Thrombosis: A Laboratory Diagnosis of Cerebral Sinus Venosus Thrombosis (CSVT) with Cardiac Myxoma

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Abstract

Cerebral sinus venous thrombosis (CSVT) is a venous thromboembolism (VTE) is very rare about 0.5%-3% of all types of stroke, often found in young patients, estimated incidence in adults 3-4‰ and children 7‰, ratio of girls to boys 3:1.[3,4,5,6] The main causes of CSVT differ in developed and developing countries. In preantibiotics, the main cause of CSVT is a septic process. Currently, it is generally due to the process aseptic. According to Bushnell et al. conversion to bleeding is reported to occur in 30-35% patient. Autopsy findings show that 10% of the causes of death are from cerebrovascular disease CSVT.[3,4,5] We report a case of CSVT in a 83-year-old female patient. The patient had a diagnosis of CSVT with cardiac myxoma delivered to the laboratory from emergency room installation on the 28th December 2017, 12.40 WIB for routine hematology examination, PT, APTT, D-dimer, glucose while, SGOT, SGPT, urea, creatinine, electrolytes, calcium and magnesium with clinical evidence of decreased consciousness, convulsions and weakness of the right extremity.

Keywords: *Blood, Cardiac, CSVT, Sinus, Thrombosis.*

A. INTRODUCTION

Thrombosis is formation of an abnormal mass in a creature's circulatory system life comes from the components of blood. The abnormal mass is called a thrombus and if it is detached from the blood vessel wall it is called an embolus (Setiabudy, 2007).

Based on the composition of the thrombus can be divided into 3 types, namely white thrombus usually at present in arteries and composed mainly of platelets, red thrombus found in the vein is composed mainly of fibrin and erythrocytes, and a mixed thrombus is its composition a combination of white thrombus and red thrombus. Composition of a thrombus influenced by the velocity of blood flow in the place where the thrombus is formed. Generally, a thrombus containing lots of platelets forms in areas with poor blood flow rapidly, whereas a thrombus containing lots of erythrocytes and fibrin is formed in area of stasis (Setiabudy, 2007).

In 1845 Virchow first suggested the existence of three main factors that plays a role in the pathophysiology of thrombosis, namely disorders of the blood vessel wall, changes in blood flow and changes in blood coagulation. These three factors are called the triad of Virchow's (Setiabudy, 2007).

Based on the triad of Virchow's, there are three factors that play a role in pathophysiology thrombosis, namely blood vessel wall abnormalities, changes in blood flow and changes in power blood clot. These three factors are interrelated, but the magnitude of the role of each factor are not same. In arterial thrombosis the most important factor is the wall abnormality blood vessels, while in venous thrombosis the most important thing is the presence of stasis and hypercoagulability (Setiabudy, 2007).

According to Setiabudy (2007), the pathophysiology, the risk factors for venous thrombosis are circumstances conditions leading to stasis and hypercoagulability. Risk factors for venous thrombosis include:

1. Immobilization,
2. Operation,
3. Extensive tissue trauma,
4. Violence,
5. Pregnancy,
6. Contraceptive pills,
7. Antithrombin deficiency,
8. Protein C deficiency,
9. S protein deficiency,
10. FXII deficiency,
11. The molecular structure of plasminogen is abnormal,
12. Paroxysmal nocturnal hemoglobinuria,
13. Factor V Leiden/APC resistant,
14. Prothrombin G20210A

Cerebral sinus venous thrombosis (CSVT) is a venous thromboembolism (VTE) is very rare, about 0.5%-3% of all types of stroke, often found in young patients, estimated incidence in adults 3-4% and children 7%, ratio of girls to boys 3:1 [3,4,5,6].

The main causes of CSVT differ in developed and developing countries. In preantibiotics, the main cause of CSVT is a septic process. Currently, it is generally due to the process of aseptic. According to Bushnell et al. conversion to bleeding is reported to occur in 30-35% patient. Autopsy findings show that 10% of the causes of death are from cerebrovascular disease CSVT (Alvis-Miranda et al., 2013; Bushnell & Saposnik, 2014; Basu & Dutta, 2012).

Based on the triad of Virchow's, there are three factors that play a role, namely damage to the blood vessel walls, hypercoagulability and stasis (Setiabudy, 2007; Alvis-Miranda et al., 2013; Basu & Dutta, 2012; Uemura, 2016).

In developed countries, the most frequent risk factors are related to congenital thrombophilia. like factor V Leiden mutation, deficiency of protein C, protein S and

AT III, systemic like vasculitis lupus erymatosus, polyarteritis nodosa especially in younger patients (Alvis-Miranda et al., 2013; Basu & Dutta, 2012; Uemura, 2016).

Infection is the most common cause of cavernous sinus thrombosis and the most important cause lateral sinus thrombosis, hematogenous spread from infection to face, nose, orbits, paranasal sinuses and ears. The causative pathogen is generally Staphylococcus aureus, Streptococcus sp., Gram negative bacteria originating from dental infections, fungi that it usually originates from infection in diabetic patients. Table 1 lists the risk factors related to CSVT (Alvis-Miranda et al., 2013; Basu & Dutta, 2012).

Table 1. Risk factors associated with CSVT

Innate	Got
Homocysteinem	Anti cardiophilin/ anti phospholipid positive
Factor V leiden mutation	Brain tumor
G20210A prothrombin mutation	Head trauma
MTHR Mutation 677TT	Intracranial hypotension, dehydration
AT III deficiency	Extracerebral neoplasia Dural fistula Haematological disorders Nephrotic syndrome Systemic vasculitis CNS infection *Bacterial meningitis *Cerebral malaria Drugs *Cisplatin *Methotrexate Steroids Neurological surgery Lumbar puncture Pregnancy and postpartum

Source: Alvis-Miranda et al. (2013)

Risk factors related to sex, including the use of oral contraceptives (OC), pregnancy, postpartum, and hormone replacement therapy. Age groups that are not related to these sex-related risk factors, namely children and elderly patients.

Clinical manifestations of CSVT very greatly, influencing factors, including location and extent of thrombosis, age, underlying disease and risk factors. According to Bousser et al there are 4 types of clinical manifestation patterns in CSVT (table 2) (Alvis-Miranda et al., 2013; Bushnell & Saposnik, 2014).

Table 2. Pattern of clinical manifestations in CSVT

Type	Characteristics
Focal syndrome	Motor weakness, sensory deficits, aphasia and seizures
Intracranial hypertension	Headache, nausea, vomiting and papilledema
Subacute encephalopathy	Loss of consciousness

Cavernous sinus syndrome	Optalmoplegic pain, chemosis and proptosis

Source: Alvis-Miranda et al. (2013)

According to Bushnell & Saposnik (2014), and Basu & Dutta (2012), the diagnosis of CSVT is based on:

1. Clinical manifestations of stroke without any risk factors for arterial thrombosis,
2. There are risk factors for CSVT,
3. Examination of D-dimer (550 ng/mL), results within normal limits do not rule out presence CSVT, with a sensitivity of 93.9% and a specificity of 89%,
4. To confirm CSVT, imaging examinations are necessary, namely:
   a. CT scan of brain with contrast and coronal section
   b. Brain MRI
   c. MRI angiography
   d. MR venography
   e. Transcranial Doppler (TCD)

   Guidelines for The American Heart Association (AHA) and the European Federation of Neurological the Societies (EFNS) recommend imaging the brain using MRI/MRV, as well as CT/CT venography in the absence of an MRI. One of the strengths of MR is the existence of recent sequences, ie eg T2 increases the detection of isolated cortical vein thrombosis as a hypointense area. The best sequence for detecting sinus thrombosis is T1 and T2 which show hyperintense. The combination of MRI and MRV is gold standard diagnosing CSVT (Pizzi et al., 2016).
5. Establish the cause of CSVT.

Usually, in lateral sinus thrombosis due to an infection in the ear (Basu & Dutta, 2012). The occurrence of intracranial hypertension is caused by obstruction of venous flow and malabsorption of cerebrospinal fluid found in 15-40% of CSVT patients (Bushnell & Saposnik, 2014). Focal neurologic deficits occur due to increased pressure in the venous blood flow blockage resulting in edema, infarction and massive bleeding produce clinical manifestations of focal neurological deficits, such as hemiparesis, aphasia, ataxia, hemianopia, neglect, etc.

Analysis Clinical manifestations of CSVT found in women are headaches 96%, seizures 24%, nausea/vomiting 66%, decreased awareness 48%, focal motor deficits 12%, speech disturbances 24%, whereas in men the clinical manifestations found were headaches 66.7%, nausea/vomiting 11.1%, decreased consciousness 44.4% and 44.4% focal motor deficit (Setiabudy, 2007; Alvis-Miranda et al., 2013).

Supportive and symptomatic treatment, such as antibiotics, anticonvulsants, lowering intracranial pressure, eg Mannitol, Glycerol. Steroid use is not recommended, as it may lead to further hypercoagulability and worsen the prognosis. The main treatment uses anticoagulants with a therapeutic dose or target APTT 2X normal on administration of intravenous Heparin with dose adjusted, treatment with thrombolytics such as urokinase and rTPA gave good results in one study, but heparin was given afterward (Bushnell & Saposnik, 2014).

Prognosis generally good, complete improvement in women with no risk factors (81%) is better than men (71%). Only 5.1% of patients with serious permanent disability, although 70-85% of patients recover completely after 2 months. Recurrence of thrombosis occurs in patients with risk factors for thrombosis or patients with venous thrombosis in the lower extremities, 0% in the first year, up to 12% in 6.5 years later (Alvis-Miranda et al., 2013).

Cardiac myxoma is a benign tumor of the heart, about 50% of cardiac tumors originate from multipotential primary mesenchymal cells (Thyagarajan et al., 2017). Sure, most cases are approximately 90% sporadic or isolated or non-syndromic cardiac myxoma, the prevalence is 0.0017-0.003% and 10% is inherited in an autosomal dominant manner (Carney's complex) or myxoma syndrome (Thyagarajan et al., 2017; Anvari et al., 2009; Malezewski, 2016).

Characteristics of Carney's complex or thesyndrome of myxomas is myxoma (heart or other endocrine organs (cutaneous ormucosal), Schwannoma and skin neoplasms), endocrinopathy (Cushing's syndrome and diagnostic muco cutaneous pigmentation [18,20]. Criteria for Carney's acromegaly) and spotty complex usually when 2 or 3 clinical manifestation findings are found in table 1. Some of the terms often associated with Carney's complex are related to affected/suffered clinical manifestations, such as PPNAD, namely pigmented nodular adrenocortical disease-high cortisol, then LAMB, namely lentigines (flat skinpigmentations), atrial myxomas, blue nevi and NAME, namely nevi, atrial myxoma, myxoid neurofibroma, ephelides (freckles) (Malezewski, 2016).

Table 3. Carney's Complex Diagnostic Criteria

Clinical manifestations
1. Spotty skin pigmentation with a typical distribution (lips, conjunctiva, vaginal and penile mucosa)
2. Myxoma (cutaneous and mucosal)*
3. Cardiac myxoma*
4. Myxomatous breast*
5. Pigmented nodular adrenocortical disease (PPNAD)*
6. Acromegaly associated with a growth hormone-producing adenoma*
7. Large-cell calcifying sertoli cell tumor (LCCSCT)*
8. Thyroid carcinoma* (any age) or multiple, hypoechoic nodules on ultrasound in prepubertal children
9. Psammomatous Melanotic Schwannoma (PMS)*
10. Blue nevus, epitheloid blue nevus (multiple)*
11. Breast ductal adenomas (multiple)*
12. Osteochondromyxoma*
Additional Criteria
Regarding first degree relative
PRKAR1A gene mutation

Note: *with histopathological confirmation

Two-thirds of Carney's complex patients were found to be familial, the rest were de novo mutations in the PRKAR1A gene on chromosome 17q (Maleszewski et al., 2017; Negi et al., 2013). Shown in Figure 1:

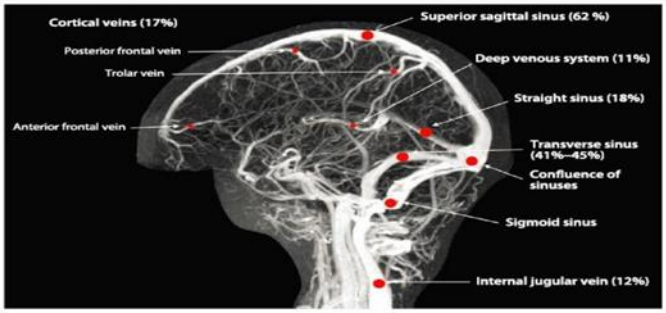

Figure 1. Anatomy of the Cerebral Veins and Venous Sinuses

Source: Bushnell & Saposnik, (2014).

Mutations in the form of missense, nonsense, frameshift and splice site variants as well as relatively large deletions have been reported by Horvarth et al. The presence of pathogenic variants, although relatively small, only one splice site will be changing protein expression.

The PRKA1A gene is a tumor suppressor gene, encoding a subunit which regulates IK protein kinase A, is the main mediator of cyclic AMP (cAMP) signals in mammals. PRKAR1A aberrant with one-third found mutations in the PRKAR1A gene, according to Li et al. 70% related to DNA infection caused by HSV-1 and or HSV-2 (Anvari et al., 2009; Malezewski, 2016).

Then, Abnormal PRKAR1A gene expression cannot differentiate syndromic from myxoma non syndromic (Anvari et al., 2009; Greenwood, 1968).

Figure 2. Location of the PRKAR1A gene on Chromosome 17q

Source: https://ghr.nlm.nih.gov/gene

The PRKA1A gene encodes the formation of a type 1 alpha regulatory subunit of protein kinase A. Pada Figure 2 describes the mechanism of action of protein kinase A consisting of four protein subunits, two called regulatory subunits (control whether this enzyme is turned on or off). Two of other is the catalytically active subunit. Protein kinase A remains turned off when the regulatory subunit attached to another subunit of the enzyme. To activate protein kinase A, the regulatory subunit must detach from the enzyme. This enzyme promotes cell growth and division (proliferation). More than 117 mutations in the PRKAR1A gene have been found to cause Carney's complex. Most of these mutations result in abnormal type 1 alpha regulatory subunits quickly broken down (degraded) by cells. The lack of this regulatory subunit leads to protein kinases A becomes more active, which causes uncontrolled cell proliferation. Signs and symptoms of Carney's complex are related to unregulated cells in many parts of body (Maleszewski et al., 2017).

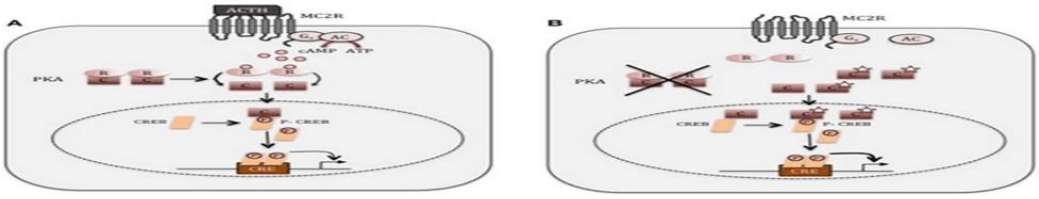

Figure 3. Mechanism of action of normal and abnormal protein kinase A
Source: https://ghr.nlm.nih.gov/genePRKAR1A

Sporadic cardiac myxomas are more common in women with an average age of 60 years. where as in Carney's complex it is generally found at a young age with an average age of 20 years old [15,17,20].

Figure 4. Illustration of the Location of Cardiac Myxoma
Source: Thyagarajan et al. (2017).

For the initial diagnosis of choice is echocardiography, which can assess the size, location, attachment, movement and distinguish myxoma from other tumors [15,19]. In figure 4, showing an atrial myxoma on echocardiography [14] Other options as adjunct to cardiac MRI [15].

Macroscopically, myxoma anatomy is stalked and smooth; the consistency is soft, villied, and spongy brittle on the surface, sometimes there is a calcification, called lithomyxoma [15,19]. Most of the myxoma surfaces are coated with thrombus.15,19 Weighing between 15-180 grams with a size of 2-6 cm.15 Smooth myxomas are large in size so they often cause obstruction, whereas myxomas are villous and brittle often cause embolism [15,17]. Atrial myxomas are the cause very rare stroke, <1% of all causes of ischemic stroke. Stroke is the initial clinical manifestation in 50% of cases of atrial myxoma and 75% of cases in left atrial myxoma.

Atrial myxoma results in a triad of complications, namely the presence of obstruction related to the size and location of the tumor, followed by pulmonary and systemic embolism and constitutional symptoms [16,20,21].

From Goswami et al's study, symptoms were found in patients diagnosed with left atrial myxoma constitutional symptoms such as breathlessness in 80% of patients, other palpitations, fainting, leg edema and pain chest, about 30% cause secondary emboli [15]. In patients diagnosed with myxoma right atrial obstruction is found resulting in intracardiac flow disturbances, pulmonary and systemic embolism and constitutional symptoms [15]. In right atrial myxoma, if the location is close to the tricuspid valve there are symptoms of right heart failure, such as leg edema, congestion liver, tightness and ascites [15].

Tumors on the right or left side of the heart can cause obstruction to blood flow

lead to congestive heart failure, venous thrombosis and pulmonary embolism [20]. Symptoms can occur at any time but are most often found with a change in body position. Pedunculated myxoma can have a "wrecking ball effect", resulting in stasis. It can also be a nidus for infection to cause infective endocarditis

The embolus consists of tumor fragments (tumor cells), fibrin clots or both. Embolization of left atrial myxoma generally goes to the central nervous system and arteries in the retina, can also on the lower extremities, generally iliac and femoropopliteal, internal organs such as the spleen, adrenal glands, kidneys and abdominal aorta [15]. Symptoms include shortness of breath, hemiplegia, fainting, blindness, arrhythmias and chest pain. Symptoms of Raynaud's phenomenon, skin pigmentation, abdominal pain, diarrhea and other peripheral embolism symptoms [15]. From the results of studies due to cardiac myxoma around 10% coronary embolization, 20-35% with neurological complications and 9-22% embolic stroke [15].

Left atrial myxoma always be a differential diagnosis in cases of multiple cerebral infarction [15]. Embolus can cause inflammation of the blood vessel walls and penetrates into the blood vessel walls resulting in subintimal proliferation resulting in a weakness of the integrity of the vessel wall blood and the formation of an aneurysm.

Constitutional symptoms include fatigue, loss of appetite, fever, joint pain and weight loss, symptoms that arise due to the release of pro-inflammatory cytokines interleukin 6 (IL-6), causes an increase in the number of leukocytes, gamma globulin, erythrocyte sedimentation rate and C-reactive protein (CRP) in laboratory tests cultured showed increased specific mRNA for IL-6, IL-6 facilitates cell proliferation and differentiation and release of acute phase proteins during inflammation [15].

Cardiovascular symptoms were found in 67% of patients, ie. heart failure, non-exercise chest pain, palpitations, syncope and myocardial infarction. role of ILs, namely mimic infective endocarditis. The role of BFGF, namely remodeling of the cardiac matrix. Role VEGF, namely angiogenesis and formation of coronary collaterals improves blood supply to the injured myocardium [16,18,21].

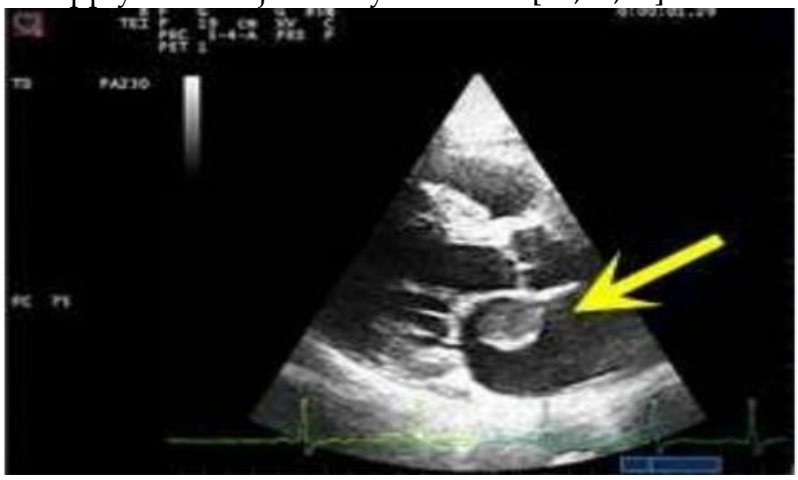

Figure 5. Atrial myxoma on Echocardiograph

Sources: Jain et al. (2015).

On auscultation of the heart with the help of a stethoscope you will hear a "tumor plopped" (sound that caused by tumor movement), a murmur similar to mitral

stenosis during diastole, this sound changes when the patient's position changes.[19] EKG shows atrial fibrillation.

Two theories of histogenesis in myxoma. First, according to Krikler, et al stated that myxoma expresses Schwann cells and neuroendocrine differentiation markers, such as proteins gene product (PGP), neuron specific enolase (NSE) and synaptophysin, for suspected myxoma originate from the endocardial sensory nerve tissue. Second, according to Pucci, et al stated that cells Myxoma stroma is a reactive neuropeptide and endothelial marker, as it is suspected myxoma is derived from multipotent mesenchymal cells suitable for neural differentiation and endothelial. In addition, glands were detected in some myxomas overlapping immunoreactive patterns between endocrine cells from the normal human gut supports the entrapped embryonic foregut hypothesis [24].

Microscopic picture found stellate fusiform and polygonal cells shapes within the mucopolysaccharide stroma are shown in Figure 5. Immunohistochemical results were strongly positive for vimentin, moderately positive against epithelial membrane antigen (EMA), CD34, carcinoembryonic antigen (CEA) and mildly positive for cytokeratin 7 and negative for desmin, cytokeratin and smooth muscle antigen (SMA) [18]. Sometimes fibrocytes, smooth muscle cells, lymphocytes and plasmocytesare seen in the matrix. Approximately 10% of cases found calcification.15,18 Calretinin is a specific marker to distinguish myxoma from mural myxoid thrombus.[15]

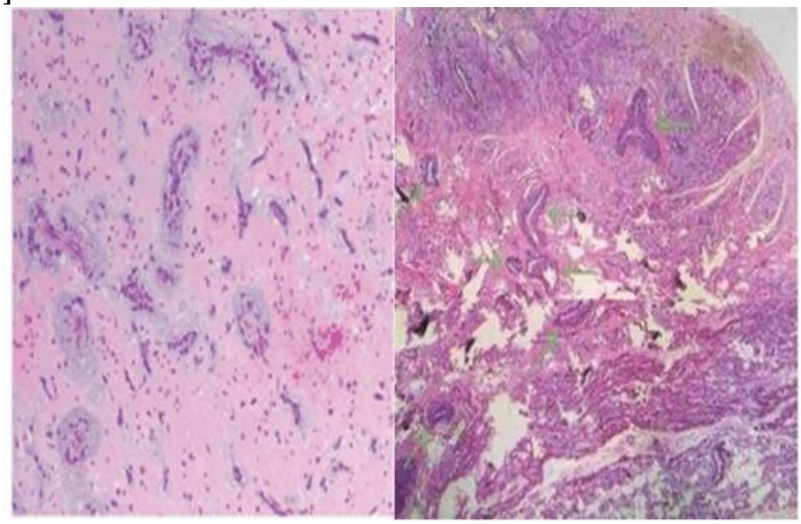

Figure 6. Atrial myxoma stained with H&E
Source: Yuan et al. (2017)

Molecular genetic examination to detect heterozygous germline pathogenic PRKAR1A with sequence analysis, if not found then proceed to detect gene-targeted deletion/ duplication analysis to detect intragenic deletion/duplication by PCR technique quantitative, long-range PCR, MLPA, gene targetes microarray to detect single-exon deletions/duplications in table 2. [28,30]

The treatment of choice for cardiac myxoma is definitive therapy, namely gene therapy, direct enzyme replacement (there are no clinical trials for this disease). Supportive therapy, ie surgical removal of the tumor [15,16,19]. Some patients also

need to replace the valve the mitral valve, can be performed at the same time of operation. Treatment of consequent symptoms myxoma should be done, such as administering diuretics in pulmonary congestion, if functional left ventricle in good systolic there is no indication for beta blockers, spironolactone, ACE inhibitors. [15]

Therapy for prevention of primary clinical manifestations (cardiac dysfunction, stroke, embolism others that cause sudden death) and secondary (can prevent abnormalities metabolic), including anti-arrhythmic, anti-coagulant and anti-platelet administration to prevent ischemic stroke.

B. RESULT AND DISCUSSION

A 83-year-old female patient, had a diagnosis of CSVT with cardiac myxoma delivered to the laboratory from emergency room installation on the 28th December 2017, 12.40 WIB for routine hematology examination, PT, APTT, D-dimer, glucose while, SGOT, SGPT, urea, creatinine, electrolytes, calcium and magnesium with clinical evidence of decreased consciousness, convulsions and weakness of the right extremity.

The patient was admitted to the emergency room installation of hospital with a diagnosis of cerebral sinus venous thrombosis (CSVT) with cardiac myxoma.

Table 1. Laboratory examination results on Dec 28th 2017, 12.40 WIB

Checking type	Flags	Results	Unit	Reference
Routine hematology				
Hemoglobin (Hb)	*	**15.0**	g/dL	12-14
Hematocrit	*	**44**	%	37-43
Erythrocyte		5.1	10^6/uLfL	4.0-5.0
MCV MCH		87	pg	82-92
MCHC		29	g/dL	27-31
RDW-CV	*	34	%	31-36
Leukocytes		14.3	10^3/uL	12.2-15.0
Platelets		**10.3**	10^3/uL	5.0-10
HEMOSTASIS				150-400
PT		11.3	Second	11.3-13.8
APTT	*	**24.4**		27.5-40.3 (Mean: 33.9)
D-dimer	*	**2230**	ng/mL	*Cut off* <500 *to exclude*

Checking type	Flags	Results	Unit	Reference value
Electrolyte	*			
Sodium		138	mmol/L	136 – 146
Potassium		4.3	mmol/L	3.5 - 5.0
chloride		**115**	mmol/L	98 – 106
Calcium		9,1	mg/dL	8.8-10.2
Magnesium		2,1	mg/dL	1.9-2.5

The patient 84 years old female patient with clinical description of loss of consciousness, seizures and right limb weakness. After obtaining additional data from laboratory results dated December 28, 2017 at the RSPON Laboratory, it was concluded that dehydration or hemoconcentration due to decreased consciousness and impaired swallowing which is characterized by increase in Hb and Ht. Repeated hematology results showed Hb and Ht results were within limits normal. Increased

blood chloride levels while normal sodium may occur in hypoalbuminemia or due to retention of chloride as a compensatory mechanism of the body Albumin levels at the time of admission to the hospital were not carried out, but after being suggested from the data. In addition, hypoalbuminemia was found but tended to be normal because of this patient. If the patient is classified as elderly or the patient is likely to have received albumin therapy. Hyperchloride may be caused as a compensatory mechanism of the body against acid balance. As a base, chloride competes with bicarbonate in binding sodium, so it plays a role in acid base balance. If the bicarbonate level decreases, chloride will increase as compensation. [29] Increased Hb levels and high hematocrit values cause Hyperviscosity affects cerebral blood flow. Mild leukocytosis is probably due to inflammation; about 35% of embolization occurs in all cases of left atrial myxoma due to myxoma having villi consistency and brittle.

Embolus can cause inflammation of the vessel wall and embolization of myxoma the left atrial is generally headed to the central nervous system, consistent with high hs-CRP results and low albumin, albumin is an acute phase protein which is negative, the results of repeated hematology are still mild leukocytosis, possibly because the myxoma has not been removed due to urinary tract infection in the presence of urinalysis results obtained leukocyturia and bacteriuria, suggest a urine culture. Decreased albumin levels due to impaired function liver synthesis can be ruled out with PT results that are still within normal limits, besides that decreased albumin due to protein loss can also be ruled out because the urinalysis results are not found proteinuria. APTT results are shortened with PT within normal limits, there may be an increase in factor VIII, which is one of the acute phase proteins. 2 After get additional data, normal APTT results are obtained, maybe already receiving anticoagulant therapy, namely heparin.

The increase in D-dimer is probably due to activation of the blood clotting system. Activation This clotting system causes increased formation of thrombin from prothrombin with releases prothrombin fragments 1 and 2 (F1,2). thrombin will be bound by antithrombin so that thrombin-antithrombin complex (TAT) is formed. The thrombin that is formed will also change fibrinogen to fibrin monomers by releasing fibrinopeptide A, fibrinopeptide B (FPA and FPB), fibrin monomer will undergo polymerization to form fibrin polymer which then under the influence of FXIII cross-linking will occur so that cross-linked is formed fibrin, then plasmin will break down cross-linked fibrin to produce D-dimer. Therefore, the parameter that can be used as a marker of coagulation activation is D-dimer to support or rule out the diagnosis of venous thrombosis [2,4,5]. To rule out the presence of risk factors for arterial thrombosis several tests are carried out, namely platelet aggregation, blood glucose, lipid profile. In this patient, the number was obtained Platelets within normal limits and normoaggregation on platelet aggregation examination. Rate fasting glucose and HbA1C increased in the prediabetic category with glucose 2 hours post prandial within normal limits, based on PERKENI 2015 screening test Oral Glucose Tolerance (OGTT) was performed to establish the diagnosis of Type Diabetes Mellitus 2 (DMT2) and pre diabetes in the high-risk group who do not show classic symptoms DM to

find out whether there is impaired fasting glucose tolerance or glucose tolerance disturbed. Examination of the lipid profile found dyslipidemia, namely increased levels High triglycerides and LDL cholesterol and decreased HDL cholesterol are risk factors. The greater the occurrence of arterial thrombosis, it is still possible for a stroke to occur, therefore further treatment for dyslipidemia must be carried out.

Based on the results of brain MRI and MRV on November 8 on 2017 which is standard gold for the diagnosis of CSVT obtained images of thrombus in the superior sagittal sinus and sinus transverse right with venous infarction with foci of bleeding in the lobe left fronto temporo parietal, right parietal. these radiological results confirmed the diagnosis of CSVT in these patients [4,5,11].

To find the most frequent risk factors for CSVT associated with congenital thrombophilia, such as factor V Leiden homozygous mutation, deficiency of protein C, protein S and AT III, vasculitis such as systemic lupus erythematosus, polyarteritis nodosa especially in younger patients, where as the onset of CSVT in this patient was at the age of 83 years. Use of oral contraceptives (OC), pregnancy, childbirth, and hormone replacement therapy are risk factors associated with gender, except for children and elderly patients, this patient even if it is a woman, but elderly patients. [3,5,10]

The risk factors underlying the occurrence of CSVT in these patients are probably due to the patient 83 years old, there is immobilization and myxoma in the left atrial based on the results Echocardiography on November 23 2017 which can cause flow obstruction blood, causing venous thrombosis. Based on the triad of Virchow's there are three factors that play a role, namely damage to the blood vessel wall, hypercoagulability and stasis. In the pathophysiology of thrombosis, the most important thing in venous thrombosis is the presence of stasis and hypercoagulability. In left atrial myxoma, all three can occur. On myxoma can stasis occurs due to the "wrecking ball effect" of the myxoma mass [37]. Cultured myxoma cells showed increased specific mRNA for IL-6, IL-6 facilitates proliferation and cell differentiation and release of acute phase proteins during inflammation, this condition gives rise to hypercoagulability. In left atrial myxoma there is damage to the blood vessel wall due to about 35% of embolization occurs in all cases of left atrial myxoma due to consistency villous and fragile myxoma. Embolus can cause inflammation of the vessel wall blood and penetrate the vessel wall resulting in subintimal proliferation cause weakness of the integrity of the vessel wall and the formation of aneurysms, embolization of left atrial myxoma generally leads to the central nervous system [38].

Results of blood gas analysis (AGD) showed an increase in pH and a decrease in pCO2, with HCO3 within normal limits there may be respiratory alkalosis due to alveolar hyperventilation associated with seizures, loss of consciousness and CSVT. The results of blood gas analysis (ABG) can provide valuable information about a patient's respiratory and metabolic status. In this case, the ABG showed an increase in pH and a decrease in pCO2, with HCO3 within normal limits. These findings suggest respiratory alkalosis, which is often caused by alveolar hyperventilation. This type of hyperventilation can occur due to various reasons such as seizures, loss of

consciousness, or CSVT. Respiratory alkalosis is characterized by a decrease in pCO2 and an increase in pH due to hyperventilation [35]. This imbalance can cause symptoms such as lightheadedness, dizziness, and tingling sensations [36]. However, in some cases, respiratory alkalosis may not present with any symptoms, and the condition may resolve on its own. It is important to determine the underlying cause of respiratory alkalosis to ensure appropriate management of the patient's condition. In the case of CSVT, prompt diagnosis and treatment are essential to prevent potentially life-threatening complications. From physical examination got a respiratory rate of 18X/minute (within normal limits) there is a possibility of alkalosis metabolism associated with compensatory hypoventilation. To determine whether if the respiratory alkalosis is pure or mixed, then the calculation is carried out based on the amount of compensation, before doing a calculation whether AGD results are feasible or no, namely:

1. Practically using the formula po2 + pCO2 ÿ140 mmHg, we get a pO2 of 94 mmHg added pCO2 27 = 121 mmHg (ÿ140 mmHg), AGD results can be trusted.
2. By comparing the supposed H ions of the pH conversion (any increase in pH of 0.1 from pH 7, the level of H ions should be 100X0.8 and so on with H ions from the tool based on calculation of 24X(pCO2/HCO3), if the difference is < 10% then the ABG results can be used by clinicians. pH 7.49 is equivalent to pH 7.5, so H ions should be 100X0.8X0.8X0.8X0.8X0.8 got 32.76. The H ion from the 24X device (pCO2 27 mmHg/HCO3 21 mmol/L) was 30.86. based on these results, the H ion delta is (32.76-30.86)/32.76 X 100% obtained 5.8% (< 10%), ABG results can be used by clinicians. Next, determine whether the resultsAGD is pure or mixed.

Respiratory alkalosis pH 7.49 (ÿ), pCO2 27 (ÿ), pure or mixed? Decrease in pCO2 = 10 mmHg ÿ decrease in HCO3 = 4 mmol/L HCO3 reduction should be = 13 X 0.4 = 5.2 mmHg (HCO3 should be 18.8 mmol/L). The decrease in HCO3 that occurs = 3 mmHg (HCO3 that occurs 21), meaning that it is mixed with metabolic alkalosis.

The most common clinical manifestations of CSVT occur in nearly 90% of patients and are found in 96% of women are headaches due to local processes on the walls of cerebral veins and sinuses dural there are many nerve endings that are sensitive to pain and intracranial hypertension, however aphasic patient so cannot be assessed. Cerebral venous sinus thrombosis (CSVT) is a rare but potentially serious condition that affects the veins in the brain. The most common clinical manifestations of CSVT occur in almost 90% of patients, with headaches being the most frequent symptom. In women, this symptom is found in 96% of cases (Masuhr 2004). The headaches are caused by local processes on the walls of cerebral veins and sinuses dural, where many nerve endings are sensitive to pain and intracranial hypertension. However, in some cases, patients may experience other symptoms such as seizures, changes in mental status, or focal neurological deficits. Unfortunately, some patients may not be able to communicate their symptoms due to aphasia, making assessment challenging for healthcare professionals. It is crucial to identify the symptoms of CSVT

promptly, as early diagnosis and treatment can help prevent potentially life-threatening complications .Other clinical manifestations encountered in the patient this is hemiparese, aphasia, seizures and decreased consciousness that occurs because of the increase pressure of blood flow in the blocked vein because it must maintain perfusion so that resulting in edema, infarction and bleeding that cause clinical manifestations focal neurological deficit. In patients found generalized seizures, the occurrence of seizures in CSVT This is caused by edema and neuronal damage which also causes an increase intracranial pressure causes loss of consciousness, with good treatment, temporary loss of consciousness. Presence of edema, infarction and bleeding is supported with the results of MRI and MRV of the brain on November 8th 2017, MRI obtained an overview thrombus in the superior sagittal sinus and right transverse sinus accompanied by venous infarction with foci of bleeding in the left frontotemporoparietal lobe, right parietal and on the 30th November 2017, from MRI obtained compared to CT on November 8th 2017, visible subacute hematoma on the left temporal with extensive perifocal edema and prolonged bleeding in right and left parietal lobe sulci, acute hematoma is not visible, obtained from MRV sinus thrombosis in the middle 1/3 of the superior sagittal sinus, the left transverse sinus is no longer visible, possibly a normal variant.

C. CONCLUSION

A case has been presented, a woman, 84 years old, with Cerebral Sinus Venosus Thrombosis in cardiac myxoma. The diagnosis of CSVT was made based on radiological results, namely MRI and MRV of the brain CSVT was obtained with a picture of edema, infarction and bleeding which caused a deficit focal neurological disorder such as hemiparesis, seizures, aphasia and loss of consciousness. Results Echocardiography revealed left atrial myxoma and laboratory results were obtained increased D-dimer which is a marker of coagulation activation, supported by other laboratory results, namely the presence of dehydration, inflammation, accompanied respiratory alkalosis metabolic alkalosis. There are no known risk factors for arterial thrombosis in the form of diabetes mellitus excluded from fasting blood glucose and HbA1C results suggest prediabetes an oral glucose tolerance test was performed, the lipid profile results obtained dyslipidemia. Causes of CSVT in this patient is myxoma in the left atrial which often causes complications in the form of: Obstruction of blood flow causes stasis and underlying hypercoagulability CSVT.

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REFERENCES

1. Setiabudy, R. D. (2007). *Pathophysiology of thrombosis*. Jakarta: FKUI Publishing House.
2. Sutanto, I., & Setiabudy, R. D. (2007). *Relationship between laboratory abnormalities and thrombosis*. Jakarta: Balai FKUI Publisher.
3. Alvis-Miranda, H. H., Castellar-Leones, S. M., Alcala-Cerra, G., & Moscote-Salazar, L. R. (2013). Cerebral sinus venous thrombosis. *Journal of neurosciences in rural practice*, *4*(04), 427-438.
4. Bushnell, C., & Saposnik, G. (2014). Evaluation and management of cerebral venous thrombosis. *CONTINUUM: Lifelong Learning in Neurology*, *20*(2), 335-351.
5. Basu, D., & Dutta, K. (2012). *Cerebral venous sinus thrombosis*. Kolkota.
6. Salottolo, K., Wagner, J., Frei, D. F., Loy, D., Bellon, R. J., McCarthy, K., ... & Bar-Or, D. (2017). Epidemiology, endovascular treatment, and prognosis of cerebral venous thrombosis: US center study of 152 patients. *Journal of the American Heart Association*, *6*(6), e005480.
7. Kılıç, T., & Akakın, A. (2008). Anatomy of cerebral veins and sinuses. *Handbook on cerebral venous thrombosis*, *23*, 4-15.
8. Silvis, S. M., Middeldorp, S., Zuurbier, S. M., Cannegieter, S. C., & Coutinho, J. M. (2016, September). Risk factors for cerebral venous thrombosis. In *Seminars in thrombosis and hemostasis* (Vol. 42, No. 06, pp. 622-631). Thieme Medical Publishers.
9. Uemura, M., Tsukamoto, Y., Akaiwa, Y., Watanabe, M., Tazawa, A., Kasahara, S., ... & Nishizawa, M. (2016). Cerebral venous sinus thrombosis due to oral contraceptive use: postmortem 3 T-MRI and autopsy findings. *Human Pathology: Case Reports*, *6*, 32-36.
10. Chen, H. M., Chen, C. C. C., Tsai, F. Y., Shy, C. G., Wu, C. H., Chen, W. S., & Hung, H. C. (2008). Cerebral sinovenous thrombosis: neuroimaging diagnosis and clinical management. *Interventional Neuroradiology*, *14*(2_suppl), 35-40.
11. Pizzi, M. A., Alejos, D. A., Siegel, J. L., Kim, B. Y., Miller, D. A., & Freeman, W. D. (2016). Cerebral venous thrombosis associated with intracranial hemorrhage and timing of anticoagulation after hemicraniectomy. *Journal of Stroke and Cerebrovascular Diseases*, *25*(9), 2312-2316.
12. Verhagen, M. J., van Es, A. C., Lycklama à Nijeholt, G. J., Jellema, K., Coutinho, J., & Van Den Wijngaard, I. R. (2017). Successful mechanical thrombectomy in a comatose patient with cerebral venous sinus thrombosis: a case report. *Interventional Neuroradiology*, *23*(4), 437-440.
13. Jain, S., Maleszewski, J. J., Stephenson, C. R., & Klarich, K. W. (2015). Current diagnosis and management of cardiac myxomas. *Expert Review of Cardiovascular Therapy*, *13*(4), 369-375.
14. Thyagarajan, B., Kumar, M. P., Patel, S., & Agrawal, A. (2017). Extracardiac manifestations of atrial myxomas. *Journal of the Saudi Heart Association*, *29*(1), 37-43.
15. Di Vito, A., Mignogna, C., & Donato, G. (2015). The mysterious pathways of

cardiac myxomas: a review of histogenesis, pathogenesis and pathology. *Histopathology*, *66*(3), 321-332.
16. Anvari, M. S., Boroumand, M. A., Karimi, A., Abbasi, K., Ahmadi, H., Marzban, M., ... & Abbasi, S. H. (2009). Histopathologic and clinical characterization of atrial myxoma: a review of 19 cases. *Laboratory Medicine*, *40*(10), 596-599.
17. Yuan, S. M., Yan, S. L., & Wu, N. (2017). Unusual aspects of cardiac myxoma. *Anatolian Journal of Cardiology*, *17*(3), 241.
18. Greenwood, W. F. (1968). Profile of atrial myxoma. *The American Journal of Cardiology*, *21*(3), 367-375.
19. Kontogiorgi, M., Kalodimou, V. E., Samanidis, G., Vartela, V., Tasouli, A., Ghiatas, A., ... & Michalis, A. (2013). Recurrent cardiac myxoma in a 25 year old male: a DNA study. *World Journal of Surgical Oncology*, *11*, 1-5.
20. Malezewski, J. J. (2016). Cardiac myxoma pathology: Definition, epidemiology, etiology. Retrieved from https://emedicine.medscape.com/article/1612513-overview
21. PRKAR1A gene. *Genetic Home Reference*. Retrieved from https://ghr.nlm.nih.gov/genePRKAR1A
22. Maleszewski, J. J., Anavekar, N. S., Moynihan, T. J., & Klarich, K. W. (2017). Pathology, imaging, and treatment of cardiac tumours. *Nature Reviews Cardiology*, *14*(9), 536-549.
23. Novendstern, S. L., Silliman, S. L., & Booth, R. P. (2001). Cerebrovascular complications of atrial myxoma. *Hospital physician*, *37*(8), 39-48.
24. Negi, R. C., Chauhan, V., Sharma, B., Bhardwaj, R., & Thakur, S. (2013). Atrial myxoma: a rare cause of ischemic stroke. *J Assoc Physicians India*, *61*(4), 280-2.
25. Côté, I., Sinclair, J., Woulfe, J., Glikstein, R., & Veinot, J. (2015). Cerebral metastasis presenting after complete primary resection of atrial myxoma: case report. *Canadian Journal of Neurological Sciences*, *42*(6), 457-460.
26. Chong, J. Y., Vraniak, P., Etienne, M., Sherman, D., & Elkind, M. S. (2005). Intravenous thrombolytic treatment of acute ischemic stroke associated with left atrial myxoma: a case report. *Journal of Stroke and Cerebrovascular Diseases*, *14*(1), 39-41.
27. Stratakis, C. A., & Raygada, M. (2010). *Carney complex*. American Society of Clinical Oncology.
28. Laksana, E. (2006). *SIRS, Sepsis, Acid-Base Balance, Shock and Fluid Therapy. Semarang: Anesthesia and Intensive Therapy Section of Dr. Kariadi Hospital*. (Faculty of Medicine Diponegoro University).
29. Please RA CELL. (2018). *General Lecture Material for Sub-Specialist Doctor Education Participants Clinical Pathology*.
30. Soelistijo, S. A., Novida, H., Rudijanto, A., Soewondo, P., Suastika, K., & Manaf, A. (2015). *Consensus on Management and Prevention of Type 2 Diabetes Mellitus in Indonesia*. Jakarta: PB PERKENI.
31. Immanuel, S. (2017). *Interactive Case Study of Blood Gas Analysis*. Jakarta: Education Ongoing Clinical Pathology.

32. Moenadjat, Y., Madjid, A., Siregar, P., Wibisono, L. K., & Loho, T. (2017). *Gangguan Keseimbangan Air-Elektrolit dan Asam-Basa.* Jakarta: BPFKUI.
33. Masuhr, F., Mehraein, S., & Einhäupl, K. (2004). Cerebral venous and sinus thrombosis. *Journal of neurology*, *251*, 11-23.
34. Drummond, W. H., Gregory, G. A., Heymann, M. A., & Phibbs, R. A. (1981). The independent effects of hyperventilation, tolazoline, and dopamine on infants with persistent pulmonary hypertension. *The Journal of pediatrics*, *98*(4), 603-611.
35. Karatas, M. (2008). Central vertigo and dizziness: epidemiology, differential diagnosis, and common causes. *The neurologist*, *14*(6), 355-364.
36. Das, D., Acharya, D., Das, T., & Pramanik, S. (2021). Left atrial myxoma swinging like a ball valve thrombus:"The wrecking ball effect". *Indian Journal of Case Reports*, 207-210.
37. Power, S., Matouk, C., Casaubon, L. K., Silver, F. L., Krings, T., Mikulis, D. J., & Mandell, D. M. (2014). Vessel wall magnetic resonance imaging in acute ischemic stroke: effects of embolism and mechanical thrombectomy on the arterial wall. *Stroke*, *45*(8), 2330-2334.