Unresponsive and late intravenous immunoglobulin of giant aneurysms after kawasaki disease

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ABSTRACT

Giant aneurysm is rare complication of Kawasaki disease (KD) and has highest risk for arteriole occlusion. We report an 8.5 years old boy who was diagnosed with giant aneurysm, after diagnosed with KD. Echocardiography during acute phase was found lesions at left main ostium coronary artery (LMCA), left anterior descending artery (LAD), and right coronary artery (RCA). Patient was treated with single dose intravenous immuno globulin (IVIG) at 14th of illness. Recurrent fever, hypoalbuminemia, rising c-reactive protein (CRP), and thrombocytosis occurred after IVIG administration, patient then given methylprednisolone pulse dose. Coronary angiography showed giant aneurysm LMCA, proximal left circumflex artery (LCx), proximal RCA, proximal LAD and total occlusion proximal RCA but no ischemia found through electrocardiogram tests. The patient control regularly with aspirin, warfarin, and bisoprolol therapy. The patient does not have any complian. Unresponsive and late intravenous immunoglobulin therapy in KD are significant risk factors for coronary artery lesions.

Keywords: Giant aneurysm, Kawasaki disease, coronary artery aneurysm, unresponsive to immunoglobulin therapy, coronary artery occlusion


INTRODUCTION

Kawasaki disease first time discovered in 1967 by Tomisaku Kawasaki in Japan.1 Kawasaki disease is an self-limiting acute systemic microvasculitis that often occurs in children.2 Coronary artery aneurysm is one of the complications that can be fatal. It is one of the most common acquired heart disease in developing countries, including Indonesia.3 Coronary artery aneurysm is enlargement of coronary arteries that can localized or generalized.4 Coronary aneurysm occurs primarily in the proximal end portion of the blood vessels and the left anterior descending coronary artery (LAD) coronary artery.5 Giant coronary artery aneurysm is aneurysm that has diameter exceed 8 mm.6 Regression or reduced size of an aneurysm that occurs spontaneously is within 1-2 years after onset in 32-50% of cases, but if it may not regress, it will persist and develop into coronary artery occlusion and stenosis, which could trigger an acute myocardial infarction and sudden death.7,8

Nowadays, It is known the efficacy of immunoglobulin therapy (IVIG) in the acute phase can reduce the incidence of coronary artery aneurysms up to 5%.9,10 Administration immunoglobulin within 7 until 10 days of illness with dose immunoglobulin is 2 g/kg single infusion.
Resistant to immunoglobulin occur in approximately 10% of the patient.\(^2\)

Detection of coronary artery complications in the acute phase is done through echocardiography. Echocardiography has high sensitivity and specificity in diagnosing arterial dilatation and proximal thrombus in the coronary arteries, but less reliable for the detection of distal aneurysm and stenosis. The gold standard for evaluating the existence and severity of abnormalities of the coronary arteries is coronary angiography (CAG). By coronary angiography, the anatomy of the coronary arteries can be seen in more detail and it enables us to see artery stenosis or occlusion due to thrombosis.\(^1\) We present a case of giant aneurysm at left main coronary artery (LMCA) and multiple aneurysms with total occlusion at proximal right coronary artery (RCA), after administering single dose IVIG therapy.

**CASE ILLUSTRASION**

An 8.5 years old boy came to pediatric cardiology polyclinic for control after Kawasaki disease. From examination no complaints were perceived. Patients with a history of Kawasaki disease 11 months before. The boy had symptoms fever for almost 10 days, bilateral conjunctival injection, enlargement unilateral cervical lymph node, dry and cracking lips and polymorphous rash at body, hand and feet. Blood count examination revealed trombosit count (PLT) 216000 /µL, CRP 77,3 mg/L, LED I 8 mm, and LED II 120 mm. From thorak imaging, it revealed that the heart dan lung were still in normal limit. ECG examination was normal. Based on echocardiography, it showed cardiac manifestation of acute phase kawasaki with dilatation in both ostium coronary >2 SD which are left main coronary artery (LMCA 3,28 mm of 2 SD 3,6), left artery descending (LAD 2,96 mm of 2 SD 2,8), and right coronary artery (RCA 3,31 mm of 2 SD 2,8 mm), with mild TR, mild MR and decrease left ventricle (LV) systolic function with ejection fraction (EF 44%). Kawasaki disease was confirmed.

The boy got therapy of intravenous gamma globulin 2 gram/kg single dose drip in 12 hours, aspirin 80 mg/kg/day divided in 4 doses and ranitidine at 14th of illness. The boy had recurrent fever three days after intravenous gamma globulin therapy and then given methylprednisolone pulse dose continued with high dose oral prednisone. The serial echocardiography and ECG showed in figure 1-7.

One week later, the patient underwent invasive coronary angiography to evaluate distal segment of coronary artery and to find out if occlusion of artery coronary existed. It revealed giant aneurysm...
LAPSUS

Figure 5  ECG when patient diagnosed with giant aneurysm

Figure 6  Giant aneurysm with dilated LAD, RCA and LMCA

Figure 7  Giant aneurysm at proximal LAD, total occlusion at proximal RCA, and aneurysm at LMCA, proximal LCx, proximal RCA

Figure 8  Echocardiography when coronary angiography at LMCA, proximal LAD, proximal LCx, proximal RCA and total occlusion at proximal RCA.

On 3rd days after coronary angiography, the patient was discharged with aspirin 100 mg a day and warfarin 0,5 mg a day. Parents were refused refered to coronary artery bypass graft surgery (CABG) procedure. The patient checks up to cardiology polyclinic every month regularly with aspirin, warfarin, and bisoprolol therapy and evaluation echocardiography was planned later.

DISCUSSION

According to Diagnostic Guidelines of the Japan Kawasaki Disease Research Committee, the clinical criteria for Kawasaki disease are fever minimum for 5 days along with 4 or more major clinical symptoms such as conjunctival injection, cervical lymphadenopathy, oral mucosa changes, polymorphous rash, and swelling or redness of the extremities. In this case, the patient was a 7 years old boy, had fever for 10 days and 4 mayor clinical symptoms (bilateral conjunctival injection, enlargement unilateral cervical lymph node, dry and cracking lips and polymorphous rash at body, hand and feet) of kawasaki disease. He had diagnosed with Kawasaki disease based on clinical symptoms.

Several underlying risk factors for coronary artery abnormalities including age at diagnosed (<1 year or > 9 years old), male gender, longer duration of fever before diagnosed, lower albumin level, lower hemoglobin level, higher platelet count and nonresponse to initial intravenous immunoglobulin. A response to treatment was defined as the absence of fever within 36 hours after starting the initial IVIG infusion. In this case, patient is a boy, suffered high fever which lasted for 10 days, with history of hypoalbuminemia, mild anemia, trombositosis, and the fever recurent less than 36 hours after therapy of intravenous immunoglobulin.

As much as 85-90% of patients show positive response to initial IVIG therapy and high dose of aspirin, however, IVIG resistance could occur to 10-20% of patients. Patient is considered to experience resistance if they suffer lasting or recurring fever at the minimum 36 hours after given their first IVIG dose. IVIG resistance shows the indication of arteritis process, which has high risks of developing into coronary artery aneurism. The IVIG resistance management is still a controversy, many health center give second dose of IVIG at 2 g/kg/day in 48 hours after the first dose if the fever lasts or recur. Corticosteroid can be considered to be given to patients with IVIG resistance, those with acute symptoms (under 1 year old of age, persistent rise of CRP, liver dysfunction, hypoalbumin, anemia, and shock), or those with peripheral aneurysm. Corticosteroid can be given as methylprednisolone pulse dose 30 mg/kg or as low dose oral prednisone (0.5 to 2 mg/kg/day). In this case, the patient suffered recurrent fever 36 hours after given IVIG. The fever lasted until the 21st day since the onset of disease.
Aside from fever, the patient suffered from pitting edema with hypoalbuminemia (1.5 mg/dL), rising CRP (160.8) and thrombocytosis (PLT 555,000). The patient then given methylprednisolone 30 mg/kg/ day 3 days in a row, then continued with high dose of oral prednisone 2 mg/kg/day every 24 hours. Aspirin are continued to be given.

The main complication of Kawasaki disease is in coronary artery. Coronary artery abnormalities develop in 5–10% of patients with Kawasaki disease. Coronary artery abnormalities are divided into dilatation and aneurysm coronary artery. Coronary artery aneurysms are more common in male gender. Echocardiography is an imaging tool which has high sensitivity and specification in diagnosing dilatation even the proximal coronary artery thrombus. According to the classification by American Heart Association, aneurysm is divided into small size (internal diameter 5 mm), medium (internal diameter 5-8 mm), or giant (internal diameter >8 mm). Common site for coronary aneurysm is the proximal segment and middle right coronary artery (RCA) at 68%, followed by proximal anterior descending (LAD) at 60%, and left circumflex arteries (LCx) at 50%. Coronary aneurysm in the left main stem (LMCA) seldom occurs, only happens to 0.1% of the population. In this case, through echocardiography discovered that the patient suffered from giant aneurysm of LAD, dilated RCA and LMCA, mild MR. The saccular RCA was dilated (prox 7,16 mm; distal 4 mm), dilated LMCA (9-10,07 mm), dilated LAD (9mm).

Coronary angiography shows images of coronary artery anatomy more detailed than echocardiography. Coronary angiography can detect coronary artery stenosis or thrombosis occlusion and the scope of collateral artery development in Kawasaki disease. Coronary angiography is generally recommended 6-12 months after the onset of disease or earlier if there is any clinical indication. In order to get information about more detailed coronary artery segment, stenosis and thrombosis occlusion, therefore the patient must go through coronary angiography. Its revealed giant aneurysm at LMCA, proximal LAD, proximal LCx, proximal RCA and total occlusion at proximal RCA.

Activation of platelet is an important factor in disease acute phase and it lasts during the phase of convalescence and chronic, therefore it is necessary to give anti-platelet agents in the treatment of each disease phase. In order to prevent thrombosis in aneurysm and myocardial infarction, patient with giant aneurysm is given aspirin therapy and anticoagulan low molecular weight heparin or warfarin. The International normalized ratio (INR) is maintained at the rate of 2 to 2.5. In this case, patient with giant aneurysm, aside from given aspirin therapy in low dose, is also combined with warfarin therapy. Evaluation of haal hemostasis is done every month with INR target was 2.

Occlusion is often found in giant and medium aneurysm. One study states that 16% of coronary aneurysm will experience occlusion during follow up, and 78% will have occlusion in 2 years since onset. Coronary artery occlusion caused acute myocardial infarction and sudden deaths. Acute myocardial infarction triggered by sudden coronary occlusion due to thrombosis. The prognosis giant aneurysm without myocardial infarction is good. Otherwise the prognosis is poor if the patients has decreased left ventricular ejection function. In this case, the patient had total occlusion at proximal RCA. The patient doesn't have symptoms leading to myocardial infarction. From the ECG examination no ischemic appearance. From echocardiography the ejection fraction is still normal.

SUMMARY

Intravenous immunoglobulin should be administered in 7-10 days, which are 85-90% of patients show positive response to initial IVIG therapy, however, 10-20% cases may unresponsive to IVIG. Unresponsiveness to IVIG is high risks of developing coronary artery aneurism or giant aneurysm. Giant aneurysm is one of the complications that can be fatal after Kawasaki disease.

REFERENCES