Case Report:
DENGUE FEVER WITH PERIMYOCARDITIS

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ABSTRAK

Perimyocarditis (PM) merupakan salah satu komplikasi demam berdarah dengue (DHF). Komplikasi ini sering tidak terdiagnosis oleh karena klinisi sering terfokus pada dengue syok syndrome (DSS) dengan gambaran klinis yang hampir sama. Dilaporkan lebih dari 70% penderita demam berdarah dengue yang mengalami DSS disertai dengan PM, walaupun PM dapat juga terjadi tanpa DSS. Presentasi klinis PM bervariasi dari gejala klinis ringan sampai terjadi syok kardiogenik. Kelompok virus B Arthoropod borne Virus (Arbovirus) type DEN-2 dan DEN-3 penyebab DHF yang sering menimbulkan PM. Diagnosis PM didasarkan pada keberadaan myocarditis dan tanda-tanda perikarditis. Terjadinya perikarditis merupakan kelanjutan dari myocarditis. Gejala myocarditis berupa sesak, palpitasi, nyeri dada, perubahan ECG, disfungsi ventrikel kiri dan peningkatan penanda jantung (CKMB/troponin) atau terdapat gambaran myokarditis pada MRI. Diagnosis perikarditis akut apabila terdapat minimal dua kriteria dari manifestasi klinis yaitu: nyeri dada, frictional rub pada auskultasi, terdapat perubahan ECG berupa ST elevasi, dan adanya efusi perikard pada gambaran echokardiografi. Pengobatan PM menggunakan NSAID, kortikosteroid bahkan imunosupresan bila diperlukan. ***(FMI 2015;51:118-124)***

Kata kunci: *DHF, DSS, pericarditis, myocarditis*

ABSTRACT

Perimyocarditis (PM) is one of the complications of dengue hemorrhagic fever (DHF). This complication is often not be diagnosed because clinicians often focused on dengue shock syndrome (DSS) with similar clinical picture. It is reported that more than 70% of patients who experienced dengue hemorrhagic fever (DSS) is accompanied by the PM, although the PM can also occur without DSS. The clinical presentation of PM vary from mild clinical symptoms to cardiogenic shock. The virus group of B Arthoropod borne virus (Arbovirus) type DEN-2 and DEN-3 is the cause of DHF that often lead to PM. PM diagnosis was based on the existence of signs of myocarditis and pericarditis. Pericarditis is a continuation of the occurrence of myocarditis. Myocarditis symptoms such as tightness, palpitations, chest pain, ECG changes, left ventricular dysfunction, and increase in cardiac markers (CKMB/troponin) or there is a profile of myocarditis in MRI. Acute pericarditis is diagnosed if there are at least two criteria of the clinical manifestations: chest pain, frictional rub on auscultation, ECG changes such as ST elevation, and the presence of pericardial effusion in the echocardiography. PM treatment is using NSAIDs, corticosteroids, and immunosuppressants if needed. ***(FMI 2015;51:118-124)***

Keywords: *DHF, DSS, pericarditis, myocarditis*

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INTRODUCTION

Dengue hemorrhagic fever (DHF) is still a public health problem in Southeast Asia. In Indonesia until 2010 dengue cases are still found in every provinces. Since 1968, Indonesia had became a country with the highest incidence of dengue fever in South East Asia (WHO Regional Office for South-East Asia Regional Office for South-East Asia 2011, Tim Editorial Jurnal 2010). The disease is caused by a virus group B Arthoropod borne dengue virus (Arbovirus) now known as the genus flavivirus and has four serotypes, the DEN-1, DEN-2, DEN-3, DEN-4. One serotype infections will cause antibodies to serotypes in question and cannot provide protection against other serotypes. The transmission is through *Aedes aegypti* mosquito that bites the patient who is having viremia (WHO Regional Office for South-East Asia 2011, Nagaratnam et al 1973). DBD complications often overlooked are myocarditis and pericarditis. Clinical manifestations vary from asymptomatic to cardiogenic shock due to myocardial cell damage which can result in death. In the field the clinician often simply fixed to dengue shock syndrome when they face DHF patients with shock without thinking about the possibility of perimyocarditis as a cause of the shock (Nagaratnam et al 1973, Lee IK et al 2010). This case report is expected to provide

information to the clinicians on perimyocarditis, which still has fairly high incidence in patients with DHF.

CASE REPORT

Male 39 years presented with fever since five days before being admitted to a hospital. He did not improve with medication for fever. Signs of bleeding were not found. The patient also complained chest pain and shortness of breath. Physical examination revealed blood pressure 70/50 mm Hg, pulse 90 x/min, breathing 28 x/minute, the body temperature of 38^{o}C, head and neck examination revealed no anemia and icterus. Thorax: S1 and S2 single, smooth wet ronchi in basal lung and audible friction rub. Emergency unit laboratory results: hemoglobin 14.2, leukocytes 2.9, HCT 45, platelets 35, SGOT 31, SGPT 42, random blood glucose 122, serum creatinine 1.78, BUN 71. Laboratory tests the following day in ICCU revealed positive troponin, positive Ig-M dengue, and positive Ig-G dengue. Tourniquet test was also positive. Supportive examination included electrocardiogram that revealed almost nonspecific ST-elevation in all leads except the AVR and V1, chest radiographs obtained cardiomegaly while echocardiography obtained minimal pleural effusion.

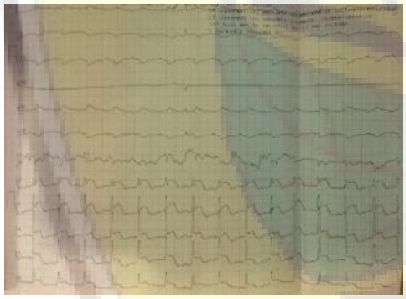


Figure 1. Electrocardiogram result

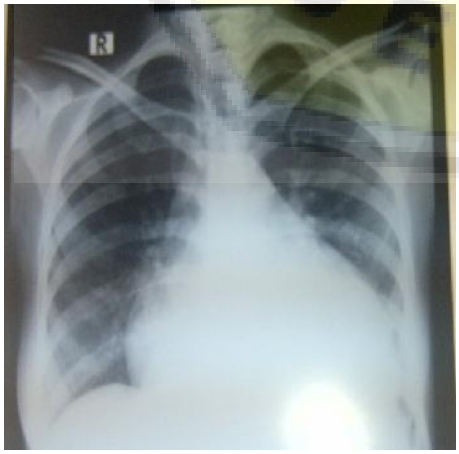
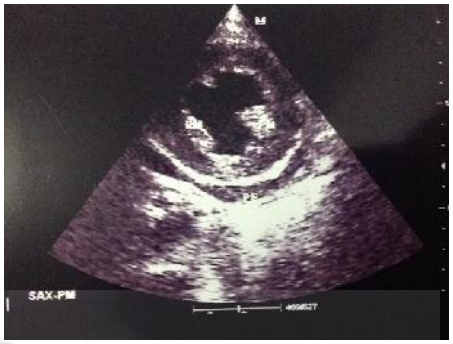


Figure 2. Chest radiograph reveals cardiomegaly



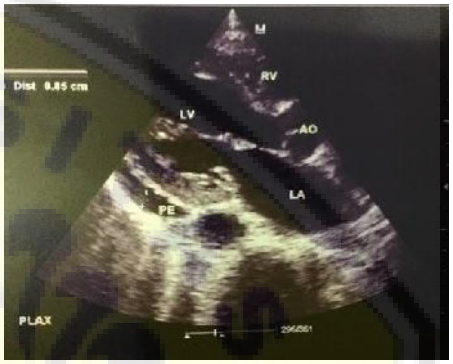


Figure 3 & 4. Echocardiography reveals minimal pleural effusion.

From the data, the patient was diagnosed with acute perimyocarditis and cardiogenic shock with differential diagnosis of dengue shock syndrome. The patient was planned for cardiac MRI examination and endomyocardial biopsy, but because of financial reasons both these examinations were not carried out. Therapies provided were noradrenaline pump to overcome the shock, ibuprofen 3 x 500 mg and prednisone 1 mg/kgbw for 1 month through the outpatient clinic basis as well as supportive medications.

The first day of treatment the patient came in a state of shock. The first suspiction was that the patient had dengue shock syndrome. To improve hemodynamic, he was provided with fluids and inotropics. On the second day, the blood pressure began to improve 100/70 mmHg but the patient's condition was still weak and congested. Echocardiographic examination in ICCU obtained pericardial effusion with an ECG overview showing ST-segment elevation in all leads except for V1 and AVR. Examination of troponin in the ICCU showed increase. Above data confirmed the diagnosis of dengue with complication of perimyocarditis. The therapy was added with ibuprofen 3 x 500 mg for 3 days, followed by prednisone 1 mg/kg bw. On the third day, the general condition of the patient was getting better and on the fourth day the patient was transferred to the ward. On the sixth day echocardiographic examination revealed

no pericardial effusion and ECG returned to normal profile.

DISCUSSION

Manifestations of bleeding in patients with DHF due to antibodies formed in the infection between previous dengue virus with other dengue virus types so that the formed antigen antibody complexes mediating the secretion of vasoactive mediators increases vascular permeability, causing hypovolemia and shock. Dengue virus infects CD4+, and CD8+ T cells and generate cytotoxic factor. The formed cytotoxic factors trigger increased capillary permeability. The infected CD4+, CD8+ T cells will produce IFN-γ, TNF-α, and TNF-β that contribute to the pathogenesis of secondary dengue. Secondary infection with dengue virus of different types will produce high anti-dengue IgG antibody titers (WHO Regional Office for South-East Asia 2011, Gurugama et al 2010).

DBD systemic complications may occur, ranging from shock, systemic hemorrhage, to multiorgan failure. The incidence of cardiac complications in patients with dengue is not anything new or remarkable, but these events are often not diagnosed because most cases are asymptomatic and clinicians often fixed only on the DSS when dealing with DHF shock patient. Seventy percent of 17 patients with DHF/DSS suffered from myocardial hypokinesis of the left ventricle with an average of fraction ejection approximately 40% due to acute myocarditis (WHO Regional Office for South-East Asia 2011). The latest report from Sri Lanka showed that 62.5% of 120 adult patients with DHF had abnormalities in their ECG as a manifestation of perimyocarditis (Lee et al 2010, Ravindral et al 2007). In this case we suspected cardiac complications, such as acute perimyokarditis, with the highest cause is viral infection such as adenovirus, arbovirus, coxsackie, Epstein Barr virus, cytomegalovirus, and hepatitis B virus. This suspicion was supported by clinical data on this patient, which showed perimyocarditis and the cause of the DHF was the virus group of Arbovirus (Freixa 2010, Kindermann et al 2012).

Dengue virus attacks the myocardial through three phases: acute phase, at this phase virus is mediated into myocytes through specific receptors, followed by the activation of NK cells and macrophages and T lymphocytes phase of subacute, and chronic phase. In subacute phase, the virus injured myocytes cells and replicates within the myocytes. Then, myocyte necrosis occurs and causes the activation of the immune system, the T-specific lymphocytes and cytokines (TNF-α, IL-1, and IL-6). Activation of the immune system can lead to molecular mimicry. This molecular mimicry resulting in cytokines and antibody activation so that it produces certain heart proteins that interfere heart contractions. The mechanism of myocarditis on dengue virus or other viruses is the same (Miranda et al 2013). Therefore, during the transition phase we shall be aware of acute and subacute cardiac complications in DHF.

Chronic phase is characterized by the persistence of the autoimmune process and the occurrence of myocardial remodeling and dilated cardiomyopathy (Kindermann et al 2012, Miranda et al 2013). Dengue viruses often reported to cause cardiac complications are viruses DEN-2 and DEN-3. Endocarditis is never reported since dengue immune complexes formed in dengue infection cannot be trapped in the valve chamber (Wiwanitkit 2008). Pericarditis dengue itself is rarely seen or standing alone and usually manifests with acute perimyocarditis (Nagaratnam et al 1973). Dengue infection starts in the myocardium that will spread to the pericardium and cause perimyocarditis (Nagaratnam et al 1973, Wiwanitkit 2008).

Shock that occurs in dengue cases may occur due to dengue virus infection that mediates increased vasoactive mediators and the permeability of capillaries, resulting in hypovolemic shock (Ravindral et al 2007). Literatures wrote that shock in dengue fever with heart complications is cardiogenic syock as a manifestation of complications of acute perimyocarditis virus due to the action of the viruses in cardiac myocytes cells (Kindermann et al 2012). In this case, the author suspected that the occurring shock in the patient was cardiogenic due to perimyocarditis since the patient showed no evidence of bleeding. Whole blood evaluation during treatment showed no hemoglobin decrease during the shock and after receiving fluid therapy. The diagnosis of acute perimyocarditis is established on the presence of acute pericarditis accompanied by myocarditis symptoms (tightness, palpitations, and chest pain), ECG changes (tachycardia, AV block, extra-systoles, or changes in ST segment/T), left ventricular dysfunction, and increased cardiac markers (enzyme CKMB, troponin I or T) or the presence of myocarditis profile in MRI (Freixa 2010). The diagnosis of acute pericarditis is established when there are at least two criteria of clinical manifestations: chest pain, frictional rub on auscultation, ECG changes such as ST elevation, and increased pericardial effusion or novel pericardial effusion on echocardiography profile (Freixa 2010, Imazio & Trinchero 2007). Perimyocarditis definite diagnosis is confirmed by endomyocardial biopsy (Kindermann et al 2012). This case meets the criteria to establish the diagnosis for perimyocarditis. T

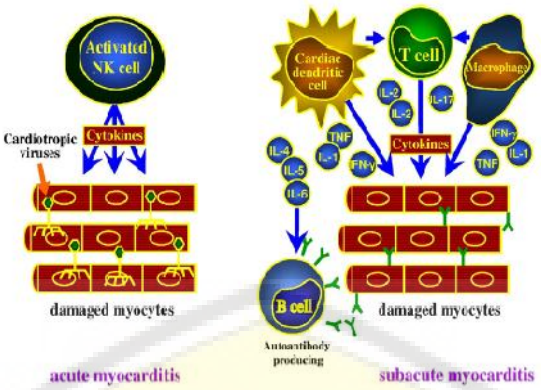


Figure 5. Pathophysiology of viral myocarditis (Kindermann et al 2012)

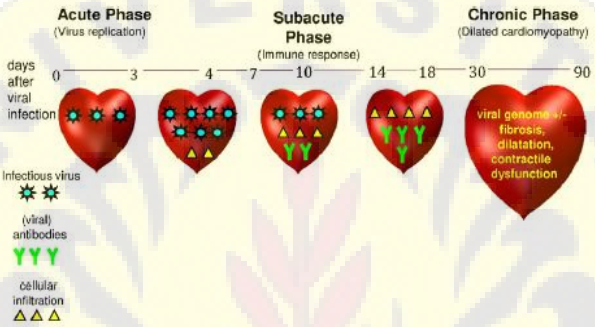


Figure 6. Phases in viral myocarditis (Kindermann et al 2012)

Table 1. Similarity between the literature and the patient's data

	Patients	Literature
Dengue Fever Criteria		
Fever 2-7 days	+	+
Spontaneous bleeding/	+	+
Trombositopenia (< 100.000/pl)	+	+
Hematocrit increase > 20%	+	+
Hypotension or shock in SSD	+	+
Serologic examination with IgM or IgG	+	+
Pericarditis Acute Criteia (minimally two criteria)		
Frictional rub in auscultation	+	+
ECG changes as ST elevation	+	+
New pericardial effusion in echocardiography	+	+
Chest pain	+	+
Perimyocarditis Acute Criteria (minimally 2)		
Accompanied symptoms (dyspnea, palpitation, chest pain)	+	+
EKG (AV block, PVC, ST/T changes)	+	+
CKMB increase or troponin	+	+

Increased troponin or CKMB value is fairly relevant examination related to acute perimyocarditis. Troponin I is more sensitive than CKMB as a marker of myocardial damage. Troponin particularly increases in patients with early onset of acute myocarditis (Freixa 2010, Dennert et al 2008, Schultz et al 2009). Increased troponin due to acute myocardial infarction can be removed in the absence of ECG changes evolution during treatment and no risk factors in this patient. This patient was not performed endomyocardial biopsy and MRI due to financial reason and that the patient lived outside of town where there was no facilities of cardiac MRI and cardiac biopsy.

Perimyokarditis acute therapy through immuno-suppressant drugs such as siklosporine (cyclophospha-mide) or corticosteroids and NSAIDs (Freixa 2010, Miranda et al 2013).

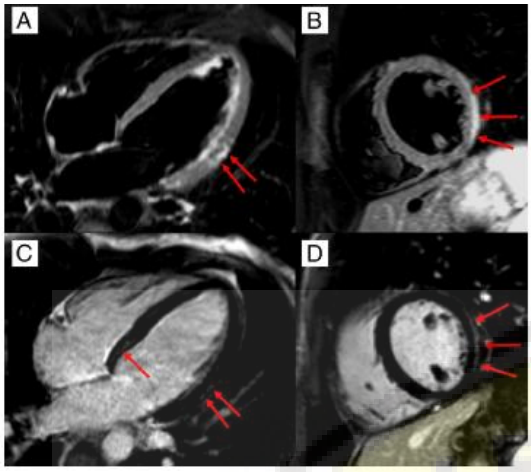


Figure 7. Cardiac MRI of perimyocarditis (Kindermann et al 2012). Section A and C show the cut of the long axis, while parts B and D of the short axis. Focal myocardial edema edema is apparent subepicardium appear in the middle of the left ventricle (arrows).

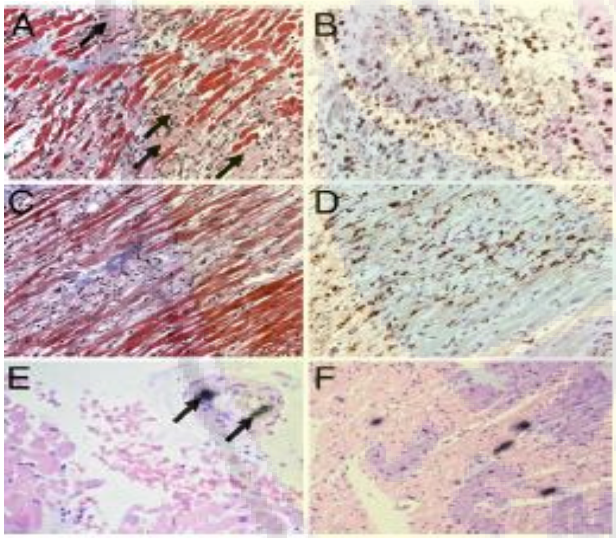


Figure 8. Histoimmunopathology of acute perimyocarditis (Kindermann et al 2012). Section A and B is the profile of acute myocarditis, visible necrotic cell and the cluster of mononuclear cells including CD3 and T cells. Sections C and D is the profile of chronic myocarditis where necrotic myocytes are surrounded with CD68 and macrophages, tissue fibrosis appears in section D (blue color). In section E and F we detect ribonucleic acid of enterovirus in some myocites.

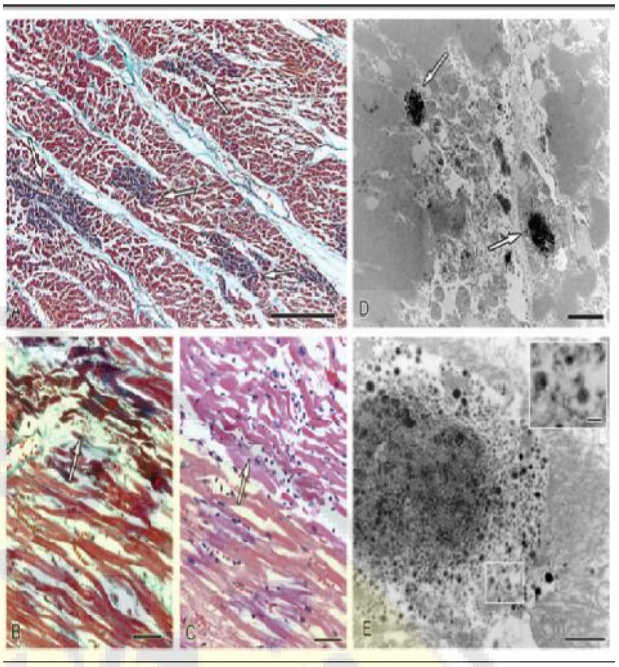


Figure 9. Virus-infected myocites (Miranda et al 2013). Part A shows diffuse myocite necrotic foci, while the B and C necrotic myocites are more apparent. Part C shows mononuclear cells and part D shows dengue-like virus cluster. Part E, using high magnification, dengue-like virus is more evident in myocite.

The research data showed that corticosteroids provide improvement of heart function. First-line therapy in cases of acute perimyocarditis is NSAID using ibuprofen of 300-800 mg/6-8 hours. Alternatively, we use aspirin of 800 mg/6-8 hours. The second choice is colchicine 2 mg/day for two days, lowered to 0.5 mg/12 hours as maintenance. The next option is a class of immunosuppressants, such as cyclosporin or corticosteroids. Recommended corticosteroid is prednisone 1-1.5 mg/kg for 1 month and then lowered slowly and continued with NSAIDs before corticosteroid therapy ends. When starting dose reduction of corticosteroids, colchicine dose of 1 mg/day may be added, which is divided into two doses. Other supportive drugs associated with viral infections can also be given.

The patients in this case received aspilet therapy 3 times 800 mg orally for 2 days, followed with oral prednison 1 mg/kg for 1 month and lowered slowly through the outpatient clinic. The therapy has produced good results as seen in clinical improvement such as improvement in cardiac function parameters as well as increases in blood pressure cannot be found pericard effusion post-treatment.

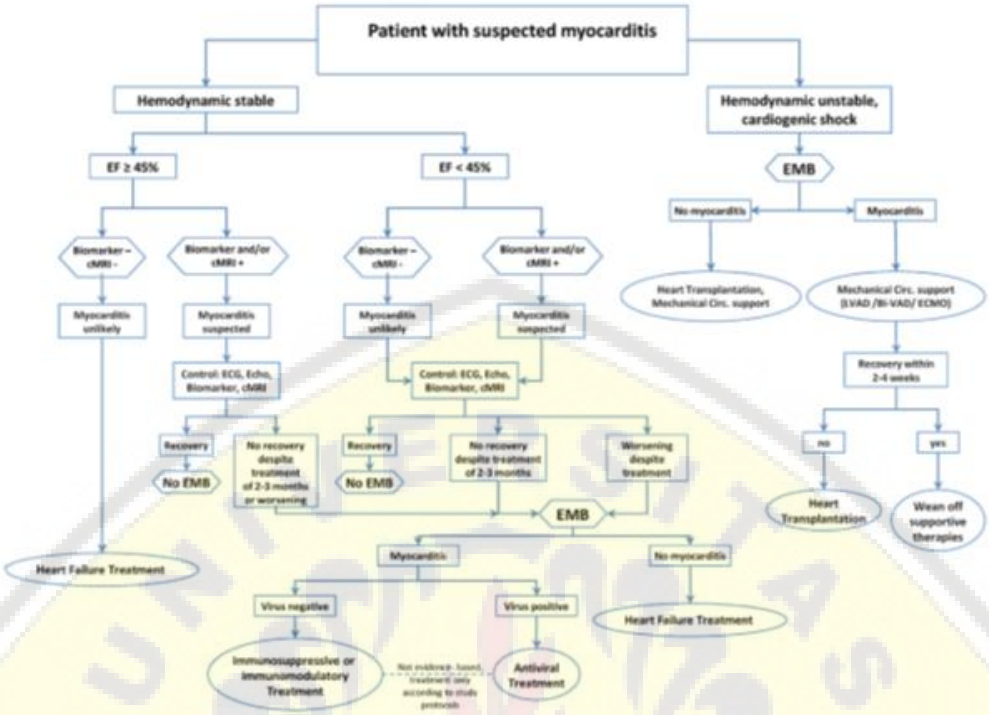


Figure 10. Management flow of patients with suspected viral myocarditis (Kindermann et al 2012)

CONCLUSION

Perimyocarditis complication due to DHF is often overlooked as it is confused by other similar complications. Perimyocarditis often accompanies DHF, increasing the morbidity and mortality risks. Perimyocarditis diagnosis is established based on two pericarditis criteria with accompanying symptoms, ECG changes, increased heart enzyme, or MRI examination. The definitive diagnosis is established by endomyocardial biopsy. The management of DHF cases with acute perimyocarditis is performed simultaneously. The provision of plasma volume, antipiretics, and supportive medications are primarily to overcome DHF symptoms. Acute perimyocarditis itself is managed by providing NSAID and immunosuppressants, with cyclosporin or corticosteroids as the first line.

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