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Hemorrhagic Pericardial Effusion in Systemic Lupus Erythematous (SLE) Prompt Diagnosis and Treatment

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Abstract: ***Background: Pericardial effusion can be as cardiac manifestation of systemic lupus erythematous (SLE), which is usually serous fluid. Hemorrhagic pericardial effusion is unusual clinical sign of SLE. Pericardial effusion is an abnormal accumulation of fluid in the pericardial cavity it can be either serous, serosanguineous, or hemorrhagic. The most common causes of hemorrhagic pericardial effusion are malignancy, tuberculosis, trauma and complication of myocardial infarction. The aim of this report is to recognize unusual clinical sign of SLE and to decide early treatment for life saving in SLE case. Case: A 13 years old female presented with shortness of breath, difficult to lying on the bed but get better on sit position. Echocardiography investigation showed pericardial effusion. Pericardiocentesis then become the choose of treatment, it was showed bloody fluid. Clinical and laboratory examination did not showed sign of malignancy, tuberculosis, trauma, nor myocardial infarction. Further investigation then guide the diagnosis to SLE, which full filled 6 point out of 16 point of SLICC criteria. High dose methylprednisolone (HDMP) was as the choose of initial treatment followed by cyclophosphamide. After first HDMP administration, patient got dramatically improvement by the production of pericardial effusion. Patient was discharge in the good condition. Conclusion: SLE can occur in unusual manifestation like hemorrhagic pericardial effusion. Early SLE diagnosis will prompt a thorough evaluation and diligent follow-up which can minimize the disease comorbidities and improve its outcomes.***

Keywords: systemic lupus erythematous, hemorrhagic pericardial effusion

1. Introduction

Pericardial effusion is an abnormal accumulation of fluid in the pericardial cavity. Pericardial fluid can be either serous, serosanguineous, or hemorrhagic. The most common causes of moderate to large pericardial effusions are iatrogenic, infection, malignancy, chronic idiopathic effusion, post-acute myocardial infarction, autoimmune disease, radiation, renal failure with uremia, and hypothyroidism and most frequent causes of bloody pericardial effusions are malignancy, post-procedural (transcatheter interventions and pacemaker insertion), post-pericardiotomy syndrome, complications of myocardial infarction, idiopathic, uremic, aortic dissection, and trauma. In addition, tuberculosis is a frequent cause of hemorrhagic effusion in endemic areas [1].

Cardiac disease affects between 15 and 50% of patients with SLE. The cardiac manifestations of SLE include pericarditis, myocarditis, arteritis of the coronary arteries, endocarditis and conduction system abnormalities. Pericarditis is seen most often, occurring in up to 75% of all cases. It is also one of the diagnostic criteria for SLE. Large pericardial effusions can cause cardiac tamponed however rare. There is a 1–2.5% reported incidence of tamponed due to either idiopathic or drug induced SLE [2]. Cardiac manifestations can be mild and asymptomatic. However, they can be frequently recognized by echocardiography and other noninvasive tests. Echocardiography is a sensitive and specific technique in detecting cardiac abnormalities, particularly mild pericarditis, valvular lesions, and myocardial dysfunction [3]. Pericardial effusion in SLE usually serous fluid, it is one of the diagnostic criteria for SLE meanwhile hemorrhagic pericardial effusion is unusual clinical sign of SLE. Forty percent of SLE patients are said to have pericardial effusion by echocardiography while only about 25% actually manifest clinically. Even so, demonstration of LE cells in the pericardial fluid is far uncommon than in pleural fluid cytology with only rare documented reports. The literature review of LE cell positive serous effusions by Park et al in 2007 found only one case of pericardial effusion showing LE cells among 16 case reports [4].

Systemic Lupus erythematous (SLE) is a severe, chronic autoimmune disease that results in inflammation and eventual damage in a broad range of organ systems; kidney, joint, skin, heart, pulmonary, hematology, neurological system and blood vessels. It is likely that lupus is a multifactorial disease of unknown etiology in which significant immunological abnormalities have been

identified. Hormonal, genetic and environmental factors have been implicated in its etiology. SLE is a relatively rare disease in childhood but the prevalence is increase in adolescence, approximately 20% of individuals with SLE will have their disease onset prior to the age of 16 years. SLE generally presents between the ages of 5-15 years, rare in children younger than 5year. Females are most commonly affected with female-to-male of 4.5-5:1 prior to puberty, raised to 9-10:1 after puberty [5]-[7].

There is no specific diagnostic test for SLE, and diagnosis is difficult due to variability of clinical symptoms and signs. Physicians have commonly relied on the American college of rheumatology (ACR) criteria for the classification of SLE. These criteria were preliminary developed in 1971, revised in 1982 and updated in 1997. A child can be classified as having SLE if at least four of the 11 criteria are present in order to address the limitations of ACR criteria. The systemic lupus international collaborating clinics (SLICC) developed SLICC criteria in 2012, which exhibited higher sensitivity and lower specificity than ACR criteria. The SLICC criteria include 11 clinical and 6 immunologic items. It requires 4 items with at least one clinical and one immunologic item or biopsy proven nephritis compatible with lupus in presence of an ANA or Anti ds-DNA. The SLICC criteria has been validated in children, showing better sensitivity and fewer miss-classifications than the ACR criteria. Of note, both criteria are classification rather than diagnostic criteria and some patients need treatment despite not fitting these classification criteria. Malar rash, discoid rash (DLE), photosensitivity, alopecia, oral/nasal ulcers, polyarthralgia/myalgia, polyarthritis, pleurisy/ pericarditis and peritonitis, leukopenia, thrombocytopenia, hemolytic anemia, hematuria, proteinuria, azotemia, psychosis/seizures, peripheral/cranial neuropathies are the classic features of SLE. Pericarditis and pericardial effusions in SLE are well recognized in SLE but the incidence is rare. Common initial presentations of SLE included constitutional symptoms, renal disease, musculoskeletal and cutaneous involvement. Less frequently involved at SLE presentation were the neuropsychiatric, pulmonary and cardiac systems, with pericarditis reported in 3–24% of cases at presentation [6], [8], [10].

2. Case Report

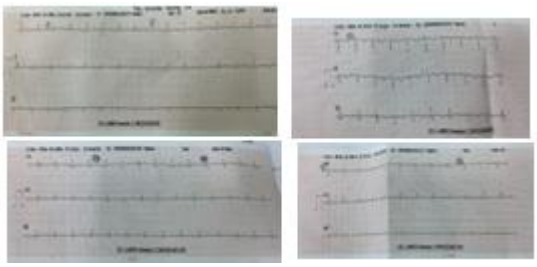
A female, 13 years old, Balinese, came to the emergency ward at Sanglah Hospital in Denpasar on 1st June 2018 with chief complaints shortness of breath since 1 week ago and getting worse since 3 days ago. The shortness of breath feel when she pull in the air, no sign of blue skin. She usually lying or sleep in the bed with minimally 2 pillow behind her back since 1 year ago. But since 3 days ago she sleep with half-sit position and if she lying the shortness of breath getting worse. History of hair loss since 1 month ago and getting worse since 1 week ago. Then she decided to cut her hair it shortly. Rash on the face when exposed to sunlight denied. Pain and swelling on the joint denied. Seizures and headache denied. She has urine like tea but not remember when it is starts.

Physical examination found the patient's general condition is look breathless, awareness compost mentis. The vital sign showed normotension, tachycardia, takipneu and no fever. The status nutrition patient was well nourished. On the status of generalist obtained conjunctiva look pale, neck not found enlarged lymph nodes and in thoracic examination found the sound of heart is muffled. First and second heart sound is normal, without murmur. Lungs sound within normal limits with vocal fremitus weak in the left side of thorax compared with right side. On abdominal examination found no distension, bowel sounds audible within normal limits. There were no inguinal lymph node enlargement. The upper and lower limb without oedema and feels warm. The hair's patient look short and thin.

Complete blood count was showed in table 1, the hemoglobin was decrease from 7,03 g/dL to 5,69 g/dL although patient has been given PRC transfusion. This indicates that there has been active bleeding in patient. The result reticulocyte was 2,2%. Blood smear result hypochromic microcytic, anisopoikilocytosis. Urinalysis gained protein +1, blood +3 with leucocytsedimen 8/HPF and erytrocytsedimen 756/HPF. Renal function gained BUN 28,8 and creatinine 2,05 (GFR 41,3ml/min/1,73m2). On thorax x-ray show pericardial effusion. On electrocardiography gained sinus tachycardia with low voltage (< 10mm) wave QRS (Picture 1). On echocardiography gained large pericardial effusion (estimate 1.203 mL) with pericardial thickening, fibrotic +, normal LV systolic function (EF 70%) and patient was planned pericardiocentesis urgent.

Table 1: Complete blood count (CBC)

Parameter	1/6/18	6/6/18	10/6/18	27/6/18	Unit
WBC	10,96	9,52	20,99	13,47	10^3/µL
Neu	9,11	8,11	19,26	10,49	10^3/µL
Lym	**1,05**	**0,80**	**1,43**	**2,14**	10^3/µL
Mono	0,68	0,59	0,28	0,80	10^3/µL
Eos	0,04	0,01	0,00	0,01	10^3/µL
Baso	0,07	0,15	0,03	0,04	10^3/µL
RBC	3,42	2,53	4,87	4,56	10^6/µL
HGB	**7,03**	**5,69**	**11,19**	**10,93**	g/dL
HCT	22,59	19,97	34,03	34,09	%
MCV	66,0	78,99	69,90	74,77	fL
MCH	20,53	22,51	22,98	23,97	Pg
MCHC	31,11	28,50	32,88	32,06	g/dL
RDW	15,03	22,95	20,06	22,56	%
PLT	239,0	**94,92**	164,0	365,0	10^3/µL



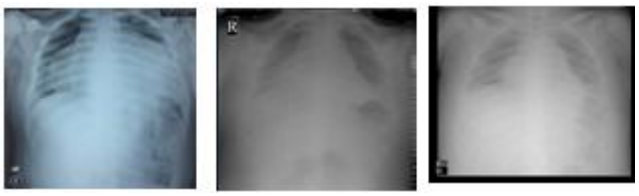
Picture 1: Electrocardiography shows sinus tachycardia with low voltage which suggest pericardial effusion

Pericardiocentesis was performed with total aspiration 250 ml of hemorrhagic fluid. Patient was performed pericardiocentesis six times with total aspiration 1500 mL of hemorrhagic fluid. On pericard analysis gained lactat dehydrogenase (LDH) 598 UI/l, proteins 7.2 g/L, albumin

2.6 g/L, rivalta : positive , mono : 30%, poly : 70%, Cell count 1900 with full erytrosit. LDH serum 291 with protein 9.2. The picture of pericardial effusion shows in picture 2. The result of cytology is chronic inflammation, which contain mostly neutrophil PMN cells and slightly visible lymphocyte and macrophage distribution, such as large erythrocytes and not showed LE cell. Pericardial cultures were negative. Polymerase chain reaction (PCR) for detection of Mycobacterium tuberculosis in the fluid was negative. Patient have not been found clinically significant improvement after pericardiocentesis. Patient still feel breathless and there is still production of blood in pericardial. Because of the condition is not improving, patient is decided to giving methylprednisolone pulse dose, although the result of serological examination of SLE is not available yet. ANA IF results was >1:1000 and antibody anti dsDNA result was 743,9.

Picture 2: Pericardial fluid

The working diagnosis in this patient is systemic lupus erythematous with hemorrhagic large pericardial effusion, overweight. Patients undergoing planning with high dose methylprednisolone (HDMP) 30mg/kg/time, 3 days consecutively, then methylprednisolone 1mg/kg/time for 2 weeks and cyclophosphamide low dose 500 mg every 2 weeks for 6 time (3 months). The condition after first HDMP is getting better. The production of pericardial effusion was decrease and followed by increase of hemoglobin without transfusion. The patient is discharged from hospital with condition no chest pain, no dyspnea, can lying in the bed and no production of pericardial effusion. The final echocardiography result after treatment is mild loculated pericardial effusion. The image of thorax x-ray getting better after treatment and show on picture 3.



Picture 3: Thorax x-ray before and after treatment. From left to right: before treatment, after HDMP, after 1st cyclophosphamide

3. Discussion

SLE is one of the most common autoimmune connective tissue diseases in childhood, where it tends to present more severely than in adults. Common initial presentations of SLE included constitutional symptoms, renal disease, musculoskeletal and cutaneous involvement. Less frequently involved at SLE presentation were the neuropsychiatric, pulmonary and cardiac systems, with pericarditis reported in 3–24% of cases at presentation. SLE is a relatively rare disease in childhood, approximately 20% of individuals with SLE will have their disease onset prior to the age of 16 years. SLE generally presents between the age of 5-15 years, rare in children younger than 5year. Females are most commonly affected with female-to-male of 4.5-5:1 prior to puberty, raised to 9-10:1 after puberty [6],[7],[10].

The diagnosis of SLE can be made by clinical/laboratory judgment of an expert rheumatologist and there is not any diagnostic criteria for early detecting it yet. The 1997 American College of Rheumatology (ACR) criteria and its complementary criteria; the 2012 Systemic Lupus International Collaborating Clinics (SLICC) criteria, both are designed for classification of SLE and they are not diagnostic. The 2012 SLICC criteria are very complex/extended criteria and it can be used when the ACR criteria cannot classify SLE. Right now there is newest criteria for diagnosis of SLE with entitled "2015 ACR/SLICC revised criteria for diagnosis of SLE". If we meet 4 point or more that's mean definite diagnosis of SLE, if we meet 3 points highly suggestive SLE, 2 points probable SLE and one point possible SLE are the diagnosis [8],[9].

The result of pericard analysis is LDH 598 U/L (240-480 u/L), protein 7,2 gr/dl (6,0-8,0 gr/dl), albumin 2,6 gr/dl (3,5-5,2 gr/dl), Rivalta: positive, mono: 30%, poly: 70%, cell 1900 with full erythrocyte. The result of cytology examination is chronic inflammation and not showed LE cell. Differential diagnosis of SLE associated pericardial effusion includes idiopathic, infectious (viral, bacterial, tuberculosis), post myocardial infarction, traumatic and neoplastic. In a retrospective study of 81 patients who were diagnosed of SLE, causes of pericarditis included active SLE (93%), and suspected tuberculosis (TB) (5%), with 2% inconclusive [12].Another SLICC criteria that full filled in this case is hematology criteria that is thrombocytopenia with thrombocyte count is 94,92/mm3 (1 point) and lymphocyte count was $<$ 1500 /mm3 in $\geq$ 2 times examination (1 point) and hemolytic anemia because in blood smears appears picture of anisopoikilocytosis (1 point). Serologic test contained on SLICC criteria such as ANA tests, anti dsDNA, anti Sm, anti-phospholipid, and low serum complement (C3/C4). In this case, with result of anti dsDNA is 743,9 (< 100), it is gained 2 point. Total SLICC point in this case is 7, that's mean definitive diagnosis of SLE.

Kidney disease in SLE (also known as lupus nephritis (LN)) is a common manifestation of SLE and constitutes an important prognostic factor for such patients. Up to 50% of SLE patients have abnormalities of renal function or urine (proteinuria, hematuria or cellular casts) early in the course of the disease, whereas approximately 80% may later develop overt abnormalities of renal function. According to the 2012 Systemic Lupus International Collaborating Clinics Classification (SLICC) criteria for the diagnosis of SLE, kidney disease is present when a patient with SLE presents with persistent proteinuria (>0.5 g/24 h) or cellular red cell casts. LN is a major determinant of morbidity and mortality in SLE patients. A South African study has shown that over half of 226 SLE patients from a lupus clinic had either died or been lost to follow-up at 55 months, and LN was the only significant factor associated with mortality on multivariate

analysis, with a 5-year survival rate of 60% [11]. In this case, according to urinalysis there is hematuria with erythrocyte sediments count is 756 and decrease 59% of glomerulus filtration rate (GFR 41,3ml/min/1,73m2), so this patient diagnose with lupus nephritis.

SLE classification according 2015 ACR/SLICC revised, classification degree of disease to determine treatment, such as:

1) Mild-moderate : no involving vital organ
2) Severe : involving vital organ (cerebral lupus, nephritis, hemolytic anemia, serosisitis)
3) Lupus crisis : life threatening (seizure, decrease of consciousness, cardiac tamponade, progressive decrease of renal function)

Treatment of severe SLE is high dose methylprednisolone 30mg/kg/time until 3 days consecutively, then tapering off. This HDMP followed by cyclophosphamide low dose 500 mg every 2 weeks for 6 time (3 months) [13].

SLE Disease Activity Index (SLEDAI), developed at the University of Toronto in 1992, is a global score reflecting all aspects of disease activity. It is a weighted scale for 24 parameters and the score can range from zero to 105. Various manifestations are scored based on their presence or absence in the previous ten days of evaluation. Higher scores indicate more severe disease activity. SLEDAI has certain limitations in that it does not score some life-threatening manifestations such as pulmonary hemorrhage and hemolytic anemia. It is heavily weighted for central nervous system and does not take into account the severity of manifestations. Gladman et al defined that an increase in SLEDAI score of more than three was a flare, SLEDAI score that was within three points of the previous score was persistent disease and a score of zero was remission. A change of SLEDAI score of more than 12 is a severe flare according to another study. Global scores like SLEDAI can be problematic at times in that the score may be the same whether the patients are improving, stable or worsening. For instance, a rash can improve and still be present, or deteriorate and yet the score may be same.15 Serological tests are commonly used to assess the disease activity and predict lupus flare. During active disease, usually there is a fall in complement levels and a rise in anti-double stranded deoxyribonucleic acid (anti dsDNA) levels [14],[15].

4. Conclusion

SLE can occur in unusual manifestation like hemorrhagic pericardial effusion. Early SLE diagnosis will prompt a thorough evaluation and diligent follow-up which can minimize the disease comorbidities and improve its outcomes.

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