

Case Report

Systemic Lupus Erythematosus (SLE) with Lupus Nephritis in a 15 Year-Old Male – A Case Report

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Abstract: Systemic lupus erythematosus is a chronic autoimmune inflammatory disease that can affect any part of the body. Lupus Nephritis is one of the most common, and most important, serious manifestations of SLE particularly for male. We present a case of 15 year old male that is diagnosed with a systemic lupus erythematosus (SLE) based on 6 of the American College of Rheumatology (ACR), diagnostic criteria developed namely: malar rash, arthritis, photosensitive, kidney disorders (hematuria), immunological disorders (positive anti-dsDNA), and blood disorders (anemia, leucopenia). The result of the kidney's biopsy indicated the patient already developed Lupus Nephritis.. The patient responded very well with corticosteroid. Although male patient with SLE is not commonly seen, the manifestations are life threatening and early detection of disease will lead to better outcome of the patient. Antimalaria drugs Hydrochloroquine is useful in patients with SLE glomerulonephritis. In consequences of their numerous beneficial effects, antimalarials appear to have a protective effect on survival in SLE.

Keywords: Systemic Lupus Erythematosus, Lupus Nephritis, Male SLE, Hydrochloroquine

1. Introduction

Systemic erythematosus lupus (SLE) is a chronic multifaceted autoimmune inflammatory disease that can affect any part of the body. Inflammation results in swelling, pain and other symptoms. Although almost every organ can be affected, the organs most often involved are the skin, joints, kidneys, cells forming blood, blood vessels, and the central nervous system. [1]

The pathogenesis and etiology of SLE remains incompletely understood but most likely involves the interaction of genetic, hormonal, and environmental factors. SLE can occur in children and adults, most often in women of reproductive age. Compared to adults, children and adolescents with SLE have more severe disease and wider involvement of organs. However, lupus in males may take a more severe course, in particular with an increased incidence of renal disease, serositis, thromboses and discoid skin disease. It is substantially more common in females of

child-bearing age where the reported female: male ratio is 8-15:1. Pre-pubertal and post-menopausal ratios are much lower at 2-6:1 and 3-8:1, respectively. [2]

This predominance in females probably related to the effect of endogenous sex hormones, which have complex effects on the immune system. The influence of sex hormones is also seen in animal models of the disease. Typically, in most mouse models, females have worse outcomes, and administration of estrogens exacerbates while androgens ameliorate disease. There is no doubt that males are protected in incidence, from SLE, and this has been ascribed to many things. In particular, the role of oestrogen and other gonadal hormones in the alteration of immune cell function. It is generally recognized that the male hormone, testosterone, is immunosuppressive, whereas the female hormones, estrogen, stimulates immune response. Lower testosterone levels have been observed in male and female patients with SLE. Several studies also indicate that testosterone also interacts with the immune system by

suppressing both cellular and humoral responses. Estrogen seems to play an important role in promoting autoimmune-related immune response. Sex hormones have been shown to interact with the immune system, including the B cell and T cell compartment, dendritic cells and cytokine networks. It is thought that female sex hormones caused the enhanced autoimmune reactivity and contribute to the immunological perturbations that result in SLE. The female hormonal influences include supporting the survival of autoreactive B cells and modifying their maturation towards a marginal zone phenotype, while male hormones produce the opposite effects. [3] The abnormal expression of estrogen or its receptors may lead to immunological diseases, including SLE. Another possible explanation for the female predominance in SLE is genetic susceptibility. At least 3 gene variants located on the X chromosome have been shown to be associated with increased risk of developing SLE (Interleukin-1 receptor-associated kinase 1, Methyl CpG binding protein 2, and toll-like receptor 7 [2, 4, 5])

Renal involvements in systemic lupus erythematosus (SLE), also known as lupus nephritis (LN), are a serious relatively common complication, with up to 90% of SLE patients acquiring pathological, often irreversible, impairment in renal function. Renal disease in SLE is a source of major morbidity and mortality; it develops in approximately 60% of patients with SLE, with a reported 5-22% of these patients progressing

to end-stage renal disease requiring dialysis or transplant. Studies have shown that lupus nephritis is more frequent in men than in women, furthermore, a higher prevalence of Class IV, diffuse proliferative nephritis, and active glomerular disease amongst males. It has been shown that the main female hormone, 17 β estradiol, is capable of inhibiting inflammatory and proapoptotic process and protecting the renal tissue. In contrast, the male hormones, testosterone and dehydroepiandrosterone, have the opposite effect. Female gender is therefore considered a protective factor in many kidney disease. It has been suggested that sex hormones mediate the effect of gender on chronic renal disease, through the interaction with the renin-angiotensin system, the modulation of nitric oxide synthesis, and the down regulation of collagen degradation. Androgen may contribute to continuous loss of kidney cells through the stimulation of programmed cell death which is activated in several chronic kidney diseases. [5, 8].

The diagnosis of SLE is established by fulfilling at least 4 of the 11 classification criteria made by the *American College of Rheumatology* 1997. (Table 1). In addition, in 2012 *Systemic Lupus International Collaborating Clinics* (SLICC) issued criteria for diagnosing SLE disease. For its use in pediatric SLE, the SLICC criterion is more sensitive than the ACR criteria, although its specificity is lacking. [1, 5, 7, 14]

Table 1. American College of Rheumatology (ACR).

No	Criteria	Definition
1	Butterfly rash	Flat or raised erythema that persists in the cheek area, tends to spread to the nasolabial fold
2	Discoid	Spots of erythema that arise with adherent keratotic scaling and follicular plugging, in long lesions may occur scarring atrophy
3	Photosensitive	patches on the skin resulting from sun exposure, on history or physical examination
4	ulceration mouth	ulcers mouth or nasopharynx, usually painless
5	Arthritis	Arthritis non erosive in two or more joints peripheral, characterized by tenderness, swelling or effusion
6	Serositis	a. Pleuritis A history of pleuritic pain or pleural friction rub or pleural effusion on a physical examination, or b. Pericarditis Proven by ECG or heard pericardial friction rub or pericardial effusion on physical examination
7	Kidney disorders	a. Persistent proteinuria > 0.5 g / day or +3 examination if a quantitative examination cannot be done, or b. Cellular cast: erythrocytes, hemoglobin, granular, tubular or mixed
8	Nerve disorders	Seizures Not caused by drugs or metabolic disorders (uremia, ketoacidosis or electrolyte imbalance), or Psychosis Not caused by drugs or metabolic disorders (uremia, ketoacidosis or electrolyte imbalance)
9	Blood disorders	There is one blood disorder Hemolytic anemia with reticulocytosis Leucopenia: <4000 / mm ³ at > 1 examination lymphopenia: <1500 / mm ³ in > 2 examinations thrombocytopenia: <100,000 / mm ³ without drug intervention There is one abnormality
10	Immunological disorders	Anti-ds-DNA above normal titer Anti-Sm (Smith) (+) Phospholipid (+) based on antibodies abnormal anticardiolipin serum IgG or IgM levels lupus (+) anticoagulants using standard false syphilis (+) test, for at least 6 months and confirmed by the discovery of Treponema palidum or treponema antibodies
11	Antinuclear antibodies	ANA (+) tests

Lupus nephritis is classified based on the renal histology findings. [11] International Society of Nephrology/Renal Pathology Society (ISN/RPS) 2003 classification of lupus nephritis consists of class I is defined as minimal mesangial

lupus nephritis with mesangial accumulation of immune complexes identified by immunofluorescence, or by immunofluorescence and electron microscopy, without concomitant light microscopic alterations. Class II is defined

as mesangial proliferative lupus nephritis characterized by any degree of mesangial hyper cellularity (defined as three or more mesangial cells per mesangial area in a 3-micron thick section) in association with mesangial immune deposits. Class III is defined as focal lupus nephritis involving less than 50% of all glomeruli. Affected glomeruli usually display segmental endocapillary proliferative lesions or inactive glomerular scars, with or without capillary wall necrosis and crescents, with sub endothelial deposits (usually in a segmental distribution). Class IV is defined as diffuse lupus nephritis involving 50% or more of glomeruli in the biopsy. In the affected glomeruli, the lesions as described below may be segmental, defined as sparing at least half of the glomerular tuft, or global, defined as involving more than half of the glomerular tuft. Class V is defined as membranous lupus nephritis with global or segmental continuous granular sub epithelial immune deposits, often with concomitant mesangial immune deposits. Class VI (advanced-stage lupus nephritis) designates those biopsies with $\geq 90\%$ global glomerulosclerosis and in which there is clinical or pathologic evidence that the sclerosis is attributable to lupus nephritis. [1, 8, 9]

2. Case Report

A 15 year old male presented with a history of frequent fever that was reduced with antipyretics for the last three months and joint pain and swelling in the last two months. The joint pain involved the shoulders, knees, ankles and hands. The patient went to a local hospital and being diagnosed with typhoid fever. Two week after being discharged from the hospital the patient had a joint pain and swelling that was worsening. Having severe joint pain and swelling for the last two weeks, the patient went to a physician clinic and the doctor performed Anti-dsDNA-NcX examination with the results of more than 3,200 units, the patient was finally referred to our hospital: Wahidin Sudirohusodo Teaching Hospital at Makassar, Indonesia for further treatment.

On physical examination, the general condition of the patient was moderate. The patient was neither having jaundice nor cyanosis but suffered from malnutrition. Systemic cardiovascular and respiratory system did not reveal any abnormality; however, the patient had a history of hypertension. On examination of the skin and extremities, malar or butterfly rash found on the face and rash with edema in both lower limbs. The patient also suffered from photosensitivity. There was weight loss of approximately 10 kilograms for the last two months. The patient did not have a family member with a history of the same complaints or with other autoimmune conditions

From complete blood examination, hemoglobin was obtained 7.5 gr / dL, leukocytes 3.090 / mm³, erythrocytes 2.99 x 10⁶/ mm³, platelets 283.000 / mm³, ferritin 465.27 ng / ml, the smear of peripheral blood, the impression of anemia is normocytic normochromic suspected of the cause of chronic disease accompanied by leukocytes with signs of

infection.

The patient was diagnosed with systemic lupus erythematosus (SLE) based on 6 of the *American College of Rheumatology* (ACR) diagnostic criteria developed namely: malar rash, arthritis, photosensitive, kidney disorders (hematuria), immunological disorders (positive anti ds DNA), and blood disorders (anemia, leucopenia). From the biopsy of the kidney's patient it was indicated that the patient had a Class IV Diffuse Lupus Nephritis according to the International Society of Nephrology/ Renal Pathology Society 2003 Classification where more than 50% of the involved glomeruli had diffuse segmental sclerosing lesions or Class IV Diffuse glomerulonephritis with sclerosing lesions according to WHO morphologic classification of Lupus Nephritis (modified in 1982). After the diagnosis of SLE, corticosteroids were prescribed and the patient evolved with clinical improvement.

3. Discussion

Systemic lupus erythematosus evolves with periods of activity and varying periods in which patients area symptomatic or mildly symptomatic. The involvement of different of organs or systems may occur simultaneously or subsequently. SLE typically affects females at far greater rates than males; however male SLE patients often have more severe disease than females. Since 1975 a number of articles have been published in difference between male and female SLE. In general, the results revealed that male patients develop similar typical clinical manifestation of lupus as in females, although male SLE may have some distinguishing frequencies of organ involvement notably haematological, neurological involvement or nephritis. The gender disparities have been reported in clinical manifestations and in serological and hematological indices as well. SLE complicated with nephritis is more frequent in men than women, and several groups identified male gender as a risk factor for progression to renal failure. [3, 11, 12]

Nephritis has been reported to afflict 27–45% of patients with SLE. Approximately 10–30% of the patients' progress to end-stage renal disease and despite improvements in overall care, long-term mortality remains high. Involvement of the kidney is suspected when there is a worsening of renal function on routine labs or if the patient is noted to have an abnormal urinalysis. It is interesting to note that contrary to popular belief, only 25–50% of the patients have abnormal renal function. [13]

Childhood-onset SLE represents 10-20% of all SLE case, and is associated with greater disease severity than adult-onset SLE, including more rapid renal damage that developed within 5-10 years of disease onset. Other studies of clinical characteristics indicated that men younger than 33 at the time of diagnosis were more likely to develop lupus nephritis, and that patients of Asian descent tend to have more severe disease, including the renal manifestations. [15]

The patient was diagnosed with SLE based on the classification of the American College of Rheumatology. The

serology examination of SLE shows high titre of ANA and Anti-dsDNA. Anti-dsDNA antibodies are highly specific for SLE and are present in about 61-93% of children with active disease, especially with active nephritis. [16] In our patient, the Anti-dsDNA showed positively high that indicated the need for renal biopsy.

Children with SLE have often an aggressive clinical course with more frequent renal involvement as compared to adults. Boys were reported to have a higher prevalence of several renal disease and poorer outcome. [5] Renal involvement is a major cause of morbidity and mortality in SLE pediatric patients and it has an important role in selecting immunosuppressant therapy in patients. In the project *Euro-Lupus* involving 1000 pediatric SLE patients, a 10-year survival rate of 88% was found in SLE patients with nephritis compared to 94% of patients without nephritis. It is estimated that as many as 50% of SLE patients have kidney disorders, and as many as 80-90% are diagnosed in the first year, and the remainder in the first or second year. [17] Renal disease is manifested by hypertension, edema of the lower extremities, retinal change and clinical manifestation associated with electrolyte abnormalities, nephrosis, or acute renal failure. Renal disease is more frequently observed in children than in adults. [18] We observed the manifestation of renal disease in our patient that was hypertension, edema of the lower extremities.

From the renal biopsy examination, it showed that the patient had a Class IV Diffuse lupus nephritis where it involved $\geq 50\%$ of all glomeruli with diffuse segmental sclerosing lesions with proliferative mesangial cells. It seemed that the patient had rapid progressed in kidney due to lupus and it was in agreement with the findings of Schwartzman-Morris et al. that both in the adult and pediatric lupus populations, male patients had greater disease severity, including rapid clinical progression to diagnosis, progression to renal injury and failure, and greater renal-related morbidity. [4] It is also reported in some series with biopsy results have shown a higher incidence of proliferative nephritis in males [6] that coincides with our male patient's renal biopsy.

There are many challenges to reaching a lupus diagnosis. Lupus is known as the 'great imitator' because its symptoms mimic many other illness. Lupus symptoms can also be unclear, can come and go, and can change. A majority (63%) of people with SLE surveyed report being incorrectly diagnosed. Of those reporting incorrect diagnosis, more than half of them (55%) report seeing four or more different health care providers for their lupus symptoms before being accurately diagnosed. [20] Before being referred to our hospital, the patient already visited two health care providers for the last three months and the symptoms of fever and joint pain came and disappear for regular treatment of antipyretic before the joint pain worsened and at the time of diagnosis has been established he already had a complication of lupus nephritic. As nearly ninety percent of those diagnosed with SLE are female between the ages of childbearing, male should not discount the potential that they too can have it or discount the seriousness of the disease and its effect on the

body if left untreated.

The severity of the disease in a child's SLE is worse than that of most SLE in adults. However, the progress in the diagnosis and the treatment of SLE so far has increased the survival rate dramatically over the past 50 years. At present, the 5-year survival rate for child with SLE is ~95%, and the 10-year survival rate remains ~80-90%. Lupus nephritis carries significant morbidity and mortality. In the 1990s, the renal survival (survival without dialysis) rates of lupus nephritis ranged from 83% to 92% in 5 years and 74% to 84% in 10 years. Considering the long-standing disease, children and adolescents with SLE face a high risk of future morbidity and mortality, especially atherosclerosis and malignancy. Renal disease that fails to remit with immunosuppressive therapies is a major risk factor for subsequent deterioration of renal function and poor outcome. Given the complex and chronic nature of SLE, children and adolescents with SLE should be treated carefully by pediatric rheumatology. [17, 22]

Since symptoms and severity vary from person to person, treatments are individually tailored to meet a person's particular circumstances that are based on the clinical manifestations and tolerance of the treatment. The mainstay of therapy for renal involvement in patients with SLE is corticosteroids, immunosuppressive agents and antihypertensive medications. All current widely-accepted treatment regimens for LN incorporate high-dose corticosteroids for rapid control of inflammation and either MMF or cyclophosphamide to control inflammation and autoimmunity. [21] The patient during hospitalization have gotten corticosteroid administration i.e. methylprednisolone and responded with clinical improvement and therefore it was not given any combination with other drugs such as immunosuppressive drugs.

Our childhood-onset SLE patient already develop lupus nephritis that can lead to permanent renal damage and chronic kidney disease and showed a good response with corticosteroids medications with the clinical manifestation of SLE subsided. Nevertheless, SLE still has the potential to behave aggressively, leading to end stage organ disease and even death. However, aiming at reducing the progression of the disease and preventing long term toxicity from drugs to lower the morbidity and mortality of the disease, drugs that is useful in preventing and treating patients with more severe forms of the disease are needed. In the era of new and more expensive therapies for the treatment of connective tissue diseases, Anti-malarial drugs with extensive potential benefit effects need to be explored. In lupus nephritis, anti-malarial therapy is associated with reduced corticosteroid use, reduced disease activity, extended time to end stage renal disease, and, with adjunctive immunomodulatory treatment, improved duration of renal remission. Their immunomodulatory effects are mediated by mechanism that are anti-inflammatory, immunosuppressive and photoprotective. In 2005, the investigators of LUMINA study reported that HCQ use was associated with reduced risk of developing renal disease in

SLE patients. Strong evidence also supports the use of antimalarial drugs in patient with lupus nephritis: treatment with these agents is associated with reductions in the prevalence of renal disease (Class IV glomerulonephritis, elevated serum creatinine, and hypertension); disease activity; glucocorticoid requirements; and progression to chronic kidney disease. [22] The efficacy of antimalarials, especially hydroxychloroquine (HCQ), in preventing SLE flares is well documented. However, many studies show that the percentage of SLE patients treated with HCQ remains low. By blocking the toll-like receptor 7 and 9 in plasmacytoid dendritic cells, HCQ inhibits interferon-alpha production which plays a crucial role in SLE pathogenesis. As a consequence, some studies have suggested that HCQ, which is inexpensive, has a protective effect on survival in SLE patients. The benefits of HCQ results from its direct effects on SLE activity and from its indirect effects, such as its antithrombotic properties and its ability to protect against diabetes or hyperlipidemia which may contribute to reduce the high cardiovascular risk of SLE patients. Studies also have shown that HCQ is useful in patients with SLE glomerulonephritis. In consequences of their numerous beneficial effects, antimalarials appear to have a protective effect on survival in SLE. [23]

4. Conclusion

Systemic lupus erythematosus is a disease of unknown etiology with a variety of presenting features and manifestations. Symptoms vary from person to person, depend on what part of the body affected, and can be mild, moderate or severe. Although the disease course similar between male and female but male had more disease activity at the diagnosis than woman. The diagnosis of SLE should always be considered in patient with systemic involvement, which would certainly avoid any delay in management and prevent irreversible damage to target organs.. Lupus Nephritis is one of the most common, and most important, serious manifestations of SLE particularly for male. However, improved diagnosis and disease management may lower the morbidity and the mortality rate of SLE. Antimalarial drugs use in lupus nephritis therapy can reduced corticosteroid use, reduced disease activity, extended time to end stage renal disease, and, with adjunctive immunomodulatory treatment, it can improved duration of renal remissions.

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