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Management of systemic lupus erythemathous with polymyositis overlap syndrome

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ABSTRACT

There has been an increase in SLE cases among children in Sanglah General Hospital. In the rare case, there is a possibility SLE occurs not as a single entity but overlap with another connective tissue disease. Polymyositis is a disease with a primary symptom of muscle weakness associated with muscle pain and swollen. Polymyositis very rarely becomes overlapping syndrome with SLE, occurring in 4-6% of SLE patients. The aim of this study is to describe clinical findings and management of SLE and Polymyositis. This case is a 12-year-old girl presented with arthralgia and myalgia since one month before admission, accompanied by a 1-month episode of relapsing fever, decrease in appetite, facial rash, photosensitivity, muscle weakness numbness and tingling sensation on the right foot. Diagnosis of SLE was based on the diagnostic criteria of the American College of Rheumatology. Neurologic examination and electromyography were significant for the decrease in motoric power on the right lower limb, gastrocnemius atrophy, steppage gait, and reduction of the sensory sensation of right L4-S1 dermatome. Hence, the diagnose of SLE and polymyositis was concluded. This is a case of SLE overlap syndrome with polymyositis. The patient was treated with prednisone 2 mg/kg/day for 2 weeks, and also given ibuprofen 10 mg/kg/dose for pain relief, continued with azathioprine plan for one year. The patient showed an excellent result with the disappearance of symptoms and normal laboratory examination. The conclusion of the study is SLE overlap syndrome with polymyositis treated with prednisone and ibuprofen continue with azathioprine showed good outcome with the disappearance of symptoms and normal laboratory examination.

Keywords: Systemic Lupus Erythematous, polymyositis, children, overlap syndrome
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ABSTRAK

Peningkatan kasus SLE terjadi pada anak di Rumah Sakit Umum Sanglah, pada kasus yang jarang SLE bukan sebagai satu kesatuan namun tumpang tindih dengan penyakit jaringan ikat lainnya. Polymyositis adalah penyakit dengan gejala utama kelemahan otot yang berhubungan dengan nyeri otot. Polymyositis sangat jarang menjadi sindrom yang tumpang tindih dengan SLE, namun terjadi pada 4-6% pasien SLE. Tujuan dari penelitian ini adalah untuk menggambarkan manajemen dan temuan klinis pada SLE dan Polymyositis. Kasus ini seorang perempuan berusia 12 tahun yang mengalami artralgia dan mialgia selama 1 bulan, disertai demam selama 1 bulan, penurunan nafsu makan, ruam pada wajah, fotosensitifitas, mati rasa, kelemahan otot dan kesemutan pada kaki kanan. Diagnosis SLE dibuat berdasarkan kriteria diagnostik *American College of Rheumatology*. Pemeriksaan neurologis dan elektromiografi signifikan menunjukkan penurunan kekuatan motorik pada tungkai kanan bawah, atrofi gastrocnemius, steppage gait, dan penurunan sensasi sensorik pada dermatom L4-S1 kanan. Oleh karena itu dapat disimpulkan kasus ini adalah kasus sindrom SLE overlap dengan polymyositis. Pasien diobati dengan prednison 2 mg/kg/hari selama 2 minggu, dan juga diberikan ibuprofen 10 mg/kg/dosis untuk menghilangkan rasa sakit, dilanjutkan dengan pemberian azathioprin yang direncanakan selama satu tahun. Pasien menunjukkan hasil yang baik dengan hilangnya gejala dan pemeriksaan laboratorium normal. Kesimpulan dari penelitian ini adalah sindrom SLE overlap dengan polymyositis yang diobati dengan prednison dan ibuprofen dilanjutkan dengan azathioprin menunjukkan hasil yang baik dengan hilangnya gejala serta hasil pemeriksaan laboratorium yang normal.

Kata kunci : Systemic Lupus Erythematous, polymyositis, children, overlap syndrome
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INTRODUCTION

Systemic Lupus Erythematous (SLE) is a heterogenic autoimmune disease caused by the formation of antibodies against our own cellular nucleus, causing widespread clinical manifestation on one or more organs and pathologically characterized by wide inflammation of blood vessel and connective

tissue.[1] The incidence of SLE varies accordingly in each country; in the United States, the prevalence of SLE averaged 51/100.000 per population. In other countries data revealed an estimated 2.9/100.000 – 400/100.000.[2] Women tend to be 9 times more prone to have SLE compared to men. Sixty-five per cent of SLE occurred in the age of 16-55 years old. The aetiology of SLE is yet to be defined. Multifactorial pathogenesis including genetics, environment, and hormonal component, is estimated to be involved. Monozygotic twins have a higher risk compared to dizygotic. Ninety percent of SLE patients were women, this is expected to be related to the effect of hormone against X chromosome, yet the underlying mechanism is still undefined.[3,4]

SLE is clinically manifested by a chronical and relapsing onset of a disease, and symptoms included continuous or intermittent fever, red rashes, buccal ulcer, and arthritis. Patients also experienced constitutional symptoms including fatigue, decrease in body weight, and anorexia.[3,5] The American College of Rheumatology (ACR) in 1997 or Systemic Lupus International Collaborating Clinics (SLICC) in 2012 classification is the standard guideline in classifying SLE with a sensitivity of 96% and specificity of 100%.[1,2] Recommended laboratory examination included inflammation indicator, autoantibody test, organ-specific functional tests and examinations to monitor therapeutic effect. Initially, during the acute phase, laboratory examination would reveal an increase in LED but a normal C-RP.[2,3] Hematologic examination could manifest as anaemia, leucopenia, and/or thrombocytopenia. Urinary examination manifest as proteinuria, hematuria, and a cast of heme glandular, or red blood cell on the urine. Antinuclear antibody (ANA) test could be used as a screening test for patients with SLE, with a positive result in 90-100% of SLE patients. Anti-dsDNA is a pathognomic criterion for SLE.[6,7,8]

Management of SLE aims to control inflammation, achieve remission phase, increase the quality of life, decrease exacerbation, prevent serious organ damage, and decrease death.[1,2] The mainstay therapy for SLE is glucocorticoid with close monitoring of side effects. Other options include Disease Modifying Anti Rheumatic Drugs (DMARDs) types of drug. Non-steroid anti-inflammation drugs could be used to manage musculoskeletal symptoms.[1,2]

CASE ILLUSTRATION

This is a case of 12 years and 9-month girl from Buleleng Bali. The Patient presented with arthralgia for 1 month before admission, 10th October 2016. The pain was reported to move from one joint to another, except in the right leg where the pain persisted. The pain was not alleviated by rest. The pain was severe enough to impede walking and felt persistently throughout the day. Arthralgia was also accompanied by myalgia. The joint involved was palpated to be warm. The numbness was thought from the right foot to the dorsum foot. The numbness and tingling sensation were felt persistently

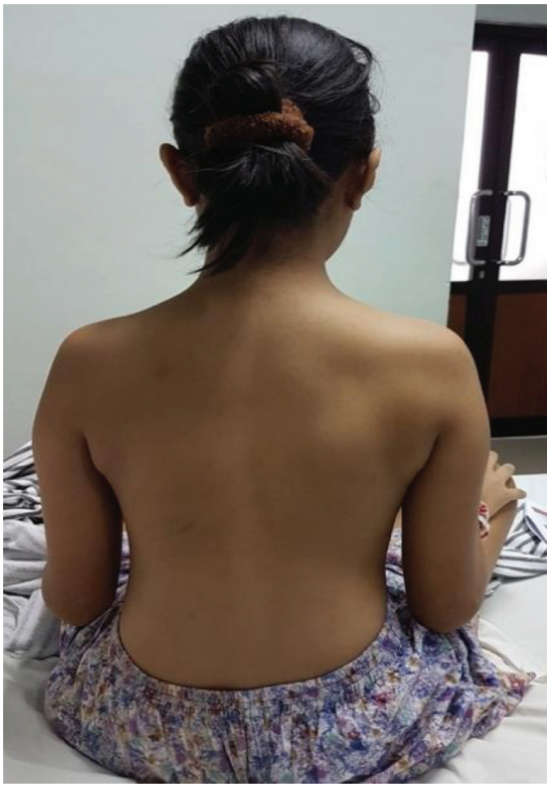

Figure 1 Spine asymetrical deformity

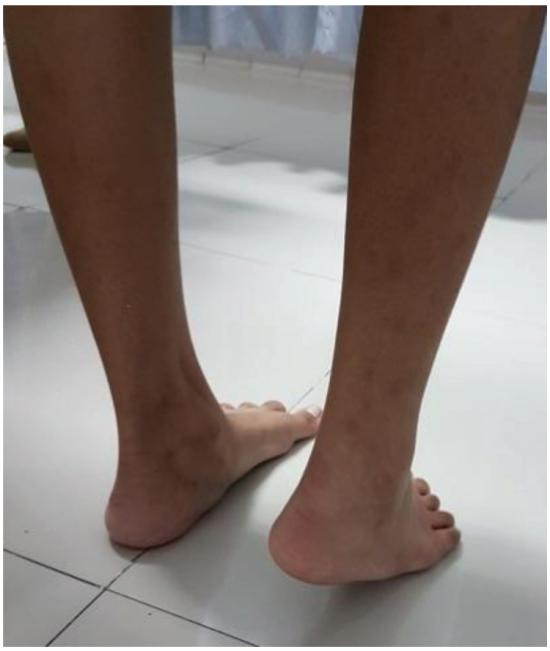

Figure 2 Legs and gait disorder

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Table 1 pGALS screening problems

pGALS screening Documentation		
Pain symptoms?	Right Leg	
Problem on using shirt?	No problem	
Problem when walking?	Problem when walking	
	Visible	Movement
Gait	+	+
Arms	-	-
Legs	+	+
Spine	+	-
pGALS screening found problems including: Gait and Legs		

Table 2 Classification criteria of systemic lupus erithemathous

SLICC 2012 criteria	ACR 1997 criteria
Requires ≥ 4 criteria (at least 1 clinical and 1 laboratory criteria)	- Butterfly rash
Clinical Criteria:	- Discoid lupus eash
- Acute cutaneous lupus	- Photosensitivity
- Chronic cutaneous lupus	- Oral or nasal mucocutaneus lesion
- Oral or nasal mucocutaneus ulceration	- Non erosive arthritis
- Alopecia	- Nephritis
- Arthritis	- Proteinuria > 0,5 g/24 hours, positive cylinder cell
- Serocitis	- Enchepalopathy (seizure, psychosis)
- Renal Involvement	- Peluritis or pericarditis (serocytis)
- Neurologic (convulsion, phycosis, myielitis	- Cytopenia (leukopenia <4000/mm3, atau limfopenia <1500/mm3, atau trombositopenia <100.000/mm3, not caused by drugs
- Hemolytic Anemia	- Positive immuoserology
- Leukopenia (<4000/µL) or limfopenia (<1000/µL)	✓ Antibody against dsDNA
- Trombositopenia (<100.000/µL)	✓ Antibody against nuclear antigen Sm
	✓ Antibodiyantifosfolipid positive, based on :
Immunologic criteria:	• Anticardiolipin antibody IgG or IgM
- ANA	• Lupus anticoagulant antibody
- Anti-dsDNA	• False positive result for syphylis serologic test with treponema pallidum immobilization test or fluoresent treponemal antibody absorbsion test
- Anti-Sm	- Postive anti nuclear antibody test Four out of 11 positive criteria had shown a 96% sensitivity and 96% sensitivity.
- Antifosfolipid Ab	
- Low complement level (C3, C4, CH50)	
- Direct coombs test (not calculated if there were hemolytic anemia)	

and was not alleviated by rest. The patient also experiences fever for 1 month before admission with the same onset of arthralgia. Fever started in the afternoon and worsened during the evening with a maximum temperature of 39.5˚C. The patient had a decrease in appetite for 1 month. The patient also had a 4 kg decrease in body weight in one month. Since admission, the arthralgia persisted, also

accompanied by numbness and tingling sensation on the right dorsum pedis.

From the physical examination, the patient presented with alert consciousness. Her blood pressure as 110/70, pulse was 96 times/minute, her respiratory rate 24 times/minute, and the axillary temperature was 37˚C. She was 37 kg (75-90th percentile) and 143 cm (95th) percentile with a body index of 18.09 kg/m^2 and good nutritional status (Waterlow 101%). General examination revealed butterfly rash (+) on her face. Examination of lower extremities presented with: right drop foot, warm palpation on the joints and muscle especially on the right ankle, muscle atrophy, no swelling, nor redness was observed and steppage gait was positive. Neurologic examination revealed: decrease in motoric function (444) of the right lower limb, gastrocnemius atrophy with a diameter of 25.5 cm (left 26.5 cm) and a sensory deficit of the L4-S1 of the right lower limb. A pGALS (Paediatric Gait Arms Legs and Spine) screening (Table 1) was conducted and revealed problems on gaits and leg.

Laboratory examination revealed a hypochromic microcytic anemia, positive thrombocytopenia, positive ANA test, with a titer of 1:100, homogenous pattern. Anterior-posterior/Lateral rontgen examination of right and left cruris displayed metatarsal 1 and right-left digiti 1 phalanx osteoartopathy. Right and left AP/Lateral ankle rontgen presented with right and left ankle osteoarthopathy. Other laboratory examination revealed a complement C3 of 87.2 mg/dL; ANA profile PM-Scl100 (PM100) (+), nucleosomes (NUC) +.

DISSCUSSION

Systemic Lupus Erythematous (SLE) is a heterogenic autoimmune disease that occurs due to antibody production against the body's own cell nucleus component with broad clinical manifestations involving several organs; it is characterized by widespread inflammation on blood vessels and connective tissues, it has an episodic disease pathway intercepted by remission episodes.[1] SLE incidence varies from 2.9/100.000-400/100.000. SLE is seldom found in children aged below 5 years old, women are 9-fold more susceptible compared to man.[2] Sixty five percent of SLE patients had an onset from of 16 to 55 years old, 20% are below 16 years old and 15% started to experience SLE since 55 years old. In children 60% of SLE began by the age of 10 years old or above, 35% had an onset from 5 to 10 years old, and only 5% had SLE before 5 years old. [3,4]

The etiology of SLE is still unclear, many evidences suggest that SLE pathogenesis is multifactorial, involving genetic, environmental, and hormonal factors against the immune system. Multiple genetic factors hold a significant role in the pathogenesis. SLE prevalence was found higher in children whom had a family history of SLE. Ninety percent of SLE patients are female, this is related to the hormonal influence that affects the gene on chromosome X, yet the exact mechanism has yet to be elucidated.[2,3] In this case, the patient was a 12 years and 9 months old girl, with no family history of SLE. Other risk factors such as food, drugs, and infectious agents were not found.

Clinical manifestation of SLE varies from a chronic disease with intermittent arising symptoms to fatal acute phase. Clinical manifestation also differed based on the age; pre pubertal ≤ 8 years, pubertal age 8-13 years old, and post pubertal age 13-18 years old. Common symptoms included persistent or intermittent fever, red rash, ulcer on the mouth (mucositis) which occurred twice as often in children compared to adults, and arthritis. Other constitutional symptoms included fatigue, loss of weight and anorexia.[3,5] In this case, the patient was in her pubertal age, she presented with intermittent fever for 4 months before admission, loss of appetite, and also accompanied by loss of weight. A journal study was conducted to elucidate SLE manifestation in puberty age that would then be used for long term monitoring of this patient. A journal search resulted with the title "Differential manifestations of prepubescent, pubescent and post pubescent pediatric patients with systemic lupus erythematosus: A retrospective study of 96 Chinese children and adolescents" by Chiang et al., in Pediatric Rheumatology 2012, with 3b level of evidence, and B strength of recommendation. The summary of this journal: pubertal groups of SLE patients tend to present kidney involvement, leucopenia, and positive to lower C3 and C4 level compared to pre pubertal group. Puberty group also show higher positive anti-Sm antibody compared to groups of post pubertal patients.[8]

SLE is diagnosed based on a classification made by the American College of Rheumatology (ACR) in 1997 or Systemic Lupus International Collaborating Clinics (SLICC) in 2012, as seen on Table 2.

Diagnostic approach using these criteria have a sensitivity of 96% and specificity of 100%.[1,2] Most patients with SLE have ANA, yet low or moderate titer of these antibodies have low specificity towards diagnosis. Meanwhile patients with antibodies against dsDNA and Sm almost always have ANA.[3]

In this case, the patient had butterfly rash on both part if the cheeks that spread up until the nose and forehead. Patient also presented with

photosensitivity, arthritis, cytopenia (thrombocytopenia) and positive ANA test. The ACR 1997 and CLICC 2012 criteria was fulfilled.

Laboratory examination for SLE included inflammation indicator autoantibody test, organ involvement evaluation, and examination to observe the effect of therapy, including drug toxicity. During acute phase of the disease, inflammation indicator will increase, such as erythrocyte sedimentation rate but the C-reactive protein (CRP) would still be within the normal limits.[2,3]

Hematologic examination could reveal anemia. Anemia in SLE could be caused by chronic disease, hemolytic anemia, bleeding, renal insufficiency, drugs, infection, hypersplenism, myelodysplasia, myelofibrosis, and aplastic anemia. Hemolytic anemia is caused by the attachment of IgG antibodies and complements on the erythrocytes. Patients with SLE could also present with leucopenia and Lymphopenia. While trombocytopenia had been reported in 25-50% cases. Anticoagulant assay could reveal an increase in aPTT and prothrombin. Urinalysis on SLE patients had shown proteinuria, hematuria, cast, granular heme or red blood cell on the urine.[2,3] In this case, we found a picture of anemia caused by chronic disease, lymphopenia, thrombocytopenia, normal LED, normal CRP, normal kidney function, and normal urine analysis.

Antinuclear antibody (ANA) could be used in screening patients suspected with SLE or other connective tissue disease. The prevalence of positive ANA test in several autoimmune disease included; 90-100% in SLE, 60-80% in systemic sclerosis, 40-70% in Sjogren's syndrome, 30-80% in polymyositis/dermatomyositis, and 30-50% in rheumatoid arthritis. An ANA titer of ≥1:160 was regarded as significant.[6,7] In this case the ANA test was positive with a titer of 1:100, the titer was still not significant to establish the diagnosis of SLE. A journal search was conducted to know the sensitivity and specificity of ANA test to diagnose SLE, A journal with the title "Sensitivity and specificity of ANA and anti-dsDNA in the diagnosis of systemic lupus erythematosus: A comparison using control sera obtained from healthy individuals and patients with multiple medical problems" by Wichainum et al. in Asian Pac J Allergy Immunol 2013 was found. With 2c level of evidence B strength of recommendation. The conclusion of the journal: ANA and anti-dsDNA provide high sensitivity and specificity for patients with SLE. An ANA titer ≥ 1:80 provide 98% sensitivity and 92% specificity.

Anti-dsDNA antibody is a pathognomonic criterion for SLE and demonstrated a high titer when nephritis was active; it could be used as a marker of disease activity.[8] A positive anti-ds-DNA was found in 73% of SLE patients and harboured significant diagnostic and prognostic value. An increase in ant ds-DNA represents an increase in disease activity.[9] In addition to ds-DNA, ANA consist of other types of variation including histone protein, nucleosome, centromere protein, and extractable nuclear antigens (ENA) (Smith antigen (Sm), Ro, La, ribonucleoprotein (RNP), and others. ANA profile is found in 95% of patients with active SLE.[10,11] In this case, the patient had a negative anti-dsDNA, positive anti-nucleosomes and positive anti-PM Scl 100.

In this case, the patient had an ANA profile of negative anti-dsDNA, positive anti-nucleosome and positive anti-PM Scl 100. A journal search was conducted to know whether anti-nucleosome could be used as an SLE diagnostic marker. A journal with the title "Are anti-nucleosome antibodies a better diagnostic marker than anti-dsDNA for systemic lupus erythematosus? A systematic review and a study of metaanalysis" by Bizzaro et al. in Autoimmunity Reviews 2012 was found, with 1a level of evidence and A grade recommendation. The journal concludes: anti-nucleosome antibody examination has good accuracy in diagnosing SLE, even though the positive anti-nucleosome result could not distinguish other types of connective tissue disease. ANA examination is superior for SLE diagnosis compared to anti-dsDNA antibody.

In SLE, the level of C1, C4, C2 and C3 are usually low but could be normal in cutaneous lupus. Immune complex causes inflammation lesion through activation of the complement cascade. The decrease in complement is related to the degree of SLE progression primarily related to kidney complication.,[12,13] in this case, the C3 complements were within the normal limit, and the patient did not have any kidney involvement.

SLE could be accompanied by another connective autoimmune disease, in these cases, it is regarded as overlap syndrome. Soft tissue diseases that are often included in the overlap syndrome among them are: SLE, systemic sclerosis, polymyositis, dermatomyositis, rheumatoid arthritis (RA), Sjogren's syndrome, eosinophilic granulomatosis with polyangiitis (EGPA), autoimmune thyroiditis, antiphospholipid antibody syndrome.[14] Myositis is a disease with a main symptom of muscle weakness related with muscle pain and oedema.It occurs more commonly in women compared to men, with a ratio of 2:1 and more prevalent in patients > 20 years old, especially in patients 45-60 years old. This disease seldom occurs in children.[14,15] Increase in creatinine kinase could be found in lab result. Meanwhile, the increase in muscle signal could be found in MRI examination and muscle weakness/or damage observed in EMG examination and muscle biopsy.[15] Myositis is a rare complication of SLE, occurring in less than 4-6% of SLE cases.[14] In this

case, we found a presentation of muscle weakness and pain. In EMG examination, we found the weakness of muscle innervated by the right median nerve and right peroneus nerve.

The main goal of SLE treatment is to control inflammation, reach remission phase, increase the quality of life, avoid heavy exacerbation, prevent severe organ damage and decrease death.[15] The non-steroid anti-inflammation drug could be used to overcome musculoskeletal symptoms, with a primary choice of ibuprofen 10mg/kg/dose every 8 hours. Anti-malaria drugs are used in discoid lupus cases with a prime selection of sulphate hydroxychloroquine 6-7 mg/kg/day in 1-2 doses for 2 months and decreased to 5mg/kg/day. Long term evaluation requires retinal evaluation for every 6 months. Glucocorticoid therapy is the mainstay therapy for SLE. The dosage and frequency are determined by the degree of disease and organ involved. Lower dosage of prednisone (<0.5mg/kg/day) are used to treat fever, dermatitis, or as bridging therapy. Higher dosages (1-2 mg/kg/day divided with a maximum dose of 80mg/day) were used to treat lupus crisis, nephritic symptoms, neurologic symptoms and hemolytic anaemia. Intravenous methyl prednisone with a dosage of 30mg/kg/times for three days oral prednisone 15-60 mg/day (0.5-2mg/kg/day) continued by dosage tapering were used in severe cases. Disease-Modifying Anti Rheumatic Drugs (DMARDs) were given after methylprednisone pulse. Cyclophosphamide, MMF and Azathioprine are used as mainstay therapy. Cyclophosphamide is given after methylprednisolone pulse therapy. It is given with a dosage of 500 mg/LPT/times intravenously every 2 weeks for 12 cycles or 6 months, followed by Cyclophosphamide maintenance every 3 months. Mycophenolate mofetil (MMF) is used after methylprednisolone pulse therapy as steroid-sparing while tapering. It is given with a dosage of 1200 mg/m^2 for 6 months and decreased 50% afterwards for 6 months. Azathioprine is used after 12 Cyclophosphamide or after the first 6 months of MMF therapy, with a daily dosage of 0.5-2.5 mg/kg/day for 6 months. Treatment for polymyositis consists of prednisone 1mg/kg/day for 6 weeks and decreased slowly.[15,16] In this case, the patient was treated with prednisone 2 mg/kg/day for 2 weeks and also given ibuprofen 10 mg/kg/day for pain relief, continue with azathioprine plan for one year.

The prognosis for SLE had improved, with a 10-year survival rate of 90%. Death was related to direct consequences of SLE including, kidney failure, malignant hypertension, central nervous system damage, pericarditis, and autoimmune cytopenia. Other cause of death included, drug side effect, for example, atheroma disease from chemotherapy, neoplasm due to immunosuppressed state, or infection. Infection and sepsis are the leading cause of death in SLE, not just due to corticosteroid therapy but also due to immune deficiency of the SLE itself.[1,2] The number of death decreases due to improvement in treatment, earlier diagnosis, and possibility in more widespread palliative medication.[2]

Polymyositis had shown good response on medication despite residual muscle weakness in 30% of patients. Osteoporosis is a main complication of long term steroid use and causes significant morbidity. Adverse prognostic factors include old age, omen, African American race, pulmonary interstitial disease, positive Jo-1 and anti-SRP, malignancy, late therapy, dysphagia, dysphonia, and involvement of heart and lungs. The survival for 5 years averages 80%. Mortality is often related to malignancy or lung complication.[15,17] In this case, the patient experienced weakness, muscle pain, and decrease in sensory quality caused by SLE and polymyositis. The occurrence of overlap syndrome prompts the question on the patient's prognosis. Therefore a journal search was conducted and a journal with a title "Association of clinical features and prognosis with age at disease onset in patients with systemic lupus erythematosus" by Feng et al. in the sage pub, 2014 were found. The journal had 2b level of evidence and Grade B recommendation. The journal concludes: The onset of the disease is related to the SLE disease status. Earlier onset (age >18-≤ 45 years old) have the best survival rate followed by juvenile-onset (age ≤ 18 years old) and late-onset (age > 45 years). Infection was the primary cause of death.

CONCLUSION

This is a case of 12 years and a 9-month girl who presented with arthralgia for one month. Arthralgia was also accompanied by myalgia, persistent fever, and decrease in body weight, numbness, and tingling sensations. The patient was assessed with systemic lupus erythematosus with suspected polymyositis overlap syndrome. Myositis is a rare complication of SLE occurring in less than 4-6% of SLE cases. Further studies are needed to elucidate the therapeutic and prognostic significance of polymyositis overlap syndrome in SLE.

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