Contents
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Editorial
3 Editor’s note
YI Kasimir

Review
5 Role of interleukin-17 in the pathogenesis of rheumatoid arthritis
JA Ongkowijaya, B Setiyohadi, Sumariyono, YI Kasimir

Original Article
10 Correlation of autoantibodies with the Disease Activity Score 28 and radiographic hand joint damage in rheumatoid arthritis patients
IARW Manuaba, Sumariyono, H Isbagio

Case Report
31 Arthritis in leprosy without specific skin lesion
S Dewi, B Setiyohadi

41 Multiple autoimmune syndrome (Graves’ disease, systemic lupus erythematosus, and systemic sclerosis) in a young woman in Jakarta
S Dewi, B Setiyohadi, Mikoagow

CONTACT DETAILS

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Editor’s note

YI Kasjmir

This is the third issue of the Indonesian Journal of Medicine. For a scientific journal, we are admittedly still at a very young age. It was back in 2007 that the idea to have a periodical publication in the field of rheumatology first came, with the first edition finally available to our readers in 2009. As a scientific journal, the continuity of the Indonesian Journal of Rheumatology depends on the support from our readers in the form of letters to editor or other articles, contributions from rheumatologists in Indonesia as well as other countries, and reviews from our international editorial board members. We hope that all of those contributions would enable this journal to become one that represent Indonesian population.

The population of Indonesia consists of various ethnic groups, whose ancestral origin continues to be a matter of debate among experts. According to Koentjaraningrat, it was the Austro-Melanesoid people that first came to Indonesia, followed by the Paleo-Mongoloids in two waves of migration. They spread and eventually inhabited all of Indonesia, with occasional intermingling in places where those two races met. Today, the descendants of the Austro-Melanesoid people could mostly be found in the eastern part of Indonesia, with a few remaining as isolated tribes in the inner part of Riau, while the descendants of the Paleo-Mongoloids occupy most of the other parts of Indonesia.¹ The diversity of ethnic groups also owes in part to the geographic position of Indonesia which lies in the main sea route connecting the eastern and southern parts of Asia.²

The demographic variation of Indonesia gives rise to a broad range in the manifestation of musculoskeletal disorder, which makes defining a pattern that represent Indonesian population a challenge. For example, there is a relatively higher prevalence of systemic lupus erythematosus among individuals of Chinese origin, low incidence of subcutaneous nodule as the manifestation of rheumatoid arthritis (RA), and relatively mild presentation of disease.³ Those remarkable characteristics may have a genetic basis which still need further investigation.

In this issue of the Indonesian Journal of Rheumatology, a review article by Ongkowijaya (see page 5) study the role of interleukin (IL)-17 in the pathogenesis of RA. Studies in recent years had found that, besides the well-known tumor necrosis factor α and IL-1, there are other cytokines which also play role as proinflammatory cytokines in the pathogenesis of RA, with IL-17 being one of them. Those studies showed that IL-17 acts as an effector which induces and maintains the inflammatory process in RA. More research will provide us with a better knowledge of the role of IL-17 in the pathogenesis of RA and lead us toward the use of IL-17 as a new target of RA therapy.⁴ Furthermore, the role of IL-17 and underlying genetic variance in causing the difference in the characteristics of RA in Indonesia are also open to further study.

There are three original articles about RA in this issue. Manuaba et al⁵ (see page 10), on the basis of the fact that the course of RA is often difficult to predict, attempt to investigate the correlation of autoantibodies with disease activity and radiographic hand joint damage in RA patients, while Sumariyono et al⁶ (see page 15) and Aji et al⁷ (see page 21) study the correlation of several clinical and laboratory findings with joint damage in RA patients. We hope that the result of these studies may contribute to the search for a reliable predictor of joint damage in RA.

There is also an original article about systemic lupus erythematosus (SLE) by Sari et al⁸ (see page 24) who investigate the prevalence of atherosclerosis in female SLE patients under 40 years old as well as the correlation between atherosclerosis risk factors and carotid intima-media thickness. In contrast with previous studies, this study only involved women under 40 years old in order to minimize the influence of age in the formation of atherosclerotic plaque. Thus, the role of SLE itself and other risk factors such as long-term steroid medication in the pathogenesis of atherosclerosis in SLE could be better understood.

In this issue we have several reports about cases less commonly encountered in daily clinical practice, such as Behçet’s disease, multiple autoimmune syndromes (Graves’ disease, systemic lupus erythematosus, and systemic sclerosis), and erosive osteoarthritis. There is also an article about arthritis in leprosy, in which the authors report the occurrence of arthritis in a patient who initially presented with peripheral neurological symptoms without the typical skin lesion of leprosy. We hope that those reports may enrich our knowledge as well as increase our awareness of those disorders in our clinical practice.
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Role of interleukin-17 in the pathogenesis of rheumatoid arthritis

JA Ongkowijaya, B Setiyohadi, Sumariyono, YI Kasimir

ABSTRACT

Rheumatoid arthritis (RA) is a systemic autoimmune disorder with an unknown etiology. It typically affects the peripheral synovial joints symmetrically. The roles of T and B cells, macrophages, plasmocytes, host tissue cells (synoviocytes, chondrocytes), and osteoclasts in RA are more defined. In RA, cytokines secreted by cells implicated in adaptive and natural immunity have important roles in causing inflammation, articular destruction, and other comorbid diseases related to RA. Other than the clear roles of interleukin (IL)-1 and tumor necrosis factor α, there are other cytokines that are suspected of having roles in the pathogenesis of RA, IL-17 for instance. Interleukin-17 is a proinflammatory cytokine, produced by Th17 cells, and has pleiotropic effects on various cells contributing to the pathogenic condition of RA. Several studies showed that this cytokine maintains the inflammation and causes more destruction of joint cartilage. Advances in the understanding of the role of IL-17 elicits the idea to modulate IL-17 and/or Th17 cells as the potential targets of therapy in RA.

Rheumatoid arthritis (RA) is a systemic autoimmune disorder indicated by chronic polyarthritis and synovitis that results in joint damage. It typically affects the peripheral synovial joints symmetrically. The clinical course of the disease is prolonged and accompanied by systemic complaints. The manifestations are varied and early intensive management is needed to prevent joint damage and physical handicap. The disease had been described by Landre Beauvais since 1800 and the terminology of RA was first introduced by Garrod in 1859. The etiology of RA is still unknown despite advances in the understanding of its pathogenesis. Several aspects that are also suspected of having roles in the pathogenesis of RA are as follows: (1) genetic factor or specific gene polymorphism; (2) pathogenic immune response and infectious agent-induced inflammation; (3) autoimmunity toward synovium and cartilage components; (4) interference of regulation of proinflammatory cytokines production; and (5) transformation of constituent cells in the synovial into tissue invasive, autonomous cells.

The perception that RA pathogenesis is a multifactorial process that needs a combination of genetic, environmental, and immune factors, has been accepted by most experts. However, the understanding of how the components are correlated with each other is still unclear. There is a possibility that those factors have roles as risk factors. They, combined with other factors, can cause the disease through mechanisms and pathways that are not yet fully understood.

Synovial membrane in RA contains activated T cells and B cells, macrophages, and plasmocytes. It is also known that host tissue cells, such as synoviocytes, chondrocytes, and osteoclasts, are also involved in mediating bone and joint cartilage damages. Recruitment process, activation, and effectors of each contributors mentioned earlier are regulated through a network of cytokines.

ROLE OF CYTOKINES IN RHEUMATOID ARTHRITIS

Cytokines are protein secreted by cells implicated in adaptive and natural immunity that regulate various fundamental processes of the cells, such as inflammation, tissue reparation, cell growth, fibrosis, angiogenesis, and immune response. To understand about the role of cytokines in RA, comprehensive analysis is needed. Tissue availability from pathogenic site (synovial joint) facilitates investigation and identification of role of cytokines.

In RA, cytokines secreted by those cells have important roles in causing inflammation, articular destruction, and other comorbid diseases related to RA. Disease activity is also closely related to cytokines changes.

Interleukin (IL)-1 and tumor necrosis factor α (TNFα) are major proinflammatory cytokines that have roles in inflammation in RA; both have overlapping roles such as causing inflammation, promoting inflammatory cells’ adhesiveness, and causing angiogenesis and bone resorption. Tumor necrosis factor α is a cytokine secreted by macrophage and is the center of cytokines that have roles in pathogenesis of RA. Brennan et al reported higher level of IL-1 in synovial culture of RA patients than that of osteoarthritis patients. Treatment with anti-TNFα monoclonal antibody can suppress IL-1 level. Further studies showed that suppression of TNFα also decreases other
cytokines production such as granulocyte macrophage colony-stimulating factor (GM-CSF), IL-6, IL-8, and IL-9. It shows that there is a coordinated cytokine network in causing an inflammation.\textsuperscript{5,6}

There is an imbalance between proinflammatory and anti-inflammatory cytokines, in which the proinflammatory ones are dominant. Raza et al\textsuperscript{12} reported that the level of proinflammatory cytokines produced by T cell, macrophage, and fibroblast, such as IL-2, IL-4, IL-13, IL-17, IL-15, basic fibroblast growth factor, and epidermal growth factor increase more evidently in RA patients as compared to non-RA arthritis patients.

Although the blocking of TNFα and IL-1 shows good response, there is still the possibility of failing to control the disease course of RA. It shows that there are other factors that also have roles, IL-17 for instance. Interleukin-17 is suspected of having role because firstly, it is similar to TNFα in its proinflammatory characteristic and secondly, it is produced by T cells, while the role of T cells is not yet fully understood.\textsuperscript{6,13}

**ROLE OF INTERLEUKIN-17 IN RHEUMATOID ARTHRITIS**

Interleukin-17 is a cytokine produced by T cells. It was first assumed as a product of Th1 cells, but then it was found that IL-17 is produced by Th17 cells which are similar to Th1 cells as derivation of CD4+ Th cells pathway. The differentiation into Th-17 cells is influenced by IL-23, IL-6, and IL-1B and it undergoes negative regulation influenced by IL-4, IL-10, and interferon γ (IFNγ).\textsuperscript{13–16} Interleukin-17 is a member of IL-17 superfamily which consists of 6 members: IL-17A to IL-17F. Interleukin-17A is the strongest of them and is also known as IL-17. Interleukin-17 is a protein with a molecular weight of 17 kDa and secreted in dimeric form with 155 amino acids.\textsuperscript{16,17}

Interleukin-17 is a proinflammatory cytokine and has pleiotropic effects on various cells, including macrophages and fibroblasts, and is a strong candidate for effector cytokine contributing to the pathogenic condition of RA.\textsuperscript{16–20} Chabaud et al\textsuperscript{17} and Kohno et al\textsuperscript{22} measured IL-17 level of synovial tissue supernatant of RA patients, osteoarthritis patients, and healthy people. They found high level of IL-17 in RA patients, but not in osteoarthritis patients nor in healthy people. Shahrara et al\textsuperscript{23} also found similar result. Higher levels of IL-17 in serum and in synovium of RA patients were also reported.\textsuperscript{15,18} A study by Chabaud et al\textsuperscript{17} showed that intra-articular injection of IL-17 to mice will induce joint cartilage degradation, while Jovanovic et al\textsuperscript{25} reported treatment with IL-17 can initiate and maintain the inflammatory response.

Interleukin-17 is produced by cells of immune system that have roles in inflammatory process in RA patients.\textsuperscript{13} It will stimulate the transcription activity of nuclear factor-κB and IL-6 and the secretion of IL-8 by fibroblast, endothelial cells, and epithelial cells, and induce T cell proliferation.\textsuperscript{17,26} Furthermore, IL-17 will stimulate synoviocytes to produce GM-CSF and prostaglandin E2, which means that IL-17 may have a role in promoting mediators in arthritis pathogenesis and functions as the controller of inflammatory response.\textsuperscript{17,27} Interleukin-17 will stimulate macrophages’ production of IL-1 and TNFα,\textsuperscript{25} support the production of IL-1–mediated IL-6 by synoviocytes, and the synthesis of IL-1, IL-6, and IL-8 induced by TNFα.\textsuperscript{17} It shows that IL-17 synergizes with TNFα and IL-1, and the combination of those three will cause more tissue destruction.\textsuperscript{23,26}

A study in mice showed the role of IL-17 in causing joint inflammation. Interleukin-17-deficient mice showed the important role of IL-17 in the activation of T cell-mediated immune responses. Interleukin-17-deficient mice that were induced to have arthritis showed evident inflammatory suppression, as well as prevention of the development of destructive arthritis in IL-1 receptor antagonist deficient mice after inactivation of IL-17.\textsuperscript{17,28}

![Figure 1 Effects of interleukin-17 on various cells implicated in rheumatoid arthritis. (Adapted from Miossec et al, 2003)\textsuperscript{3}](image)

Interleukin-17 has double effects in joint cartilage, such as blocking the metabolism of chondrocytes in intact joint cartilage and inducing proteoglycan destruction. Matrix synthesis by chondrocytes is suppressed by increasing nitric oxide production. Interleukin-17 also stimulates aggregcanase activity to degrade the matrix of joint cartilage.\textsuperscript{24,25} Cai et al\textsuperscript{29} explained that the effect is independent of IL-1 and will be even greater if it synergizes with IL-1. Van Bezooinen et al\textsuperscript{30}
also showed that IL-17 synergizes with TNFα to induce joint cartilage destruction. Meanwhile, Koshy et al31 stated that to stimulate release of metalloproteinase, IL-17 can work by itself or combined with proinflammatory cytokines produced by macrophage (IL-1 and TNFα).

Interleukin-17 is a cytokine of T cell which is potent in stimulating osteoclastogenesis. Interleukin-17, combined with TNFα, will increase osteoclast resorption and the expression of receptor activator for nuclear factor-κB ligand (RANKL) in osteoblasts. RANKL is a regulator of osteoclastogenesis and can be blocked by osteoprotegerin (OPG).8,32 Lubberts et al17 also found that in IL-17–deficient mice, there was an obvious suppression of bone erosion if induced to be chronic arthritis. It seems that the mechanism of IL-17 to stimulate bone erosion is through loss of balance between RANKL and OPG.

In animal model, increase of IL-17 in joint with arthritis will cause influx of polymorphonuclear cells; thus, there will be a release of oxygen radical and proteolytic enzymes from those cells. This condition will aggravate the destruction of exposed joint.30 On the contrary, Yamada et al33 found that Th1, but not Th17 cells, predominate in the joints of patients with rheumatoid arthritis. In spite of that, murine studies using IL-17 inhibitor or anti–IL-17 monoclonal antibody showed promising results.34–36 In addition, a recent study by Genovese et al37 found that a humanized anti–IL-17 monoclonal antibody, added to oral disease-modifying antirheumatic drugs improved signs and symptoms of RA, with no strong adverse safety signal noted.

Figure 2  Role of interleukin-17 in the pathogenesis of rheumatoid arthritis. APC, antigen-presenting cell; IL, interleukin; TNFα, tumor necrosis factor α; RANKL, receptor activator for nuclear factor-κB ligand; MMP, matrix metalloproteinase.
CONCLUSION
Rheumatoid arthritis is indicated by chronic inflammation affecting connective tissues throughout the body, but it is mainly affecting diarthrodial joints. Roles of some cytokines are defined in the pathogenesis of RA. Other than the clear roles of TNFα and IL-1, there are many evidences that support the role of other cytokines; IL-17 is one of them. Several studies showed that this cytokine induces and maintains the inflammation, especially in RA. Advances in the understanding of the role of IL-17 elicits the idea to modulate IL-17 and/or Th17 cells as the potential targets of therapy in RA.

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Correlation of autoantibodies with the Disease Activity Score 28 and radiographic hand joint damage in rheumatoid arthritis patients

IARW Manuaba,1 Sumariyono,2 H Isbagio2

ABSTRACT

Background: Rheumatoid arthritis (RA) is a systemic chronic inflammatory disease of the joint that causes deformity or disability leading to a decreased function in RA patients. According to the 1987 American College of Rheumatology, rheumatoid factor (RF) is used as one of the diagnostic criteria because until today it is still considered as the primary autoantibody in RA although it has a lower specificity than that of anti-cyclic citrullinated peptide (anti-CCP). Besides RF and anti-CCP, anti-RA33 is another autoantibody found. The presence of the three autoantibodies in RA patient serum is important because it is the starting point of the pathogenesis of the autoimmune process in RA.

Methods: This is a cross-sectional study using consecutive sampling. Forty six subjects, all suffering from RA, were recruited for this study. All of them were tested for RF, anti-CCP, anti-RA33 titers using enzyme-linked immunosorbent assay (ELISA) method and had their hand radiograph taken to obtain the Sharp score to evaluate joint damage. During this study, 28-joint Disease Activity Score (DAS28) (4 parameters) was also evaluated using erythrocyte sedimentation rate as one of the parameters.

Results: The study found that the correlation between the three antibodies and DAS28 was not statistically significant: RF (r = 0.200, p = 0.091), anti-CCP (r = 0.117, p = 0.220), and anti-RA33 (r = 0.126, p = 0.202). There was a significant correlation between anti-CCP and the Sharp score (r = 0.300, p = 0.021). The correlation between the other two autoantibodies and the Sharp score was not statistically significant: RF (r = 0.194, p = 0.098), anti-RA33 (r = 0.156, p = 0.150).

Conclusion: There was a significant correlation between anti-CCP autoantibody and radiographic hand joint damage in RA patients so that it could be used as an indicator for occurrence of an erosive or a more severe RA.

Rheumatoid arthritis (RA) is one form of systemic chronic inflammatory rheumatic disease in which up to this day its etiology has not been fully explained yet. The course of RA disease has clinical characteristics that result in joint damage, functional disability, lower quality of life, and shorter life expectancy.1,2 Until today, the diagnosis of RA is made based on the criteria from the 1987 American College of Rheumatology (ACR) in which its validity is now being questioned especially in regards to diagnosing early RA because the rheumatoid factor (RF) is present in only 50% of early RA and the radiographic findings showing erosion which is characteristic of early RA is found in only 13%.3 This limitation should draw our attention because diagnosis must be made as early as possible in RA management; thereby, enabling us to predict erosive RA so that disease-modifying antirheumatic drugs could be administered as soon and aggressively as possible to slow down the process of joint damage.

Some studies reported that in the course of the RA disease, RF or anti-cyclic citrullinated peptide (anti-CCP) is correlated with the occurrence of a more erosive RA. On the other hand, the clinical feature of RA seems to be different among various ethnic groups and not all RA patients have positive RF or anti-CCP. These findings led us to a new paradigm: is RA a single disease or has it a particular subset related to genetic risk factors?3 Also in its natural course, questions remain whether these autoantibodies of all the ethnic groups are related to joint damage in RA patients so that they could be used as the predictors of erosive RA.

The natural course of RA disease is difficult to predict—which patient has a tendency to have progressive disease with persistent inflammation and joint destruction, which patient has slow progress of disease, and which patient has fluctuating disease. It is hoped that the understanding of the correlation between RF, anti-RA33, and anti-CCP with 28-joint Disease Activity Score (DAS28) and joint damage in RA patient could be beneficial for monitoring the patient and for administering treatment more effectively.

Based on the above points, questions for this study were made: do the titers of RF, anti-RA33, and anti-CCP have positive correlation with DAS28 and joint damage in hand radiograph of RA patients?
METHODS
This is a cross sectional study using consecutive sampling. Forty six subjects, all suffering from RA, were recruited for this study. All subjects were tested for their RF titer using IMTEC-RF IgM from HUMAN, anti-CCP titer using IMTEC-CCP-Antibodies from HUMAN, anti-RA33 titer using IMTEC-RA33 antibody from HUMAN using enzyme-linked immunosorbent assay (ELISA) method and hand radiography was performed for calculation of Sharp score to evaluate joint damage. During this study evaluation of DAS28 (4 parameters) using erythrocyte sedimentation rate as one of the parameters was conducted.

RESULTS
Of 46 subjects in this study, 40 subjects (87%) were female and 6 subjects (13%) were male. The majority, 44 subjects (95.7%), were married. Although the subjects in this study were RA patients who underwent regular follow-ups at the rheumatology clinic at Cipto Mangunkusumo General Hospital, Jakarta, they were of various ethnic groups: Javanese 15 subjects (32.6%), Sundanese 12 subjects (26.1%), Batak 7 subjects (15.2%), Betawi 3 subjects (6.5%), Minang 3 subjects (6.5%), Lampung 2 subjects (4.3%), and 1 subject (2.2%) each for the following ethnic: Kalimantan, Malay, and Acehnese.

Mean age of the subjects was 48.61 years old, and if categorized in decades: 1 subject (2.2%) was in the 20–30 year old age bracket, 8 subjects (17.4%) was in the 30–40 year old age bracket, 15 subjects (32.6%) in 41–50 year bracket, 18 subjects (39.1%) in 51–60 year bracket, and 4 subjects (8.7%) in 61–70 year bracket. In this study the majority was in the 51–60 age bracket.

Disease activity evaluation using DAS28 findings were as follows: 13 subjects (28.3%) had high disease activity (DAS28 >5.1), 19 subjects (41.3%) had moderate disease activity (DAS28 3.2–5.1), 8 subjects (17.4%) had low disease activity (DAS28 2.6–3.2), and 6 subjects (13%) were in remission (DAS28 <2.6).

The outcome of Sharp score used as a dependent variable in this study was evaluated by a consultant radiologist. An intraobserver reliability analysis was conducted that showed the observer intraclass correlation coefficient values were high: joint narrowing score was 0.9848, erosion score 0.9674, and total Sharp score 0.9618. The limitations in this study did not allow the evaluation of the Sharp score to be conducted by two or three observers.

Other characteristic data such as: clinical signs of pain and swelling, visual analog scale (VAS) global health score, DAS28 score, duration of disease (months), autoantibodies level, and Sharp score based on mean and median values of the subjects are elaborated in table 1.

Table 1 Characteristics of subjects

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Mean (SD)</th>
<th>Median</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>48.61 (9.23)</td>
<td>50.0</td>
</tr>
<tr>
<td>Number of children</td>
<td>3.25 (2.57)</td>
<td>3.0</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>24.60 (3.64)</td>
<td>24.25</td>
</tr>
<tr>
<td>Tender joint count</td>
<td>5.41 (6.28)</td>
<td>3.0</td>
</tr>
<tr>
<td>Swollen joint count</td>
<td>2.54 (3.67)</td>
<td>0.0</td>
</tr>
<tr>
<td>VAS global health score</td>
<td>17.50 (17.76)</td>
<td>10.0</td>
</tr>
<tr>
<td>ESR, mm/hr</td>
<td>58.50 (32.10)</td>
<td>52.50</td>
</tr>
<tr>
<td>DAS28 score</td>
<td>4.24 (1.37)</td>
<td>4.3</td>
</tr>
<tr>
<td>RF titer, IU/mL</td>
<td>57.13 (75.29)</td>
<td>22.77</td>
</tr>
<tr>
<td>Anti-CCP titer, IU/mL</td>
<td>828.48 (1264.74)</td>
<td>57.6</td>
</tr>
<tr>
<td>Anti-RA33 titer, IU/mL</td>
<td>49.85 (99.83)</td>
<td>7.65</td>
</tr>
<tr>
<td>Disease duration, months</td>
<td>55.24 (42.70)</td>
<td>39</td>
</tr>
<tr>
<td>Joint narrowing score</td>
<td>5.37 (6.26)</td>
<td>3.0</td>
</tr>
<tr>
<td>Bone erosion score</td>
<td>3.50 (4.70)</td>
<td>2.0</td>
</tr>
<tr>
<td>Total Sharp score</td>
<td>8.76 (9.62)</td>
<td>5.0</td>
</tr>
</tbody>
</table>

BMI, body mass index; VAS, visual analog scale; ESR, erythrocyte sedimentation rate; RA, rheumatoid arthritis; DAS28, 28-joint Disease Activity Score; RF, rheumatoid factor; anti-CCP, anti-cyclic citrullinated peptide.

Correlation of RF with DAS28 and joint damage in hand radiograph
We found that 19 subjects (41.3%) were RF negative (level ≤15 IU/mL) and 27 subjects (58.7%) were RF positive. Data normality test using Kolmogorov-Smirnov method found that the RF titer, DAS28, and Sharp score showed abnormal distribution so that the bivariate statistical analysis used was nonparametric statistical test. The result of Spearman’s correlation test between RF titer and DAS28 showed that they were not significantly correlated (r = 0.200, p = 0.091). The test between RF titer and joint damage in hand radiograph using Sharp score also showed that they were not significantly correlated (r = 0.194 and p = 0.098).

Correlation of anti-CCP with DAS28 and joint damage in hand radiograph
The test of anti-CCP titer found that 20 subjects (43.5%) were anti-CCP negative (level ≤25 IU/mL) and 26 subjects (56.5%) were anti-CCP positive. Data normality test using Kolmogorov-Smirnov method, either for the anti-CCP titer or the Sharp score, had an abnormal distribution so that the bivariate statistical analysis used was nonparametric statistical test. The Spearman’s analysis test outcome showed that the correlation between anti-CCP and DAS28 was not significant (r = 0.117, p = 0.220), but we found a significant correlation between anti-CCP and Sharp score (r = 0.300, p = 0.021). The correlation above showed that the higher the anti-CCP titer, the more hand joint damage based on the Sharp score found. The scatter diagram of the correlation between anti-CCP titer and joint damage in hand radiograph based on the Sharp score could be seen in figure 1.
Correlation of anti-RA33 with DAS28 and joint damage in hand radiograph

The outcome of anti-RA33 titer test showed that 32 subjects (69.57%) were anti-RA33 negative (level <15 IU/mL) and 14 subjects (31.43%) were anti-RA33 positive. Data normality test using Kolmogorov-Smirnov method showed that the anti-RA33, DAS28, and Sharp score were of abnormal distribution; therefore, a nonparametric statistical test was used for the bivariate statistical analysis. The Spearman’s test for the correlation between anti-RA33 and DAS28 showed that the correlation was not significant (r = 0.075, p = 0.311). The correlation between anti-RA33 and joint damage in hand radiograph using the Sharp score showed that the correlation was not statistically significant (r = 0.156, p = 0.150).

DISCUSSION

Rheumatoid factor has been known to be one of the autoantibodies that play a role in RA pathogenesis. Rheumatoid factor is an autoantibody against Cγ22-Cγ3 interface Fc region of the immunoglobulin molecule in which its presence in the serum is quite sensitive but not too specific. High RF titer in the serum is reported to be correlated with the severity of joint damage and extra-articular manifestations in RA.

RA patients are in a state of active inflammation of the joints as a result of the differentiation of CD20-CD28+ plasma cells in the synovial fluid produced by a structure resembling the germinal centre of the lymphoid tissue. T cells play an important role in stimulating lymphocyte B cells to shift from the production of IgM RF to secretion of IgG or IgA RF to initiate the immune mechanism in RA. The presence of IgM RF is dominant in RA patient serum while IgG and IgA are dominant in synovial fluid. The differences in RF isotypes are based on the differences in the molecular shape. IgM RF is a pentamer and forms a complex with IgG, IgA RF is monomer and polymer, and IgG RF is a monomer and could form self-associated complex. IgG RF itself could form a large complex that will play a role in RA joint inflammation and IgA RF is more associated with causing bone erosion. Knijff-Dutmer et al reported the result of RF test using the fluoroimmunoassay method that showed IgM RF was weakly correlated with the Sharp score (r = 0.19) and it seemed that IgA RF was more correlated with joint damage based on radiography. Valbracht et al reported that the RF isotype played a role in the course of RA disease—those with high titer were more correlated with a more severe disease activity and the occurrence of joint damage especially if there was a high anti-CCP level. A study conducted by De Rycke et al found that if RF is combined with the presence of shared epitope then it would be correlated with joint damage according to the radiographic score progression. The RF titer is more independent particularly it is more correlated with the occurrence of rheumatoid nodule in RA patients.

The fact that rituximab treatment significantly affects only RA patients with positive RF led to a new insight that the pathogenesis of RA with positive RF is different from that with negative RF. The genetic study in a group of RF-negative RA patients found that there was no shared epitope (SE) allele such as that of positive RF. A study conducted by Bas et al found that RA with positive IgM RF was correlated with the severity of erosion in joint damage based on the Larsen score compared to those in seronegative RA, particularly those with a disease duration of >12 years. Mewar et al reported that subjects with S2 allele (K-R-A-A in position 71–74) were associated with severe or more erosive RA (p = 0.0059) and was associated with the high RF titer. Erosive RA is affected not only by RF titer level but also the presence SE allele. Today we know that RA has a particular subset that is associated with SE allele that affects the severity of the course of RA disease.

This study failed to show statistically significant correlation between RF titer with DAS28 and hand joint damage. Some subjects were RF seronegative; several literatures mentioned genetic analysis of RA seronegative did not have SE allele and showed a different pathogenesis from that of RA with RF seropositive. There is an assumption that the SE allele in polymorphic genes is different in each ethnic group in Indonesia; however, whether this could affect the statistical significance had not been researched in this study. This study used a cross-sectional method so that the titer level obtained was only at one point in time and only measured the IgM RF which could also affect the statistical significance. Further studies comparing the seropositive RA group with seronegative RA using other RF isotype and using the cohort method is recommended.

In RA, we could find a variety of antibodies against structures produced by keratinized epithelial cells which include antikeratine antibody, antiperinuclear factor, and antiflagrade antibody. The target molecules of these antibodies among others are flagraine, vimentine, and other peptides. Peptidylarginine deiminase enzyme is in charge of converting the arginine epitope to citrulline that has autoantigenic characteristic in which individuals who have a genetic risk
for RA expresses the citrulline protein fragment through the MHC class II T cell molecule. Next, B cell response to citrulline antigen forms (anti-CCP) autoantibodies that later stimulates the chronic inflammatory process that is the basis of RA pathogenesis. Various studies reported that anti-CCP has higher specificity, which is between 94–96%, compared to that of RF. One study conducted by Vallbracht et al reported that although the three RF isotypes were negative in RA patients, anti-CCP could be found positive in 34.4% of them. Various studies found that anti-CCP has high sensitivity and specificity so that if RF is negative, anti-CCP test should be next carried out.

Some cohort studies found that anti-CCP in the serum is found long before RA is diagnosed; therefore, anti-CCP is considered as predictor for the occurrence of RA in the future in patients with polyarthritis. For diagnosing RA, anti-CCP is 20% more sensitive than RF. It is proven that RA patients with positive anti-CCP have the associated genetic risk factors, among others: human leukocyte antigen shared epitope alleles (HLA-SE), protein tyrosine phosphatase nonreceptor type 22 (PTPN22), complement component 5-TNF receptor-associated factor 1 (C5-TRAF1), and TNFα-induced protein 3-oligodendrocyte lineage transcription factor 3 (TNFAIP3-OLIG3). The presence of HLA-DRB1*0401 and HLA-DRB1*0404 causes increased affinity of a peptide to bind with HLA-DRB1 during the conversion of arginine to citrulline. In the next stage, the CD4+ T cell is activated which stimulates B cell activation resulting in the production of anti-CCP and at the end the formation of immune complex that triggers the inflammatory process through the upregulation of the proinflammatory cytokine. This evidence shows that anti-CCP plays a dominant role in the development of chronic inflammation of the joints in RA. RA patients with a continuously high positive anti-CCP titer and presence of SE allele will likely have joint damage.

In this study, the correlation between anti-CCP and DAS28 was not statistically significant, probably because the anti-CCP titer at one point of time was not enough to prove its correlation with RA activity. The correlation between anti-CCP and joint damage according to the Sharp score was significantly positive with a correlation coefficient of 0.30. This outcome is in line with the subjects of this study who were nonsmokers. A study by Mattey et al reported that smoking will elevate anti-CCP titer and this also occurs to those who have HLA-DRB1 SE.

Result of other studies supported our study, among others: Avouac et al that reported high specificity of anti-CCP of 95–96% in RA and Bas et al, Meyer et al, and Bukhari et al that reported anti-CCP had high specificity (96%) and positive subjects were strongly correlated with the occurrence of erosive RA whose severity is in line with the duration of RA disease. Forslind et al and Syversen et al reported that anti-CCP was correlated with radiographic joint damage and could be used as an independent predictor for progression and radiographic RA damage so that it could be used as an indicator for the rheumatologist in clinical practice to determine whether a more aggressive treatment is needed. According to a study conducted by Lee et al, 81% of RA patients with erosion showed reactive anti-CCP. Liao et al suggested revision of the RA diagnostic criteria of the 1987 ACR by including anti-CCP as one of the criteria to replace rheumatoid nodule. They found that the sensitivity was higher at 55% and specificity remained high at 91%.

This study could not provide enough evidence to support the correlation between anti-RA33 and DAS28 nor joint damage of the RA hand according to Sharp score. The anti-RA33 titer taken was at one point of time and 50% of the subjects were negative resulting in an insignificant correlation in the statistical analysis. Despite this fact, Mediwake et al reported an optimistic result in which anti-RA33 could be used to differentiate erosive RA from erosive SLE. A further study is needed to prove this fact.

CONCLUSION

The anti-CCP autoantibody is significantly correlated with joint damage in hand radiograph of RA patients; therefore, it could be used as an indicator for the occurrence of an erosive or a more severe RA.

REFERENCES


**Predictor of joint damage in rheumatoid arthritis**

Sumariyono, H Isbagio

**ABSTRACT**

**Objective:** This study was implemented to determine the joint damage predictor in rheumatoid arthritis (RA).

**Methods:** A cross-sectional study was conducted on outpatients of the rheumatology clinic at Cipto Mangunkusumo General Hospital who had suffered from RA for more than 2 years during the period from October 1, 1999 to June 30, 2000. During this period, we obtained 23 RA patients who fulfilled the inclusion and exclusion criteria. We evaluated the patients’ medical data that included gender, education, age of onset, rheumatoid factor (RF), C-reactive protein (CRP), and erythrocyte sedimentation rate (ESR). Then we carried out examinations and tests including X-ray of hand and wrist joints, RF, CRP, and ESR. The degree of joint damage was evaluated using the Larsen score.

**Results:** Twenty-three patients—all women, mean age of onset was 36.7 years, mean duration of disease was 62.8 months, educational level with high school degree or above were found in 19 cases (82.6%), and RF (+) at initial treatment were found in 10 cases (43.5%). The mean ESR at initial treatment was 77.9 mm/hr and CRP at initial treatment was between 0 and 768 mg/dL. The Larsen score ranged between 0 and 768 mg/dL. The Larsen score was significantly higher in the group with positive RF at initial treatment compared to that in the group with negative RF at initial treatment (p = 0.031). C-reactive protein and ESR at initial treatment and the age of onset did not have any significant correlation with the Larsen score, but there was a significant correlation of CRP and ESR during the study with the Larsen score.

**Conclusion:** RF level was the most significant predictor in determining the degree of joint damage according to the Larsen score while initial positive RF had lower significance level.

Rheumatoid arthritis (RA) is a chronic systemic inflammatory disease which has a variety of disease course and very unpredictable prognosis ranging from mild to severe outcome. The natural course of RA disease could be categorized into 3 types: (1) monocyclic, characterized by one attack cycle followed by remission; (2) polycyclic, consisting of intermittent subtype and continuous subtype; and (3) progressive, characterized by spreading involvement to other joints. Most RA course of disease is chronic and fluctuating so that, if not treated, can cause progressive joint damage, deformity, disability, and early death. According to Fuch, of the medically-treated RA patients, only 15% had remission or had normal functional status after 10 years of disease onset, while according to Edward D, of the RA patients studied during a mean of 11.9 years, only 17% were without disability. The joint damage in RA occurs mostly in the first two years of the disease.

The prognosis of the disease can be evaluated with some parameters, such as remission level, functional status, and the degree of joint damage. The above three parameters are not always correlated with each other. An RA patient may have a severe joint damage with an impaired functional status although it is in complete remission. The opposite could also occur, in which an RA patient with a minimum joint damage may not be in remission or may be in flare-up but has impaired functional status. Radiographic image is believed to be “the true biological endpoint” of inflammation and enzymatic degradation of cartilage and subchondral bone. In addition, evaluation for prognosis using the output of degree of joint damage is an objective method that can be calculated.

Today there are some theories and studies attempting to determine factors that can predict the RA joint damage. Factors that are strongly suspected include rheumatoid factor (RF), C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), presence of early joint erosion, human leukocyte antigen (HLA) associated with RA, and shared epitope. Other factors are disease activity score, gender, disability index, age of onset, type of onset, extra-articular symptoms, thrombocyte, hemoglobin, matrix metalloproteinase, anti-cyclic citrullinated peptide, and educational level.

To the extent of our knowledge, until today there has not been any research on predictor of RA joint damage in Indonesia; thereby, we conducted a study to determine the factors that can predict the RA joint damage of patients in Jakarta.

**METHODS**

This is a cross-sectional study conducted at the Division of Rheumatology of the Department of Internal Medicine, University of Indonesia School of Medicine/Cipto Mangunkusumo General Hospital (CMGH), Jakarta from October 1, 1999 until June 30, 2000. The inclusion criteria included RA patients who fulfilled the 1987 American College of Rheumatology (ACR) criteria, underwent treatment at the rheumatology clinic at CMGH, suffered RA for more than two years, had age of onset of more than 16 years old, was either in polycyclic or...
progressive category, had laboratory test result of ESR and or CRP and or RF during initial treatment, and gave consent to be part of the study. The exclusion criteria included those who suffered from other types of arthritis or refused to take part in the study.

Based on the medical records in the rheumatology clinic at CMGH, patients’ medical records with diagnosis of RA were selected. An evaluation was carried out based on the medical record. If it met the 1987 RA criteria according to the ACR, the patient was asked to perform a follow-up at or visit the rheumatology clinic at CMGH. If it was not possible, the patients would be visited at their home. The patient’s history was taken and physical examination was performed. If the patient obviously met the inclusion criteria and did not meet the exclusion criteria, she would be included as sample in the study. The medical data recorded were (1) name, age, gender, address, and education level; (2) age of onset; and (3) RF, ESR, and CRP at the initial treatment. During the study, RF, CRP, ESR, and radiograph of left and right hand and wrist joints were examined and later Larsen score was determined.

Positivity and level of rheumatoid factor at the initial treatment was taken from the patient’s medical record. Rheumatoid factor test at the initial treatment used a semiquantitative method using dilutions. It was positive if the dilution factor was $\geq 160$. During this study, RF test was conducted using RapiTex RF, a semiquantitative method for RF examination in which the value is positive when RF is greater than or equal to 20 IU/mL.

Table 1  Rheumatoid factor changes from initial treatment to the time of the study

<table>
<thead>
<tr>
<th>Group</th>
<th>Rheumatoid factor I</th>
<th>Rheumatoid factor II</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>negative</td>
<td>negative</td>
</tr>
<tr>
<td>2</td>
<td>positive</td>
<td>negative</td>
</tr>
<tr>
<td></td>
<td>negative</td>
<td>positive</td>
</tr>
<tr>
<td>3</td>
<td>positive</td>
<td>positive</td>
</tr>
</tbody>
</table>

C-reactive protein at the initial treatment and during the course of disease was taken from the medical record while CRP during the study was examined using RapiTex CRP which is a semiquantitative method for CRP examination.

Erythrocyte sedimentation rate at the initial treatment and during the course of disease was taken from the medical record while during this study ESR test was conducted again.

The degree of joint damage was determined by using modified Larsen score. In this method, radiographs in postero-anterior view of the left and right wrist, hand, and fingers were done. The joints evaluated were those of the wrist, metacarpophalanx (MCP), proximal interphalanx (PIP), and interphalanx I. The film of the radiograph was evaluated by comparing with a standard film.

The degree of damage of each joint was then totaled up. This total value was the Larsen score that ranged from 0 to 110. In this study, what was meant by modification was the modification of the joints being evaluated. In the original method the joint being evaluated was not mentioned. In our modification, the ones being evaluated were of the wrist, MCP, and PIP. The distal interphalangeal joint was not examined because it rarely suffered RA. Reading and evaluation of the radiographic findings were performed by a radiologist specializing in musculoskeletal field in the Department of Radiology at CMGH, Jakarta.

A correlation analysis between age of onset, duration of disease, educational level, ESR, CRP, RF respectively and modified Larsen score was performed. Variables that had a significant correlation with the Larsen score in the bivariate analysis were then analyzed using linear regression with duration of disease as the control variable to determine variables that were significant in determining the Larsen score.

RESULTS

Of the 42 RA outpatients visiting the rheumatology clinic at CMGH Jakarta from October, 1999 until June, 2000, 23 RA patients fulfilling the criteria were recruited. The patients in this study were all women aged between 23 and 59 years with a mean age of 41.9 years, in which 65% of them were less
than 50 years old. In terms of level of education, 4 patients (17.4%) had a level of < or = middle school and 19 (82.6%) had a level of > or = high school. Laboratory findings could be seen in table 2. Twenty three patients had Larsen scores ranging between 0 and 68 with a mean of 21.7, SD 17.3, and 95% CI 14.2-29.3.

### Table 2 Data of laboratory findings (N = 23)

<table>
<thead>
<tr>
<th>Test Type</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initial ESR, mm/hr, mean (SD) (range)</td>
<td>77.9 (36.1) (14—138)</td>
</tr>
<tr>
<td>Intra-study ESR, mm/hr, mean (SD) (range)</td>
<td>69.5 (26.3) (13—103)</td>
</tr>
<tr>
<td>Initial CRP, mg/dL, range (SD)</td>
<td>0—768 (237)</td>
</tr>
<tr>
<td>Intra-study CRP, mg/dL, range (SD)</td>
<td>0—768 (184)</td>
</tr>
<tr>
<td>Initial RF titer, range</td>
<td>0—5120</td>
</tr>
<tr>
<td>Positive initial RF, n (%)</td>
<td>10 (43.5)</td>
</tr>
<tr>
<td>Negative initial RF, n (%)</td>
<td>13 (56.5)</td>
</tr>
<tr>
<td>Intra-study RF titer, range</td>
<td>0—2560</td>
</tr>
<tr>
<td>Positive intra-study RF, n (%)</td>
<td>11 (48)</td>
</tr>
<tr>
<td>Negative intra-study RF, n (%)</td>
<td>12 (52)</td>
</tr>
</tbody>
</table>

ESR, erythrocyte sedimentation rate; CRP, C-reactive protein; RF, rheumatoid factor.

### Association between independent variables and Larsen score

#### Age of onset

The age of onset ranged between 18 and 55 years with a mean of 36.7 years. The majority (78.3%) had age of onset between 21 and 50 years. From the result of bivariate analysis, there was no significant linear correlation between the age of onset and the degree of joint damage according to the modified Larsen score ($r = 0.188$, $p = 0.391$).

#### Duration of disease

The duration of disease of the RA patients ranged between 26 and 168 months with a mean of 62.8 months. From the result of bivariate analysis, it seems that there was no significant linear correlation between the duration of disease and the degree of joint damage according to the modified Larsen score ($r = 0.312$ and $p = 0.148$). This was probably caused by one disturbing observation (sample no. 18). If that one observation is ignored/eliminated, there would be a significant linear correlation between the duration of disease and the degree of joint damage according to the modified Larsen score ($r = 0.457$ and $p = 0.032$).

#### Level of education

The majority of patients (83%) had a high school degree or above. In group 1 (< or = middle school), the mean Larsen score was $32.25 \pm 20.71$ with a median of 30.0 while in group 2 (> or = high school), the Larsen score was $19.53 \pm 16.53$ with a median of 19.0. The trend of the median Larsen score was lower in those with higher education than in those with lower education although in the Mann-Whitney test, there was no significant difference between the two groups ($p = 0.255$).

#### Erythrocyte sedimentation rate

At the initial treatment, there were two patients with normal ESR, one patient without initial ESR data, and the rest with elevated ESR. The initial ESR ranged between 14 and 138 mm/hr with a mean of 77.9 mm/hr. From bivariate analysis, there was no significant correlation between the initial ESR and the Larsen score ($r = 0.000…$, $p = 0.999…$). During the period of this study, we performed ESR tests. Of the 23 patients studied, ESR was between 13 and 103 mm/hr with a mean of 69.7 mm/hr. From bivariate analysis, there was a significant linear correlation between the ESR during the study and the degree of joint damage according to the Larsen score ($r = 0.427$, $p = 0.042$).

#### C-reactive protein

During the initial treatment, 12 patients did not have initial CRP data. There were only 11 patients who had CRP data with scores ranging between 0 and 768 mg/dL with a mean of 192 mg/dL. From bivariate analysis, there was no significant correlation between the CRP at initial treatment and the Larsen score. During the period of study, the CRP values of 23 patients were between 0 and 768 mg/dL with a mean of 178.6 mg/dL. From bivariate analysis, there was a significant correlation between CRP and the degree of joint damage according to the Larsen score ($r = 0.549$, $p = 0.007$).
Rheumatoid factor

During the initial treatment, RF test was performed on 20 patients using semiquantitative method, 2 patients using quantitative method, and one patient using qualitative method. From the last three patients above, only the positivity of RF was recorded. Positive RF was found in 10 (43.5%) cases with 95% CI 30-70%. The value of Larsen score in the positive initial RF group was 30.5 ± 19.9 while the value of Larsen score in the negative initial RF group was 15.0 ± 12.1.

From the T-test analysis, there was a significant difference in the value of Larsen score between the two groups (p = 0.031). The RF values of the 20 patients whose initial RF were examined semiquantitatively ranged between 0 and 5120. From bivariate analysis, we found that rs = 0.388 and p = 0.091.

During this study we also evaluated the role of RF changes, that is, the RF during initial treatment and the RF during the period of study. According to one-way analysis of variance (ANOVA), there was a significant difference in the Larsen score between those who always had negative RF and those who had once positive RF (either during the start of treatment or during the period of study) (p1-2 = 0.015), and between those who always had negative RF and those who always had positive RF (p1-3 = 0.034).

![Figure 3 Mean value and 95% CI of the Larsen score of rheumatoid factor (RF) 1, 2, and 3 change group. Larsen score in group 1 = 10.3 ± 11.2, group 2 = 24.4 ± 10.1, group 3 = 33.0 ± 24.9.](image)

### Multivariate analysis

As the number of cases (N) = 23 in this study, multivariate analysis was limited to include only two independent variables. It was decided that the duration of disease became the control variable because it is an important factor of joint damage.

### Level of initial rheumatoid factor and duration of disease

The result of the linear regression analysis between the initial RF level and the duration of disease, and the degree of joint damage according to Larsen score is seen in table 3.

![Table 3 Linear regression analysis between initial rheumatoid factor (RF) level and the duration of disease and Larsen score](image)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Coefficient B</th>
<th>95% CI B</th>
<th>t test significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>RF 1</td>
<td>0.0079</td>
<td>0.003–0.01</td>
<td>0.003</td>
</tr>
<tr>
<td>Duration of disease</td>
<td>0.215</td>
<td>0.017–0.41</td>
<td>0.035</td>
</tr>
<tr>
<td>Constant</td>
<td>2.275</td>
<td>−10.177–14.727</td>
<td>0.705</td>
</tr>
</tbody>
</table>

R² = 0.575, regression analysis of variance (ANOVA) test significance = 0.001.

From the result of the above analysis, we can see that 57.5% change in the Larsen score after two years was determined by the duration of disease and the RF level at initial treatment with a level of significance of 0.001. For every 20 fold dilution of RF, the Larsen score changed as much as 0.158.

### Positivity of initial rheumatoid factor and the duration of disease

The linear regression analysis between the positivity of RF and the duration of disease, and the degree of joint damage according to Larsen score can be seen in table 4.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Coefficient B</th>
<th>95% CI B</th>
<th>t test significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duration of disease</td>
<td>0.094</td>
<td>−0.114–0.302</td>
<td>0.357</td>
</tr>
<tr>
<td>Positive initial RF</td>
<td>13.492</td>
<td>−1.203–28.187</td>
<td>0.070</td>
</tr>
<tr>
<td>Constant</td>
<td>9.967</td>
<td>−4.507–24.441</td>
<td>0.166</td>
</tr>
</tbody>
</table>

R² = 0.237, regression analysis of variance (ANOVA) test significance = 0.067.

From the result of the analysis above, 23.7% change of the Larsen score was determined by the duration of disease and the positivity of initial RF with a level of significance of 0.067. After 2 years or more, patients with positive initial RF had 13 points higher in the Larsen score for the degree of joint damage than that of patients with a negative initial RF.

### Change of positivity of rheumatoid factor and duration of disease

The change of RF positivity is categorized into 3 groups as seen in table 1. For linear regression analysis between the change of RF positivity and the duration of disease, and Larsen score, a dummy variable of RF change was created first as follows:

\[
\Delta A = \begin{cases} 
1 & \text{if the RF change was equal to 1} \\
0 & \text{if the RF change was not equal to 1} 
\end{cases}
\]

\[
\Delta B = \begin{cases} 
1 & \text{if the RF change was equal to 3} \\
0 & \text{if the RF change was not equal to 3} 
\end{cases}
\]

<table>
<thead>
<tr>
<th>Variable</th>
<th>Coefficient B</th>
<th>95% CI-B</th>
<th>t test significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duration of disease</td>
<td>0.070</td>
<td>−0.140–0.279</td>
<td>0.494</td>
</tr>
<tr>
<td>Delta A</td>
<td>−11.181</td>
<td>−28.886–6.524</td>
<td>0.202</td>
</tr>
<tr>
<td>Delta B</td>
<td>8.586</td>
<td>−8.378–25.550</td>
<td>0.303</td>
</tr>
<tr>
<td>Constant</td>
<td>18.252</td>
<td>−0.935–37.438</td>
<td>0.061</td>
</tr>
</tbody>
</table>

R² = 30.4%, regression analysis of variance (ANOVA) test significance = 0.070.
From the outcome of the above analysis, 30.4% change in the Larsen score was determined by the duration of disease and the change of RF positivity with a level of significance of 0.070.

DISCUSSION

The ratio of men to women in RA patients is 1:3. In this study all the cases comprised of women. In reality, there were male RA patients visiting the rheumatology clinic but they did not fulfill the criteria, therefore, they were not included in this study. A 1997 data of the rheumatology clinic at CMGH showed that the ratio of men to women was 1:8. This is different from data mentioned in literatures. This study could not analyze the role of gender on the degree of joint damage according to Larsen score because all of the patients were women.

The role of age of onset as a predictor of joint damage in RA is still controversial. One author stated that the age of onset of over 50 years is associated with a more severe joint damage but another stated that a young age of onset is the one that is associated with a more severe joint damage. However, both authors did not explain why the age of onset affects degree of joint damage. Our study did not find any significant correlation between the age of onset and the degree of joint damage according to Larsen score. This is in line with the results of a study conducted by Peltoma et al that found the course of disease and progression of radiographic abnormality did not differ between patients with the age of onset of less than 55 years and that of over 55 years.

Joint damage in RA mainly occurs in the first two years of onset of disease, afterwards damage still occurs but at a slower rate, so that it makes sense if the duration of disease also determines joint damage in RA. However, after two years the degree of joint damage slows down and is affected by various factors such as RF, disease activity, and the degree of inflammation so that we must evaluate whether after two years, the duration of disease should be an important predictor of degree of joint damage in RA. In this study, we found that after an average of five years suffering from RA, only three patients (13%) had a Larsen score of 0 while the rest (87%) already had joint damage ranging from mild to severe. A study by Pincus et al also showed the same result on 58 RA patients in which the erosion in the first and eighteenth year were 73% and 96.5%, respectively. Our study found no significant correlation between the duration of disease and the degree of joint damage according to Larsen score, but if one particular observation is eliminated/ignored, a significant linear correlation exist between the duration of disease and joint damage according to Larsen score. This occurred because after more than two years of suffering RA, joint damage progress more slowly so that the duration of disease plays a lesser role in predicting the degree of joint damage in RA.

C-reactive protein is one of the inflammatory markers that is most responsive towards a change in inflammatory condition. Combe reported that the CRP level in severe RA is significantly higher than that in mild RA. Leuwen et al reported that initial CRP level was significantly associated with progression of joint damage after three years. Our study found no significant correlation between initial CRP level and the degree of joint damage according to Larsen score. Our study only found 11 patients who had their initial CRP level written in the medical record and factors affecting the result of CRP tests at initial treatment could not be controlled so that they could have affected the outcome of the study. Joint damage is really the end result of a whole process especially through inflammatory process that occurred in the joints of RA patients so that the ones that are correlated to the joint damage should be the cumulative inflammatory markers (CRP, ESR) evaluated at certain intervals and calculated using area under curve (AUC). This is supported by a study conducted by Leuwen et al that found a significant correlation between CRP AUC and the progression of 3-year joint damage.

In our study, CRP level during the period of study showed a significant correlation with Larsen score (r = 0.549, p = 0.007). This outcome is in line with the outcome of a study conducted by Matsuda Y that found CRP level after 6 months of treatment was a predictor of the progression of joint damage in early RA. This could occur because CRP level after 2 years displayed the CRP level after patients receive either nonsteroidal anti-inflammatory drugs or disease-modifying antirheumatic drugs (DMARDs) treatment, but if after 2 years of treatment the CRP level was still elevated, it showed that the patient had severe RA that was not responsive to treatment so that it could be assumed that during the 2 years or more of illness, CRP level was also high. This assumption is not entirely true because the course of RA disease often fluctuates: in one period it would be in remission and in another it would be recurrent.

From the data above, we could learn that RA patients who still had elevated CRP levels after adequate treatment would probably experience a more severe joint damage in the future so that patients in this category need to be treated more aggressively with DMARDs.

Our study showed that the correlation between ESR and joint damage had almost the same result as that of CRP test but with a lower level of significance (r = 0.427, p = 0.043). Some studies showed the same results with CRP.

Rheumatoid factor is an autoantibody against Fc IgG. This autoantibody mainly consists of IgM, but other immunoglobulins (G, A, D, and E) are also found. The role of RF in the pathogenesis of RA includes its capability to form an immune complex and activate complement.

The positive RF at initial treatment in this study was found in 43.5% of cases with 95% CI = 30–70%. This outcome is almost the same as that found in other countries in which positive RF was found in 60-90% of cases. Our study found a significant difference in Larsen scores between patients with positive initial RF and those with negative initial RF (p = 0.031). This study also found a correlation between initial RF level and Larsen score with a lower level of significance (r = 0.388, p = 0.091). This is also in line with the result of studies conducted by Mottonen, Paimela, and van Zeven. The change from initial RF value to RF value taken during the study also showed a correlation with the degree of joint damage in which the difference in Larsen score was significant enough between patients whose RF were always negative, once been...
positive, and always positive. Linear regression test found that initial RF level was a significant predictor in determining joint damage after 2 years in which for every 20 IU/mL change in RF would be followed by a 0.158 change in Larsen score after 2 years with a level of significance of 0.003. This could be stated by the following equation:

\[
Y \text{ (Larsen score)} = 2.275 + 0.215 \text{ duration of disease} + 0.0079 \text{ RF level}
\]

The outcome of the linear regression test for positivity of initial RF and the duration of disease showed a lower level of significance. This was possibly caused by small number of samples. The outcome of this study was in line with the statement made by Hazes JM who stated that at that time (October 2000) the IgM rheumatoid factor was the only strong predictor of joint damage.26

Based on this study, we could learn from the result that RA patients with positive RF, especially those with high levels of RF, should immediately be treated aggressively to reduce the possibility of joint damage in the future.

CONCLUSIONS

In this study we found out that positive RF and higher level of RF at the beginning of treatment were the significant predictive factors for joint damage after two-year duration of disease in female RA patients. C-reactive protein and ESR after two-year treatment were linearly correlated with Larsen score in RA patients. After two years, the duration of disease was still the important factor of joint damage in RA patients.

REFERENCES

Correlation of matrix metalloproteinase-9 level, erythrocyte sedimentation rate, rheumatoid factor, and the duration of illness with radiological findings in rheumatoid arthritis patients

G Aji,1 IARW Manuaba,2 JA Ongkowijaya,3 B Setiyohadi,3 Sumariyono3

ABSTRACT

Background: Rheumatoid arthritis (RA) is a common autoimmune disease of the joint indicated by chronic inflammation of synovium, cartilage destruction, and osteopenia. The end results of RA are joint deformity and disability that will decrease the quality of life of the patients. Until now there is not a specific marker to assess the process of joint and bone damage in RA. Available markers such as C-reactive protein and erythrocyte sedimentation rate (ESR) indicate more about the inflammatory status of the patient. The discovery of matrix metalloproteinases (MMPs) enzyme overexpression in RA has brought a new hope for the discovery of more specific markers of joint damage.

Objective: To study the correlation of MMP-9 level, ESR, rheumatoid factor (RF), and the duration of illness with joint damage in RA patients.

Methods: A cross-sectional study was conducted on RA outpatients in rheumatology clinic at Cipto Mangunkusumo General Hospital, Jakarta from January to October 2009. From the patients who fulfilled the inclusion criteria and did not fulfill the exclusion criteria, blood sample was collected for MMP-9 level, RF, and ESR examinations; hand radiography (posterior-anterior view) was also taken.

Results: From the study of 46 patients, we found a significant correlation between MMP-9 level and radiographic feature of bone erosion (r = 0.3, p = 0.02) and between the duration of illness and Sharp score (r = 0.36, p = 0.014). There was no correlation between ESR and radiological findings nor between RF and radiological findings. Linear regression analysis showed the duration of illness as the most influencing factor to radiological findings in RA patients.

Conclusion: We found a significant correlation between MMP-9 level and radiographic feature of bone erosion, and between the duration of illness and radiological findings in RA patients.

Matrix metalloproteinases (MMPs) are a group of enzymes first known to be involved in morphologic changes of tadpole. This group of enzymes, later known to be able to degrade the substrate of extracellular matrix, is categorized based on the degraded specific substrate. Until now there have been more than 20 MMPs enzymes found. It is assumed that MMPs can interfere with cell behavior including cell apoptosis, migration, and proliferation.1

Matrix metalloproteinase-9 has telopeptidase activity toward collagen and aggrecanase, the minor components of joint cartilage, thus MMP-9 is presumed to play a role in bone resorption. Rheumatoid arthritis (RA) itself is an autoimmune disease mainly affecting the joints besides other organs. The disease is indicated with symmetrical synovitis and bone erosion with the final result of joint deformity. There is a rather complex cytokine network in RA, but the dominant proinflammatory cytokines are tumor necrosis factor α (TNFα) and interleukin-1.2

Posthumus et al and Young Min et al reported that the high level of MMP-3 was correlated with the progression of radiographic joint damage, hence the high level of MMP-3 at the initial time of diagnosis is the reason to give anti-TNFα.3,4 However, Tsukuhara reported that genetic polymorphism promoting MMP-3 in AR patient in Japan did not influence the joint damage. It was different from the RA population in Europe.5 Gruber et al stated that there was increase of MMP-9 level in RA patients. Chang et al also reported the increase of MMP-9 level in RA patients in Taiwan. Matrix metalloproteinase-9 was thought to play a role in joint damage in RA.6,7

It is assumed that MMP-9 plays more roles than other MMPs in joint damage in RA. Meanwhile, other “traditional” inflammatory markers such as rheumatoid factor (RF) and erythrocyte sedimentation rate (ESR) are still being used often to predict radiological damage. Based on those ideas, we wanted to study the correlation of MMP-9 level, ESR, RF, and the duration of illness with radiographic joint damage in RA patients.

METHODS

Study design

This was a cross-sectional study conducted at rheumatology clinic at Cipto Mangunkusumo...
General Hospital (CMGH), Jakarta involving 46 RA patients from January to October 2009. The sample size was calculated using formula for correlation coefficient for single sample. Dependent variable in this study was radiological Sharp score, while the independent variables were MMP-9 level, ESR, RF level, and the duration of illness.

**Subjects**
Inclusion criteria were RA patients fulfilling the 1987 American College of Rheumatology criteria and agreed to be included in the study. Patients with chronic kidney disease, malignancy, chronic obstructive pulmonary disease, and systemic infection were excluded from the study. The study protocol had been approved by the appropriate local ethical board. All patients were then asked to give informed consent.

**Measurement**
Blood was collected for MMP-9 level, RF level, and ESR examinations. Matrix metalloproteinase-9 was examined in duplicate using enzyme-linked immunosorbent assay method from Bender MedSystem GmbH performed at Integrated Laboratory (Makmal Terpadu) at University of Indonesia School of Medicine, Jakarta. The result was in ng/mL. ESR was stated in mm/hour and RF was in IU/mL. Hand radiography with posterior-anterior view was also performed on the subjects with computed tomography at Department of Radiology at CMGH using Kodak CR975 System. The images were then interpreted by consultant radiologist and reported as Sharp score. Sharp score is a cumulative of two scores: joint space narrowing score in 16 hand joint area (0 = no joint space narrowing to 4 = no joint space) and bone erosion score in 17 hand joint area (0 = no bone erosion to 5 = extending erosion).

**Statistical methods**
The collected data were analyzed using Statistical Package for the Social Sciences (SPSS) program. We used multivariate analysis for statistical test of subject characteristics and bivariate analysis for correlation test using Pearson’s correlation test (or Spearman’s test for abnormally distributed data), then continued with multivariate analysis.

**RESULTS**
Of the 46 subjects we found the characteristics as follows: 40 subjects (87.0%) were female and 6 subjects (13.0%) were male. Mean age was 48.61 years and mean duration of illness was 4.83 years. Mean tender joint count was 5.42 and mean swollen joint count was 2.54. Mean total Sharp score, erosion score, and joint space narrowing score were 8.76, 3.50, and 5.37, respectively (table 1).

**DISCUSSION**
In this study we found that ESR and RF did not correlate with joint damage in RA patients. This result is different from previous studies done overseas. Caruso et al8 and Combe et al9 reported that ESR was the prognostic factor for radiographic joint damage, while Vitttecoq et al 10 reported that RF was the predictor for radiographic progression in RA patients. The difference in results could be caused in part by the study design used: those studies were prospective study, while ours was a cross-sectional study. We found a significant correlation between MMP-9 level and bone erosion score (r = 0.3, p = 0.02). It fitted the theory that MMP-9 has telopeptidase activity toward collagen, thus it is assumed to play a role in bone damage (r = 0.299, p = 0.043).

From the analysis of receiver operating characteristic curve, we obtained the cut-off point of 95.02 ng/mL for MMP-9 level with 72.72% sensitivity and 40.00% specificity. On the other hand, the cut-off point for the duration of illness was 39.0 months with 75.0% sensitivity and 63.33% specificity. In multivariate linear regression analysis we found the duration of illness as the most influencing factor to radiographic joint damage (r = 0.299, p = 0.043).

<table>
<thead>
<tr>
<th>Characteristics of subjects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Characteristics</td>
</tr>
<tr>
<td>Age, years</td>
</tr>
<tr>
<td>Tender joint count</td>
</tr>
<tr>
<td>Swollen joint count</td>
</tr>
<tr>
<td>ESR, mm/hr</td>
</tr>
<tr>
<td>RF level, IU/mL</td>
</tr>
<tr>
<td>MMP-9 level, ng/mL</td>
</tr>
<tr>
<td>Duration of illness, years</td>
</tr>
<tr>
<td>Joint space narrowing score</td>
</tr>
<tr>
<td>Bone erosion score</td>
</tr>
<tr>
<td>Total Sharp score</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Sharp score r (p Value)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MMP-9 level</td>
<td>0.181 (0.115)</td>
</tr>
<tr>
<td>RF level</td>
<td>0.194 (0.098)</td>
</tr>
<tr>
<td>ESR</td>
<td>0.104 (0.246)</td>
</tr>
<tr>
<td>Duration of illness</td>
<td>0.361 (0.014)</td>
</tr>
</tbody>
</table>
| MMP-9, matrix metalloproteinase-9; RF, rheumatoid factor; ESR, erythrocyte sedimentation rate.

There was not any correlation of MMP-9 level, ESR, or RF with the total Sharp score, but there was a significant correlation between the duration of illness and the total Sharp score (table 2). We also found a significant correlation between MMP-9 level and bone erosion score (r = 0.3, p = 0.02).
resorption. Engsig et al stated that MMP-9 plays important role in osteoclasts recruitment and migration to diaphysis in long bone formation, in conformity with theory stating that MMPs also play a role in cell behavior.\textsuperscript{11} Recruited osteoclasts in RA will become hyperactive through the receptor activator for nuclear factor-κB (RANK) protein in osteoclasts membrane, thus the osteoclasts would become active and resorp the bone. In this study, the duration of illness was significantly correlated with radiological findings ($r = 0.36$, $p = 0.014$). It fitted the study of Caruso et al which stated that the duration of illness was the most important factor that correlates with radiographic joint damage.\textsuperscript{8}

**CONCLUSIONS**

We found a significant correlation between MMP-9 level and radiographic bone erosion, and between the duration of illness and radiological findings in RA patients. Further studies are needed to investigate the role of MMPs in RA.

**REFERENCES**

Atherosclerosis prevalence and the correlation between atherosclerosis risk factors and carotid intima-media thickness in below 40-year-old women with systemic lupus erythematosus

RM Sari,1 YI Kasjmir,2 D Antono,3 S Setiati4

ABSTRACT

Objectives: To determine the prevalence of atherosclerosis in female systemic lupus erythematosus (SLE) patients aged below 40 years old and the factors correlated with carotid intima-media (CIM) thickening.

Methods: A cross-sectional study was conducted on 80 female SLE respondents aged below 40 years old who were either in- or outpatient of Cipto Mangunkusumo General Hospital, Jakarta. History of disease and treatment was taken, and laboratory test and ultrasonography of the carotid artery to evaluate CIM thickness were performed.

Results: The prevalence of atherosclerosis was 40%, comprising of CIM thickening and/or presence of atherosclerotic plaque in the carotid artery. The median values of CIM thickness in the right common carotid artery, right carotid bulb, left common carotid artery, and left carotid bulb were 0.040 cm, 0.04535 cm, 0.0430 cm, and 0.047 cm, respectively. There was also a positive correlation reported of CIM thickness with increased age, the duration of SLE disease, and the duration of steroid treatment.

Conclusions: We found a positive correlation of CIM thickness with age, the duration of SLE disease, and the duration of steroid treatment in female SLE patients aged below 40 years.

Systemic lupus erythematosus (SLE) is an autoimmune disease with a broad clinical manifestation including that of the coronary artery (10%).1–7 Female SLE patients have 50 times the risk of suffering a myocardial infarction with a death rate varying between 6 to 16%.4,6–8 The mechanism of premature atherosclerosis is as follows: arterial inflammation, arterial intima and media layer degeneration, immune response as a reaction to the immune complex, fibroblast and smooth muscle proliferation, and the presence of prothrombic condition.4,9–10 Setiawan reported that endothelial dysfunction was present in 10% of SLE patients that underwent flow-mediated dilatation.17

The risk factors for acquiring premature atherosclerosis in SLE patients are: old age, long duration of disease, high disease activity, kidney involvement, steroid treatment, hypercholesterolemia, absence of immunosuppressive therapy, and hydroxychloroquine.4,7,11–15,16–24 Bulkey and Robert reported that steroid administration of more than 1 year was associated with stenosis of the coronary artery lumen in 42% of SLE patient.25 In addition, Petri et al also reported a decrease in serum cholesterol level by 8.9 mg% after administration of 200 mg or 400 mg of hydroxychloroquine.26

Ultrasoundography (USG) of the carotid artery is recommended by the American Heart Association as a diagnostic tool for subclinical atherosclerosis.7,23,27 Roman et al reported that the prevalence of atherosclerotic plaque was 37.1%.28 Doria et al found carotid intima-media (CIM) thickening in 28% of patients and atherosclerotic plaque in 17% of patients.29 Sato et al reported that atherosclerotic plaque was found only in SLE patient group (36%).30 Selzer et al reported that 32% of SLE patients had a minimum of one focal atherosclerotic plaque.31 The same result was also reported by Manzi et al in which 40% of SLE women had atherosclerotic plaque.32 However, Jimenez et al did not find any differences in CIM thickness between the SLE patient group and the control group.33 Besides traditional factors, the SLE disease itself is a risk factor for atherosclerosis.4,5,11,13,20,21,34–46 Carotid artery USG was used to evaluate the diameter of the artery, thickness of CIM, presence of plaque and its extent.22,47,48 Increased CIM thickness is associated with increased risk of cardiovascular incidence.7,49–51 Ziembicka et al, who conducted a study on 558 respondents with a mean age of 58.8 years, reported that there was a significant correlation between CIM thickness and the severity of the coronary artery disease that was evaluated using coronary angiography (p<0.00001).52

The objective of this study was to determine the prevalence of atherosclerosis in female SLE patients below 40 years old to find the role of SLE disease in the prevalence of atherosclerosis and also to find the correlation between risk factors for atherosclerosis and CIM thickness evaluated using carotid artery USG.
METHODS
The study was conducted in the Department of Internal Medicine, Cipto Mangunkusumo General Hospital, Jakarta from November 2008 until April 2009 using a cross-sectional study design. The samples were female SLE outpatients and inpatients with a maximum age of 40 years who fulfilled the 1997 update of 1982 American College of Rheumatology revised criteria. The exclusion criteria are patients with a neck mass or neck ulcer and patients that could not be examined in supine position.

Variables measured
Risk factor for atherosclerosis
Interviews were done to find the characteristics of samples that included age, duration of disease, presence of hypertension or diabetes mellitus, type and duration of treatment given (steroid, chloroquine, immunosuppressants). Measurement of blood pressure and body mass index were performed. Assessment of disease activity was conducted once using the Mexican SLE Disease Activity Index (Mex-SLEDAI) scoring system. Laboratory tests were done to assess the disease activity, determine the random blood glucose level, total cholesterol, high-density lipoprotein (HDL) cholesterol, low-density lipoprotein (LDL) cholesterol, and blood triglyceride. Random urine test and 24-hour quantitative urine protein test were also conducted to detect any kidney disorder.

Carotid artery ultrasonography examination
The measurement of CIM thickness was performed using Philips Sonos 5500 B-mode ultrasound by a certified operator. In patients with supine position, examination of CIM thickness was performed on the following locations: left/right mid-common carotid artery (LCCA/RCCA) and left/right carotid bulb and each from the following angles: anterior, lateral, and posterior. The results of the examination of CIM thickness were reported in centimeters and derived from the mean CIM thickness of 3 locations examined (anterior, lateral, and posterior).

The normal value of the common carotid artery intima-media (IM) thickness is determined based on the following equation:

$$\text{IM thickness of the common carotid artery} = 0.04 \text{ cm + } \{(age - 21) \times 0.001 \text{ cm}\}$$

The above equation is determined based on the results of previous studies conducted by Maarifat who reported that the mean CIM thickness of the normal population at the mean age of 21 years was 0.04 cm and the normal growth of the common carotid artery in women was 0.001 cm a year.\textsuperscript{56,57} For normal IM thickness of the carotid bulb, the reference value used was 0.83 cm which is the maximum thickness of IM of the carotid bulb in the normal group at ages 35-39 years according to a study conducted by Lim and Kooner.\textsuperscript{53}

Atherosclerosis was reported if there was CIM thickening in at least one location: left/right mid-common carotid artery or left/right carotid bulb and/or the presence of atherosclerotic plaque in one or more of the above locations. Atherosclerotic plaque was defined if the CIM thickness was >0.13 cm in at least one location.

Statistical methods
Data processing was conducted using Statistical Package for the Social Sciences (SPSS) version 17.00. Bivariate analysis was conducted between risk factors for atherosclerosis and CIM thickness using the Pearson’s correlation test or its alternative (Spearman’s test).

RESULTS
Of the 80 respondents studied, the mean age was 26.93 years (table 1) with an educational level of mostly high school degree or its equivalent.

Table 1 Distribution of variables contributing to atherosclerosis

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Absence of chloroquine (3 months minimum)</td>
<td>70 (87.5)</td>
</tr>
<tr>
<td>Active SLE (Mex-SLEDAI score ≥ 2)</td>
<td>48 (60)</td>
</tr>
<tr>
<td>Daily dose of steroid (prednisone) &gt; 10 mg/day</td>
<td>48 (60)</td>
</tr>
<tr>
<td>Long-term steroid treatment (&gt;12 months)</td>
<td>46 (57.5)</td>
</tr>
<tr>
<td>Kidney involvement</td>
<td>45 (56.2)</td>
</tr>
<tr>
<td>Hypertriglyceridemia</td>
<td>32 (40)</td>
</tr>
<tr>
<td>Hypercholesterolemia</td>
<td>27 (33.8)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>22 (27.5)</td>
</tr>
<tr>
<td>Duration of disease &gt; 5 years</td>
<td>13 (16.3)</td>
</tr>
<tr>
<td>Obesity</td>
<td>13 (16.3)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Smoker</td>
<td>0 (0)</td>
</tr>
</tbody>
</table>

SLE, systemic lupus erythematosus; Mex-SLEDAI, Mexican SLE Disease Activity Index.

In the distribution of risk factors for atherosclerosis, absence of chloroquine treatment (87%), daily steroid dose of more than 10 mg (60%), and active SLE disease (60%) ranked the highest in the list (table 2).

Table 2 Distribution of characteristics based on risk factors for atherosclerosis

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Absence of chloroquine (3 months minimum)</td>
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<td>48 (60)</td>
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</tr>
<tr>
<td>Diabetes mellitus</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Smoker</td>
<td>0 (0)</td>
</tr>
</tbody>
</table>

SLE, systemic lupus erythematosus; Mex-SLEDAI, Mexican SLE Disease Activity Index.

From the assessment of SLE activity using the Mex-SLEDAI score, the disorder mostly found was kidney disorder (36.3%), followed by lymphopenia (30%), mucocutaneous disorder (18.8%), complaints of unexplained fatigue (17.5%),
and hematological disorder such as hemolysis (15%), leucopenia (10%), and thrombocytopenia (7.5%).

The prevalence of atherosclerosis was 40%, as seen in more detail in table 3.

**Table 3** Prevalence of atherosclerosis in female systemic lupus erythematous patients

<table>
<thead>
<tr>
<th>Criteria</th>
<th>n  (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CIM thickening without carotid plaque</td>
<td>28 (35)</td>
</tr>
<tr>
<td>CIM thickening with carotid plaque</td>
<td>3 (3.8)</td>
</tr>
<tr>
<td>Carotid plaque without CIM thickening</td>
<td>1 (1.2)</td>
</tr>
<tr>
<td>Atherosclerosis</td>
<td>32 (40)</td>
</tr>
</tbody>
</table>

CIM, carotid intima-media.

The distribution of CIM thickness in all respondents can be seen in table 4.

**Table 4** Carotid intima-media (CIM) thickness evaluated using B-mode ultrasound

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Median (range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>RCCA IM thickness, cm</td>
<td>0.0400 (0.030–0.070)</td>
</tr>
<tr>
<td>Right carotid bulb IM thickness, cm</td>
<td>0.0435 (0.030–0.183)</td>
</tr>
<tr>
<td>LCCA IM thickness, cm</td>
<td>0.0430 (0.030–0.073)</td>
</tr>
<tr>
<td>Left carotid bulb IM thickness, cm</td>
<td>0.0470 (0.030–0.090)</td>
</tr>
</tbody>
</table>

All data have abnormal distribution.

RCCA, right mid-common carotid artery; IM, intima-media; LCCA, left mid-common carotid artery.

The Pearson’s correlation test or its alternative (Spearman’s test) that was performed between the risk factors for atherosclerosis and CIM thickness showed a positive correlation between age and CIM thickness in RCCA, LCCA, right and left carotid bulb, and also a positive correlation between the duration of SLE disease and CIM thickness in LCCA. In addition, there was a positive correlation between the duration of steroid treatment and CIM thickness in RCCA, right carotid bulb, and LCCA.

Pearson’s correlation test showed no significant correlation of total cholesterol level, LDL cholesterol level, systolic blood pressure, duration of chloroquine treatment, proteinuria level, or score of disease activity with CIM thickness of SLE patients.

**DISCUSSION**

This study was focused on below 40-year-old SLE patients. As we know, older age is one of the risk factors for premature atherosclerosis in SLE patient. Some previous studies also reported high prevalence of atherosclerosis in above 40-year-old SLE patients. In those patients, we could not assess whether the atherosclerosis was influenced predominantly by older age or by the disease itself. In this study, we wanted to learn more about SLE as the main risk factor for premature atherosclerosis; therefore, we chose SLE patients below 40 years old as respondents.

Prevalence of premature atherosclerosis in SLE patients is influenced by traditional risk factors and risk factors associated with the SLE disease itself. The study showed the distribution of prevalence of hypertension was 27.5%, obesity was 16.3%, hypercholesterolemia was 33.8%, and hypertriglyceridemia was 40%. As the respondents’ mean age of 26.93 years old was a relatively young age, it was more likely that the prevalence of hypertension, obesity, and dyslipidemia that occurred was associated with the effects of treatment or the SLE disease itself rather than purely associated with the traditional risk factors. Jimenez and Manzi reported that SLE patients who had hypertension, dyslipidemia, hypercholesterolemia, hypertriglyceridemia, and elevated apolipoprotein B level had a higher risk of developing atherosclerosis. However, Svenungson reported that there was no significant correlation between blood pressure, body mass index score, and diabetes mellitus of SLE patients with a history of cardiovascular disease and of SLE patients without a history of cardiovascular disease or those of the control group.

This study found that more than half of the respondents were aged between 21 and 30 years old with a mean of 26.93 ± 6.342 years. The mean age of SLE patients found in this study was the youngest mean age compared to the studies done in other countries. This is interesting because sunlight, which is found more abundant in Indonesia as a tropical country, may be one of the triggers for an earlier onset of SLE so that the mean age of SLE patients in Indonesia was younger than in the four-seasonal countries.

For the duration of disease variable, the median was 31 months. Compared to previous studies, the median of duration of disease was the shortest although it is reported that the

**Tabel 5** Pearson’s correlation coefficients between atherosclerosis risk factors and carotid intima-media (CIM) thickness

<table>
<thead>
<tr>
<th>Risk factors</th>
<th>CIM thickness</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>RCCA</strong></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>0.227 (0.021)</td>
</tr>
<tr>
<td>Duration of SLE disease</td>
<td>0.182 (0.053)</td>
</tr>
<tr>
<td>Total cholesterol level</td>
<td>−0.028 (0.399)</td>
</tr>
<tr>
<td>LDL cholesterol level</td>
<td>−0.048 (0.335)</td>
</tr>
<tr>
<td>Systolic blood pressure</td>
<td>0.045 (0.347)</td>
</tr>
<tr>
<td>Duration of steroid treatment</td>
<td>0.195 (0.041)</td>
</tr>
<tr>
<td>Duration of chloroquine treatment</td>
<td>−0.284 (0.134)</td>
</tr>
<tr>
<td>Proteinuria level</td>
<td>−0.056 (0.311)</td>
</tr>
<tr>
<td>Mex-SLEDAI score</td>
<td>−0.014 (0.449)</td>
</tr>
<tr>
<td><strong>Right bulb</strong></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>0.289 (0.004)</td>
</tr>
<tr>
<td>Duration of SLE disease</td>
<td>0.182 (0.053)</td>
</tr>
<tr>
<td>Total cholesterol level</td>
<td>−0.065 (0.283)</td>
</tr>
<tr>
<td>LDL cholesterol level</td>
<td>−0.107 (0.177)</td>
</tr>
<tr>
<td>Systolic blood pressure</td>
<td>0.045 (0.346)</td>
</tr>
<tr>
<td>Duration of steroid treatment</td>
<td>0.202 (0.036)</td>
</tr>
<tr>
<td>Duration of chloroquine treatment</td>
<td>0.007 (0.489)</td>
</tr>
<tr>
<td>Proteinuria level</td>
<td>−0.069 (0.273)</td>
</tr>
<tr>
<td>Mex-SLEDAI score</td>
<td>0.040 (0.360)</td>
</tr>
<tr>
<td><strong>LCCA</strong></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>0.389 (0.0001)</td>
</tr>
<tr>
<td>Duration of SLE disease</td>
<td>0.189 (0.047)</td>
</tr>
<tr>
<td>Total cholesterol level</td>
<td>0.080 (0.239)</td>
</tr>
<tr>
<td>LDL cholesterol level</td>
<td>0.100 (0.189)</td>
</tr>
<tr>
<td>Systolic blood pressure</td>
<td>0.060 (0.298)</td>
</tr>
<tr>
<td>Duration of steroid treatment</td>
<td>0.238 (0.017)</td>
</tr>
<tr>
<td>Duration of chloroquine treatment</td>
<td>−0.159 (0.271)</td>
</tr>
<tr>
<td>Proteinuria level</td>
<td>0.062 (0.291)</td>
</tr>
<tr>
<td>Mex-SLEDAI score</td>
<td>−0.117 (0.151)</td>
</tr>
<tr>
<td><strong>Left bulb</strong></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>0.387 (0.0001)</td>
</tr>
<tr>
<td>Duration of SLE disease</td>
<td>0.070 (0.268)</td>
</tr>
<tr>
<td>Total cholesterol level</td>
<td>−0.014 (0.450)</td>
</tr>
<tr>
<td>LDL cholesterol level</td>
<td>0.037 (0.372)</td>
</tr>
<tr>
<td>Systolic blood pressure</td>
<td>0.110 (0.166)</td>
</tr>
<tr>
<td>Duration of steroid treatment</td>
<td>0.124 (0.135)</td>
</tr>
<tr>
<td>Duration of chloroquine treatment</td>
<td>0.0004 (0.499)</td>
</tr>
<tr>
<td>Proteinuria level</td>
<td>−0.035 (0.380)</td>
</tr>
<tr>
<td>Mex-SLEDAI score</td>
<td>0.054 (0.316)</td>
</tr>
</tbody>
</table>

Data are given as r (p value). RCCA, right mid-common carotid artery; LCCA, left mid-common carotid artery; SLE, systemic lupus erythematous; LDL, low-density lipoprotein; Mex-SLEDAI, Mexican SLE Disease Activity Index.
maximum duration of disease was 222 months. The low value of duration of disease shows that the survival rate was still low in the SLE patients of this study.

All the respondents in this study were given steroid as a main treatment. As many as 57.7% respondents were given steroid treatment for more than 12 months with a median duration of steroid treatment of 19 months and a median daily dose of steroid of 15 mg/day (equivalent to prednisone). A steroid daily dose of more than 10 mg/day and a steroid treatment of more than one year were reported as risk factors that accelerate the onset of atherosclerosis in SLE patients. Bulkey and Robert in 1975 conducted an autopsy to examine the hearts of 36 SLE patients who were given steroid treatment of more than one year and reported that 42% of patients had stenosis of more than 50% of the lumen of the coronary artery. Bulkey and Robert in 1975 conducted an autopsy to examine the hearts of 36 SLE patients who were given steroid treatment of more than one year and reported that 42% of patients had stenosis of more than 50% of the lumen of the coronary artery. MacGregor and Petri also reported that a daily dose of prednisone of more than 10 mg/day in SLE patients could increase the incidence of dyslipidemia (hypertriglyceridemia, hypercholesterolemia, hypertriglyceridemia, hypercholesterolemia) 6,21,42

It is apparent that steroid was the first choice of treatment in this study although it is known that long term steroid treatment has side effects that includes diabetes mellitus, hypertension, dyslipidemia that is also a risk factor for atherosclerosis. This steroid treatment is like a double edged knife—if the dose is more than 10 mg/day, it will increase the incidence of dyslipidemia that is associated with the incidence of atherosclerosis risk, but Roman also reported that the incidence of atherosclerotic plaque is associated with low dose of steroid. It means the SLE disease was not yet well controlled in those cases.

Chloroquine treatment for at least three months is considered to have a protective effect against atherosclerosis through its hypolipidemic effect; however, in this study only 12.5% respondents were treated accordingly. Hydroxychloroquine, which has a positive effect in treatment of skin and joint disorders, is also reported to be able to decrease the total cholesterol, LDL cholesterol, and triglyceride level so that it could reduce the risk of atherosclerosis. 13,26,43 Wallace et al found that lower levels of cholesterol, triglyceride, and LDL-C cholesterol were significant in female SLE patient group that were given hydroxychloroquine treatment without steroid administration. 41 The low frequency use of chloroquine was caused by its use in SLE that was limited for only musculoskeletal involvement, while according to the description of organ disorders in the Mex-SLEDAI score in this study, mucocutaneous involvement was 18.8% and arthritis involvement was 3.8%.

The assessment for disease activity using Mex-SLEDAI score showed that 60% of the respondents were in the active form of the disease with a median score of 3. The high score of disease activity was likely caused by the SLE condition that was actually still active during initial treatment or there was a period of fluctuating disease activity because the respondents did not undergo the treatment program regularly. This was possibly associated with the low awareness and low income levels of the respondents. The low income level was reflected in the occupational status of the respondents. Only 27.5% of the respondents held a job and 78.7% got treatment using the welfare facility.

The USG examination of the carotid had 93.4% sensitivity and 94% specificity to evaluate the process of atherosclerosis. The features found on the carotid arterial wall is a reflection of the features found on the coronary arterial wall. A thickening of CIM that precedes plaque formation or discovery of plaque in carotid artery could be used as a window to evaluate the process of atherosclerosis in coronary artery. 7,23,27 Images of USG can visualize the arterial wall in each stage of atherosclerosis from the normal stage to total arterial occlusion stage. The measurement of IM of carotid artery could be used as a marker of the development of atheroma and is associated with the incidence of coronary heart disease, stroke, and peripheral arterial disease. 27

As this study was conducted on respondents with a young mean age, it is hoped that measurement of CIM thickness gives a clearer picture of the carotid artery condition caused by the effect of SLE disease itself or by the side effect of treatment. Other factors such as hypercholesterolemia, hypertriglyceridemia, and obesity are considered as caused by the SLE disease or the side effects of steroid treatment rather than as comorbid.

Table 6 Studies on the prevalence of atherosclerosis in systemic lupus erythematosus (SLE) patients

<table>
<thead>
<tr>
<th>Researchers</th>
<th>Study design and results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Manzi, USA, 1992</td>
<td>A cross-sectional study of 175 female SLE patients found that the prevalence rate of atherosclerosis was 40% and the mean age was 50.5±11.7 years.</td>
</tr>
<tr>
<td>Roman et al, New York, 2003</td>
<td>A case-control study of 394 SLE patients found that the prevalence rate of atherosclerotic plaque was 37.1% and the mean age was 52 years.</td>
</tr>
<tr>
<td>Doria et al, Italy, 2003</td>
<td>A prospective cohort study of 78 SLE patients found that the prevalence rate of atherosclerotic plaque was 17% and the mean age was 45.7 years. There was also carotid intima-media (CIM) thickening in 28% of the patients with a mean age of 43.3 years.</td>
</tr>
<tr>
<td>Selzer et al, USA, 2004</td>
<td>A cross-sectional study of 214 female SLE patients without cardiovascular disease found that the prevalence rate of atherosclerotic plaque was 32% and the mean age was 52.6±9.7 years.</td>
</tr>
<tr>
<td>Sato et al, Japan, 2007</td>
<td>A case-control study of 78 female SLE patients who were clinically stable for at least 3 years with a fixed dose of prednisone of more than one year found that the prevalence rate of atherosclerotic plaque was 36% and the mean age was 42.3 years (premenopause) and 56.8 years (postmenopause).</td>
</tr>
<tr>
<td>This study</td>
<td>A cross-sectional study of 80 SLE patients with a maximum age of 40 years old found that the prevalence rate of atherosclerosis (with thickening of CIM and/or atherosclerotic plaque) was 40% and the median age was 24.8 years old.</td>
</tr>
</tbody>
</table>

The high prevalence rate of atherosclerosis in this study was caused by the differences in normal CIM thickness reference values of healthy respondents used. The previous study used the same reference value of normal CIM thickness for all age groups. This study used a reference value of normal common carotid intima-media (CCIM) thickness that was calculated based on an equation determined by the researcher.
Based on the study conducted by Maarifat in 2005, the mean value of the CCIM thickness in the Indonesian healthy subjects aged 21 years was 0.04 cm and the Atherosclerosis Risk in Communities (ARIC) study by Howard in 1993 found the normal growth of the common carotid arterial wall was 0.001 cm/year in healthy female respondents. Therefore, the equation for normal CCIM thickness could be determined. By using the reference value of normal CIM thickness based on age, we can determine any increase of CCIM thickness in each stage of age so that we can anticipate the steps for further treatment to prevent atherosclerosis.

In the Pearson’s correlation test or its alternative (Spearman’s test) between the risk factor for atherosclerosis and CIM thickness, we found a positive correlation between increased age, longer duration of SLE disease, and/or longer duration of steroid treatment and CIM thickness.

Aging and duration of SLE disease were reported to have a positive correlation with CIM thickness. A previous study conducted by Selzer and Manzi found that old age is associated with increased risk of CIM thickening and development of atherosclerotic plaque.31,32 Manzi et al and other studies also reported a significant correlation between the duration of SLE disease and the prevalence of atherosclerotic plaque.32 Swaak et al also reported the prevalence of myocardial infarction (5%) and coronary artery disease (8%) in patients that have suffered SLE for ten years.5

There was also a report of a positive correlation between long duration of steroid treatment and CIM thickness. This is in line with the theory that steroid is one of the risk factors for atherosclerosis that is formed because of the effects of dyslipidemia, hypertension, diabetes mellitus, and obesity. Manzi et al also reported that female SLE patients administered with a longer duration and a higher cumulative dose of prednisone had a higher risk of developing atherosclerotic plaque.32 In addition, Bulkey also reported the presence of more than 50% stenosis in the coronary artery lumen in SLE patients who had undergone steroid treatment continuously for more than one year.

Steroid, which is a drug of choice for SLE treatment, must be administered wisely because treatment with steroid has two effects: anti-inflammatory and atherogenic effect. In these cases, steroid must be administered appropriately in terms of dose and duration of treatment. Regular monitoring must be conducted to anticipate the possibilities of side effects that occur.

We understand that atherosclerosis develop as a result of various factors including inflammation factor that is characterized by an imbalance between proinflammatory cytokine and anti-inflammatory cytokine. Because of limited funds and examination methods, an examination of inflammation marker could not be performed in this study. In addition, the cross-sectional study design used here did not allow the researcher in this study to directly evaluate the cause and effect association between the risk factors and the prevalence of atherosclerosis.

The limited reference value of normal CIM thickness in the Indonesian population that is limited to a certain age group as reported by Maarifat in 2005 forced the researcher to create an equation to determine the normal thickness value of the common carotid intima-media.

**CONCLUSIONS**

Atherosclerosis occurred in 40% young aged female SLE patients as CIM thickening and/or carotid plaque. There was positive correlation of CIM thickness with age, duration of SLE disease, and duration of steroid treatment in female SLE patients aged below 40 years.

**REFERENCES**

56. Maarif NN. Thickness of intima-media complex of common carotid artery in group of 20–30 years old patients at Department of Radiology at University of Indonesia School of Medicine/Cipto Mangunkusumo General Hospital (Ketebalan kompleks intima media arteri karotis komunis pada kelompok khusus usia 20–30 tahun di bagian radiologi FKUI-RSCM). Theses. University of Indonesia; 2005.


Leprosy patients could display a great variability of signs and symptoms. An overabundance of rheumatic manifestations, occurring alone or in varying combinations, are associated with leprosy, particularly with lepra reactions. A study involving seventy cases of leprosy found that rheumatic manifestations were seen in 61.42% of cases: arthritis in 54.28% and soft tissue rheumatism in 17.14%. Enthesitis was seen in 2.84% of cases. Rheumatic manifestations may be the primary complaint, thus delaying accurate diagnosis. Musculoskeletal involvement in leprosy is the third most frequent manifestation after dermatological and neurological involvements. It can occur at any time during the infection. Articular inflammation in leprosy, which closely mimics other rheumatic disorders, usually occurs in reactive states, particularly erythema nodosum leprosum (ENL). About 1–5% of leprosy patients are reported of developing arthritis (synovial inflammation) at some stage of the disease but this rate increases to over 50% during lepra reactions.

Here we report a case of arthritis in leprosy without any typical skin lesion thus causing a delay in diagnosis.

**CASE REPORT**

A 72-year-old woman was admitted at the immunology clinic complaining that her left hand had become smaller than her right hand within one year. The skin on her left hand was anesthetic with occasional tingling sensation. She reported no skin lesion on other parts of her body. There were not any significant constitutional symptoms and family history of arthritis or leprosy.

Physical examination showed normal vital signs, but her left hand was atrophic with tight, shiny anesthetic skin and pencil-like fingers. We did not find any arthritis or tremor. She had no leonine facies or any skin lesion on other parts of her body.

**Laboratory examination revealed:** hemoglobin 12.5 g/dL, hematocrit 37.5%, leukocyte count 7.9 x 10^3/mm³, platelet count 287 x 10^3/mm³, erythrocyte sedimentation rate 35 mm/hr, C-reactive protein 4.6 mg/dL, blood glucose 102 mg/dL, blood urea nitrogen 30 mg/dL, serum creatinine 0.5 mg/dL, aspartate aminotransferase 44 IU/L, alanine aminotransferase 31 IU/L, total protein 7.8 U/L, albumin 4.41 U/L, globulin 3.49 U/L, total cholesterol 161 mg/dL, low-density lipoprotein cholesterol 63 mg/dL, and high-density lipoprotein cholesterol 71 mg/dL. The urinalysis showed normal results. The latex rheumatoid factor test was negative. Antinuclear antibodies were negative and there were no antibodies toward extractable nuclear antigens. Radiography of the hands and wrists showed normal bones.

The patient was first diagnosed with vasculitis and carpal tunnel syndrome. However, we found no histopathologic feature of vasculitis on biopsy. The electromyography did show motoric neuropathy of the median nerve and sensoric neuropathy of the ulnar nerve, but we found no swelling of the lining of the flexor tendons (tenosynovitis) or evidence of joint dislocations, fractures, or arthritis that can narrow the carpal tunnel and put pressure on the nerve. She was then given steroid (prednisolone 32 mg/day) and calcium 1,500 mg/day.

One month after therapy, she complained of gradual pain, stiffness, swelling, and redness of fingers II and III of her left hand. There was no clear history of Raynaud’s phenomenon. On physical...
examination we found swelling of the fingers of her left hand, with arthritis of interphalangeal joints of fingers II and III (figure 2). Still there was no typical skin lesion on the fingers or on any other parts of her body.

She then underwent slit skin smear for acid-fast bacilli, which showed negative result. Skin biopsies were subsequently performed and histopathological examination revealed thickening of collagen and epitheloid granuloma in dermis, thus representing scleroderma, but borderline tuberculoid (BT) leprosy was also suspected. Fite-Faraco staining showed no acid-fast bacilli. She then underwent serological test with enzyme-linked immunosorbent assay (ELISA) for anti-phenolic glycolipid-I (anti–PGL-I). We found that IgM was normal (456 U/mL, cut off 605 U/mL) but there was slight rise of IgG (666 U/mL, cut off 630 U/mL). The diagnosis of BT leprosy was then made. The World Health Organization (WHO) multidrug therapy (MDT) 1982 regimens for paucibacillary (PB) leprosy, comprising of rifampicin 600 mg once a month and dapsone 100 mg q.d., was started immediately.

Five months after therapy, the size of both hands had become similar. Her arthritis symptoms had improved, although the complaint of recurrent numbness and tingling on her left hand persisted (figure 3). The dose of prednisolone was then tapered and MDT for PB was continued.

Figure 3 Five months after therapy: similar sizes of both hands, with swelling of fingers II and III of the left hand.

DISCUSSION

Leprosy, or Hansen’s disease (HD), is a chronic granulomatous infection caused by *Mycobacterium leprae*. It has a global prevalence of 5.7 per 10,000 populations. At the end of 2005, the global prevalence of leprosy was estimated by the WHO to be around 1 per 10,000 population. It is estimated that 12–20 million people suffer from leprosy worldwide. Leprosy is endemic in Indonesia. Data from the Ministry of Health of the Republic of Indonesia showed that the prevalence of leprosy in Indonesia was 0.76/10,000 population in 2008.

Leprosy exhibits a wide spectrum of presentation, varying from the tuberculoid to the lepromatous pole, with immunologically unstable borderline forms in between, depending upon the immunity status of the individual. Traditionally, patients are classified according to the Ridley-Jopling scale, which includes indeterminate leprosy, tuberculoid leprosy, borderline tuberculoid leprosy, borderline leprosy, borderline lepromatous leprosy, and lepromatous leprosy. Tuberculoid leprosy represents a sufficient cell-mediated immune response. Patients may have one or two hypopigmented, erythematous, and anesthetic macules with a raised margin. Lepromatous leprosy may occur in the setting of immune dysfunction or if the patient is anergic to *M. leprae*. These patients may have widespread disease that involves the skin, upper respiratory tract, anterior chamber of the eye, testes, lymph nodes, periosteum, and superficial sensory and motor nerves. Cutaneous findings include diffuse, erythematous macules, papules, and nodules. The clinical system of classification for the purpose of treatment includes the number of skin lesions and nerves involved as the basis for classifying the patients into multibacillary (MB) or PB.

The presentation of leprosy can be variable. The skin lesions of leprosy have a great similarity to various other lesions, hence the term “the great imitator”. Sometimes, these skin lesions may be misdiagnosed because the physician does not consider leprosy. Although leprosy affects primarily the skin and the peripheral nervous system, it also secondarily involves the liver, spleen, testes, kidney, bone marrow, and eyes. Any peripheral or cutaneous nerve may be involved, but the ulnar nerve is the most commonly affected. In addition, leprosy patients may also suffer from reactions which are acute and episodic inflammatory states unrelated to secondary infection and which occurs during the natural course of the disease.

The diagnosis of our patient was delayed because she had no symptom of arthritis or typical leprosy skin lesion before being treated with systemic corticosteroids. The diagnosis was confused clinically because she had developed neurological signs with atrophy of the left hand without the evidence of vasculitis or carpal tunnel syndrome. Although histopathological examination of skin biopsy revealed the presence of epitheloid granuloma, the diagnosis of BT leprosy was still doubted. The diagnosis of leprosy was finally made by serological test with ELISA, in which there was a slight rise of IgG anti–PGL-I. It fitted the theory that the rapid lateral flow test for anti–PGL-I antibody of *M. leprae* was highly positive at the beginning and moderately positive at the follow-up.

In BT leprosy, inflammation associated with active and reactive BT lesions may usually cause asymmetrical swelling of the hands and feet, particularly if the skin lesions are present at these sites. Our patient had asymmetrical oligoarthralgia even though there was not any identifiable active leprosy skin lesion on the site of arthritis.

Pathogenesis of arthritis in leprosy remains unclear until now. Some experts stated that arthritis in leprosy is a reactive arthritis with immunological basis. Some others classified it as infective arthritis based on the presence of leprosy bacilli in synovial tissue or joint fluid. Arthritis could present either within a reactional state or without the reaction. The pathological effects of leprosy on the skeleton are primarily a consequence of neuropathy leading to denervation, direct
bony changes, secondary infection and the sequelae of trophic ulcers.14

In patient with leprosy, the following superficial peripheral nerve trunks may be palpably hypertrophied: facial, great auricular (neck), ulnar (elbow), median (wrist), radial cutaneous (wrist), lateral popliteal (neck of fibula), and posterior tibial (medial malleolus). The most commonly affected is the posterior tibial nerve followed by the ulnar nerve at the elbow, whose involvement results in clawing of the fourth and the fifth fingers, and loss of dorsal interosseous musculature and loss of feeling in the ulnar nerve distribution. Median nerve involvement impairs thumb opposition and grasp, while radial nerve dysfunction, though rare in leprosy, results in wristdrop. Three major nerve branches supply sensory and motor function to the hand and arm, listed in order of the frequency of their involvement in leprosy: the ulnar, the median and the radial nerve branches. Abnormality in any one of these peripheral nerve branches can result in a change from a normal sensory feedback and muscle function of the hand. Leprosy patients are somewhat unique in that they can also develop temperature-associated loss of sensory end-organs superficially in skin in areas not typical to a specific peripheral nerve area of innervation. On the palm in early stages of the disease, a loss of feeling has most often been related to specific nerve branches, thus an ulnar, median, or radial nerve loss. While leprosy can affect the peripheral nerve branches or superficial areas of the skin, other diseases and injuries can affect the same peripheral nerve branches. Information learned from patients with multiple nerve involvement has increased our understanding of the normal hand and of the role insensitivity and muscle loss plays in deformity and disability. An understanding of the mechanics of deformity from sensory and motor loss provides insight into prevention and correction.3

Specific bony lesions in leprosy are rare with an incidence of between 3 and 5% among hospitalized patients, and are mainly confined to the small bones of the face, hands and feet. These lesions are characterized by granulomatous tissue reactions, which are destructive and manifest radiographically as focal areas of increased rarefaction. The margins are thin, but may be sclerotic. Obliteration of the cavity may result from its collapse with flattening of the articular surface. In the hands and feet, the disease mainly involves the proximal and/or the middle phalanges. It may present as thinning of the endosteum with corresponding widening of the medullary canal localised to the area of the metaphysis. Fusiform swelling of the soft tissues overlying the corresponding part of the affected digit is more common. This is occasionally associated with enlarged nutrient foramina. Leprous osteitis in the hands commonly involves the distal ends of the proximal and middle phalanges, whereas it usually affects the metatarsal heads in the feet. If the disease progress and the trabeculae be destroyed, the radiographs reveal a “honeycomb and cystic” appearance. With healing, radiographic changes become sharply defined as cysts with sclerotic margins. The articular surface can also be involved and the intrinsic forces in the hand may result in fracture, subluxations and rigid clawing of the fingers.10,12–14 In our patient there is no lesion on the hand radiograph.

It is vital to prevent the development of nerve palsies and ulcers. Primary prevention is by early detection and the use of antileprosy drugs. Secondary prevention is by health education and self-awareness of the patient; hygiene of the anaesthetic foot with attention to cracks and fissures, early detection of tenderness and adequate rest; awareness of potential injury mainly during work and cooking; appropriate foot wear.14 Multidrug therapy is the mainstay of treatment. The current multidrug therapy recommended by the WHO in adults with MB disease is rifampicin 600 mg orally once a month, dapsone 100 mg orally daily, and clofazimine 300 mg orally once monthly with additional 50 mg daily. The WHO recommends that it be continued for 12 months but patients with initial high bacterial loads may need longer treatment. For PB disease (bacteriological index 2+) the regimen is rifampicin 600 mg orally once monthly and dapsone 100 mg orally daily for six months.

Any patient who develops peripheral nerve damage during the last six months of treatment should receive a four- to six-month course of oral steroids.

There is usually stiffness of the fingers. Physiotherapy with active exercises, massage, passive stretching and wax baths and splinting should be undertaken before giving consideration to tendon transfer procedures.

Impairment of nerve function can occur before diagnosis and during or after multidrug therapy. Patients with multibacillary leprosy and pre-existing nerve damage are at the highest risk of impairment of nerve function during and after treatment. These patients should be under surveillance for two years from diagnosis. Regular clinical evaluation should include nerve palpation, motor testing of the small muscles of the hand. Steroids may also be given to reduce inflammation.3,6 After the treatment with MDT for PB disease and continued with low-dose steroid (4 mg/day), her joint disease had responded well but she had permanent neurological damage presented as recurrent numbness and tingling of her left hand, some of which might have been avoided if the diagnosis had been made earlier.

CONCLUSION
Symmetric polyarthritis involving the peripheral joints is the most common rheumatic manifestation in leprosy patients. This article reported the case of a patient affected with leprosy who developed asymmetrical oligoarthritis without any of the skin lesions characteristic of leprosy infection. There was a delay in diagnosis because of nonspecific feature that resulted in persistent nerve damage, which might have been prevented if the diagnosis had been made earlier.

REFERENCES


Complete manifestations of Behçet’s disease

V Umami,1 B Setiyohadi2

Behçet’s disease (BD) is a chronic, relapsing, inflammatory disease characterized by recurrent oral aphthae and any of several systemic manifestations that include genital aphthae, ocular disease, skin lesions, neurologic disease, vascular disease, or arthritis. Hippocrates may had described BD in the fifth century B.C.; however, the first official description of the syndrome was attributed to the Turkish dermatologist Hulusi Behçet in 1924. In 1930, the Greek physician Adamantiades reported a patient with inflammatory arthritis, oral and genital ulcers, phlebitis, and iritis.1 Since then, the syndrome has been referred to as BD.1,2

The manifestations of BD are thought to be caused by an underlying vasculitis. Although this disease is recognized worldwide, the prevalence is highest in the eastern Mediterranean, the Middle Eastern, and East Asian countries, thus the nickname Silk Road disease. The disease tends to be more severe in areas where it is more common. Prevalence rates all over the world are increasing, probably because of improved recognition and reporting. Behçet’s disease occurs primarily in young adults. The mean age at onset is between 25 and 30 years. The incidence of disease in males and females is approximately equal along the Silk Road, but in Japan, Korea, and Western countries the disease occurs more frequently in women. Case confirmation can be challenging because many patients labeled as having BD have oral ulcers as the primary or sole manifestation.3

CASE REPORT

A 35-year-old man was referred to the Division of Rheumatology by the Department of Dermato-Venereology with chief complaint of having pain in his ankle for 3 days. The pain had worsened with activity and caused difficulty in walking or moving the ankle. There was no fever, swelling, or any history of trauma. During physical examination, we found tenderness of achilles tendon without any other sign of inflammation. There was also history of pain and stiffness in his shoulder and knee 2 weeks prior, but those symptoms had disappeared without treatment.

Five years prior to admission, the patient started to develop painful and irritating multiple oral ulcers. This symptom persisted despite treatments given by general practitioners and dentist, and continued for years without improvement (figure 1).

One year prior to admission, the patient had multiple ulcers on his genitalia. The lesions were located in the glans and ventral part of penis, scrotum, and inguinal (figure 2). There was no history of multiple sex partners or previous sexually transmitted disease. He was subsequently referred to the Department of Dermato-Venereology.

At the same time, the patient also complained of having skin lesions in the form of red acne-like papules. These lesions were found on his chest (anterior and posterior), face, and neck (figure 3). The dermatologist performed some laboratory investigation and administer topical ointment and methylprednisolone 24 mg a day for a week. After a few months of therapy, the skin and genital lesions disappeared, but the oral lesions persisted.

Figure 1 Multiple oral ulcers.

Figure 2 Genital ulcers: (A) scrotum and inguinal; (B) scrotum; (C) glans penis; (D) ventral part of penis.

Figure 3 Acneiform lesions on chest and face.
Case Report

Two weeks prior to admission, the patient complained of blurred vision of his right eye. There was history of redness, but there was neither pain nor discharge from the eye. The Department of Ophthalmology then confirmed that the patient had panuveitis of the right eye.

Routine laboratory investigation only revealed leukocytosis (14.55 × 10³/mm³). The X-ray of the pelvis and foot were normal. The investigation of C-reactive protein was 51 mg/L, antinuclear antibodies was positive with titer of 1/100 and a speckled pattern, anti–double-stranded DNA was negative, and complement component (C)3 and C4 were within normal limit. We also performed the examination of antibody for一些 viruses and parasites infection like herpes simplex virus (HSV), cytomegalovirus (CMV), and Treponema pallidum. We found positivity of IgM of HSV II and IgG of anti-CMV. The rapid test for human immunodeficiency virus of this patient was negative.

We gave the patient high dose of steroid at the beginning of therapy: methylprednisolone at 1 mg/kg bodyweight for 2 weeks and then tapered it down. The patient also received topical corticosteroid as the treatment for his eye. After 2 weeks of treatment, the symptoms of blurred vision did not show any improvement, but the arthralgia had diminished. An additional treatment with acyclovir for 1 week were also administered, but with no effect on his symptoms. We then made the decision to give the patient azathioprine with a dose of 50 mg to 150 mg. His symptoms improved, and he reported 80% recovery of his vision. The patient was then confirmed to have attained remission from the disease.

DISCUSSION

The common clinical feature in patients with BD is the presence of recurrent and usually painful mucocutaneous ulcers. Aphthous oral ulcers is usually the first and most persistent clinical feature of BD. Lesions occur in crops and some patients may have them during most of the course of the disease. Aphthae occur as ulcers that are 2 to 12 mm or larger. These are discrete, painful, round or oval red-rimmed lesions that affect mainly the nonkeratinized mucosa of the cheeks, the border of the tongue, the soft palate, and the pharynx. Genital ulcers resemble oral aphthae but occur less frequently. They occur as single or multiple lesions of the vulva and in the vagina, or on the scrotum or penile shaft. Skin lesions are also common in BD.3

Oral aphthae are present in almost all patients with Behçet’s, and the differential diagnosis of recurrent oral ulcers includes herpes simplex, benign aphthous ulcers, inflammatory bowel disease, Stevens-Johnson syndrome, and other systemic rheumatic diseases such as systemic lupus erythematosus. Herpes can be ruled out with culture or Tzanck preparation. Dental prosthetics and oral hygiene products can cause oral irritation and ulceration. Medications such as methotrexate can cause oral ulcers. Other causes of oral ulcers or stomatitis include pemphigoid, pemphigus vulgaris, cicatricial pemphigoid, lichen planus, and linear IgA disease.5

Many other disorders may be associated with the presence of small vessel cutaneous vasculitis, inflammatory eye disease, neurologic disease, vascular disease, arthritis, or unexplained systemic illness. These include systemic lupus erythematosus, inflammatory bowel disease, sarcoidosis, reactive arthritis, psoriatic arthritis, ankylosing spondylitis, juvenile arthritis, familial Mediterranean fever and other periodic febrile syndromes, other vasculitides, multiple sclerosis, systemic infections such as tuberculosis, human immunodeficiency virus, syphilis, and malignancies.5 Based on history, physical examination, and laboratory investigations of serum antibody for some viruses, we can rule out the other differential diagnosis and conclude that this patient have the manifestations of BD. The International Study Group criteria for the diagnosis of BD are shown in table 1.

Table 1 International Study Group criteria for Behçet’s disease2

<table>
<thead>
<tr>
<th>Recurrent oral ulceration</th>
<th>Minor aphthous, major aphthous, or herpetiform ulceration observed by physician or patient, which recurred at least 3 times in one 12-month period</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plus 2 of:</td>
<td>Aphthous ulceration or scarring, ulceration observed by physician or patient</td>
</tr>
<tr>
<td>Recurrent genital ulceration</td>
<td>Anterior uveitis, posterior uveitis, or cells in vitreous on slit lamp examination; or retinal vasculitis observed by ophthalmologist</td>
</tr>
<tr>
<td>Eye lesions</td>
<td>Erythema nodosum observed by physician or patient, pseudofolliculitis, or papulopustular lesions; or acneiform nodules observed by physician in postadolescent patients not receiving corticosteroid treatment</td>
</tr>
<tr>
<td>Skin lesions</td>
<td>Positive pathergy test Read by physician at 24 to 48 hours</td>
</tr>
</tbody>
</table>

Cutaneous lesions occur in over 75 percent of patients with BD. The skin manifestations vary and may include acneiform lesions, papulo-vesiculo-pustular eruptions, nodules, erythema nodosum (septal panniculitis), superficial thrombophlebitis, pyoderma gangrenosum-type lesions, erythema multiforme-like lesions, and palpable purpura. Biopsy of erythema nodosum lesions reveal a septal panniculitis, with medium vessel vasculitis in up to half of lesions.5 The skin lesion of this patient were acneiform. Unfortunately, we did not performed skin biopsy because this patient have already received steroid treatment.

Acneiform lesions may be more common in those with associated arthritis.5,8 This is comparable with the symptoms of arthralgia of this patient which came at the same time as skin lesion. An intermittent, symmetric oligoarthritis of the knees, ankles, hands, or wrists affects one half of the patients with BD; arthralgia is also common. An erosive or destructive arthropathy is unusual. Inflammatory cells of the synovium and synovial fluid are primarily polymorphonuclear leukocytes.3

Ocular disease occurs in 25 to 75 percent of BD patients. Ocular inflammation typically follows mucocutaneous symptoms by a few years, but it often progresses with a chronic, relapsing course affecting both eyes. This manifestation may require systemic immunosuppressive treatment and may irreversibly impair vision, and even progress to blindness if left untreated.3

Overall, the clinical manifestations of this patient were characterized for BD. The symptom of recurrent oral ulcers

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36 Indonesian Journal of Rheumatology 2010, Vol 03
came first followed by genital ulcer and skin lesion with arthralgia. Panuveitis was confirmed after few years of first manifestation.

The positivity of antibody for HSV II and CMV was related to the pathogenesis of BD. Studies suggest a possible pathogenic role of certain bacterial antigens that have cross-reactivity with human peptides. The cross-reactive self-antigens may include the heat shock proteins, a family of 60 to 90 kDa proteins produced by many cells in response to stress. These proteins have significant sequence homology between human and bacteria. T cells and/or antibodies may recognize epitopes shared by both host and infectious organism heat shock proteins, thereby initiating and/or perpetuating Behçet’s disease.3,9,10

European League Against Rheumatism (EULAR) recommendations for the management of BD stated that any patient with BD and inflammatory eye disease affecting the posterior segment should be on a treatment regime that includes azathioprine and systemic corticosteroids.11

Eye involvement in BD follows a remitting and relapsing course and the recurrent inflammatory attacks result in irreversible damage and visual loss. Suppression of the inflammation and the prevention of recurrences of ocular attacks should be the goals. Azathioprine is widely accepted as the initial agent for ocular involvement of BD.11

Placebo-controlled randomized controlled trial (RCT) showed that azathioprine 2.5 mg/kg/day decreased hypopyon uveitis attacks (number needed to treat (NNT) = 4), stabilized visual acuity, and decreased the development of new eye disease (NNT = 2). Moreover, the 7-year follow-up of these patients showed that the beneficial effect of azathioprine continued in the long-term. Local and systemic corticosteroids for eye involvement, especially during attacks, are generally used with no evidence from RCTs. Corticosteroids rapidly suppress the inflammation but potential side effects, including cataracts and glaucoma, can cause concern.11

From the review of 880 Turkish patients with Behçet’s uveitis, 68 percent were male, mean age of onset was 28.5 years for men and 30 for women. Ocular disease was bilateral in 78.1 percent, and panuveitis was the most common finding. Risk of losing useful vision at 10 years was 30 percent for men and 17 percent for women, but prognosis was better in the 1990s than in the 1980s.12 Surprisingly, this patient showed remarkable improvement after we added azathioprine 50 mg to 150 mg a day. Hopefully, the visual loss in this patient will reverse to normal. However, it is important to remember that BD typically has a waxing and waning course characterized by exacerbations and remissions.

CONCLUSION

Behçet’s disease is a chronic, relapsing, inflammatory disease characterized by recurrent oral aphthous ulcers and numerous potential systemic manifestations. These include genital ulcers, ocular disease, skin lesions, neurologic disease, vascular disease, and arthritis. The disease is believed to be caused by vasculitis. The disease is characterized by exacerbations and a relapsing/remitting course.

Azathioprine revealed good improvement in ocular involvement of BD and this immunosuppressant is recommended by EULAR. However, frequent ophthalmologic examinations are essential for patients with ocular disease, and periodic monitoring of the eyes is recommended for all patients. A careful history and examination, with attention to the vascular and neurologic systems, should be part of the physician’s assessment.

REFERENCES

Erosive osteoarthritis

JA Ongkowijaya, B Setiyohadi, Sumariyono

Osteoarthritis (OA) is a degenerative joint disease characterized by the erosion of cartilage joints, hypertrophy of the marginal bone, subchondral sclerosis, and the morphological and biochemical changes of synovial membrane and joint capsule. This clinical syndrome is characterized by joint pain caused by degeneration of the joints. It is the most common joint disease to afflict the elderly and it occurs more often with age.1–3

Erosive osteoarthritis is a subset of OA in which there is a destruction of the joints as a result of inflammation.3,4 Changes mainly occur on the distal interphalangeal (DIP) joints, proximal interphalangeal (PIP) joints, carpometacarpal (CMC) joints, and very rarely occur on other joints of hand or of other body parts.3–5

The diagnosis is in accordance with the criteria of American College of Rheumatology (ACR) for OA and is supported by the existence of bone erosion on the radiological image. The management of this disease is merely for palliative purpose.3,5,6

CASE REPORT

A 54-year-old male, works as a teacher, complained of having swollen fingers and pain at the tips of his fingers for eight years. The intensity of pain was increasing, especially when being pressurized. The patient rarely complained of stiffness in his hand. These symptoms did not show up on the joints of any other body parts. There was no fever or skin lesion. Bending motion could be done without any difficulty. He had been on medication but without any significant improvement. The patient claimed to never have suffered any serious illnesses i.e. diabetes mellitus, hypertension, tuberculosis, and high uric acid level. There was also no family history for those illnesses.

The result of physical examination finds the patient in good general condition, compos mentis. Blood pressure was 120/70 mmHg, pulse was 80 beats/minute, and he was afebrile. General physical examinations were normal. He had normal gait and normal extremities except on hand (figure 1). On local status, there were findings of Heberden’s nodes on left and right DIP II–V joints with tenderness and deviation toward radial of left DIP IV and right DIP V joints. The pain was measured with visual analog scale and gave the score of 5.

Some of the tests conducted, such as pelvic rock sign, lateral compression, single leg raised, Patrick’s test, and Schober’s test showed negative results.

Laboratory examination showed: hemoglobin 13.5 g/dL, leukocyte count 8.9 × 10³/mm³, platelet count 286 × 10³/mm³, erythrocyte sedimentation rate 35 mm/hr, high-sensitivity C-reactive protein (hs-CRP) 2.070 mg/L (normal value <10.000 mg/L), negative rheumatoid factor, negative anti-cyclic citrullinated peptide, uric acid 6.3 mg/dL, aspartate aminotransferase 38 IU/L, alanine aminotransferase 38 IU/L, alanine aminotransferase 38 IU/L, total cholesterol 195 mg/dL, triglyceride 97 mg/dL, high-density lipoprotein cholesterol 38 mg/dL, low-density lipoprotein cholesterol 130 mg/dL, ureum 19 mg/dL, creatinine 1.2 mg/dL, albumin 3.6 g/dL, and globulin 3.2 g/dL. Urinalysis test showed negative on protein and glucose, and microscopic examination was within normal limit.

Radiological examination showed no abnormalities on the chest X-ray. Pelvic X-ray was also normal along with its sacroiliac joint. Hand X-ray (figure 2) showed luxatio of right DIP IV and left DIP IV joints, juxta-articular porosis, and sclerosis of distal of medial phalanx and proximal of distal phalanx of fingers II-V of both hands along with the narrowing of DIP joints of both hands. There was no calcification. Impression is in accordance with the image of bilateral hand rheumatoid arthritis.

Based on the history along with physical and laboratory examinations, the patient was diagnosed with erosive OA and treated with methotrexate 5 mg/week, folic acid 1 mg q.d, 50 mg diclofenac sodium b.i.d, and omeprazole 20 mg q.d.
Indonesian Journal of Rheumatology 2010; Vol 03

DISCUSSION

Osteoarthritis is the most common form of arthritis, characterized by a slowly progressive degeneration of cartilage joints. Its main predilection is the weight bearing joints. It has a greater prevalence among women and its incidence is increasing with age.1,3–5 This is the case of 54-year-old male who has been felt on both hands for eight years.

Symptoms commonly felt by patients with OA are joint pains, morning stiffness, or stiffness after resting, usually lasts for less than 30 minutes.3,5 American College of Rheumatology has developed a diagnostic criteria for hand OA as follows: (1) pain, aching, or stiffness in the hand; (2) hard tissue enlargement of two or more of 10 hand joints; (3) less than three swollen MCP joints; (4) hard tissue enlargement of two or more DIP joints; or (5) deformity of two or more of 10 hand joints. Diagnosis is confirmed by the presence of (1), (2), (3) and (4) or (1), (2), (3) and (5) or (1) plus 3 from (2)–(5). The 10 hand joints referred above are the DIP II & III, PIP II & III, and CMC. By these criteria the sensitivity and specificity for diagnosing hand OA is 92% and 98%.3 This case met all the criteria.

There are several subsets of osteoarthritis: primary and secondary, local and generalized, hypertrophic and atrophic, inflammatory or noninflammatory, with and without chondrocalcinosis or calcium phosphate crystal deposition, and rapidly progressive.7 Erosive OA is a primary OA with a more severe inflammation, bone abnormality (erosion), and ankylosis in some cases. Kellgren and Moore was the first to describe this condition in 1952. At first, the term inflammatory OA was used to emphasize the commonly encountered clinical symptom, i.e. the inflammatory process, but now the more commonly used term is erosive OA.8–11

Erosive OA is a rare type of OA. It is found commonly on postmenopausal women. Genetic factors also play role; HLA DR2 is a suspected risk factor for erosive OA.5,11,12 Erosive OA began with a sudden pain accompanied by stiffness in the morning of the DIP joints, which then spreads to the PIP joints, commonly symmetrical, while regular OA is usually slow and generalized. It rarely afflicts foot joints or any other large joints.3,8,9 Laboratory findings are generally nonspecific although there are reports of a higher CRP level in erosive OA than in a regular OA.5,8,13 This case occurred in a 54-year-old male and afflicted the DIP joints II-V on both hands. Laboratory results were within normal limits.

Radiological finding of erosive OA are periarticular osteoporosis and subchondral erosion. In contrast to the erosion of rheumatoid arthritis that occurs in the marginal, erosion in erosive OA occurs in the central, accompanied by marginal proliferation resulting in a “gull-wing” appearance. In psoriatic arthritis, marginal erosion also occurs along with marginal periostitis. The patient’s hand X-ray showed evidence of bone erosion and juxta-articular osteoporosis.3,8

Differential diagnoses of erosive OA are rheumatoid arthritis and psoriatic arthritis. This case had similar radiological image with rheumatoid arthritis but afflicts the DIP joints and showed neither symptoms nor signs supporting the diagnosis of rheumatoid arthritis or psoriatic arthritis.3

Currently there are no standard treatments for erosive OA so that the first treatment recommended is similar to those of regular OA, pharmacological and non pharmacological. The recommended pharmacological therapy is simple analgesics, nonsteroidal anti-inflammatory drugs, and intra-articular and topical steroid.5,6 For cases less responsive to standard therapy, it can be considered administrating methotrexate, hydroxychloroquine, or anti-TNFα. Several studies have reported satisfactory result with these drugs.10,14,15 The patient in this case was given doses of methotrexate 5 mg/week, folic acid 1 tablet q.d., diclofenac sodium 50 mg b.i.d., and omeprazole 20 mg q.d.

SUMMARY

We reported a case of erosive osteoarthritis, which is a subset of OA. The diagnosis of hand OA is based on ACR criteria and supported by the radiological image in the form of subchondral erosion and juxta-articular osteoporosis. There are currently no standard treatments for erosive OA, and this patient was administered with doses of methotrexate, diclofenac sodium, folic acid, and omeprazole.

REFERENCES


Multiple autoimmune syndrome (MAS) is a condition in which patients have at least three distinct autoimmune conditions. The definition of MAS is based on 91 reported cases of such associations in the literature. A review of the literature and cluster analysis of MAS disclosed systemic lupus erythematosus (SLE), Sjögren’s syndrome, and autoimmune thyroid disease (AITD) as the “chaperones” of autoimmune diseases. This entity was described by Humbert and Dupond in 1988 as a syndrome consisting of the presence of three or more autoimmune diseases in a single patient. While describing the syndrome, their observations led them to a rough classification of clusters based on the co-occurrence of autoimmune disease, which they identified as types one through three.1 In MAS-1, the authors grouped myasthenia gravis, thymoma, dermatopolymyositis, and autoimmune myocarditis together. In MAS-2, they grouped Sjögren’s syndrome, rheumatoid arthritis, primary biliary cirrhosis, systemic sclerosis (SSc), and AITD. MAS-3 consists of AITD, myasthenia gravis and/or thymoma, Sjögren’s syndrome, pernicious anemia, idiopathic thrombocytopenic purpura, Addison’s disease, type I diabetes, vitiligo, autoimmune hemolytic anemia, and SLE.1,2,3 The importance of this concept is the probability that having three autoimmune diseases simultaneously in one patient goes beyond epidemiological inferences or statistical chance. Disorders of autoimmune pathogenesis occur with increased frequency in patients with a history of another autoimmune disease. The tendency to develop another disease occurs in about 25% of these patients.3,4

We report a case in which the presence of Graves’ disease/AITD, SLE, vasculitis, and SSc with pulmonary hypertension and Raynaud’s phenomenon in one patient.

**CASE REPORT**

A 30-year-old Indonesian woman, was first diagnosed with Graves’ disease when she was 17 years old based on the presence of hyperthyroidism, diffuse goiter, and specific laboratory findings. She was an outpatient of the endocrinology clinic at Cipto Mangunkusumo General Hospital and treated with propylthiouracil 100 mg t.i.d and propranolol 10 mg t.i.d. For the past 3 years, she had been complaining of photosensitivity, hair loss, recurrent oral ulcer, and bilateral pretibial edema. She also had a history of a focal neurological deficit in the form of involuntary movement. She underwent a renal biopsy on June 2007 and was given the diagnoses of SLE with lupus nephritis and lupus cerebritis. She was treated with steroid and mycophenolate mofetil. For the past 6 months, she had been presenting clinical characteristic of Raynaud’s phenomenon and scleroderma. The symptoms became worse and her fingers developed gangrene. She had been hospitalized for two months, underwent many examinations and was given the diagnoses of SSc with pulmonary artery hypertension, Raynaud’s phenomenon, and vasculitis.

The results of her physical examination were as follows: she was comos mentis, blood pressure was 120/80 mmHg, pulse rate was 88 beats/minute, respiratory rate was 20 breaths/minute, and body temperature was 36.7°C. On head auscultation, we found lupus hair, mask-like face, moon face with salt-and-pepper appearance, no lid retraction, no proptosis, no trismus, no pale conjunctiva, and no oral ulcers. There was diffuse goiter on her neck. On heart auscultation we found loud pulmonary valve sound without audible murmur or pericardial friction rub. On the extremities, there were vasculitis in both arms and both legs, Raynaud’s phenomenon and gangrene of fingers II, III, and IV of the left hand, and thickening of the skin from fingers to trunk (shoulder, back, and neck). We also found peripheral neuropathy and moist hand. We did not find any arthritis, tremor, or edema.

**Figure 1** (A) Lupus hair; “salt-and-pepper” appearance of the face. (B) Vasculitis of the legs.
Laboratory studies disclosed the following values: hemoglobin 12.9 g/dL, hematocrit 38.5%, leukocyte count 4,31 × 10³/mm³, platelet count 295 × 10³/mm³, erythrocyte sedimentation rate 15 mm/hr, blood glucose 83 mg/dL, blood urea nitrogen 33 mg/dL, serum creatinine 0.5 mg/dL, Na 137 mEq/L, K 3.38 mEq/L, aspartate aminotransferase 61 IU/L, alaninaminotransferase 34 IU/L, total protein 7.2 U/L, albumin 3.71 U/L, globulin 3.49 U/L, total cholesterol 161 mg/dL, low-density lipoprotein cholesterol 63 mg/dL, high-density lipoprotein cholesterol 71 mg/dL, fibrinogen 268 mg/dL, D-dimer 1800 ng/mL, activated partial thromboplastin time 0.7 times control, prothrombin time 0.7 times control. The urinalysis showed proteinuria (+1), hematuria, and sediment of erythrocyte and leukocyte. The creatinine clearance test was 137.23 mL/min, and the total urine protein was 65 mg/24 hours (with a history of total urine protein of 800 mg/24 hours). Thyroid function test revealed as follows: stimulated thyroid-stimulating hormone (TSHs) 0.010 IU/mL (normal value 0.270-4.200), total T4 13.64 mg/dL (normal value 5.100-14.100), total T3 1.640 ng/mL, suppressed thyroid-stimulating hormone (T4s) 0.010 IU/mL (with a history of total urine protein of 800 mg/24 hours). Thyroid scanning showed diffuse goiter with high radioiodine uptake. Renal biopsy confirmed nephritis lupus class I. Arteriography showed total occlusion of finger II, III, and IV of the left hand. Cerebral magnetic resonance imaging was normal. Electroencephalography (EEG) showed episode of epileptiform activity on the left frontotemporal area. Ankle-brachial index (ABI) was 0.84/0.91.

The diagnoses were finally established: type 3 MAS consisting of Graves’ disease/AITD, SLE and vasculitis, SSc with pulmonary artery hypertension and Raynaud’s phenomenon. The patient was treated with warfarin 2 mg with dose titration to international normalized ratio target of 2.5-3.5 (after intravenous heparin), acetylsalicylic acid 80 mg q.d., nifedipine 10 mg b.i.d., and cilostazol 50 mg b.i.d. for Raynaud’s phenomenon; beraprost 3 × 20 mcg t.i.d. for pulmonary hypertension; cefotaxime 1 g t.i.d., and bacitracin cream; methylprednisolone pulse dose 125 mg for 3 hour, tapered down to 16 mg t.i.d., mycophenolate mofetil 500 mg b.i.d. for vasculitis and SLE; thiamazole 40 mg q.d. and propranolol 10 mg t.i.d. for AITD (Graves’ disease); calcium hydrogen phosphate 500 mg and cholecalciferol 133 IU 1 tablet t.i.d; diclofenac sodium 25 mg b.i.d., omeprazole 20 mg b.i.d., cyclophosphamide 500 mg i.v. (Euro-Lupus Nephritis protocol) 3 times per 2 weeks followed by 6 times per 4 weeks.

The clinical response to all treatments were remarkably good; the thickening of the skin and gangrene of the fingers were resolved in the fifth month of therapy.
and some of the specific mono- or polyclonal autoantibodies may be multiple organ-reactive. In conclusion, the presence of one autoimmune disease should alert one to watch for another one. The occurrence of multiple autoimmune phenomena in these cases indicates the need for continued surveillance for the development of new autoimmune disease in predisposed patients.2,3,4,9

MAS-3 consisted ofAITD, myasthenia gravis and/or thymoma, Sjögren’s syndrome, pernicious anemia, idiopathic thrombocytopenic purpura, Addison’s disease, type 1 diabetes mellitus, vitiligo, autoimmune hemolytic anemia, and SLE.3,6,7,10,11 Our case was defined as the type 3 MAS withAITD/Graves’ disease, diffuse-type SSc, and SLE.

The diagnosis ofAITD/Graves’ disease was based on the clinical characteristics (hyperthyroidism, diffuse goiter with high radioiodine uptake on thyroid scanning) and specific laboratory results (positive TRAb (2.5 mg/dL), low level of TSHs (0.010 IU/mL), and high level of free T4 (3.07 mg/dL)).

Graves’ disease is an AITD characterized clinically by the presence of hyperthyroidism, diffuse goiter, and in some patients, ophthalmopathy and dermopathy. Graves’ disease is caused by circulating antibodies directed against TRAb that activate the thyrotropin receptor causing thyrotoxicosis. The cause of Graves’ ophthalmopathy and dermopathy is still unknown, but a cross-reaction between thyroidal and orbital and/or connective tissue antigens has been postulated. In this case, it has also been documented for the diagnosis of Graves’ disease, and gave a good response to thiamazole. In several case reports, treatment of one autoimmune disease may result in the emergence of yet another disease such as SLE or systemic sclerosis. In our patient, methylprednisolone combined with intravenous cyclophosphamide for the treatment of SLE (cerebral and renal involvement) was associated with the emergence of Raynaud’s phenomenon with digital gangrene (cerebral and renal involvement) was associated with the emergence of Raynaud’s phenomenon with digital gangrene on angiography, and ABI of 0.84/0.91. We did not find the same case in her family.

Autoimmune thyroid disease occurs in 5–10% of patients with myasthenia gravis. It also seems as ifAITD is found in excess in patients with SLE and secondary Sjögren’s syndrome, as well in SLE-unaffected relatives with a diagnosis of primary Sjögren’s syndrome.4,5,6 We did not find the same case in her family.

The diagnosis of SLE with vasculitis was based on the ACR criteria for SLE. Our patient fulfilled 7 of 11 criteria, i.e. photosensitivity, oral ulcers, nonerosive arthritis, renal disorder, neuropsychiatric involvement (abnormal EEG), immunologic disorder (positive anti-dsDNA), and positive ANA (positive anti–Scl-70, anti–Rib-P protein, anti–SS-A, and anti–SS-B, with negative anti-mRNP). She also had SLE-related vasculitis (confirmed by skin biopsy) and nephritis lupus class I (confirmed by renal biopsy).

Systemic lupus erythematosus is the most diverse of the autoimmune diseases, characterized by a wide range of clinical features and the production of multiple autoantibodies. The diagnosis is based on the clinical features and the presence of a wide variety of autoantibodies, most of which are directed to double-stranded DNA, nuclear antigens, ribonucleoproteins, and cell surface antigens. The treatment includes the use of antimalarial agents, corticosteroids, and immunosuppressive agents. The primary pathological findings are those of inflammation, vasculitis, immune complex deposition and vasculopathy. The course of the disease is characterized by periods of flares and remission. The incidence of SLE varies from 2 to 7.6 cases per 100,000 individuals per year; the highest prevalence is in Afro-Carribeans, followed by Asians. The sex ratio is 9:1 in favour of females with the disease onset between the ages of 15-55. The laboratory hallmark of the disease is the presence of ANA, appearing in more than 95% of individuals with lupus. The most common pattern is a diffuse or homogeneous nuclear staining. Anti-DNA and anti-Sm antibodies are rarely seen in other conditions and have therefore high specificity for SLE.4,9,10

The diagnosis of SSc with pulmonary hypertension and Raynaud’s phenomenon-related gangrene on finger II, III, and IV of the left hand was supported by laboratory findings, i.e. positive ANA with positive anti–SS-A, anti–SS-B, and anti–Scl-70 on ANA profile; hypercoagulable state, arterial stenosis of the left hand in angiography, and ABI of 0.84/0.91.

Systemic sclerosis is a chronic disease of unknown etiology, and its classification as a systemic autoimmune rheumatic disease is supported by clinical and experimental observations that include the presence of autoantibodies and autoreactive T cells. Systemic sclerosis is a connective tissue disorder characterized by endothelial dysfunction, fibrosis, and the production of autoantibodies. Although some autoantibodies are specific markers for the disease, there has not been widespread adoption of them as specific classification criteria. Excessive collagen deposition results in skin thickening and changes in internal organs that include the lung, vasculature, gastrointestinal tract, and kidney. Endothelial damage leading to vascular dysfunction manifests as Raynaud’s phenomenon, digital ulceration and gangrene, pulmonary arterial hypertension, and renal vascular damage. Systemic sclerosis is usually subclassified as limited or diffuse depending on the extent of skin involvement. The distinction between limited and diffuse SSc varies, but most authors would concur that patients with truncal and acral involvement have diffuse disease, whereas changes of distal to the metacarpophalangeal and metatarsophalangeal joints are consistent with limited disease. There is continuing debate over the degree of acral involvement that constitutes limited versus diffuse disease. Typically, patients with limited SSc have a more insidious disease onset, and they describe Raynaud’s phenomenon for some years prior to the onset of sclerodactyly. In contrast, in those with diffuse SSc the onset of Raynaud’s phenomenon and the disease course is more acute, with most internal organ involvement occurring within 5 years.4,9 Our patient typically had diffuse SSc, based on the truncal and acral skin involvement, pulmonary arterial hypertension, and Raynaud’s phenomenon-related digital gangrene.
CONCLUSIONS
The diagnosis of MAS depends on the physician’s accuracy and the age of onset of the first autoimmune disease. Our patient presented the symptoms of AITD (Graves’ disease) and systemic autoimmune disease (SLE and SSc). The diagnosis of one disease could only be achieved when it was suspected because most of the symptoms related to pulmonary artery hypertension, skin involvement, and vasculitis might be hidden by the symptoms of other disease. The confirmation will be made only by appropriate tests (i.e. abnormal immunology tests, abnormal arteriography, the presence of TRAb, or confirming skin and renal biopsy). Each individual disease included in the MAS group should be considered and treated accordingly.4,9,10,11

The presence of one autoimmune disease should alert one to watch for another one. The occurrence of multiple autoimmune phenomena in this case indicates the need for continued surveillance for the development of new autoimmune disease in predisposed patients.

REFERENCES
Rapid and Sustained improvement
- Rapid control of signs and symptoms
- Prevent joint damage and disability
- Improve physical functions for a better quality of life

Convenient schedule and Safer administration
- IV Induction dose at week 0, 2, 6
- Maintenance dose of every 2 months
- Delivered within a professional medical environment

Assurance, Experience & Confidence
- The most widely used TNFα inhibitor
- More than 15 years of safety data collected in clinical trials
- Almost 11 years of experience of well characterized post marketing safety profile