitor	It may reduce cardiovascular events incidence, especially in patients giving clinical response
Glucocorticoid	It is related to higher cardiovascular morbidity and mortality in general population. Its role in RA treatment should be defined. Use with the lowest possible dose
NSAIDs, COX-2 inhibitors	It is related to higher cardiovascular risk. Naproxen shows smallest effect making it as drug of choice

ACE-I, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; NSAIDs, nonsteroidal anti-inflammatory drugs; DMARDs, disease-modifying antirheumatic drugs; TNF, tumor necrosis factors; RA, rheumatoid arthritis; COX, cyclo-oxygenase

Statin

Benefits of statin to CVD has been proved. Statin also has been tested in RA patients, but there has not been large enough study to conclude its effect to cardiovascular events.[35] Statin effect may be more obvious in RA patients because of its potency as antiinflammatory agent. The Trial of Atorvastatin in Rheumatoid Arthritis (TARA) study compared administration of atorvastatin 40 mg and placebo in 116 RA patients for six months. Significant improvement of disease activity score (DAS) of 28 was found in atorvastatin group. C-reactive protein level and erythrocyte sedimentation rate was reduced by 50% and 28%, respectively.[47] Similar study by El-Barbary reported decreased level of cholesterol, LDL, and TG; increased level of HDL; and improvement of disease activity parameter in atorvastatin group.[48] However, number of subjects in these studies are too small to show therapy effect to cardiovascular events. Another ongoing study, The Trial of Atorvastatin in the Primary Prevention of Cardiovascular Endpoint in Rheumatoid Arthritis (TRACE RA) involving 3,800 subjects is expected to answer this question.

Antihypertensive drugs

Hypertension is commonly found in RA patients. Therefore, control of blood pressure becomes target in the management of RA. At present, no available data can be used to determine a target for blood pressure control in RA patients. Therefore, recommendation for general population still can be used.[35] ACE-inhibitor and AT-II blocker may give beneficial effect to inflammation and endothelial function in RA patients. Thus, these two agents are drug of choice for RA patients, if indication exists to prescribe it.[46]

DMARDs

Literature has mentioned cardioprotective effect of DMARDs, especially MTX and biological agents. However, strategy to control disease activity and progression of CVD remains unclear. It is not known the limit to control inflammation in order to decrease cardiovascular risk and at what extent the therapy for RA patients can reduce cardiovascular risk.[6]

CONCLUSION

Higher risk of CVD has a great role to increase morbidity and mortality in RA patients. Evidences show this condition started early in disease activity. Early identification and management of cardiovascular risk, followed by control of these factors are necessary to decrease cardiovascular events risk. These risk factors are smoking habit, physical inactivity, nutrition, body weight, and blood pressure.

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Knee function measured by timed up-and-go test and stair-climbing test after isometric exercise of quadriceps femoris muscles in female patients with knee osteoarthritis

SC Widjanantie,[1] ABM Tulaar,[1] YI Kasjmir,[2] SB Prasetyo[3]

[1] Department of Physical Medicine and Rehabilitation, University of Indonesia School of Medicine/Cipto Mangunkusumo General Hospital, Jakarta; [2] Division of Rheumatology, Department of Internal Medicine, University of Indonesia School of Medicine/Cipto Mangunkusumo General Hospital, Jakarta; [3] University of Indonesia School of Public Health, Depok

ABSTRACT

Background: Osteoarthritis (OA), the most common form of joint disease, can result in long-term disability. Limitation of activity in OA patients may result in a decline in the strength of quadriceps femoris muscles and thus further reduce mobility. Isometric exercise has been known to increase muscle strength, decrease pain, and improve knee function.

Objective: To evaluate knee function measured by timed up-and-go test (TUGT) and stair-climbing test (SCT) as well as muscle strength in the fourth and sixth week after isometric exercise of quadriceps femoris muscles and the correlation between these variables.

Methods: Female patients with OA underwent isometric exercise of quadriceps femoris muscles 3 times a week for 6 weeks. Muscle strength (measured by tensiometer cable) and knee function (measured by TUGT and SCT) were evaluated before and at week 4 and 6 of the exercise.

Results: Thirty five female patients were recruited in this study. The majority of the patients (45.7%) were between 60 to 65 years old. Obesity was found in 62.86% of the patients. At week 6, there was significant decrease in mean TUGT and SCT (by 39.0% and 45.6%, respectively; $p<0.001$), and significant increase in mean right and left quadriceps muscles strength (by 47.9% and 36.7%, respectively; $p<0.001$). There was a weak negative correlation (nonsignificant) of the increased strength of quadriceps muscles with the increase of knee function according to TUGT (right leg: $r = -0.172$, $p = 0.323$; left leg: -0.303, $p = 0.077$) and SCT (right leg: $r = -0.031$, $p = 0.860$); left leg: $r = -0.058$, $p = 0.742$).

Conclusion: In female patients in this study, significant improvement was found in the strength of quadriceps muscles, TUGT, and SCT after 6 weeks of isometric exercise. There was no significant correlation between muscle strength and knee function according to TUGT and SCT.

Osteoarthritis (OA) is the most common form of joint disease and has been known to cause long-term disability in patients.[1] Data from the World Health Organization (WHO) showed that along with the increase in life expectancy, in 2025 there will be a 414% increase in the elderly population.[2] Since age is one of the most important risk factor for the development of OA, it is likely that there will be also an increase in the incidence of this disease.[2,3]

Wachjudi et al[2] reported that OA comprised of 69% of all rheumatic diseases in outpatient clinic, with 87% being knee OA. Data from our institution showed that from 394 patients with OA, there were 207 (52.54%) patients who were diagnosed with knee OA. Seventy eight of those patients were women older than 50 years.[4] The prevalence of OA is roughly equal in men and women under the age of 50 years old, but with older age the prevalence is higher in women.[1,5]

Knee OA manifests as knee pain and joint stiffness,[1] which will cause patients to limit their knee movement in order to reduce pain.[3] This limitation may result in disuse atrophy of the quadriceps muscles,[6] 30% loss of muscle mass in 1 week, and up to 5% reduction in muscle strength per day,[7] which will cause muscle weakness, limitation in daily activities, and reduce independence in self-care.[7]

The management of OA involves the combination of both pharmacologic and nonpharmacologic treatment.[1,2] Exercise therapy performed in medical rehabilitation facilities is one of the nonpharmacologic approaches. Several studies had shown that exercise therapy in knee OA patients resulted in significant improvement in quadriceps muscle strength, pain intensity, and knee function.[8–13] The exercise therapy may be given as isometric, isotonic, or isokinetic exercise.[10]

Knee function in OA patients is usually assessed with visual analog scale (VAS), Lequesne algofunctional index, or Western Ontario and McMaster Universities (WOMAC) Index.[14] More simple, easily applied, and yet objective indicators such as timed up-and-go test (TUGT)[15,16] and stair-climbing test (SCT)[17] have not been widely used.

The TUGT is known as the examination to evaluate mobility, balance, and movement in the elderly, which related to the risk of falling.[16] The application of TUGT as a method to evaluate knee function has been done previously by Piva et al[15] in a cross-sectional study of knee OA patients, and TUGT was shown to be reliable in the clinical settings. TUGT result is considered normal if <30

seconds.[16] The SCT is usually used to assess overall knee function before and after an intervention that will affect the mobility of the lower extremities (e.g. surgery); its use is not limited in OA only. There is not yet normal range for SCT result.[17]

In this study we attempted to assess knee function according to TUGT and SCT as well as muscle strength after isometric exercise in patients with knee OA and the correlation between those variables.

METHODS

Patients

The study was conducted at the rheumatology and medical rehabilitation outpatient clinic at Cipto Mangunkusumo General Hospital, Jakarta between December 2005 and March 2006. We recruited female patients who were aged above 50 years old and diagnosed with knee OA based on the 1986 American College of Rheumatology (ACR) criteria[18] for knee OA, had second or third degree joint damage according to the Kellgren-Lawrence scale, tibiofemoral angle of ≤15°, VAS of ≤4 (with or without the use of analgesics), preliminary TUGT score of <30 seconds, Lequesne algofunctional score of ≥8, and who were able to walk without the need for support. Patients with history of heart disease, stage 2 hypertension, neuromuscular disease, infection or abnormalities of the joints in the lower extremities, history of falling, knee trauma or surgery, and contracture of the knee joint (range of motion; ROM ≤135°) were excluded from the study.

Isometric exercise

The isometric exercises were performed 3 times a week for 6 weeks using N-K table (Enraf-Nonius, Rotterdam, The Netherlands). To determine the weight that was to be used for the exercise, first we measured the maximum weight that the patients were able to lift. Patients were seated on the N-K table with the knee flexed at 90° angle. Then they were asked to extend the knee and use the quadriceps muscles to raise a weight until the knee was at 30° flexion. The position was sustained for 6 seconds, before returning to the 90° angle flexion. After 5 seconds of rest, patients were asked to repeat the movement. The maximum weight that the patient was able to lift for 3 consecutive times was then recorded. In the isometric exercise, patients were asked to perform similar movement using 60% of the maximum weight. The movement was then repeated until fatigue occured. For each week, a new maximum weight was determined.

Outcome measurements

Muscle strength (in kilograms) was measured by tensiometer cable attached to the N-K table. The TUGT (in seconds) was performed by calculating the time needed for the patient to stand up from a chair, walk through a 3-meter long path, turn around, walk back on the path, and resume the sitting position. The SCT (in seconds) was performed by calculating the time needed for the patient to walk up a 12-step stair (each step has a height of 18 cm and depth of 28 cm), turn around, and walk down the stair to return to the first position. Measurement of the quadriceps muscle strength, TUGT, and SCT were performed before, at the beginning of week 4, and at the end of week 6 of the isometric exercise.

Statistical analysis

The comparison of quadriceps muscle strength and knee function before and at week 4 and 6 of isometric exercise were analyzed using the analysis of variance (ANOVA) or Friedman's test as appropriate. The correlation of quadriceps muscle strength with knee function was analyzed using Pearson's or Spearman's test as appropriate.

RESULTS

A total of 35 female patients were recruited in the study. The largest proportion of patients (45.7%) were aged 60 or older, followed by those aged 50–54 years old (40%), and 55–59 years old (14.3%). Most (62.86%) also had obesity (body mass index of ≥25 kg/m^2). The majority of the patients were housewives (57.1%). Most (71.4%) had second degree joint damage according to Kellgren-Lawrence scale. Almost all of the patients did regular light exercise (91.4%) with the frequency of less than 3 times a week (94.3%). Table 1 further described the characteristics of the patients.

Table 1 Characteristics of the patients

Characteristics	n (%)*
Age, years, mean (SD)	57.57 (5.75)
Body mass index, kg/m^2, mean (SD)	
<18.5	1 (2.86)
18.5–22.9	9 (25.21)
23–24.9	3 (8.57)
25–29.9	8 (22.86)
≥30	14 (40)
Education	
Elementary school	1 (2.86)
Junior high school	6 (17.1)
Senior high school	18 (51.44)
Diploma or bachelor degree	10 (28.6)
Occupation	
Housewife	20 (57.1)
Employee	7 (20)
Nurse	3 (8.6)
Teacher	3 (8.6)
Other	2 (5.7)
Kellgren-Lawrence score	
2	25 (71.4)
3	10 (28.6)
Exercise	
Irregular	32 (91.4)
Regular	3 (8.6)
Frequency of exercise	
<3 times a week	33 (94.3)
≥3 times a week	2 (5.7)

*Unless otherwise specified.

At week 4, there was significant decrease in mean TUGT and SCT (by 27.5% and 30.5%, respectively; p<0.001), and significant increase in mean right and left quadriceps muscles strength (by 29.1% and 22.0%, respectively; p<0.001). At week 6, there was significant decrease in mean TUGT and SCT (by 39.0% and 45.6%, respectively; p<0.001), and significant increase in mean right and left quadriceps muscles strength (by 47.9% and 36.7%, respectively; p<0.001) compared with baseline. Figure 1 and 2 further describe the change in TUGT, SCT, and quadriceps muscles strength during the follow-ups.

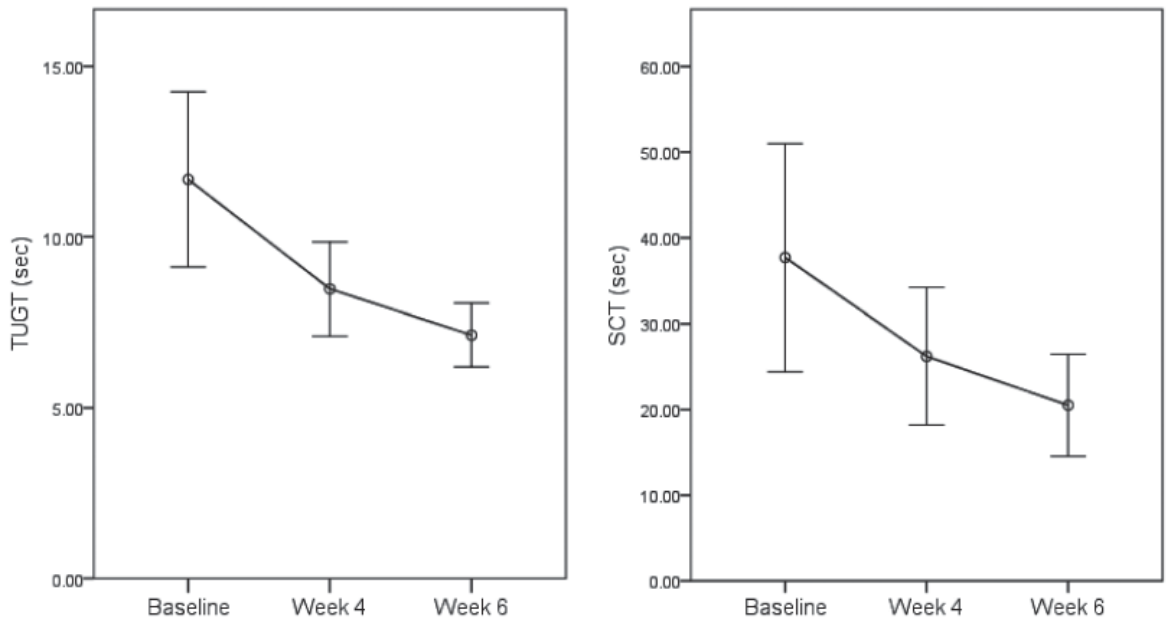

Figure 1 Timed up-and-go test (TUGT) and stair-climbing test (SCT) at baseline and at week 4 and 6 of the isometric exercise. Values shown are mean and standard deviation. TUGT at baseline, week 4, and week 6 were 11.68 ± 8.47, 8.47 ± 1.37, and 7.13 ± 0.93 sec, respectively. SCT at baseline, week 4, and week 6 were 37.70 ± 13.28, 26.21 ± 8.02, and 20.51 ± 5.95 sec, respectively. The decrease in TUGT and SCT at week 4 and 6 were all statistically significant ($p<0.001$).

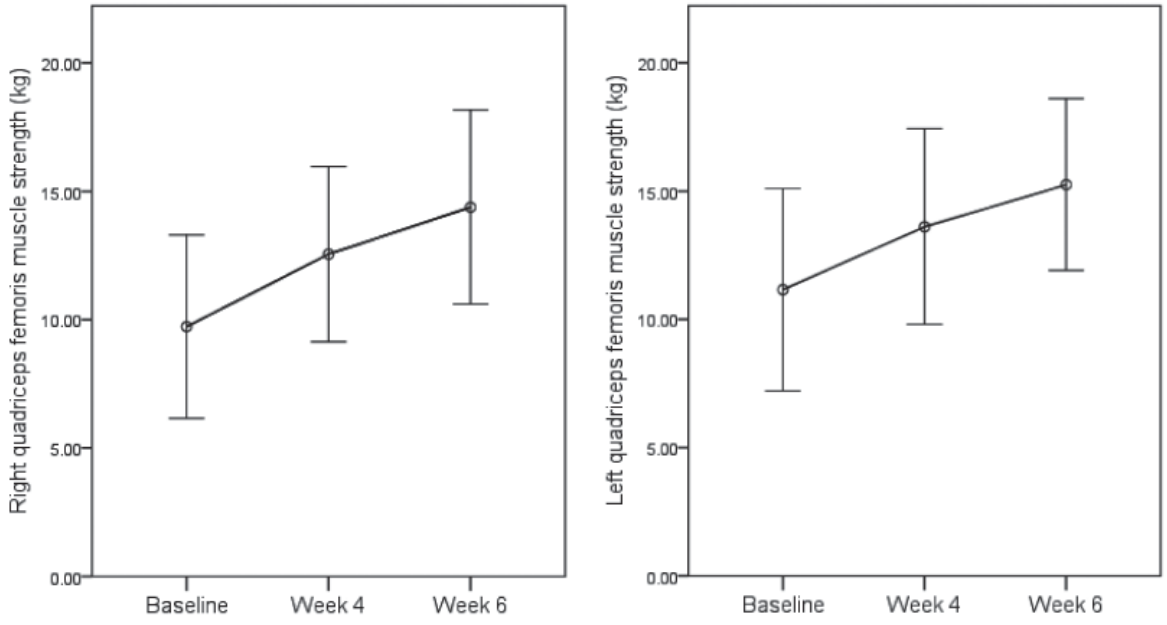

Figure 2 Quadriceps femoris muscle strength at baseline and at week 4 and 6 of the isometric exercise. Values shown are mean and standard deviation. The muscle strength of the right quadriceps at baseline, week 4, and week 6 were 9.73 ± 3.58, 12.56 ± 3.42, and 14.39 ± 3.78 kg, respectively. The muscle strength of the left quadriceps at baseline, week 4, and week 6 were 11.16 ± 3.95, 13.61 ± 3.81, and 15.26 ± 3.34 kg, respectively. The increase at week 4 and 6 was statistically significant for both legs ($p<0.001$).

Statistical analysis showed no significant correlation of TUGT and SCT with muscle strength after isometric exercise (table 2). The coefficient of determination (r^2) was 0.0296–0.1018 for TUGT and 0.001–0.0034 for SCT.

Table 2 Correlation of timed up-and-go test (TUGT) and stair-climbing test (SCT) with quadriceps muscle strength at week 4 and 6 of the isometric exercise

	Quadriceps muscle strength	
	Right leg	Left leg
Week 4		
TUGT	−0.295 (0.086)	−0.319 (0.062)
SCT	−0.121 (0.490)	−0.055 (0.754)
Week 6		
TUGT	−0.172 (0.323)	−0.303 (0.077)
SCT	−0.031 (0.860)	−0.058 (0.742)

Data are presented as r (p value).

During the study, no adverse effects of the isometric exercise were reported by the patients.

DISCUSSION

The patients in our study showed significant decrease in the time needed to perform TUGT at week 4 and 6 of isometric exercise. Generally, TUGT abd SCT are used to evaluate the functional performance and are not specific for knee function, and the improvement signified the progress of the overall physical functioning and vigor of the patients.[15–17] TUGT and SCT provide a simpler and more easily applied alternative to measure knee function in the clinical settings. TUGT requires only minimal equipment, training, or expense. It also better isolates the functional deficits; so this test could be used to plan prevention strategies and in guiding further testings and treatments.[16] Moreover, because TUGT result is also associated with cognitive function[19] and could predict the risk of falling,[20] the use of this test may be beneficial in patients with OA, who are usually in the more advanced age.

In this study, isometric exercise was chosen over other type of exercises. In isometric exercise, muscle strength improves only at the joint angle at which the exercise takes place. This specificity of exercise principle may limit how much isometric exercise can affect performance of functional tasks that feature joint movement beyond the joint angle prescribed in the isometric exercise; however, it may have a possible advantage in that it does not stress the joint over a functional ROM. Dynamic resistance exercise improves strength and functioning over the exercise ROM, but the joint is being loaded while it is moved, which may result in pain among OA patients. In contrast, reduced joint movement in isometric exercise may result in less pain during and after the exercise.[21]

Significant increase in the quadriceps muscle strength was already shown at week 4 of the isometric exercise. Isometric exercise with the knee flexed at 30° angle, if done early in the course of the disease, will help maintain a better biomechanics of knee joint.[22,23] Studies[10–12] conducted previously at our institution also had shown similar results: a 6-week program of isometric exercise with the knee flexed at 30° angle increased the strength of quadriceps muscles and was safe for knee OA patients with grade 2 and 3 Kellgren-Lawrence scale. Moreover, this exercise was also shown to decrease pain and improve knee function according to Lequesne index. Hettinger and Muller found that muscle contraction using 2/3 of the maximum strength in 5–6 seconds with interval of 20 seconds was able to increase muscle strength, a method known as brief repetitive isometric exercise (BRIME).[23] Isometric exercise of the quadriceps muscle could strengthen the supporting structures of the knee joint; thus it will decrease the effect of compression and intermittent relaxation to the patellar and tibiofemoral cartilage, meniscus, and ligament.[19,24]

Statistical analysis did not show significant correlation of TUGT and SCT with muscle strength, which may be due to the limited sample size. The weak correlation signified that TUGT and SCT were also influenced by other factors that is important in mobility, such as biomechanical association between joint, strength of the supporting muscles, flexibility of the vertebrae and hip joints, range of motion of hip and joints of the lower extremities, postural control, and balance related to neuromusculoskeletal coordination.[24–26]

Obesity was found in 62.86% of the patients. Previous studies[10–13] conducted at our institution also reported that obesity was found in the majority of their subjects. Obesity has been known as a risk factor for the development of knee OA because of the change in the biomechanics of the knee joint.[27] In OA, there may be functional decline of the muscles that support the knee, i.e. the quadriceps and hamstrings.[27,28] Besides, the decline is also physiologic as a part of aging, in which case exercise may help in improving muscle strength.[29,30]

The limitations of this study that may affect the interpretation of the result includes recruitment of only female patients, lack of a control group, and the exclusion from analysis of factors that may affect the result of our study, such as BMI, age, degree of joint damage, size and direction of osteophytes, affected knee compartment, knee-stressing activities, and use of medications.

CONCLUSION

In female patients enrolled in this study, there was significant increase in quadriceps muscle strength and knee function according to TUGT and SCT at week 4 and 6 of isometric exercise. We found no significant correlation between muscle strength and knee function according to TUGT and SCT.

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Comparison of ultrasound therapy and local steroid injection in rotator cuff tendinitis

Noviar,[1] ABM Tulaar,[1] YI Kasjmir,[2] S Sudarsono[3]

[1] Department of Physical Medicine and Rehabilitation, University of Indonesia School of Medicine/Cipto Mangunkusumo General Hospital, Jakarta; [2] Division of Rheumatology, Department of Internal Medicine, University of Indonesia School of Medicine/Cipto Mangunkusumo General Hospital, Jakarta; [3] University of Indonesia School of Public Health, Depok

ABSTRACT

Objective: To evaluate the effectiveness of ultrasound therapy compared with local steroid injection for pain relief and movement limitation in rotator cuff tendinitis.

Methods: Patients with rotator cuff tendinitis at the rheumatology and rehabilitation outpatient clinic at Cipto Mangunkusumo General Hospital were enrolled in a parallel randomized trial, in which each eligible patient were randomly assigned to one of two groups: one group received 10 sessions of ultrasound therapy given in 2 weeks, the other received a single dose of local steroid injection. Evaluation of the visual analog scale (VAS) was performed in 10 days (5 days for each week: day 1–5 and 8–12), while evaluation of the abduction as well as external and internal rotation range of motion (ROM) was performed twice a week (day 2, 5, 9, and 12). Change in the variables between the two groups at the end of the second week (day 12) was then compared.

Results: Thirty patients, divided into two groups consisting of 15 patients each, were recruited in the study. Significant decrease in VAS during the follow-ups was obtained in both groups, slightly earlier in the steroid injection group (day 2; $p = 0.041$) compared with the ultrasound group (day 3; $p = 0.001$). Significant increase in abduction ROM was achieved at the same rate (beginning at day 5) in both groups. Significant increase in internal rotation ROM was achieved at day 9 in the ultrasound group ($p = 0.043$) and day 12 in steroid injection group ($p = 0.044$). The increase in external rotation ROM in both groups was not found to be statistically significant. At the end of the second week, significant difference between the two groups was only shown in the abduction ROM, with higher increase in the steroid group.

Conclusions: Ultrasound therapy provided a comparable effectiveness to steroid injection in alleviating pain and improving ROM in patients with rotator cuff tendinitis.

Rotator cuff tendinitis is an inflammatory and degenerative process of the tendon and is the main cause of shoulder pain.[1] The most commonly affected tendon are the suprapinatus and infraspinatus tendon.[2–5]

This disease occurs as a result of overuse syndrome in the young adult (25-40 years old) and results in degenerative process in older age,[1–6] causing pain and limitation in range of motion (ROM) that is difficult to treat with nonsteroidal anti-inflammatory drugs (NSAIDs). Therefore, an additional therapy is usually needed, such as local steroid injection, transcutaneous electrical nerve stimulation, ultrasound, and other modalities.

Shoulder pain is the third most common cause of musculoskeletal disorder after low back pain and cervical pain. Estimates of the cumulative annual incidence of shoulder disorders vary from 7–25% in the Western general population. The annual incidence is estimated at 10 cases per 1,000 population, peaking at 25 cases per 1,000 population in persons aged 42-46 years. In persons aged 70 years or older, 21% of persons have shoulder symptoms, most of which were attributed to the rotator cuff.[7] Women are affected more commonly than men. There is right side predominance. In 13–47% of patients this disease affects both shoulders.[8]

In a study by Hay et al[9] who investigated shoulder pain in patients with adhesive capsulitis, steroid injection have similar effectiveness with ultrasound therapy. Van der Windt et al[10] in their study concluded that local steroid injection is more effective than ice or hot packs and electrotherapy, although it has more adverse reactions, such as facial flushing, gastric ulcer, and irregular menstrual bleeding.

In this study we aim to investigate the effectiveness of ultrasound therapy as an alternative therapy to avoid the adverse reactions of local steroid therapy.

METHODS

Patients

This study was conducted at the rheumatology and rehabilitation clinic at Cipto Mangunkusumo General Hospital, Jakarta from June until October 2005. Patients between 20–65 years old who were diagnosed with stage II rotator cuff tendinitis, had not received analgesic medication since the time of diagnosis, and visual analog scale (VAS) of more than 3 were enrolled in the study. The exclusion criteria were hypersensitivity with corticosteroid, menstrual disorders (e.g. dysfunctional uterine bleeding), and presence of local infection or fracture at the site for injection. Patients were then randomly assigned to one of the two groups: steroid injection group or ultrasound group. The initial ROM of each patient was measured with gonioscopy manufactured by Academy of Physiotherapy, Solo, Indonesia.

Treatment

Patients in the steroid group received one dose of 1 mL of triamcinolone acetonide mixed with 1 mL of lidocaine 2%, injected at a site 2 cm under the posterolateral angle of the acromion. Patients in the ultrasound group were given ultrasound therapy in 10 sessions, each with a duration of 10 minutes, performed with Sonopuls 590 (Enraf-Nonius B.V., Rotterdam, The Netherlands) using 1 MHz frequency and 1.5 Watt/cm^2 intensity, given at approximately the same location as the steroid injection.

Follow-ups

Evaluation of VAS was performed in 10 days (5 days for each week: day 1–5 and 8–12), while evaluation of the abduction as well as external and internal rotation ROM was performed twice a week (day 2, 5, 9, and 12).

Statistical analysis

Comparison was made between the change of variables in the two groups at the end of the second week (day 12). Statistical analysis of subsequent follow-ups (compared with baseline value) were performed with paired T-test, while the comparison of the post-treatment change of VAS as well as abduction, internal and external rotation ROM between the two groups were performed with unpaired T-test.

RESULTS

Thirty patients, consisting of 15 patients in each group, were enrolled in the study. Most of the patients were female (63.33%). The age range was between 42 to 65 years old. Right shoulder was the most commonly involved (50%); 11 patients (36.67%) had left shoulder involvement, and four patients (13.33%) had both their shoulders involved (table 1).

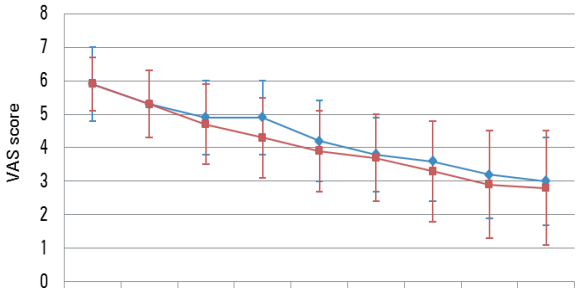
Table 1 Baseline characteristics of both groups

Characteristics	Ultrasound group (n = 15)	Steroid injection group (n = 15)
Gender, female, n (%)	9 (60)	11 (73.3)
Age	56 (5.8)	54.8 (7.4)
Visual analog scale	6.1 (1.2)	6.2 (0.8)
Abduction range of motion	103.0 (44.3)	122.0 (35.9)
Internal rotation range of motion	39.5 (16.7)	49.7 (16.8)
External rotation range of motion	79.7 (21.7)	83.7 (15.2)

Unless otherwise specified, values are presented as mean (SD).

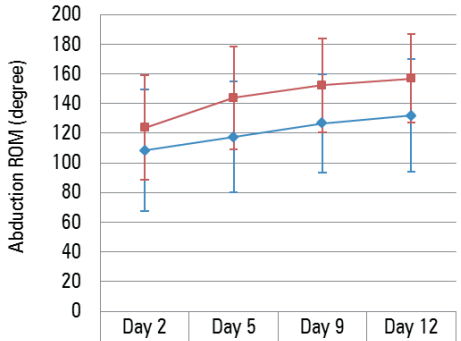
Because the pain usually occurs after waking up in the morning, most of the patients could not identify the underlying cause of their tendinitis. Five patients suspected their sport activities, either golf or badminton, which required repeated movement of the arm over the head, as the cause of their symptoms. Four patients suspected their occupation as shopkeeper, which required lifting heavy objects repeatedly, as the underlying cause. Only one subject who could recall a single traumatic event that led to the symptoms.

The decrease in VAS during the follow-ups was mostly significant, slightly earlier in the steroid injection group (day 2; p = 0.041) compared with the ultrasound group (day 3; p = 0.001) (figure 1). Significant increase in abduction ROM was achieved at the same rate (beginning at day 5) in both groups (figure 2). Significant increase in internal rotation ROM was achieved at day 9 in the ultrasound group (p = 0.043) but only seen at day 12 in steroid injection group (p = 0.044) (figure 3). There was no statistically significant increase in the external rotation ROM in both groups (figure 4). At the end of the second week, significant difference between the two groups was only shown in the abduction ROM, with slightly higher increase in the steroid group (table 2).



	Day 2	Day 3	Day 4	Day 5	Day 8	Day 9	Day 10	Day 11	Day 12
Ultrasound	5.9	5.3	4.9	4.9	4.2	3.8	3.6	3.2	3.0
Steroid injection	5.9	5.3	4.7	4.3	3.9	3.7	3.3	2.9	2.8

Figure 1 Daily evaluation of visual analog scale (VAS). Values shown are mean and standard deviation. Significant ($p<0.05$) decrease in VAS was observed at day 3, 4, 5, 9, 10, 11, and 12 in the ultrasound group and at day 2, 3, 4, 5, 8, 10, and 11 in the steroid injection group.



	Day 2	Day 5	Day 9	Day 12
Ultrasound	108.3	117.3	126.7	131.8
Steroid injection	123.7	144.0	152.3	157.0

Figure 2 Evaluation of abduction range of motion (ROM). Values shown are mean and standard deviation. Significant increase ($p<0.05$) in abduction ROM was observed at day 5 and 9 in the ultrasound group and at day 5, 9, and 12 in the steroid injection group.

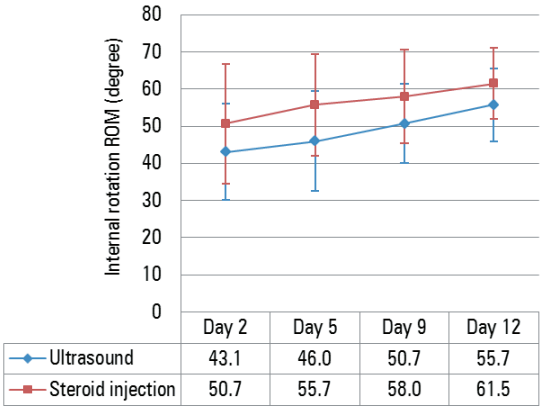


Figure 3 Evaluation of internal rotation range of motion (ROM). Values shown are mean and standard deviation. Significant increase ($p<0.05$) in internal rotation ROM was observed at day 9 and 12 in ultrasound group and at day 12 in the steroid injection group.

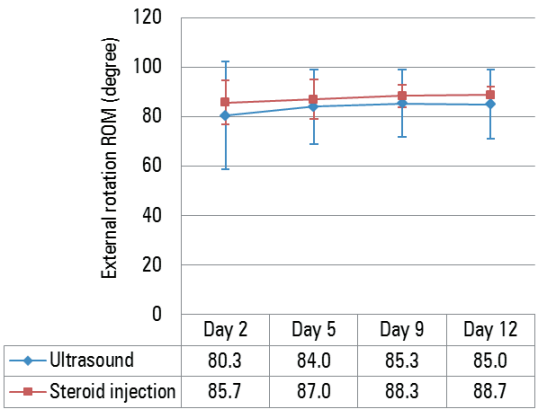


Figure 4 Evaluation of external rotation range of motion (ROM). Values shown are mean and standard deviation. The increase in external ROM in both groups was found to be nonsignificant.

Table 2 Comparison of visual analog scale and shoulder range of motion (ROM) between the two groups at the end of the second week

Characteristics	Ultrasound group (n = 15)	Steroid injection group (n = 15)	p Value
Visual analog scale	3.0 (1.3)	2.8 (1.7)	0.677
Abduction ROM	**131.8 (37.9)**	**157.0 (29.6)**	**0.049**
Internal ROM	55.7 (9.8)	61.5 (9.6)	0.078
External ROM	85.0 (14.0)	88.7 (3.5)	0.365

Unless otherwise specified, values are presented as mean (SD). Statistically significant results are in boldface.

DISCUSSION

Most of the patients with rotator cuff tendinitis were female, and right shoulder was more commonly affected than left shoulder. These findings confirmed what has been stated in literature.[8]

Compared with the baseline levels, the decrease of VAS in the two groups were mostly significant. However, there was no significant difference between the two groups, which indicated that ultrasound therapy was as effective as local steroid injection in alleviating pain in patients with rotator cuff tendinitis. This result is similar with a study by Hay et al[9] which involved patients with adhesive capsulitis.

There were significant increase of abduction ROM at day 5 and 9 in the ultrasound group and at day 5, 9, and 12 in the steroid group. The higher increase in the steroid group may be due to the direct infiltration of the steroid into the suprapinatus tendon. We performed ultrasonography to the patients and found that 83% had supraspinatus tendinitis. Since the supraspinatus muscle, together with the deltoid muscle, is the main muscle involved in the first 90° of abduction movement, this may explain the improvement seen in the group who received steroid injection.

Significant increase in internal rotation ROM was seen at day 9 in the ultrasound group and at day 12 in the steroid group. There was no significant difference between the two groups. There was also no significant difference in external rotation ROM between the two groups. While this may indicate similar effectiveness of both methods, it is also important to consider the limitation of this study such as the limited number of samples and that not all patients experienced all types of ROM limitation. Because steroid injection has more adverse effects, such as gastric ulcer, flushing, and dysfunctional uterine bleeding,[10] ultrasound therapy may provide a safer alternative to steroid injection, particularly in patients to whom steroid injection was contraindicated.

CONCLUSION

The ultrasound and steroid injection showed comparable effectiveness in alleviating pain and improving ROM limitation in patients with rotator cuff tendinitis. Because of its less adverse effects, ultrasound therapy may be used as a safer alternative to steroid injection.

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Comparison of the prevalence of hyperuricemia in families of patients with and without gouty arthritis among Balinese people

G Kambayana, TR Putra

Division of Rheumatology, Department of Internal Medicine, Udayana University School of Medicine/Sanglah Hospital, Denpasar

ABSTRACT

Background: Gout is a metabolic disorder caused by hyperuricemia, which results from changes in uric acid metabolism. Both internal (e.g., genetics) and external factors (e.g., diet, habits, comorbidities) play role in the occurrence of hyperuricemia and the difference of hyperuricemia prevalence in different populations.

Objective: To compare the prevalence of hyperuricemia in families of gout and non-gout patients among Balinese people.

Methods: This cross-sectional study was carried out at the rheumatology clinic at Sanglah Hospital, Denpasar. Samples were collected using consecutive method and consisted of gout and non-gout patients. Several characteristics (alcohol and purine consumption, medications, blood pressure, body mass index, serum uric acid level, and serum creatinine) in both groups were collected and compared. Family members (first-degree relatives) of patients in each group were also recruited and had their serum uric acid level measured and compared.

Results: A total of 46 patients and 116 family members (23 patients and 58 family members in each group) were enrolled. Among gout patients, there was significantly higher prevalence of hyperuricemia, serum uric acid level, blood pressure, and serum creatinine; and lower creatinine clearance compared with the non-gout patients. There was significantly higher prevalence of hyperuricemia among families of gout patients compared with families of non-gout patients (60.3 vs. 29.3%, respectively; $p = 0.001$), with a prevalence ratio of 2.06. Mean serum uric acid level of the family members of gout patients were also significantly higher than the family members of non-gout patients (7.24 (SD 1.74) vs. 5.92 (SD 1.63) mg/dL, respectively; $p = 0.000$).

Conclusion: Among Balinese people in this study, significantly higher prevalence of hyperuricemia and mean serum uric acid level was observed in families of gout patients compared with families of non-gout patients.

Hyperuricemia (also known as uricacidemia, hyperuricacidemia, or uricemia) is a condition characterized by an increase in the serum uric acid level.[1] Hyperuricemia is defined as serum uric acid level of more than 7 mg/dL (6 mg/dL for female).[2] Uric acid is produced from the conversion of xanthine, an end-product of purine metabolism.[3] This substance, which was discovered in 1776 by Schele, is a white crystal that has no taste or odor and undergo degradation in high temperature into hydrogen cyanide. It has low solubility in water but is soluble in glycerin or alkaline solutions, a principle that is used in urine alkalinization to prevent urate stones formation. Due to the lack of uricase enzyme in human body, uric acid could not be further catabolized into more soluble compound.

Causes of hyperuricemia can be primary of secondary, and are related to the formation and metabolism of uric acid, which are influenced by endogenous (e.g., gender, age, genetics, presence of obesity, hypertension, kidney disease, or myeloproliferative disorders) as well as exogenous factors (e.g., diet, medications, alcohol consumption, or activity).[4] Genetic variance or defects may cause disturbance in uric acid metabolism, such as an increase in production, decrease in excretion, or the combination of both.[5] Exogenous factors account for 15% of the incidence of gout.[6]

Gout is a group of heterogeneous diseases that occur as a result of the deposition of monosodium urate crystals due to supersaturation of extracellular fluid with uric acid.[7] A small proportion (<5%) of uric acid binds with plasma protein, while the majority (~98%) of uric acid in plasma and other extracellular fluid exists in the form of monosodium urate at pH 7.4. Plasma is saturated with monosodium urate at a concentration of 6.8 mg/dL at 37°C. In higher concentration (i.e., hyperuricemia), there will be supersaturation of plasma with uric acid, thereby increasing the possibility of urate crystal precipitation.[8] This crystal deposition will induce gout. The clinical manifestations of gout depend on the location of monosodium urate crystal deposition: gouty arthritis when it is deposited in joints, formation of tophus/i or tenosynovitis when deposited in soft tissue, and formation of urate stones when deposited in urinary tract, which may lead to kidney failure.[9]

There are different underlying genetic mechanisms in hyperuricemia and gout;[10] however, the positive correlation between hyperuricemia and gout has been known.[11] Epidemiological studies had shown that the majority of gout patients have hyperuricemia, although around 15% of individuals

without gout also have hyperuricemia.[12] In Indonesia, populations in Northern and Southern Sulawesi as well as in Northern and Western Sumatra have high prevalence of hyperuricemia, which is regarded to occur as a result of genetic influences.[12] In previous studies in Bali, there was a high prevalence of hyperuricemia in families with history of gout, particularly among men. In a study that involved 64 family members of 18 patients with gouty arthritis, hyperuricemia was detected in 17 individuals (26.6%); frequency of hyperuricemia in male siblings was 41.6%, male offsprings 39.1%, and female offsprings was 5.0%.[7]

The aim of this study is to evaluate whether there is significant difference in the prevalence of hyperuricemia in families of gout and non-gout patients in Balinese population.

METHODS

Study design and patients

This cross-sectional study was conducted at the rheumatology clinic at Sanglah Hospital, Denpasar, Bali between July and November 2008. Samples were collected using consecutive method. Gout patients older than 12 years old who were diagnosed based on the 1977 American College of Rheumatology criteria for gouty arthritis were recruited. As a control group, patients with diagnosis other than gouty arthritis were also enrolled. Patients who had no family member, or had chronic kidney disease stage IV–V or myeloproliferative disorders were excluded from the study. Family members (first-degree relatives older than 13 years old) of each group were subsequently recruited and had their serum uric acid level measured. All participants gave consent to be enrolled in this study.

Assessment

Several clinical and demographic data were collected from the patients: age, height, weight, blood pressure, history of alcohol drinking, medications, diet history, serum uric acid level, and serum creatinine. Serum uric acid level of the family members was also measured. Obesity was defined as body mass index of ≥25 kg/m^2. Alcohol drinker was defined as having history of at least one drink of alcoholic beverage in the last 1 month. One standard drink in this study was defined as any alcoholic beverage that contains 10 g of ethanol (1 mL ethanol = 0.79 g).[13] Medications were defined as drugs that may affect serum uric acid level: low-dose aspirin (<2 g/day), diuretics (thiazide, furosemide), antituberculosis drugs (pyrazinamide, ethambutol), and uric acid-lowering drugs (allopurinol, probenecid). High-purine diet was defined as consumption of >300 mg purine per day. Diet history was assessed using a semiquantitative food frequency questionnaire, the data of which was used to calculate the amount of purine consumption per day (in mg/day), using a method that had been validated (κ coefficient = 0.816) in a previous study[14] in Denpasar. Hyperuricemia was defined as serum uric acid of more than 7 mg/dL (male) or 6 mg/dL (female). Hypertension was defined as systolic pressure of ≥140 mmHg or diastolic pressure of ≥90 mmHg.

Statistical analysis

Differences between the two groups were analyzed by χ^2 or Fisher's exact test as appropriate (for categorical variables), or by unpaired t-test or Mann-Whitney U test as appropriate (for numerical variables). A p value <0.05 was considered as significant. Additionally, prevalence ratio of hyperuricemia among the family members of the two groups was also calculated.

RESULT

Patients

Forty six patients (23 in each group) were enrolled in this study. From analysis we found that patients with gout had significantly higher prevalence of hyperuricemia, serum uric acid level, blood pressure, and serum creatinine; and lower creatinine clearance (table 1) compared with non-gout patients.

Table 1 Characteristics of patients

Characteristics	Gout (n = 23)	Non-gout (n = 23)	p Value
Age, years, mean (SD)	49.96 (8.10)	49.52 (7.66)	0.853
Male, n (%)	22 (95.70)	22 (95.70)	1.000
Obesity, n (%)	15 (65.22)	13 (56.52)	0.763
Body mass index, kg/m^2	25.78 (12.86)	25.33 (12.30)	0.750
Alcohol drinker, n (%)	0 (0)	1 (4.30)	1.000
On medications, n (%)	0 (0)	1 (4.30)	1.000
High-purine diet, n (%)	2 (8.70)	0 (0)	0.489
Amount of purine consumption, mg/day	104.50 (337.23)	69.75 (199.99)	0.132
Hyperuricemia, n (%)	20 (86.96)	9 (39.13)	**0.002**
Serum uric acid level, mg/dL, mean (SD)	8.67 (1.72)	6.88 (1.23)	**0.000**
Hypertension, n (%)	11 (47.83)	6 (26.09)	0.222
Systolic pressure, mmHg	140.00 (60.00)	120.00 (50.00)	**0.001**
Diastolic pressure, mmHg	90.00 (20.00)	80.00 (40.00)	**0.012**
Serum creatinine, mg/dL, mean (SD)	1.39 (0.44)	1.07 (0.18)	**0.003**
Creatinine clearance (calculated), mL/min	62.90 (126.90)	82.50 (97.17)	**0.018**

When not indicated, values are presented as median (range); statistically significant results are in boldface.

Family members

A total of 116 family members (58 in each group) were enrolled in this study. The prevalence of hyperuricemia was significantly higher in family members of gout patients compared with family members of non-gout patients (60.3 vs. 29.3%, respectively), with a prevalence ratio of 2.06. Table 2 describes the characteristics of family members in more detail.

Table 2 Characteristics of the family members

Characteristics	Gout (n = 58)	Non-gout (n = 58)	p Value
Age, years	40.62 (17.98)	41.45 (15.08)	0.789
Male, n (%)	41 (70.7)	36 (62.1)	0.432
Hyperuricemia, n (%)	35 (60.3)	17 (29.3)	**0.002**
Serum uric acid level, mg/dL			
Men	7.57 (1.82)	6.82 (1.30)	**0.043**
Women	6.44 (1.25)	4.43 (0.82)	**0.000**
Overall	7.24 (1.74)	5.92 (1.63)	**0.000**

When not indicated, values are presented as mean (SD); statistically significant results are in boldface.

When the family members were further classified and compared based on family relation and gender, we found that serum uric acid level was consistently higher in family members of gout patients (table 3).

Table 3 Serum uric acid level (mg/dL) in family members

Relationship	Gout		Non-gout	
	N	Mean (SD)	n	Mean (SD)
Parents				
Father	4	7.37 (2.40)	3	6.26 (1.30)
Mother	1	7.90	5	4.48 (0.816)
Siblings				
Male	23	7.84 (1.95)	21	6.80 (1.46)
Female	12	6.28 (1.27)	11	4.35 (0.82)
Offsprings				
Male	14	7.19 (1.46)	12	6.99 (1.05)
Female	4	6.53 (1.26)	6	4.55 (0.97)
Overall	58	7.22 (1.75)	58	5.91 (1.63)

DISCUSSION

In this study, we found that the prevalence of hyperuricemia in families of gout patients was 60.3%. This result is higher compared with a previous study[15] conducted at our institution that also involved families of gout patients, which found a prevalence of 26.6%. Compared with the same study, serum uric acid level of the family members of gout patients in this study was lower (8.5 vs. 7.4 mg/dL, respectively).

The importance of genetic factors in hyperuricemia has long been known. The fact is especially evident in studies involving populations that are genetically isolated, such as indigenous peoples.[16] A study in Taiwan found that the hyperuricemia rate in adolescent was higher in indigenous tribes with high gout prevalence (57.7%) compared with non-indigenous population (48.2%) or indigenous tribes with low gout prevalence (34.0%).[17] In this study, genetic defects causing disturbance in uric acid metabolism may explain the higher prevalence of hyperuricemia in families of gout patients. Moreover, obesity and hypertension, which are the known risk factors for hyperuricemia, are also influenced by genetic factors.[18]

As has been stated, hyperuricemia occurs under the influence of internal as well as external factors and this may explain why hyperuricemia was also found in the family members of non-gout patients. Diet is an important external factor that also contributes to the result of our study. Families who live together in one house usually have similar diet. If genetic defects causing disturbance in purine metabolism are already present in the family, regular consumption of high-purine diet could further aggravate the problem.

In this study, a statistically significant prevalence of hyperuricemia and serum uric acid level was observed among families of patients with gouty arthritis; however, it is important to mention several limitations that might influence the result of this study. This was a cross-sectional study and thus we only measured serum uric acid at a given point in time, while the level of serum uric acid in the body may actually fluctuate over period of hours, and transient hyperuricemia sometimes occur in healthy individuals.[19] Also, not all family members gave consent to participate in this study and this might cause bias in the result. A more definitive result could be drawn from further, more detailed studies with better control over both the internal and external factors.

CONCLUSION

The prevalence of hyperuricemia and mean serum uric acid level was significantly higher in families of gout patients compared with families of non-gout patients among Balinese people in this study.

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Diagnostic criteria of knee osteoarthritis in rheumatology outpatient clinic, Dr. Sardjito Hospital, Yogyakarta

N Kertia, DN Wachid, PN Krishnan

Division of Rheumatology, Department of Internal Medicine, Gadjah Mada University School of Medicine/Sardjito Hospital, Yogyakarta

ABSTRACT

Background: Osteoarthritis (OA) is a chronic condition characterized by the breakdown of joints cartilage. Approximately 25% of persons 55 years of age or older have knee pain on most days and about half of them have radiographic OA in the knee. Prevalence of knee OA increases with age and it is more common in women than men. It is not easy to establish the diagnosis of knee OA since other knee disorders have similar clinical signs and symptoms.

Objective: The purpose of this study was to observe the diagnosis pattern of knee OA in rheumatology outpatient clinic at Dr. Sardjito Hospital based on clinical and radiographic criteria of American College of Rheumatology (ACR).

Method: The design of this study was cross-sectional. Data of the patients with knee OA were investigated from their medical records.

Results: There were 212 subjects diagnosed with knee OA during the year 2000–2010. Most of the subjects (90.56%) were more than 50 years old. Women were more frequent affected by OA than men. All of the subjects (100%) had knee pain. Crepitus was found in 98.11% subjects. Morning stiffness less than 30 minutes was found in 86.79% subjects. Osteophyte appearances were found in 79.72% subjects.

Conclusion: Knee pain, crepitus, and age more than 50 years old were the most frequent criteria used to diagnose knee OA. Morning stiffness less than 30 minutes and osteophyte appearances were also frequent in knee OA.

Osteoarthritis (OA) is one of the most common form of arthritis in primary care practice.[1] As the most common form of arthritis, it becomes a major contributor to functional impairment and reduced independence in elderly. Osteoarthritis of the hip and knee are two of the most important causes of pain and physical disability in community-dwelling adults.[2] Approximately 25% of persons 55 years of age or older have knee pain on most days and about half of them have radiographic OA in the knee, which the group are considered to have symptomatic OA. Prvelance of knee OA increases with age and it is more common in women than men.[3] Pain associated with OA is the chief complaint of most patients, prompting them to seek medical attention. Pain can originate from synovial membrane, joint capsule, periarticular muscles, ligaments, periosteum, and subchondral bone.[1]

Osteoarthritis is traditionally thought of as a non-inflammatory type of arthritis, despite inflammatory mechanisms may occur.[1] It is a complex disease which pathogenesis includes the contribution of biomechanical and metabolic factors, altering the tissue homeostasis of articular cartilage and subchondral bone, determine the predominance of destructive over productive processes. A key role in the pathophysiology of articular cartilage is played by cell-extracellular matrix (ECM) interactions, which are mediated by cell surface integrin. Abnormal integrin expression alters cell-ECM signaling and modifies chondrocyte synthesis, with the following imbalance of destructive cytokines over regulatory factors.[4]

Variables from medical history, physical examination, laboratory tests, and radiographs were used to develop sets of criteria that have different investigative purposes. Based on the American College of Rheumatology (ACR) clinical and radiographic criteria, knee OA can be diagnosed if there is knee pain with at least one of the three (age >50 years, stiffness <30 minutes, crepitus) and osteophytes in radiograph.[5]

METHODS

The design of this study was cross-sectional. It was conducted by collecting data from medical records from year 2000 to 2010 in rheumatology outpatient clinic of Dr. Sardjito Hospital. All subjects whom diagnosed with knee OA were included in the study. The data was processed and then compared based on the ACR clinical and radiographic criteria, age dispersion, gender, and common sites of affected knee .

RESULTS

This research consists of 212 subjects who had been diagnosed with knee OA from year 2000 to 2010. Almost patients (90.56%) were more than 50 years old. The highest age group who suffered from OA was 61-70 years (39.62%). The lowest was <41 years old with 2.36%. Full description of age distribution of the patients is enclosed in table 1 and figure 1.

Table 1 Distribution of patients with knee osteoarthritis according to age group

Age group	Number of patients	%
<41	5	2.36
41-50	15	7.08
51-60	54	25.47
61-70	84	39.62
71-80	48	22.64
>80	6	2.83
Total	212	100.00%

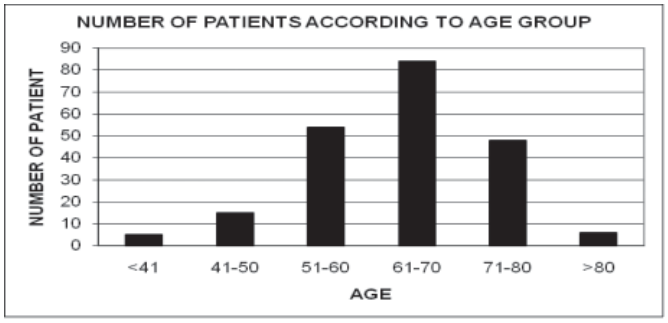

Figure 1 Number of patients according to age group

As shown in table 2, total women with knee OA was two times more than men. Overall women have higher distribution in all age groups, except for >80 years old group, which both of women and men have the same number. The highest number of women suffered from OA was in the age group of 61-70, which was 59 patients (27,83% of total patients).

Table 2 Gender distribution according to age group

Age Group	Gender	
	F	M
<41	3 (1,41%)	2 (0,94%)
41-50	12 (5,66%)	3 (1,41%)
51-60	33 (15,56%)	21 (9,90%)
61-70	59 (27,83%)	25 (11,80%)
71-80	36 (17,00%)	12 (5,67%)
>80	3 (1,41%)	3 (1,41%)
Total	146 (68,87%)	66 (31,13%)

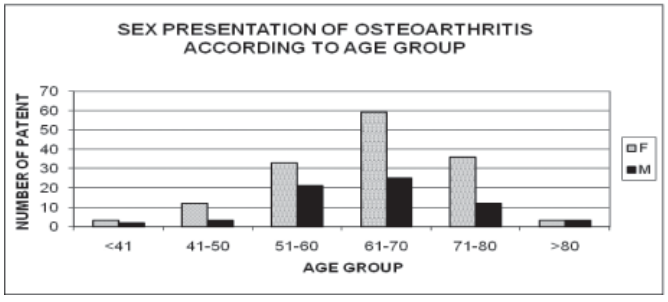

Figure 2 Gender presentation according to age group

Table 3 shows the distribution of symptoms and signs suffered by OA patients. These criteria are useful for diagnosing knee OA. From table 3, it is shown clearly that all of the patients had pain on the knee, while 208 patients (98,11%) had crepitus on active motion. Moreover, 184 patients (86.79%) had morning stiffness less than 30 minutes, while 28 patients (13.21%) had more than 30 minutes. From radiographic examination, 169 patients (79.72%) had osteophytes in their X-ray image, while 43 patients (20.28%) had no osteophyte appearence but there were subchondral sclerosis or joint space narrowing appearences.

Table 3 Clinical presentation and radiographic data of knee osteoarthritis

Pain on the knee	Absent	0 (0,00 %)
	Present	212 (100,00%)
Crepitus on active motion	Absent	4 (1,89%)
	Present	208 (98,11%)
Morning stiffness	≥ 30 minutes	28 (13,21%)
	< 30 minutes	184 (86,79%)
Osteophytes	Absent*	43 (20,28%)
	Present	169 (79,72%)

*subchondral sclerosis or joint space narrowing were present

Table 4 and figure 3 show that most of patients had bilateral OA (64,15%).

Table 4 Side of the affected knee in patients with osteoarthritis

Side	Number of patients
Right knee	36 (16,98%)
Left knee	40 (18,87%)
Bilateral	136 (64,15%)
Total	212 (100,00%)

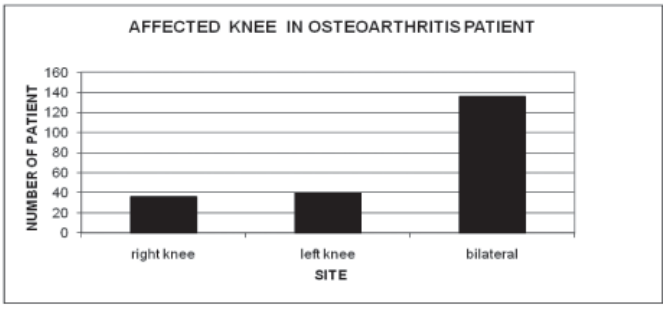

Figure 3 Affected knee in osteoarthritis patients

DISCUSSIONS

Osteoarthritis is a type of arthritis caused by the breakdown and eventual loss of cartilage of one or more joints. Cartilage is a protein substance that serves as a "cushion" between the bones of the joints. As a degenerative arthritis, it often begins in the 40s and 50s and affects almost all people to some degree by age 80.[2] It is consistent with this study that majority of patients (90.56%) with knee OA were more than 50 years old.

Primary OA is mostly related to aging. Within aging process, the water content of cartilage increases, while the protein make up of cartilage degenerates. Eventually, cartilage begins to degenerate by flaking or forming tiny crevasses. In advanced cases, there is a total loss of cartilage cushion between the bones of the joints. Repetitive use of the worn joints over the years can irritate and inflame the cartilage, causing joint pain and swelling. Therefore, it is reasonable that all subjects (100%) had knee pain. The pain associated with OA is the chief complaint of most patients, prompting them to seek medical care.[2]

The cause of pain in patients with knee OA remains unclear. Osteoarthritis has been considered as a disease which characteristic pathologic feature is loss of hyaline articular cartilage; however that tissue contains no pain fiber. Pain fibers are present in several other structures, that are often affected by pathologic processes in knee OA, including joint capsule, ligaments around the knee joint, the outer third of the meniscus, periosteum, and possibly the synovium.[6]

Osteoarthritis affects women more often than men and its prevalence and incidence increase after menopause. Many experimental, clinical, and epidemiological studies suggest that loss of estrogen at the time of menopause increases a woman's risk of getting OA. This was also supported by some preclinical studies which had been conducted on rats. Ovariectomy induced acceleration of cartilage degradation and erosion in rats indicate that estrogen deficiency accelerates cartilage turn over and increases cartilage surface erosion.[7] In this study, total number of women suffered knee OA was two times more than men.

Osteophytes can form early in the development of OA and can be seen prior to joint space narrowing. Osteophytes can have a significant clinical impact and can be a source of pain and loss of function. The latter is mainly through nerve compression, limitation of joint mobility, and obstruction of tissues and organs ossification. Osteophytes are so common as a radiographic feature of OA that they have been used to define the presence of the disease. They most often appear at the margins of the joint, originally as outgrowths of cartilage and subsequently undergo endochondral ossification.[8]

Crepitus on active motion have become one of the criteria used to diagnose OA. Crepitus on active motion simply means noise or "creck" sensation feeling by the observer's hand when there is movement of the leg in lay mans term.[9] Based on the collected data, 98.10% of the patients had crepitus on active motion.

Morning stiffness is a frequent symptom in arthritis patients. More severe joint inflammation is related with longer symptom of morning stiffness. Because OA is a degenerative and mild joint inflammation, the morning stiffnes in OA is mostly not longer than 30 minutes.[10] This research found that 184 patients (86.79%) had morning stiffness less than 30 minutes, while only 28 patients (13.21%) had at least 30 minutes morning stiffness.

CONCLUSIONS

The conclusions of this research are:

1) Most of the patients with knee OA were more than 50 years old
2) Women were mostly affected by knee OA compared to men
3) Pain was the main symptom suffered by all of the patients
4) Crepitus on active movement of the knee was the most frequent sign in knee OA
5) Most of the patients suffered morning stiffness less than 30 minutes
6) Most of the patient showed positive result of osteophytes in x-ray examination, while others showed joint space narrowing or subchondral sclerosis.

SUGGESTION

Since this data shows a little bit differences compared to ACR clinical and radiographic criteria for OA, we suggest the criteria for diagnosis of knee OA should be built depend on the epidemiological studies of each area in the world.

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Experience with cyclophosphamide in the treatment of a young woman with refractory dermatomyositis

B Setiyohadi,[1] R Sinto[2]

[1] Division of Rheumatology, Department of Internal Medicine, University of Indonesia School of Medicine/Cipto Mangunkusumo General Hospital, Jakarta
[2] Department of Internal Medicine, University of Indonesia School of Medicine/Cipto Mangunkusumo General Hospital, Jakarta;

Dermatomyositis is an idiopathic inflammatory myopathy characterized by the presence of rash and moderate-to-severe muscle weakness secondary to inflammation of the muscle. It can be a difficult condition to treat. Systemic corticosteroids are the first choice of treatment. However, about a quarter of patients either fail to respond to steroids or develop steroid-related toxicity. Second-line agents such as azathioprine and methotrexate are then added either alone, or in combination with corticosteroids. Failure of the disease to respond to second-line agents can then be a problem and this is often referred to as "refractory dermatomyositis". Unfortunately, there is neither agreement nor well-established guidelines on the best regimen or combination of immunosuppressive agents in the case of refractory dermatomyositis.

CASE REPORT

A 22-year-old woman was admitted to hospital for complaint of progressive muscle weakness that had been worsening since one week before admission.

Three months before the admission, she had complained of mild muscle weakness and generalized fatigue. There were no fever, joint aches, difficulty in climbing stairs or arising from a seated position, difficulty in raising her arms, rash, dyspnea, or swallowing problems. The patient consulted a general practitioner and was given several tablets of vitamins; the complaints did not improve. She then consumed traditional herbs, but the symptoms continue to worsen.

For the one month before admission, she was no longer able to climb stairs normally, and noticed a progressive loss of body weight (approximately 9 kg in 3 months). At the same time, a rash appeared over her cheeks and forehead, and she experienced swallowing difficulty.

One week before the admission, the patient reported her inability to arise from supine position and was unable to raise her arms without any help. She also developed a high fever with productive cough and purulent sputum. She had not consumed any over the counter drugs. There was no complaint of abdominal pain or dysphonia. The patient then consulted a neurologist and was then referred to a rheumatologist.

Physical examination showed Glasgow coma scale of 15; the patient was moderately ill with pulse rate of 96 beats/min, regular, respiratory rate of 22 breaths/min, and body temperature of 38.1°C. She was thin, with a body weight of 43 kg, height of 162 cm, and body mass index of 16.3 kg/m^2. She had muscle atrophy. There was rash over her cheeks and forehead. Chest auscultation revealed vesicular breath sound with diffuse rales; there was no wheezing. Her cardiac and abdominal physical examinations were unremarkable. There was no lymph node enlargement. Neurological examination of her proximal and distal arm and leg muscles strength scored 3 out of 5, with the impression of paresis of the ninth and tenth cranial nerve and decreased oromotor movement.

Her laboratory tests showed high erythrocyte sedimentation rate at 70 mm/hr, with haemoglobin of 11.7 g/dL, leukocyte count of 12 × 10^3/mm^3 (neutrophils 91%), and platelet count of 385 × 10^3/mm^3. The titer of aspartate transaminase (AST), alanine transaminase (ALT), and creatine kinase (CK) were high at 1,059 U/L, 390 U/L, and 21,093 U/L, respectively. Her hepatitis A, B, and C seromarkers were negative, with γ-glutamyl transferase (γ-GT) of 37 U/L. Her C-reactive protein (CRP) titer was 12 mg/L, calcium was 9.4 mg/dL, and phosphate was 3.3 mg/dL. The immunology panel showed CD4+ level of 301 cells/μL, positive antinuclear antibody (ANA) with negative ANA profile (including anti Jo-1), and normal titer of total IgE, IgA, IgM, IgG, IgM anticardiolipin antibody (ACA), IgG ACA, thyroxine (T4), and sensitive thyroid stimulating hormone (sTSH).

Her chest X-ray showed presence of infiltrates consistent with pneumonia. Sputum culture revealed *Pseudomonas sp.* sensitive to ceftazidime, ciprofloxacin, piperacilin/tazobactam, cefoperazone/sulbactam, doripenem, cefepime, cefpirome, meropenem, imipenem, levofloxacine, and gatifloxacine. Abdominal ultrasound was normal. Electromyography (EMG) and nerve conduction tests revealed diffuse myogenic lesions over her upper and lower extremities with normal motor and sensory nerve conduction velocity, consistent with clinical myositis. Her fiber optic endoscopic evaluation of swallowing (FEES) study with nasopharyngolaryngoscope revealed oropharyngeal phase of neurogenic dysphagia with silent aspiration and high risk for respiratory tract aspiration.

A diagnosis of dermatomyositis, oropharyngeal phase of neurogenic dysphagia with silent aspiration, and community acquired pneumonia with differential diagnosis of aspiration pneumonia was made. We gave the patient a total of 2100 kkal of soft diet via nasogastric tube and intravenous fluid 1500 mL/day. We began treatment with intravenous methylprednisolone 125 mg b.i.d for three consecutive days, tapered down to 125 mg q.d., 62.5 mg q.d., and 16 mg t.i.d. We also administered azathioprine 50 mg t.i.d., ceftazidime 1 gram t.i.d., and a tablet containing combination of calcium hydrogen phosphate 500 mg and cholecalciferol 133 IU t.i.d. The patient was also referred for physiotherapy program.

After a month of hospitalization with those medications, the rash, fever, and cough resolved. Serial chest X-ray confirmed the improvement of lung condition. However, there was no improvement in her swallowing problem. Furthermore, there was declining muscle strength to grade 1 out of 5 for her proximal arm and leg muscles, and 3 out of 5 for her distal limb muscles. She underwent comparative FEES study, with disappointing result. There was also re-increment of CK titer values, as were shown in table 1; thus, we decided to add methotrexate 10 mg/week to her medications.

Due to the clinical deterioration despite the administration of corticosteroid and two immunosuppressive agents, we decided to offer to the patient and her family the administration of intravenous cyclophosphamide. The drug's potential side effects were discussed. The patient and her family consented to receive cyclophosphamide. We gave her intravenous cyclophosphamide 500 mg two-weekly. The administration of methylprednisolone was continued according to the previously planned dose, but we discontinued both azathioprine and methotrexate.

After the second administration of intravenous cyclophosphamide (table 1), the patient showed improvement of muscle strength and decreased levels of AST, ALT, and CK. Her muscle test showed that the score of proximal arm and leg muscles strength were 2 and 2, respectively, and the score of her distal arm and leg muscles strength were 3 and 3, respectively. After the third course of the two-weekly injections, the patient was discharged from hospital. The plan was for her to receive six consecutive monthly injections of intravenous cyclophosphamide 500 mg.

After the nine serial cyclophosphamide injection within 6 months, her muscle test showed that the proximal arm and leg muscles strength were 4 and 4 respectively and her distal arm and leg muscles strength were normal. The AST, ALT, and CK improved at 20 IU/L, 30 IU/L, and 270 IU/L respectively. She was then switched to mycophenolate mofetil 500 mg b.i.d. and methylprednisolone 12 mg q.d. Repeated FEES showed improved swallowing reflexes. The patient was also started to regain her ability to walk.

DISCUSSION

Idiopathic inflammatory myopathies (IIM) are heterogeneous potentially debilitating—and sometimes life-threatening—diseases characterized by muscle inflammation with subsequent weakness. On the basis of well-defined clinical, demographic, histological, and immunopathological criteria, the inflammatory myopathies form three major and discrete groups, i.e. polymyositis, dermatomyositis, and sporadic inclusion-body myositis.[1,2]

An epidemiological study from Canada in 2009 revealed that the prevalence of this disease was higher in women than men, and in older individuals, which is consistent with the result of previously published data from other countries. Prevalence estimates were lowest in young men and highest in older women.[1,3]

The clinical course is quite variable among patients with this disease. In some, the illness is brief and is followed by remission that does not require continued treatment. Other patients experience exacerbations and remissions or persistent disease activity, necessitating chronic use of immunosuppressive drugs, with the frequency of clinical and biochemical relapses varying from 34 to 60 percent in different series. Mortality is now limited to less than 10%, but long-term morbidity is still present in more than 25% of patients. Factors associated with poor survival include older age, malignancy, delayed initiation of corticosteroid treatment, pharyngeal dysphagia with aspiration pneumonia, interstitial lung disease, myocardial involvement, and complications of corticosteroid or immunosuppressive treatment.[4-6]

Given the rarity of IIM and the heterogeneity of the myositis syndromes, their management is difficult and has not been universally standardized. There are few well-

Table 1 Serial evaluation of patient's aspartate aminotransferase (AST), alanine aminotransferase (ALT), and creatine kinase (CK) titer

	Adm	W1	W2	W3	W4	W5	W6	W7	W8	W9	W13	W17	W21	W25	W29	W33
AST	1,059	712	629	589	663	474	266	173	148	120	84	-	-	-	-	20
ALT	390	309	282	253	217	177	122	94	80	74	32	-	-	-	-	30
CK	21,093	10,762	8,781	7,598	11,772	4,988	2,897	1,931	1,369	967	387	-	-	-	-	270
Treat-ment	Methylprednisolone	----------														
	Azathioprine 3×50 mg	----------														
	MTX				10 mg											
	CYP serial					1		2		3	4	5	6	7	8	9

Normal values for AST, ALT, and CK are <27 U/L, <36 U/L, and <192 U/L, respectively
Adm, admission; W, week from admission day; MTX, oral methotrexate; CYP, intravenous cyclophosphamide

controlled clinical trials concerning IIM and many of the reported studies have not adequately differentiated muscle weakness, as secondary to disease activity (implying ongoing inflammation), damage (signifying permanent damage), and the patients' own perception of their disease, to evaluate the efficacy of treatment regimen. Moreover, some patients are refractory to first and second-line treatment, requiring a more potent immunosuppressive drug.[4,5,7,8]

The diagnosis of dermatomyositis was constructed based on diagnostic criteria suggested by Bohan and Peter in 1975. Muscle histology, included as part of the criteria, remains the gold standard for confirming the diagnosis of IIM, when typical changes (infiltrates of mononuclear inflammatory cells, regenerating and degenerating muscle fibers) are present in a muscle biopsy. However, because the disease is patchy in distribution, sampling error precludes 100% sensitivity. A muscle biopsy can look normal despite clinically evident muscle weakness. Furthermore, the changes in some biopsies may be too nonspecific and the degree of histopathological feature is not correlated with the degree of muscle weakness. Our patient fulfilled four out of five criteria of Bohan and Peter diagnosis criteria, i.e. symmetrical proximal muscle weakness, elevation of serum level of skeletal muscle enzymes, abnormal EMG, and typical skin rash of dermatomyositis, which is consistent with diagnosis of definite dermatomyositis although muscle biopsy was not done in our patient.[4,9]

Swallowing difficulty in our patient, as was confirmed by FEES study, is a common comorbidity found in patients with dermatomyositis, which brings serious implications. The dysphagia associated with these myopathies primarily affects the skeletal muscle–activated oropharyngeal phase of swallowing. It may precede weakness of the extremities or even present as the sole symptom. Dysphagia is associated with nutritional deficits (reflected by our patient's progressive loss of body weight), aspiration pneumonia, decreased quality of life, and poor prognosis. In their research, McCann LJ et al failed to show any correlation between swallow score and objective measures of muscle strength and function or general disease activity and function. They concluded that in the absence of a more accurate assessment method to determine which patients are most at risk of swallow dysfunction and aspiration, all patients with active dermatomyositis should be referred for swallow assessment.[10,11]

Dermatomyositis can be a difficult condition to treat. Systemic corticosteroids are the first choice of treatment. Most patients at least partially respond to corticosteroids and a complete lack of response should prompt a reconsideration of that diagnosis.[7] However, about a quarter of patients either fail to respond to steroids or develop steroid-related toxicity. Second-line agents should then be added either alone, or in combination with corticosteroids. Failure of the disease to respond to second-line agents, and side effects of these drugs, can be a problem.[7,12]

It has not been clearly defined which dermatomyositis cases should be categorized in the group of refractory dermatomyositis. Several studies apply this terminology to cases that do not respond to second-line immunosuppressive agents, while others apply it to cases that not respond to corticosteroids.[7,12] Our patient showed at least partial response to corticosteroid, as can be seen in the minimal improvement of the clinical condition (rash) and laboratory results in the first four weeks; however, there was failure in reaching a complete response despite addition of azathioprine and metotrexate. She was thus considered a case of refractory dermatomyositis.

As previously mentioned, there is unfortunately neither agreement nor well established guidelines on the best regimen or combination of immunosuppressive agents for refractory dermatomyositis. The choice depends on the severity of the disease, extramuscular manifestations, personal experience, and the relevant relative efficacy-safety profile ratio of the drug.[8] Several immunosuppressive agents, either reported by individual case reports or case series, have been used as treatment of choice in refractory dermatomyositis cases. There is not yet head-to-head comparative trial of the different immunosuppressive agents in the management of refractory dermatomyositis. For simplifying the approach, we can refer to a therapy classification for dermatomyositis that was developed by Miller. This classification categorized those agents into three major classes. First-line therapies include methotrexate, instead of corticosteroids and other adjunctive treatment (physical therapy, hydroxychloroquine, topical therapies for skin rashes, photoprotective measures, calcium and vitamin D for bone protection). Second-line therapies include azathioprine, cyclosporine, intravenous immunoglobulin (IVIG), or combinations of these agents. Third-line therapies include mycophenolate mofetil, tacrolimus, cyclophosphamide, rituximab, anti–tumor necrosis factor agents, as well as other biologicals (e.g. anakinra, alemtuzumab) and stem cell therapy. As a general rule, for patients with severe, refractory, or corticosteroid-dependent disease, combinations of second-line therapies or newer third-line therapies are frequently used.[7–9,13] In our case, disappointing result with the second-line therapy (azathioprine) necessitated the use of a third-line agent. The third line agent we chose was cyclophosphamide.

Although it has been effective in other autoimmune diseases, cyclophosphamide has had variable results in patients with IIM. A number of reports have described the use of cyclophosphamide in dermatomyositis patients, but the numbers have been too small to draw any conclusions and certainly no controlled trial evidence exists. There may be a strong case for its use in patients with dermatomyositis, particularly when associated with vasculitis, interstitial lung disease, and involvement of respiratory or bulbar muscles.[5,8,14,15]

Retrospective analysis of 12 juvenile dermatomyositis patients treated with intravenous cyclophosphamide in various doses by Riley P et al[5] in 2004 concluded that treatment with intravenous cyclophosphamide appeared to have resulted in major clinical benefit with no evidence of serious short-term toxicity. Skin, muscular, and extramuscular features of the disease improved and this improvement persisted following the discontinuation of treatment. There were no major short-term side effects resulting from the administration of this agent, as reflected from other researches of cylophosphamide use for various autoimmune diseases. The three main long-

term concerns for any patient after cyclophosphamide administration are malignancy, infertility, and gonadal failure. Reported malignancies, with peak incidence at seven years after the therapy, have been observed in those who received more than 50 g cumulative dose of cylophosphamide. Premature ovarian failure is relatively common when cylophosphamide is administered to women over 30 years of age, but very rare in those under 20 years and only with very high dose. A study conducted by Wang et al revealed that only 4% of younger than 21 year female lupus patients receiving oral cyclophosphamide with cumulative dose over 40 g suffered premature ovarian failure.[16] Martin-Suarez et al[17] revealed that none of the patients suffered ovarian failure associated with low dose (500 mg weekly) intravenous pulses of cyclophosphamide as treatment for various severe connective tissue diseases. Martin et al[18] in their study reviewing the side effects of intravenous cyclophosphamide pulse therapy in a group of 75 patients suffering from various autoimmune disorders who received a total of 451 intravenous cyclophosphamide pulses, given on monthly basis with mean follow-up period 26.7 ± 22.1 months found that infection was the most common side effect but rarely required in-patient treatment with no premature ovarian failure observed in the 25 female patients at risk.

Those risk and benefit data support the decision to choose cyclophosphamide as the third line immunosupresive agent to be administered to our patient. There are also several other agents that could possibly be chosen, e.g. IVIG and rituximab. We decided to reserve the use of these agents due to financial consideration, in case of persistent refractory condition in our patient after cyclophosphamide treatment. Fortunately, our patient showed improvement of both clinical and laboratory parameters, obviating the need to administer additional agents. No specific short-term adverse effect was observed; however, continuous long-term monitoring of potential adverse effects is needed.

Continuous efforts are being undertaken to achieve the best possible treatment for patients with IIM, but more specific immunotherapy still awaits a precise understanding of target antigen molecules and the immunopathological process responsible for these disorders. However, the availability of new agents coupled with the development of validated reliable assessment tools to evaluate disease activity and damage offers the realistic prospect of more effective treatments.[8]

Administration of immunosuppressive agents is only a small part in the big picture of holistic management of dermatomyositis cases. Other important parts of therapy include general rehabilitative measures, proper management of potential lung complications (i.e. aspiration pneumonia due to esophageal dysfunction and ventilatory insufficiency), as well as infection management, since several predisposing factors increase the patients' risk of developing infections. These factors include upper oesophageal involvement, thoracic muscle myopathy, use of immunosuppressive drugs and immune system dysfunction due to the disease itself. The literature indicates that, not only do patients have a high rate of infectious complication (up to 33%), but infection is also implicated in 46% of deaths in this patient group, which makes it a significant prognostic factor. Close follow-up of dermatomyositis patients with risk factors for developing major infections is mandatory.[19,20]

SUMMARY

We report here a case of a young woman with refractory dermatomyositis who was treated with cyclophosphamide because the patient did not show good response despite administration of methylprednisolone, azathioprine, and methotrexate, which is consistent with a case definition of refractory dermatomyositis. Published literature suggested that treatment with intravenous cyclophosphamide appears to result in major clinical benefit with no evidence of serious short-term toxicity and considerable long-term toxicity. Our patient showed good response to cyclophosphamide, as reflected by the improvement of muscle strength and decreased level of AST, ALT, and CK after the second intravenous administration of this agent. Other important parts of therapy that should be applied include general rehabilitative measures, proper management of potential lung complications, as well as infection prevention and management.

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Sclerodermatomyositis

M Febyani,[1] H Purbo D,[1] L Hamijoyo,[2] E Sutedja,[1] O Suwarsa[1]

[1] Department of Dermatology, Padjadjaran University School of Medicine/ Hasan Sadikin Hospital, Bandung;
[2] Division of Rheumatology, Department of Internal Medicine, Padjadjaran University School of Medicine/Hasan Sadikin Hospital, Bandung

The classification of rheumatic diseases is still challenging due to several reasons. First, those diseases have several differential clinical features, which giving overlap symptoms. Second, the etiopathogenesis of those diseases remains elusive. Diagnosis of overlap syndrome is made when there are more than one well-defined connective tissue diseases in one patient, which may develop simultaneously or sequentially.[1,2] The prevalence of overlap syndrome among autoimmune diseases is 25%.[2]

The term sclerodermatomyositis or scleromyositisis is used to describe an overlap syndrome in patients with scleroderma and dermatomyositis/polymyositis (DM/PM).[2,3,4] Sclerodermatomyositis usually affects adults, and it is rarely found in children.[4] The clinical features of this syndrome are myalgia or myositis, arthralgia, scleroderma-like skin changes, Raynaud's phenomenon (RP),[2,3] interstitial lung disease, calcinosis,[3] mask-like facies, dysphagia or esophageal dysmotility,[4] as well as the presence of specific antibody Pm/Scl.[2] Skin manifestations as the part of dermatomyositis include periorbital erythema and Gottron's papules.[3]

We report this case due to its very rare occurrence. According to medical records in the Department of Dermatology as well as Rheumatology at Hasan Sadikin Hospital, Bandung, this is the first case recorded in the last 10 years.

CASE REPORT

An 18-year-old, single, Sundanese female, came to our institution with chief complaint of rashes on her arms, hands, legs, and abdomen.

Since 2 years prior to this visit, she has had complaint of joint pain on both elbows, with rashes on the surface of her knees and elbows, as well as photosensitivity and oral ulcers. At that time, his physician considered systemic lupus erythematosus (SLE) as the cause of her symptoms. Laboratory test results were normal, except for leucopenia (white blood cell count of $4 \times 10^3/mm^3$). At that time, the patient also had negative antinuclear antibody (ANA) and anti–double-stranded DNA (anti-dsDNA) tests. She was given nonsteroidal anti-inflammatory drugs (NSAIDs) and subsequently showed improvement.

One year prior to admission, she started to have difficulty swallowing foods and liquids, also accompanied with rough skin on her face, rashes on her eyelids, face, chest and back, as well as photosensitivity. Afterwards, she developed erythematous rashes on her arms, abdomen and both legs, accompanied with skin tightening. She also had alopecia and weight loss.

Physical examination on admission at our institution revealed normal vital signs. There were heliotrope rashes on her palpebras, and Gottron's papules as well as Gottron's sign over the surface of her metacarpophalangeal joints and elbows. She had rashes on her neck (shawl sign, V-sign), sclerodactyly, and muscular atrophy of her upper extremities. Rodnan skin score was 19. On palpation, the skin on her abdomen, arms, hands, legs, and feet felt tight and taut. She had difficulty raising her arms and step on ladders or stand up from sitting position.

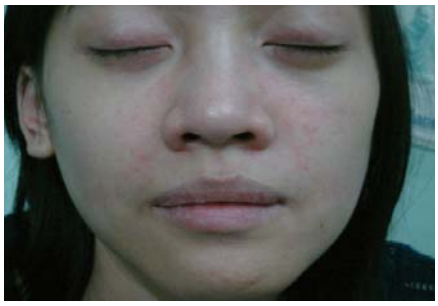

Figure 1 Heliotrophe on patient's eyes

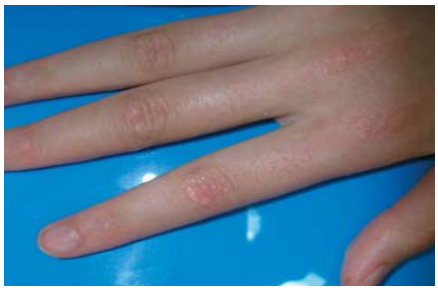

Figure 2 Sclerodactyly and Gottron's papules on PIP and DIP surface

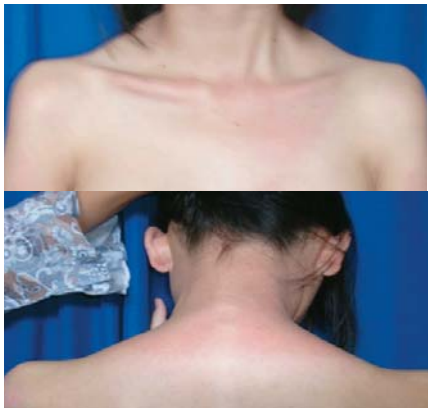

Figure 3 V sign and shawl sign

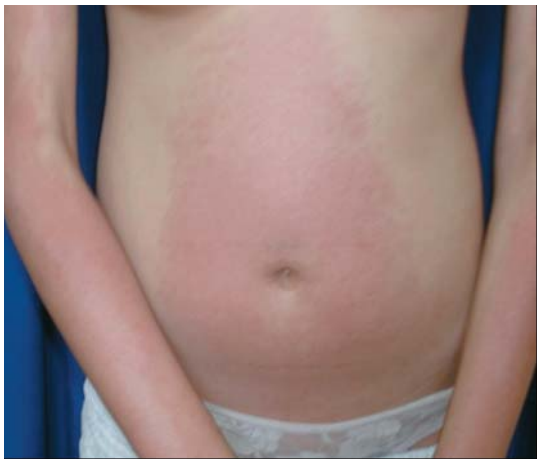

Figure 4 Rashes on the patient's arms and body

Her laboratory results were normal except for mild increase of lactate dehydrogenase (LDH) (456 U/L) and creatine kinase (CK) (20 U/L) as well as positive ANA test with speckled pattern. Anti-RNP was negative, neither anti-Jo-1 and anti-Scl-70. Skin biopsy of her femoral area revealed stratified squamous epithelium with atrophy and mild keratinization, with liquefactive degeneration of the basal layer in the center of the specimen. In dermis, a number of capillary arteries showed wall-thickening and fibrinoid degeneration. Masson's trichrome and van Gieson's stain showed thickening of some of the collagen fibrils. Direct immunofluorescence of skin biopsy specimen showed no immunoglobulin (IgG, IgA, IgM), complement component 3 (C3), or fibrinogen deposition. Electromyography (EMG) was also performed in this patient, but the result was within normal limit.

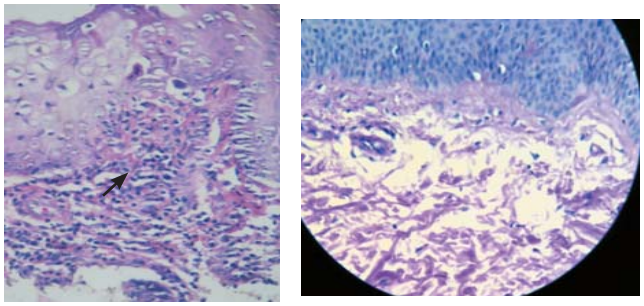

Figure 5 Histopathological specimen from patient's skin, showing liquefactive degeneration (arrow)

The patient was diagnosed sclerodermatomyositis and was given methylprednisolone 0.8 mg/kg body weight daily, methotrexate (MTX) started 7.5 mg weekly, folic acid 1 mg daily, urea and mometasone cream, as well as sunscreen cream. She was referred to the Department of Medical Rehabilitation and Department of Clinical Nutrition for further assistance with her condition.

On the follow-up at day 18, the skin rashes had reduced but the weakness and skin tautness remain. On day 43, the patient began to be able to climb stairs and rise from sitting position without help, although she still had difficulty to stand up from squatting position. The skin lesions also began to diminish, except for the skin tautness and Gottron's papules. Methylprednisolone was thus tapered down.

On day 57, CK was 32.1 U/L and LDH decreased to 434 U/L. On day 80, her condition continued to improve, Rodnan skin score was 10, and the patient could stand up from squatting position.

DISCUSSION

Dermatomyositis is an idiopathic inflammatory myopathy characterized by proximal muscle weakness and skin eruption.[5] When the skin lesions are absent, the disorder is termed polymyositis. Involvement of proximal muscles is the characteristic feature of this disease.[6,7] There are several types of dermatomyositis known: classic, amyopathic, and hypomyopathic dermatomyositis. The term classic dermatomyositis is used when myositis is accompanied with proximal muscle weakness and characteristic skin lesions. In amyopathic dermatomyositis there are skin lesions consistent with dermatomyositis which have been present for at least 6 months, without proximal muscle weakness or serum muscle enzymes abnormality. In hypomyopathic dermatomyositis, there is subclinical myositis found in laboratory examination.[7,8,9]

Creatine kinase level is important in myositis cases,[8,9,10] because of its relative sensitivity and specificity in assessing the extent of muscle fiber damage.[7,10] In 80-90% cases of myositis, CK level are usually elevated in initial measurement, but subsequently become normal due to the decrease in muscle mass or inhibition to CK activity.[10]

Measurement of other enzymes, such as aldolase, aspartate and alanine aminotransferase, and LDH can also help in making the diagnosis of myositis, particularly in patients with active disease and normal CK level.[9,10] When measurement of these enzymes is performed, it is important to consider that conditions such as liver diseases may also elevate the level of these enzymes.[10]

Erythrocyte sedimentation rate (ESR) may be elevated; however, it is not usually associated with disease activity. Elevation of rheumatoid factor (RF) may be encountered in 20% cases of dermatomyositis.[7] Electromyography is a sensitive, but not specific method in diagnosing dermatomyositis;[11] as many as 10% of patients may have normal results.[7]

In 60% of cases, skin lesions and proximal muscle weakness may occur simultaneously. Skin lesions are often accompanied by itching or burning sensation, and it may be triggered by exposure to sunlight or ultraviolet light.[7] The predominant skin lesions in dermatomyositis are symmetric, confluent, purplish erythematous macules over the extensor surface of fingers, dorsal aspects of hand, arm, deltoid area, back, and neck (shawl sign), in a "V"-like distribution over the anterior neck and upper chest (V-sign), and middle part of the face, periorbital area, forehead, and scalp.[6,11]

Characteristic lesions are often found around the eyes, appearing as a pink, scaly patch with itching, swelling, and violaceous change (heliotrope rash), or bulla.[6] Other reported skin lesions in dermatomyositis include urticaria, photosensitivity, erythema nodosum, erythema multiforme, keratosis follicularis, hypertrichosis, livedoreticularis, hyperhidrosis, psoriasiform eruption, pitting nail, and ulcer.[12]

Exfoliative dermatitis may also occur in dermatomyositis, but rare. Diffuse alopecia may occur on scalp.[9,12] Hyperpigmentation may occur later in the course of the disease.[8,12] Recurrent aphtous stomatitis was reported in one case of sclerodermatitis.[13] Periungual telangiectasia that is related to cuticular dystrophy is a characteristic lesion.[11] In patients with positive anti-synthetase antibody, there may be hyperkeratotic lesion, fissures, and linear hyperpigmentation on the palmar surface of the hand, which termed mechanic hands.[9,12]

In 20% cases, dermatomyositis is accompanied by other connective tissue diseases (overlap syndrome); thus, it is important to look for characteristic symptoms of other connective tissue diseases.[7,11] Dermatomyositis commonly overlaps with scleroderma, and it is called sclerodermatomyositis.[6]

Early in the course of the disease, weakness occurs in muscles on shoulder and waist; therefore, the patients had difficulty in performing specific movements such as moving arms upward, or stand up from sitting position. Muscle weakness may be accompanied by muscle pain and tenderness.[7] Patients with dermatomyositis often complains malaise and fatigue. Myopathy affects proximal muscle groups, particularly triceps and quadriceps,[11] with symmetrical distribution.[6,11] Later in the course of the disease, all muscle groups may be affected.[11] Other systemic disorders that also occurred in dermatomyositis were calcinosis of deep fascia and muscles,[11,12] disorder of the lung and heart, arthritis,[11] kidney, gastrointestinal system,[7,11] eyes, and malignancy.[7,12]

In 1972, Sharp et al introduce the term "mixed connective tissue disease" (MCTD), a disorder characterized by combination of two or more autoimmune diseases: SLE, progressive systemic sclerosis (PSS), dermatomyositis, or polymyositis.[14,15] The main symptoms of MCTD include Raynaud's phenomenon (93% of cases), arthralgia/joint involvement (93%), edema of the fingers and hand (71%), lymphadenopathy (71%), myositis/muscle involvement (50%), serositis (29%), hepatomegaly (21%), and splenomegaly (21%). Other symptoms include esophageal reflux, sclerodactyly, and lung involvement.[14,16] Diagnosis of MCTD should be considered when there are clinical presentation of SLE, PSS, dermatomyositis, or polymyositis in one patient.[16,17] Characteristic serological findings are high ANA titer (usually more than 1:1000) with speckled pattern, anti-RNP, and anti-U1RNP antibodies.[14,15] Antibodies such as anti-dsDNA, anti-SSa, anti-SSb, or anti-Smith are not usually found in MCTD. Although our patient had high titer of ANA, the diagnosis of MCTD can be excluded since the anti-RNP antibody was negative.

Scleroderma or systemic sclerosis (SSc) is a chronic multisystem disorder, characterized by sclerosis of connective tissue,[18,19] vascular disorder, and involvement of visceral organs.[12] The diagnostic criteria for SSc have been made by the Subcomittee for Scleroderma Criteria of the American Rheumatism Association and have been widely used, in which, for the diagnosis to be made, the patient must have (1) proximal scleroderma on the fingers, extremities, face, neck or the trunk; or (2) at least 2 of the minor criteria: (a) sclerodactyly, (b) digital pitted scarring, (c) bilateral basal pulmonary fibrosis.[12] These criteria have a sensitivity and specificity of 97% and 98%, respectively.[46,12]

Systemic sclerosis is classified into localized cutaneous SSc (lcSSc) and diffuse cutaneous SSc (dcSSc). The difference between the two type lies in the extent of skin involvement and other clinical and immunological presentations.[6,12]

Clinical manifestations in lcSSc are marked by history of Raynaud's phenomenon (in 1 to 10 years) before tightening of the skin on the distal extremities, without involvement of the trunk. In lcSSc, the classic CREST syndrome may also be found: calcinosis cutis, Raynaud's phenomenon, esophageal dysfunction, sclerodactyly, and telangiectasia.[18,20] Visceral organ involvement include pulmonary hypertension, pulmonary fibrosis, and gastrointestinal system. Vascular involvement include ischemia and ulceration of the fingers, and gangrene that may result in autoamputation.[18,19]

The patient in this case report was diagnosed with sclerodermatomyositis based on history of pain in both elbows, with difficulty in raising the arms and standing up from sitting position. Those complaints were also accompanied by skin changes on face, elbows, hands, abdomen, knees, and legs, which were characteristics of dermatomyositis. There were also history of dysphagia, difficulty opening the mouth, Raynaud's phenomenon, and tight and hard skin on arms and legs, which support the diagnosis of scleroderma.

On physical examination, we found skin lesions that support the diagnosis of dermatomyositis: heliotrope rash, Gottron's papules, and shawl sign. Those skin lesions were also accompanied by muscle atrophy, alopecia, as well as pain and stiffness of the proximal muscles. Physical examination that support the diagnosis of scleroderma were Raynaud's phenomenon, sclerodactyly, and skin hardening of the arms, hands, fingers, abdomen, and legs. The level of LDH in the patient was increased, with normal level of other muscle enzymes.

The erythematous lesion and edema in dermatomyositis commonly exhibit nonspecific histopathological appearance.[12,21] The histopathological findings in dermatomyositis include epidermal atrophy, basement membrane degeneration, vacuolar changes of basal keratinocytes, and dermal changes, such as interstitial mucin deposits with rare lymphocyte infiltration.[6,11,21]

The epidermis in SSc may appear normal, atrophic, or thickened. The dermis may appear thicker and consist of dense collagen bundles that can be visualized by trichrome staining.[22]

The histopathological examination of the patient's skin revealed atrophy, mild keratinization, liquefactive degeneration of the basal layer in the center, and thickening of the basement membrane. This appearance could also be found in dermatomyositis. Trichrome staining did not show thickening of collagen.

Positive ANA may be found in 50-80% of dermatomyositis cases, particularly in patients with overlap syndrome.[6,10] Common ANA patterns were speckled and nucleolar pattern.[7] Autoantibodies in patients with dermatomyositis are divided into 2 groups: myositis-specific and myositis-associated

antibodies. The first group is found in <50% of patients and has a worse prognosis. Antibodies such as anti–histidyl-tRNA synthetase (anti–Jo-1) belong to this group. The second group is found in 30-40% of patients, which include anti-Ro/SSA and anti-U1RNP. Anti-PM/Scl, anti-Ku, and anti-U2RNP antibodies are found in patients with overlap of dermatomyositis and scleroderma.[7] Anti-PM/Scl is found in 24% of dermatomyositis cases, but it could also be found in 8% of polymyositis cases and 3% of scleroderma cases.[15] Positive anti-PM/Scl antibodies is often associated with nucleolar pattern of ANA.[4]

More than 90% of patients with scleroderma have positive ANA.[23] Positive ANA with nucleolar pattern is specific for scleroderma; however, speckled pattern can also be found, as well as in patients with CREST syndrome,[6] dermatomyositis, or MCTD. Scl-70 autoantigen may be found in 70% of dcSSc. Anticentromere antibodies may be found in 50-96% of lcSSc patients.[24]

The patient had positive ANA with speckled pattern; however, ANA profile did not show significant increase in the level of autoantibodies.

There is a marked difference in terms of response to therapy between muscle and skin involvement.[5,11] Skin manifestations in dermatomyositis are usually more difficult to treat. The American Academy of Dermatology (AAD) recommend aggressive protection against sunlight with physical barrier, sunscreen, and topical corticosteroid.[1,5] Because patients with dermatomyositis usually have xerosis, the use of moisturizers will also be beneficial. Topical antipruritics may also given relieve to itchy skin lesions.[7,8,25] Patients are advised to use sunscreen with high SPF (>30) daily, avoid direct exposure to sunlight, cold temperatures, stress, and perform regular exercise to maintain joint mobility.[5]

Systemic corticosteroid is the therapy of choice in dermatomyositis, given as daily-dose prednisone or pulse-dose methylprednisolone.[24,25,26] The AAD recommends systemic corticosteroid for early control of muscle disease with a dose of 0.5-1.5 mg/kg/day. After control of the disease is achieved, the dose could be tapered down, usually every 4 to 6 weeks.[5,6] As many as 50-75% of dermatomyositis cases that are given corticosteroid showed complete remission.[25]

Other immunosuppressant drugs such as MTX, azathioprine, cyclophosphamide, cyclosporine,[6,25,26] and mycophenolate mofetil[26] can be given to control the disease and accelerate the tapering of corticosteroid.[25] A study that compared MTX and azathioprine showed no difference in efficacy between the two drugs, although the side effects of MTX was more tolerable.[26]

For dermatomyositis, MTX may be given early in the course of the disease or for refractory cases.[5,9] It may also be given to patients with SSc.[18,27] MTX is given when there is inadequate response to prednisone,[5] but it may also be given in combination with prednisone as first-line therapy in severe myositis.[26] Weekly dose of MTX is usually 7.5-25 mg orally.[7] Approximately 70-77% of patients who need adjuvant therapy showed response to MTX therapy.[5] Before starting initial therapy of MTX, thorough examination of the patient should be conducted, including routine laboratory examination that comprise of complete blood count and liver and kidney function test.[27] MTX may reduce diffuse skin hardening in scleroderma, but further studies are needed to confirm this.[6]

Bed rest is advised to patients with dermatomyositis who have severe inflammation; however, exercise and physical therapy are also needed as part of rehabilitation and therapy of dermatomyositis. In the evaluation, clinician should make a decision concerning the need of exercise program in each patient. The program should be arranged by physiotherapist, starting from passive and continued to active exercise. After the improvement of clinical condition, passive therapy can be continued with active therapy.[5,25]

Our patient was advised to avoid exposure to cold and sunlight. Topical therapies given were moisturizer, sunscreen, and topical corticosteroid. Systemic therapies were systemic corticoisteroid given in 0.8 mg/kg prednisone-equivalent dose and MTX with a dose of 7.5 to 10 mg per week.

The mortality rate of dermatomyositis ranges between 8.9 to 52 percent, depending on the variation of the clinical presentation.[5] Mortality in dermatomyositis is mainly caused by malignancy,[6] ischemic heart disease, and lung disease.[6,7,12] Sclerodermatomyositis usually has better prognosis.[4,7] In the last two decaces, the mortality rate of dermatomyositis has been declining, owing to the use of corticosteroid and other immunosuppressant drugs;[7] however, the risk of malignant degeneration is still high, particularly in the first 5 years since diagnosis.[28] Most patients showed good response to therapy, but in some cases there may be residual muscle pain[12] or muscle weakness[29] despite the inactivity of the disease. Relapse may occur at any time, including when the steroid dose is being tapered.[25,29]

SUMMARY

We have reported a rare case of sclerodermatomyositis, an overlap syndrome between scleroderma and dermatomyositis. Characteristic feature of the disease that were found in the patient include typical skin changes, sclerodactyly, arthralgia, muscle weakness, and positive ANA with speckled pattern. After establishing the diagnosis, the patient was given emollient and sunblock for topical treatment, oral corticosteroid, and methotrexate systemic treatment. Significant clinical improvement was observed during her follow-ups.

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Septic arthritis in malignancy

B Setiyohadi,[1] D Santosa,[2] Titis,[2] AA Abdullah[3]

[1] Division of Rheumatology, Department of Internal Medicine, University of Indonesia School of Medicine/Cipto Mangunkusumo General Hospital, Jakarta; [2] Department of Internal Medicine, University of Indonesia School of Medicine/Cipto Mangunkusumo General Hospital, Jakarta; [3] Department of Radiology, University of Indonesia School of Medicine/Cipto Mangunkusumo General Hospital, Jakarta

Septic arthritis is an infection of a joint, which can be caused by bacteria, viruses, fungi, or parasites. The infection may happen in distant sites of the body, which then spread hematogenously, or it could also result from open wounds, surgery, or unsterile injections.[1] Septic arthritis is a serious condition that, if left undiagnosed and untreated, can cause joint destruction and an irreversible loss of joint function.[2,3] Based on epidemiological data, the incidence of septic arthritis in general population is 2–10 cases in 100,000 people annually and is increased in those who have risk factors for septic arthritis, such as rheumatoid arthritis (RA) and joint prosthesis. In those with RA, the incidence of septic arthritis rises up to 30–70 cases in 100,000 people annually, and in those with prosthesis the figure is around 40–68 cases in 100,000 people annually.[4,5] Septic arthritis can affect all age groups, but it is more prevalence in the elderly and in children under 5 years old, in which the prevalence is 8.4 and 5 cases, respectively, in 100,000 people annually.[5] Septic arthritis is usually monoarticular, whereas polyarticular involvement occurs in only 10–15% of cases. The knee is involved in around 50% of cases.[6]

Septic arthritis is still a challenge for clinician since there has not been a significant decline in both morbidity and mortality in the last two decades.[2] Late recognition and therapy can cause permanent joint dysfunction and even death; thus, early diagnosis and prompt therapy is expected to decrease the morbidity and mortality rate in septic arthritis.[6]

In this case report we would like to present a case of a woman suffering from septic arthritis with an underlying immunocompromised condition of malignancy.

CASE REPORT

A 51-year-old woman was admitted to the Emergency Ward of Cipto Mangunkusumo General Hospital with a chief complaint of three-day history of tenderness on her left knee. The complaint had gradually worsened overtime and she also had difficulty in standing up and walking. The tenderness had acute onset, without any prior trauma, fever, or common cold. It was first felt when the patient was walking home from the hospital three days prior to admission, and initially she did not notice any changes on her left knee, but then after a while she noticed that her left knee had become swollen and felt warmer than the surrounding area. Up until this time, she was still able to stand up or walk, although with minimal difficulty; however, in the day after the complaint worsened and the swelling of her knee became more apparent, the patient was no longer able to bend her knee without feeling excruciating pain. There was no prior history of morning stiffness in the affected knee.

She had been diagnosed for a nasopharyngeal carcinoma since 1 year prior to the admission, and at the time of admission she was undergoing her chemoradiation therapy. She had already had 4 cycles of chemotherapy and 17 sessions of radiation.

From the initial physical examination there was obtained data as follows: blood pressure of 110/80 mmHg, pulse rate of 88 beats/min, respiratory rate of 18 breaths/min, body temperature of 36.4°C; conjunctiva was rather pale; there were multiple lymph node enlargement on both sides of her neck with a diameter of 2 cm at most; her chest and abdominal physical examination were unremarkable. The examination of her extremities revealed a swollen left knee, which on palpation felt warmer than the surrounding area, with tenderness and pain in movement. The patient was also not able to bend the affected knee.

Early laboratory examination showed hemoglobin level of 10.3 g/dL, leukocyte count of 9.6 × 10^3/μL, serum urea of 28 mg/dL, serum creatinine of 1 mg/dL, serum uric acid of 4.7 mg/dL, aspartate aminotransferase (AST) of 21 U/L, alanine aminotransferase (ALT) of 18 U/L, and serum potassium of 3.0 mEq/L. A radiographic examination of her left knee showed signs of osteoarthritis (figure 1). Her chest radiograph was unremarkable.

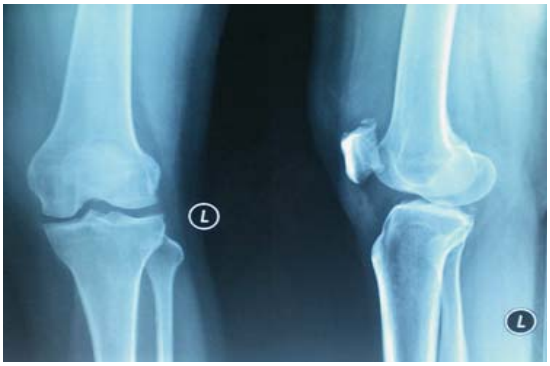

Figure 1 Radiographic examination of the left knee (anteroposterior (left) and lateral view (right)), showing formation of osteophytes on lateral and medial intercondylar eminence and lateral condyle of tibia, lateral condyle of femur, and superior anterior, posterior, and inferior posterior aspect of patella.

From the data above, the initial problems established on the emergency ward were arthritis of left knee (which at first was suspected to be due to gout), nasopharyngeal carcinoma T4N3M0 (stage IVb) on chemoradiation, anemia due to chronic disease, and hypokalemia. Initial therapy given in the emergency ward were intravenous ringer lactate solution 500 mL/12 hours, intravenous methylprednisolone 8 mg b.i.d, colchicine 0.5 mg b.i.d., and potassium supplementation 1 tablet t.i.d. Sodium diclofenac was also added to her medication to alleviate the pain, which was initially given at 25 mg b.i.d. and later was increased to 50 mg b.i.d. At the time we planned to perform magnetic resonance imaging (MRI) and whole body bone scan to exclude the possibility of a metastatic process. We also decided to postpone the chemoradiation therapy considering the patient's condition.

A synovial fluid aspiration of the left knee was performed on the emergency ward and 1 mL of yellowish fluid was obtained. It was then sent for a synovial fluid analysis, but unfortunately there was not enough sample for the analysis. The patient was then admitted to the inpatient ward.

On the third day after admission, MRI of her left knee joint was performed, showing arthrosis, synovitis, and degeneration of medial meniscus of the left knee joint (figure 2).

On the fourth day after admission, an arthrocentesis on the left knee joint was performed, which resulted in 10 mL of thick yellowish synovial fluid. The sample was subsequently sent to the laboratory for a culture and cytology examination, and it was then reassessed that the arthritis on her left knee joint was due to septic arthritis. The intravenous methylprednisolone and colchicine were stopped, and the patient was started with antibiotic therapy with levofloxacin 500 mg q.d. and ceftazidime 1 g t.i.d. An arthroscopic debridement of her left knee joint was also planned, but it was subsequently postponed due to financial problem. It was then decided that this procedure would be performed if the patient could get a free arthroscopy equipment from the Department of Orthopedics.

On the fifth day after admission, tramadol infusion in 500 mL normal saline b.i.d. was added to her medication because sodium diclofenac alone was not able to suppress her pain. Arthrocentesis was performed again on her left knee, which at this time resulted in 2 mL of yellowish synovial fluid that was sent for culture and cytology examination.

On the eighth day after admission, whole body bone scan was performed, showing no signs of metastasis to the bone.

On the ninth day, the cytology report showed only macrophage and leukocytes without any sign of malignant tumor cell. The culture showed that the bacterium infecting her knee joint was *Streptococcus anhemolyticus*, which was sensitive to amoxicillin/clavulanate, levofloxacin, and ceftazidime. The patient then received intravenous levofloxacin and ceftazidime for 14 days, followed with oral amoxicillin/clavulanate.

In the following days, the pain and tenderness of her left knee began to alleviate, accompanied by improvement of her range of motion; nevertheless, the patient was told not to use her left limb in weight-bearing activities.

On the sixteenth day after admission, an arthrocentesis procedure was reperformed, but this time it resulted in a dry tap. The plan to do an arthroscopy on her left knee was still unable to be carried out due to financial and scheduling problem, but it was decided that she could be discharged after completing her 14-day regimen of intravenous antibiotic therapy considering the improvement of her condition. Chemotherapy for the nasopharyngeal carcinoma could then recommence.

On the twenty second day after admission, the patient was discharged and her antibiotic therapy was continued with oral amoxicillin/clavulanate 650 mg t.i.d.

DISCUSSION

The symptom of joint pain is associated with a wide variety of disorder. Pain due to a problem within the joint needs to be distinguished from pain from nearby soft tissues or juxta-articular bone. If joint motion is preserved but tenderness can be elicited by palpation over one of the regional bursae, tendons, or ligaments, it is unlikely that the joint pain is due to arthritis. Arthritis is likely when the pain is aggravated by

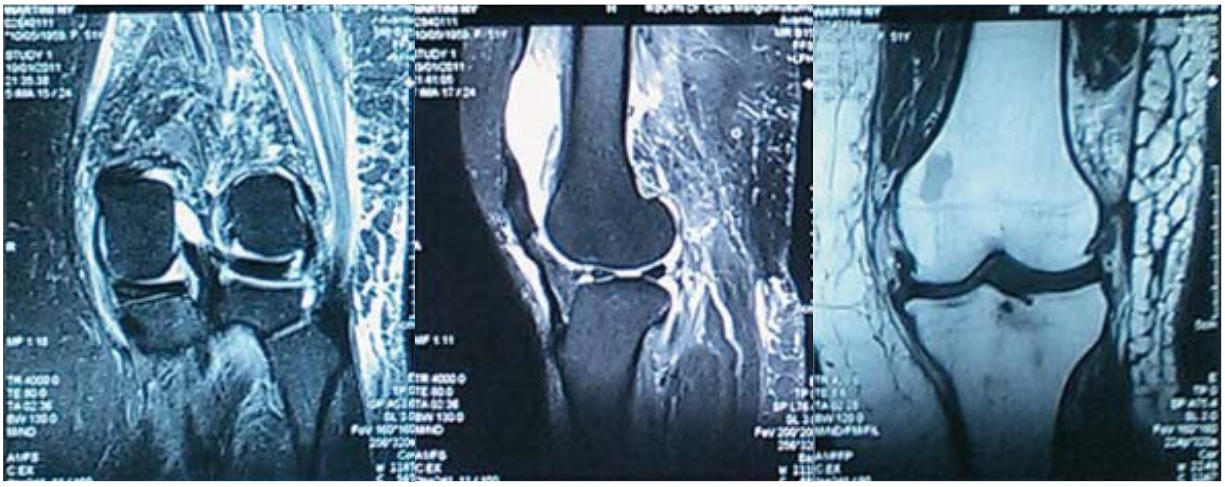

Figure 2 Magnetic resonance imaging of the left knee, showing degeneration of medial meniscus (A), accumulation of synovial fluid (B), and formation of osteophytes on medial epicondyle of femur, medial and lateral epicondyle of tibia, and intercondylar eminence (C).

movement, associated with loss of motion, and accompanied by swelling and/or erythema.[7]

The initial diagnostic evaluation of the patient with monoarticular arthritis should focus upon the possibility of an infectious etiology. Infection is a relatively common cause of acute pain and swelling in a single joint that can result in cartilage destruction within a few days if unrecognized; thus, while the history and physical examination provide important clinical clues, a definitive diagnosis often requires early performance of arthrocentesis and synovial fluid analysis.[1,8] The algorithm for the therapeutic approach to a suspected bacterial arthritis is shown in figure 3.

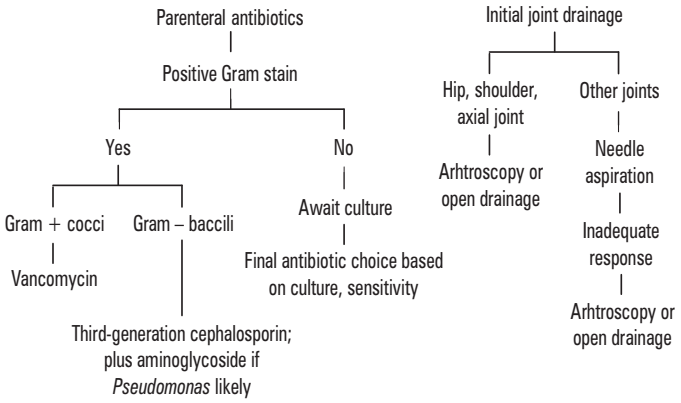

Figure 3 Algorithm for antibiotics selection and joint drainage in bacterial arthritis.[6]

In this case report, the patient had tenderness on a single joint, which is the knee joint; the pain was aggravated by movement, associated with loss of motion, and accompanied by swelling and/or erythema. The planned initial diagnostic modalities in the inpatient ward were MRI and bone scan due to suspicion of a metastatic process in her left knee. Besides, arthrocentesis procedure was also carried out with culture and cytology examination of the obtained synovial fluid. Subsequently, the result was septic arthritis with *Streptococcus anhemolyticus* as the identified pathogen.

Bacterial arthritis can result from a bite or other trauma, from direct inoculation of bacteria during joint surgery, or rarely, when infection of bone adjacent to the joint extends through the cortex into the joint space. However, in most cases, bacterial arthritis arises from hematogenous spread to the joint. Patients with hematogenously-induced bacterial arthritis may present with joint abnormalities in the absence of signs of sepsis or bacteremia. These patients presumably acquired their infection from a transient or self-limiting bacteremia.[9]

Predisposing factors for septic arthritis in adults were identified in a 2007 systematic review that included a total of 6,242 patients with acutely painful joints; 653 (10 percent) had septic arthritis and the predisposing factors and associated value as predictors (reflected by the estimated positive likelihood ratios) are summarized as follows: age greater than 80 years, diabetes mellitus, RA, prosthetic joint, recent joint surgery, skin infection and cutaneous ulcers, intravenous drug abuse and alcoholism, and previous intra-articular corticosteroid injection.[6,12]

Patients with bacterial arthritis present acutely with a single swollen and painful joint (i.e., monoarticular arthritis). The knee is involved in more than 50 percent of cases but wrists, ankles, and hips are also commonly infected.[10]

Joint pain, swelling, warmth, and restricted movement are self-reported by a majority of patients. These symptoms were noted at presentation in 85 and 78 percent, respectively, of patients with septic arthritis. A majority of patients with bacterial arthritis are febrile, although chills and spiking fevers are unusual.[11]

The most important laboratory test in the evaluation of monoarticular joint pain is synovial fluid analysis. Arthrocentesis should be attempted in all patients who have an effusion or signs suggesting inflammation within the joint.[8]

Virtually, any microbial pathogen is capable of causing bacterial arthritis. However, organisms such as *Staphylococcus aureus* and *Streptococci* have a higher propensity to cause joint infections than Gram-negative bacilli, which typically only produce these infections after trauma or in patients with severe underlying immunosuppression.[9]

MRI could be used as an early diagnostic tool, which could show an image of swollen and compression of the joint soft tissue.[12]

Treatment of acute bacterial arthritis requires appropriate antimicrobials and adequate joint drainage (figure 3).[9]

No randomized controlled studies have evaluated antibiotic regimens for bacterial arthritis. The initial choice of antimicrobial regimens is based on the coverage of the most likely organisms to cause infection. There have been no controlled trials examining the duration of antimicrobial therapy in bacterial arthritis. Treatment recommendations are based on clinical case series and cannot be generalized for all patients. Usually parenteral antibiotics are given for at least 14 days followed by oral therapy (if possible) for an additional 14 days.[9]

If the synovial fluid is purulent and/or bacteria is found on Gram's staining, prompt wide spectrum antibiotic therapy should be given. Based on the most prevalent bacterium that causes septic arthritis, which is *S. aureus*, the first choice of antibiotics are intravenous penicillin G, cloxacillin, clindamycin, or netilmicin. A de-escalation therapy must be commenced after the result from synovial fluid culture is obtained.[12]

No randomized controlled studies have evaluated joint drainage procedures in adults for bacterial arthritis; thus, recommendations are based on small retrospective studies and are dependent on the joint affected and the time from onset of infection until evaluation. Although no studies have compared drainage with no-drainage procedure, we recommend joint drainage in all patients with septic arthritis as this condition represents a closed abscess collection. The three procedures used are needle aspiration (single or multiple), arthroscopic drainage, or arthrotomy (open surgical drainage).[9]

Most peripheral joints can be drained with closed needle aspiration, although daily aspiration may be necessary.[12] If adequate drainage cannot be obtained by needle aspiration, either arthroscopy or open drainage is necessary. For knee, shoulder, and wrist infections, arthroscopy is often preferred

because of easier irrigation and better visualization of the joint.[13]

CONCLUSION

Septic arthritis due to bacterial pathogens is the most potentially dangerous and destructive form of acute arthritis; thus, early diagnosis and prompt therapy is very crucial in reducing morbidity and mortality due to septic arthritis. Patient presenting with acute pain, which aggravated by movement, associated with loss of motion, and accompanied by swelling and/or erythema mostly on a single joint should be suspected for septic arthritis. Synovial fluid analysis is an important diagnostic procedure. Prompt therapy with broad spectrum antibiotic is a must when a purulent synovial fluid is obtained from arthrocentesis. The prognosis of bacterial arthritis has not improved significantly in the past few decades, despite better antibiotics and drainage. It is extremely difficult to predict the functional outcome of individual patients during and at the conclusion of treatment. The outcome is directly related to host factors, such as prior joint damage, the virulence of the infecting organism, and the speed with which adequate treatment is begun.

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