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Unexpected Infective Endocarditis in Corrected Congenital Heart Disease: A Case Report

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Abstract

Objective: To describe patients with corrected Congenital Heart Disease (CHD) who experienced Infective Endocarditis (IE).

Methods: Two cases of IE were observed in 2019. The first case involved a 36-year-old woman with previous percutaneous transcatheter perimembranous ventricular septal defect (VSD) closure four months before admission. Echocardiography showed vegetation at noncoronary cusps of the aortic valve. Patient received antibiotics for six weeks and underwent surgery for evacuation of vegetation and device, along with VSD closure with a cardiovascular patch (Gore-tex). The second case involved a 43-year-old woman with a history of surgical closure in secundum atrial septal defect (ASD) by pericardial patch two months before admission. Echocardiography showed vegetation at the tricuspid valve. Patient received antibiotics for four weeks and planned for surgery to evacuate vegetation.

Results: IE is one of the major complications in CHD, whether uncorrected, treated, or corrected. The risk of IE increased with an invasive procedure. Post closure IE is rare. Poor dental hygiene and immunocompromised also increased patient's risk to be exposed to IE as shown in the first patient who had dental caries and the second patient who was on methylprednisolone for post-surgical pericardial effusion treatment.

Conclusion: The risk of IE increases with invasive procedures in CHD patients. Although the incidence of IE is quite rare, its possibility should become of a serious concern among physicians.

Keywords: Atrial septal defect, closure, infective endocarditis, ventricular septal defect

Introduction

Congenital Heart Disease (CHD) is the most common underlying heart condition in Indonesia in patient with Infective Endocarditis (IE). Increased survival in children with CHD and the possible use of channels and prosthesis in corrective surgery contributes to an increase in the incidence of IE even though the patient has taken prophylactic antibiotics in IE. However, CHD related IE mortality rates had decreased substantially to 10% due to improvements in IE diagnoses, antimicrobial treatment, cardiac surgery, and intervention therapy. Given the prognosis, morbidity, and expensive of IE management, IE prophylaxis has long been recommended in an effort to minimize the onset of IE.[1,2]

CHD patient have a high risk of IE in their lifetime. One complication of IE remains a major concern in patient with CHD, whether uncorrected, treated, or corrected. The prevalence of endocarditis in an adult with CHD is 11 per 100,000 people per year higher than the general population that is 1.5-6 per 100,000 people per year. Mortality IE based on contemporary grown-up congenital heart disease (GUCH) still 16% and 1-year mortality

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is 19%. Adults with repaired or palliated pulmonary atresia and corrected congenital transposition of the great arteries (TGA) have the highest incidence of IE with total cases 5.8 and 2.3 per 1000 patient-years. Patient with pulmonary stenosis (PS) or atrial septal defect (ASD) had a very low-risk incidence of IE, even in the adults with repaired or still patent arterial duct (PDA) IE non exists.[2,5] Until now, very rarely IE reported in corrected CHD patients. In this case report, we discuss IE in patient with corrected CHD and what possible risk factors may underlie the occurrence of this condition.

Case Illustration
First Case

First case, a 36 year-old Asian woman, a teacher, came to our emergency department with chief complaint weak left limb three days before hospitalization with lips deviation and slurred speech. She didn't complaint severe headache and projectile vomit. There was a history of dyspnea on the effort since childhood.

There was no history of fever before. She complained of painful in legs two months before being hospitalized and resolved with pain medication. The patient complained that there are reddish spots on the palms and soles of the feet 1 month before admission, she also complained of a lump in the tips of the fingers that felt painful one month before being hospitalized. The patient has never experienced reddish lines on the nails. The patient never experiences redness in the eyes. Her complaints of reddening urination without pain which is accompanied by pain when urination is denied. Patient did not complain about a decrease in consciousness. There were cavities that have only been known in the past two months before being hospitalized, but the patient did not go to the doctor. The patient was known as a patient with congenital heart disease since childhood. Previously, she underwent corrected VSD with Amplatzer duct occluder (ADO) 4 months before hospitalization.

In our emergency room, the patient looks moderately ill, fully alert. The blood pressure was 80/50 mmHg, 75 x/minutes of resting heart rate, 20 x/minutes of respiratory rates, and normal temperature 36,7°C. In physical examination showed jugular vein pressure normal. The thoracic examination showed there is no cardiomegaly, and there is no additional heart sound. There was pansystolic murmur with grade 3/6 in linea left sternalis border with Carvallo sign negative, and pansystolic murmur with grade 3/6 in apex referred to the axilla. Other physical examinations were unremarkable. In neurology examination showed positive light reflex in both eyes; there was no Roth spot's, eyeball movements were normal. There was a history of the parenthesis of central nerve VII and left nerve, XII. In motoric examination were found 5 in the right upper and right lower extremity and in the left upper and left lower extremity the motoric were 0. The physiologic reflex score was +2/+2 and pathologic reflex negative.

The laboratory examination showed

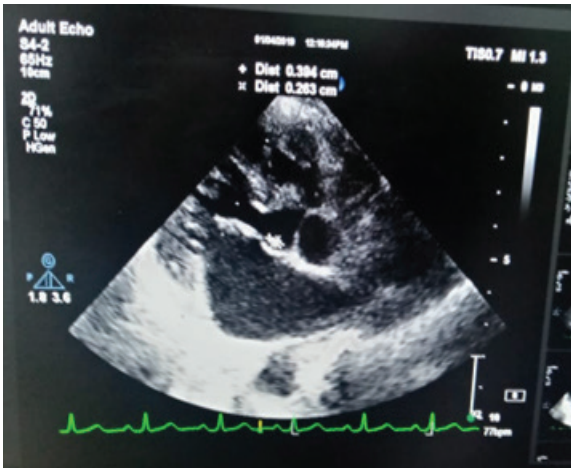

Fig. 1 Echocardiography Showed Vegetation at NCC of the Aorta

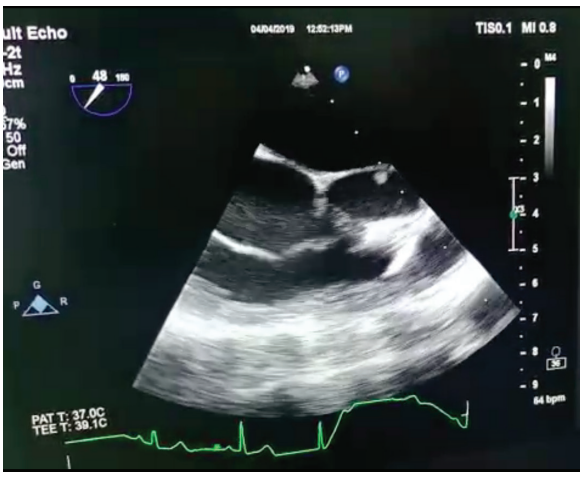

Fig. 2 Transesophageal Echocardiography Showed Multiple Vegetation Attach of the Tip of Aortic Valves

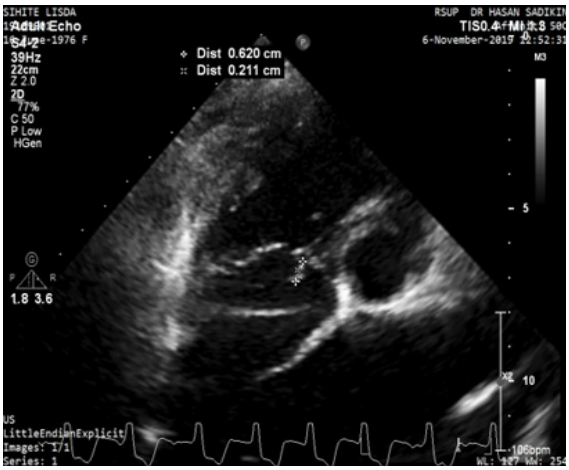

Fig. 3 Echocardiography Showed Vegetation at Tricuspid Valve

Fig. 4 Echocardiography Showed Vegetation Size was Increased

anaemia and other examination within normal limits. Electrocardiography, chest X-Ray, and Other examination within normal limits.

The patient was diagnosed on the emergency department with stroke infarct dd stroke haemorrhage, congenital heart disease VSD post transcatheter closure, *Possible Infective endocarditis. (Duke Criteria: 3 Minor criteria: Predisposing heart Condition (VSD) Osler node, Janeway lesion).* The patient was given antibiotic empiric with adjusted dose ceftriaxone 1x2 g iv dan gentamicin 3mg/kg/48 hour iv, aspilet 1x81 mg PO, paracetamol 3x 500 mg PO.

Blood culture was taken three times with a time interval between first examinations and last examination 1 hour. Results of culture showed *Enterococcus sp* which sensitive to all antibiotics except tetracycline.

Patient undergoing Echocardiography (Fig.1) examination on March 1, 2019, showed VSD perimembranous (PM) s/p device closure with suspect additional VSD PM Left to Right shunt, Moderate PS due to protruding device, Vegetation at NCC of Aorta.

Patient undergoing transesophageal echocardiography (TEE) (Fig.2) examination on March 4, 2019, showed VSD PM s/p closure, residual shunt (-); Moderate PS due to protruding part of the device (right ventricle (RV) part); small, mobile, multiple vegetation attach of the tip of aortic valves; Mild AR, eccentric jet due to mal-cooptation of aortic valves.

The patient then diagnosed with Definite Infective Endocarditis, VSD perimembranous with complication suspected of cardioembolic stroke infarction (Duke Criteria: 1 major criterion: Echocardiography positive for IE (vegetation), 3 Minor criteria: Predisposing heart Condition (VSD) Osler node, Janeway lesion), suspect additional VSD perimembranous.

The patient was given antibiotic treatment Vancomycin 3x500 mg iv for four weeks. During the treatment, there were no complications. After two weeks of therapy, the patient was taken blood culture two times with negative culture results, and antibiotic therapy continued until six weeks. After 17 days of treatment, the patient has re-evaluated echocardiography and found that vegetation disappeared. The patient then scheduled for surgery for evacuation of vegetation; the device removes and VSD closure. The patient underwent surgery on the 30th day of treatment, and an intra-operative finding was found: dislocated aplazter partially, Supracristal or Doubly Committed (SADC) position VSD, closure of VSD with Gore-tex, vegetation (-).

Second Case

Second case, a 43-year old Batak woman, a house wife, came to our emergency department with palpitations. There was no history of fever before. She never experienced pain in legs, reddish spots on the palms and soles of the feet, a lump in the tips of the fingers that feels painful, reddish lines on the nails, redness in the eyes, reddening of urination without pain or decrease in consciousness. The patient was known as a patient with congenital

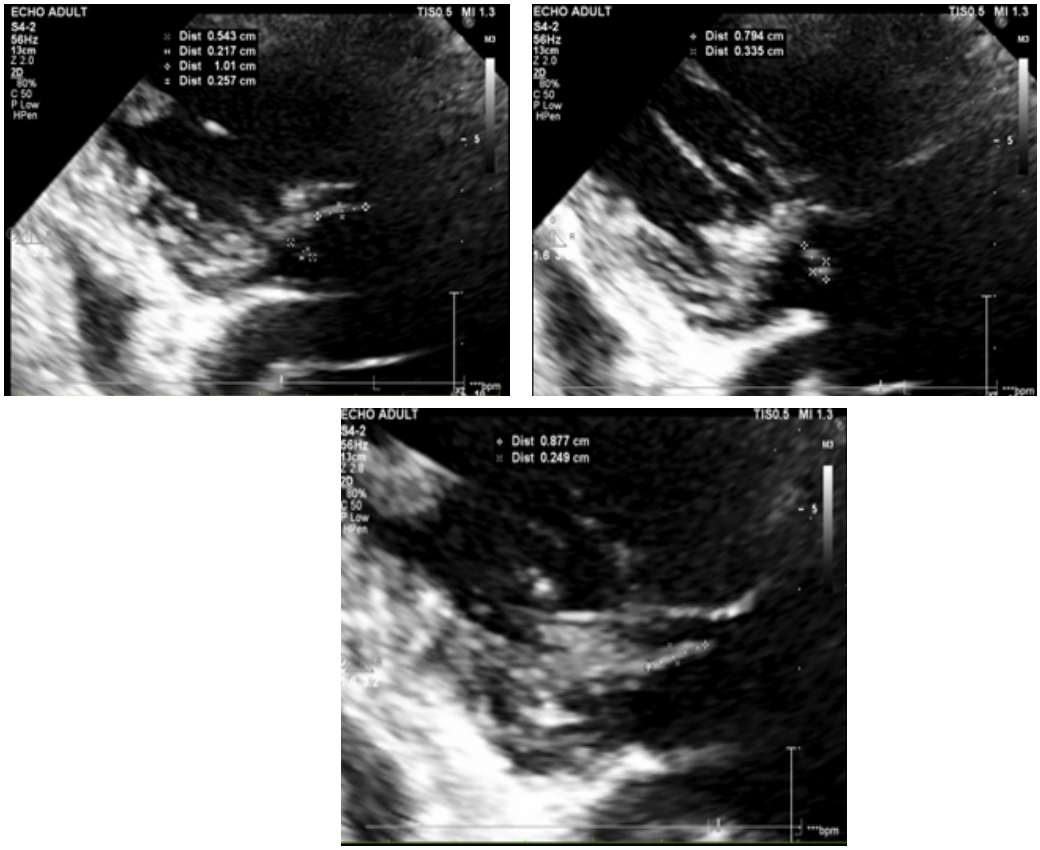

Fig. 5 Echocardiography Showed Multiple Vegetation with Various Size

heart disease. Previously, she already had corrected ASD with a pericardial patch (Gore-tex) 2 months before hospitalization. She also had a pericardial window because of severe pericardial effusion one months before admission, and she took corticosteroid 24 mg per day since one months before admission.

In physical examination, the patient looks moderately ill, fully alert. The blood pressure was 110/70 mmHg, 68 x/minutes irregularly irregular of resting heart rate, pulse was 60 beats per minutes irregularly, unequal, 20 x/minutes of respiratory rates, and normal temperature 36,8°C. In physical examination showed jugular vein pressure normal. The thoracic examination showed there are cardiomegaly and variable of heart sounds. There was pansystolic murmur with grade 3/6 in linea left sternalis border with Carvallo sign positive. Other physical examinations were unremarkable. In neurology examination showed positive light reflex in both eyes; there was no Roth spot's, eyeball movements were normal.

The laboratory examination showed anaemia and other examination within normal limits. Chest X-Ray showed cardiomegaly with the sign of pulmonary hypertension. On electrocardiography showed atrial fibrillation with right axis deviation and right ventricle hypertrophy.

Patient were taken blood culture three times with a time interval between first examinations and last examination 1 hour. Results of culture showed *Acinetobacter sp* which sensitive to all antibiotics except co-trimoxazole.

She underwent TEE (Fig.3) one day after admission, with the results ASD s/p surgical closure, multiple residual shunts, vegetation at tricuspid valve with size (2x6 mm).

The patient was diagnosed with ASD post-surgical closure with a residual shunt, AF NVR, Possible Infective endocarditis. (Duke Criteria: 1 Major criterion: echocardiogram showed vegetation, 1 Minor criterion: Predisposing heart Condition (ASD)). The patient was given antibiotic empiric with adjusted dose Ampicillin Sulbactam 4x3 gr iv and Gentamycin 1x160 mg iv.

The patient was given antibiotic treatment Ampicillin Sulbactam 4x3 gr iv and Gentamycin

1x160 mg iv for four weeks. During the treatment, there were no complications. After two weeks of therapy, the patient was taken blood culture two times with negative culture results, and antibiotic therapy continued until six weeks. After 22 days of treatment, the patient has re-evaluated echocardiography (Fig.4) and found vegetation increases in size became 3x3 mm. After 34 days of treatment, the patient has re-evaluated echocardiography (Fig.5) and found multiple vegetation with various size from 3.9x9.4 mm until 7x3 mm.

In 28 days of treatment, she got urticaria in her body, and she was found suspect allergic from ampicillin and gentamycin, so the antibiotic was replaced with ceftriaxone 2x2 gr iv in 28 days of treatment. The patient then scheduled for surgery for evacuation of vegetation, double valve replacement and ASD repair.

Discussion

Bacteremia following cardiac catheterization is rare. In a prospective study from Banai, etc., they evaluated 960 patient undergoing catheterization, only 0.4% of patient had positive blood cultures that significantly associated with cardiac catheterization. In the literature, there were 8 cases of IE after catheterization. From the 8 cases, there were found four patient with a history of valve disease and IE occurred after catheterization. Signs and symptoms of catheterization are obtained from day one until one week after the procedure.[3,6-9]

Risk factor for IE is patient with prosthetic cardiac valves, IV drug users, patient with mitral valve prolapse (MVP) or non-rheumatic heart disease (CHD, bicuspid aortic valves), rheumatic heart disease. The risk of IE increases in patient who undergo invasive procedures. Patient with old age, alcoholics, sufferers of chronic inflammatory bowel disease, poor dental hygiene, repeated dialysis, diabetes mellitus, and patient with immunosuppressants are at risk to be exposed from IE.[5,10]

Patient with a moderate risk of developing IE include patient with PDA, bicuspid aortic valve, and coarctation of the aorta, rheumatic heart disease (RHD) or hypertrophic obstructive cardiomyopathy (HCOM). Adults with CHD (GUCH), including groups with low-risk factors.[3,11]

Patient with a high risk of developing IE include patient who have prosthetic heart valves, a history of previous endocarditis, cyanotic CHD, surgically constructed systemic pulmonary shunts or conduit. Patient with prosthetic valves have 5-10 times the risk compared with native valves.[3,11]

IE related to post-closure is a rare case, but there are several case reports. There is one case report from Minnesota with one 66-year-old male with a large ASD that has been catheterized with a 32-mm ASD Amplazter occlude 30 months before the incident. A case report from India also discusses the same thing. In the first case, the treatment was done by surgery, and the patient received IV antibiotic Vancomycin for six weeks while the second patient was given Daptomycin IV for six weeks. From these two patient, significant clinical signs and outpatient were obtained after six weeks. There is one case report of IE on VSD after closure reported by Schuerman in 2005 in a 22-month-old baby girl. She is experiencing a fever one month after the closure that lasted for one month and did not respond by giving antibiotics.[12-15]

In the first case, we found several risk factors for IE namely VSD that has high risk developing of IE, and patient had undergone the invasive procedure and this increase the risk of IE. She also had cavities which is one of a risk factor for IE. Maintaining good oral hygiene and infection control can decrease the incidence of IE. It should be emphasised to patients that maintaining optimal oral health and hygiene and regular dentist visits may reduce the incidence of bacteraemia from brushing teeth, chewing food and daily activities, and thus are particularly important in reducing the risk of IE. In the second case, we consider the risk factor of IE that patient had immunocompromised state because she took corticosteroid for a long time beside she already had CHD.[15,16]

Patient with a high risk of IE should be given prophylaxis before medical treatment. Prophylactic antibiotics only needed if the patient undergoes the invasive procedure. In action in the field of cardio, prophylactic antibiotics can be given to patient who will undergo prosthetic valve implantation or pacemaker installation. Prophylactic antibiotics must be considered in patient who will undergo dental procedures. At-risk procedures involve manipulation of the gingival or periapical region of the teeth or perforation of the oral mucosa (including scaling and root canal procedures). Antibiotic prophylaxis should only be considered for patient at highest risk for endocarditis.[17]

Prophylactic antibiotics must be started

as soon as possible before the action starts and stops after 48 hours post-procedure. The recommended prophylactic antibiotic dose in patient with high risk are amoxicillin or ampicillin 2 g oral or intravenously. If the patient has an allergy to penicillin or ampicillin, 600 mg of oral or intravenous clindamycin can be given.[16]

Management of IE should be started promptly. In ESC 2015 about IE we can give empirical treatment in patient whose microorganisms have not yet been identified. Once the pathogen is identified, the antibiotic treatment must be adapted to its antimicrobial susceptibility pattern.[17]

In the first case, the patient has been given ceftriaxone 1 x 2 g iv and gentamicin 3 mg/kg / 48 hours iv, and in the second case, the patient has given Ampicillin Sulbactam 4x3 gr iv and Gentamycin 1x160 mg iv. As we know in 2015 European Society of Cardiology (ESC) guidelines about IE, in patient with unknown types of bacteria can be given gentamicin 3 mg/kg/hour iv. In the guideline mentioned, gentamicin administration can be given with vancomycin, but the patient did not get vancomycin but get ceftriaxone at the emergency room due to unavailability of drugs. Patient get vancomycin 3x500 mg iv when entering the ward.

After the results of the culture came out, we found the bacteria that causes IE in these patient was *Enterococcus spp*. Based on the 2015 ESC guidelines on IE, there are three choices of IE antibiotic therapy regimens caused by Enterococcus spp. i.e. Amoxicillin 4 x 200 mg / kg / day iv plus gentamicin 1x 3 mg / kg / day intravenous (IV) or intramuscular (IM) for 4-6 weeks or can be given ampicillin 4 x 200 mg / kg / day iv plus ceftriaxone 2x4 gr / day iv for 6 weeks or Vancomycin 2x 30 mg / kg / day plus Gentamicin 1 x 3 mg / kg / day given for 6 weeks.

Valve surgery is fundamental in the standard of care of selected IE patient. Surgical intervention can be a lifesaving procedure in complicated, critically ill endocarditis patient. Heart failure, uncontrolled and persistent infection despite optimal antibiotic therapy and recurrent emboli are the major indications for valve surgery in IE population. [17-18]

In the first case, the patient had a complication that is acute stroke. The timing valve surgery in IE patient with stroke remains controversial. Stroke is an independent risk factor for postoperative mortality in IE patient. One clinical quandary is whether early valve surgery can be safely performed within seven days after a stroke or if it is better to postpone surgery for at least one week. No randomized trials have addressed this conundrum. Investigations have suggested a better outcome for IE patient with ischemic stroke who undergo early cardiac surgery. Ruttmann *et al*. analyzed 65 patient who underwent cardiac surgery after cardioembolic (embolic) stroke (median time, four days; range, 0–38 days). Surgery in this time frame was not associated with worse patient outcomes. [18]

In the second case, the patient had locally uncontrolled infection marked by enlarged vegetation size and multiple vegetation in 22 days of treatment. Uncontrolled infection is most frequently related to a perivalvular extension or "difficult-to-treat" organism. Unless severe co-morbidity exists, the presence of locally uncontrolled infection is an indication for early surgery in patient with IE.[17]

In this case report, there were two women with CHD post corrected and experienced IE with a different risk factor. From the first case, the risk factor was cavities and didn't go to the dentist; meanwhile, in the second case, the risk factor was immunocompromised because she took methylprednisolone for treatment pericardial effusion. Although the incidence is rare, the possibility of IE must be a concern for a physician, especially for those who have other clinical condition like poor dental hygiene and immunocompromised.

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Differential Diagnosis of Fever of Unknown Origin in Drug Reaction with Eosinophilia and Systemic Symptom (DRESS)

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Abstract

Objective: To describe an unusual case of drug reaction with eosinophilia and systemic symptoms presenting as fever of unknown origin (FUO) and the diagnostic hurdles that come with the presence of differential diagnosis of FUO, which is tuberculous lymphadenitis.

Methods: A 34-year-old female with a chief complaint of fever that has lasted for 3 weeks accompanied with jaundice and skin rashes for 2 weeks was admitted with an indication of FUO. She had a history of carbamazepine consumption for trigerminal neuralgia 2 months prior. Cervical lymphadenopathy was palpable bilaterally and hepatomegaly, elevated liver enzyme, as well as hyperbilirubinemia were observed. After excluding differentials for many causes of prolonged fever, patient was treated for Drug Reaction with Eosinophilia and Systemic Symptom (DRESS) and was given intravenous steroid injections. Fine needle aspiration biopsy was performed for her cervical lymphadenopathy.

Results: Biopsy presented a mix of sialadenitis and tuberculous lymphadenopathy. Clinical improvement was observed on the second day after steroid administration. Patient was discharged on the seventh day after steroid administration.

Conclusion: FUO is one of the possible manifestations of DRESS; however, thorough investigation still needed to be done considering the possibility of more than one entity of disease that can cause FUO in patients, such as tuberculous lymphadenopathy seen in this case.

Keywords: Case report, DRESS, drug reaction, fever of unknown origin, treatment

Introduction

In some cases, fever can continue indefinitely, thus called as a fever of unknown origin (FUO). Before etiologic cause is decided, administration of empiric therapy is not recommended although in selected cases administration of corticosteroid and broad-spectrum antibiotics is allowed. In drug reaction with eosinophilia and systemic symptom (DRESS), fever is one of the possible symptoms that can manifest. Reports on FUO related to DRESS is scarce. Here, this study present a case of FUO as a manifestation of DRESS in the presence of tuberculous lymphadenopathy which discovered much later. This study will unfold its clinical picture, disease history, workup, and treatment.

Cases

A 34-year-old came female with a chief complaint of fever that lasted for 3 weeks before admission to the hospital. The patient experienced continuous fever, higher in the evening, gets better after consuming antipyretic but return after a few hours. There is no apparent symptom of infection such as

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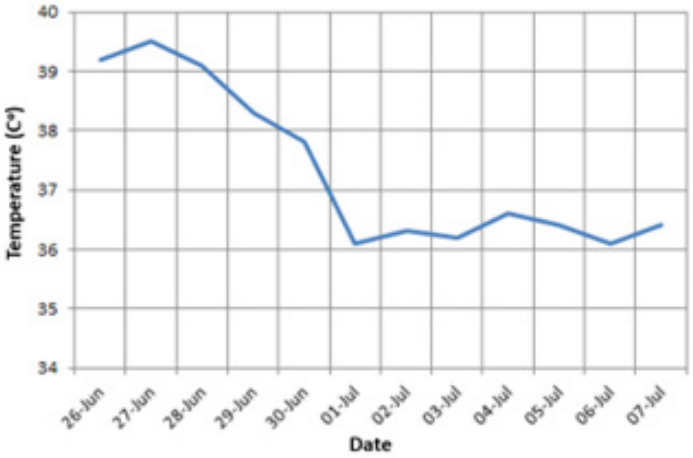

Fig. 1 Temperature Curve

cough, runny nose, dyspnea, earache, and dysuria. This complaint was accompanied by nausea, vomiting, and stomachache. Patient had a history of drug consumption in the last 2 months, for her trigerminal neuralgia that was diagnosed by her neurologist and was treated with carbamazepine tablet 2x500 mg a day. There is no history of close contact with tuberculosis patient nor history of tuberculosis medication. There is no history of prolonged cough, night sweat, although there is a loss of 2 kilograms of bodyweight for 1 month. Patient was married and have 2 children, there's no history of miscarriage, hair loss, previous skin rash or photosensitivity. Four days after the onset of her fever, she seeks treatment to a private hospital, and was told that her skin condition was caused by carbamazepine. However, after 2 weeks of hospital stay, her fever persists, and she was referred to the hospital.

The patient was compos mentis and axilla measured temperature was 39°C. She was icteric, having multiple non-tender cervical lymph node enlargement, hepatomegaly, generalized confluent skin lesion with irregular border consisted of erythematous macule and desquamation that cover her entire skin.

On laboratory examination this study found increased liver aspartate transferase (AST) 248 U/L, alanine transferase (ALT) 492 U/L, total bilirubin 5.739 mg/dL, conjugated bilirubin 5.040 mg/dL, unconjugated bilirubin 0.699 mg/dL, with negative anti-HCV, anti-HIV, and HbsAg. On blood smear microscopy, this study found atypical lymphocyte. Two ziehl-neelsen-stained sputum samples result was negative. Chest x-ray interpretation was bilateral bronchopneumonia. Abdominal ultrasound from previous hospital revealed

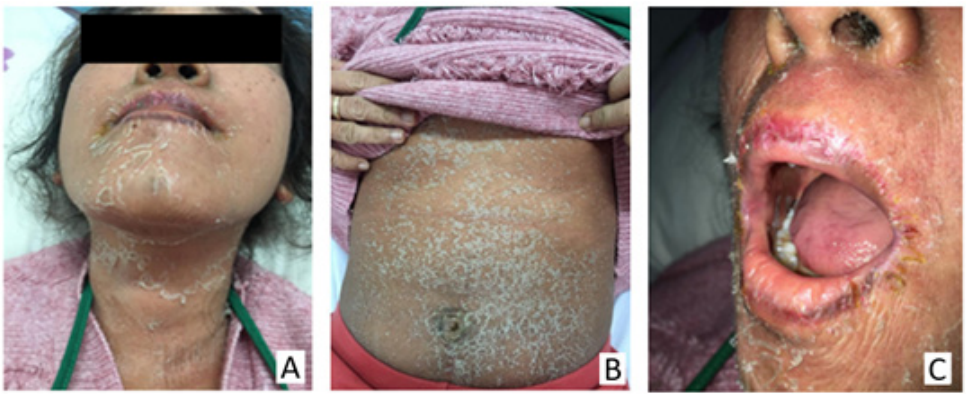

Fig. 2 (A, B) Skin Desquamation; (C) Oral Thrush with Exfoliative Cheilitis

inhomogeneous liver parenchyma with resembling starry sky that suggests inflammatory process.

She was given paracetamol 3x500 mg per oral, fluconazole 1x150 mg per oral, omeprazole 1x40 mg intravenous, curcuma 3x1 tablets per oral. From dermatology consult, this patient was suspected as having drug reaction with eosinophilia and systemic symptom (DRESS). Patient was given dexamethasone 7,5 mg intravenous per day, cetirizine 10mg per day, Vaseline for her skin.

Since steroid administration, liver function was measured regularly, and it was found that transaminase level improved along with her skin rash and jaundice. Repeat blood smear examination was done and the atypical lymphocyte was not found. All her initial symptom has already diminished, from skin rashes, lymphadenopathy, liver enlargement, and jaundice. Patients were discharged on the 13th day. Her biopsy result came out at the same day, revealing necrotic mass with fibrin, lymphocyte, epithelioid cell, and Langhans giant cell for her right cervical lymph. For her left cervical lymph shows necrotic mass, lymphocyte, polymorphonuclear cell, columnar cell, epithelioid, without Langhans giant cell. Pathology expertise concludes that her right cervical lymph was tuberculous lymphadenitis, and her left was sialadenitis. Because of that result, we give her referral for tuberculosis clinic visit after she was discharged for further treatment and evaluation.

Discussion

Fever of Unknown Origin (FUO) is an increased body temperature (higher than 38,2oC) for three weeks or more without clear etiology even after extensive evaluation for at least 1-week in hospital. There's no official guideline nor there is standardized approach to diagnose this condition.[1] According to Durack and Street, FUO can be classified into 4 type: 1) Classical FUO, fever longer than 3 weeks with unidentified cause after 3 days in hospital evaluation or more than 3 times outpatient visits, 2) Nosocomial FUO, fever that manifested after 48 hours in hospital care without clear diagnosis after 3 days in hospital evaluation, 3) Neutropenic FUO, fever with neutrophil count less than 500 cell/uL without clear diagnosis after 3 days in hospital evaluation, 4) HIV-related FUO, fever afflicting known HIV patient that was diagnosed more than 4 weeks in an outpatient setting, or diagnosed as HIV in hospital for more than 3 days.[2] The patient experience fever for 24 days before admitted in hospital, with previous 16 days inpatient care in another hospital, thus fulfilled classical FUO criteria.

There are more than 200 diseases that may became FUO differential diagnosis, subgroup of differentials that usually used in classical FUO consist of 4 categories: infection, malignancy, rheumatoid diseases, and other causes.[1] Each subgroup have distinct clinical characteristic. Malignant etiology tends to cause early anorexia and significant weight loss, while infectious etiology may cause chill without apparent weight reduction. Vasculitis and synovitis are signature clue for rheumatic etiology.3 Drug related fever can be found in 1-3% of FUO cases.[1]

Most experts suggested a wide array of standard testing panel, including blood tests, urinalysis, fecal examination, skin tests, and culture from different specimen, chest x-ray, and abdominal ultrasound. If there's still no definite diagnosis, Mourad states that its acceptable to order other tests such as hepatitis testing, liver biopsy, culture for mycobacteria, fungi, and other bacteria, echocardiography, abdominal and chest CT scan, and temporal artery biopsy for patient older than 55 years.[4] The patient disease history began when she complained of severe headache that was treated with carbamazepine, followed by appearance of fever and skin rashes. She does not have history of staying on an endemic area nor surgery. She previously had a history of hospital stay, though she did not have her medication history on that hospital with her. She already did several of the examination suggested above, which is blood exam, ziehl neelsen stain for sputum sample, chest x-ray, abdominal ultrasound. From this data, differentials were made, and rheumatologic condition was excluded from etiological possibility. Infection and malignancy were still possible at the time, considering her fever, weight loss, lymph enlargement that has yet to be examined histopathologically. From her initial blood exam, she has known to have anemia, increased conjugated bilirubin, and transaminase. Abdominal ultrasound revealed liver inflammation, previously suspected as drug induced liver injury, though after dermatology consultation, concluded that it may be related to the possibility of DRESS involvement.

Drug reaction with eosinophilia and systemic symptom (DRESS) is an adverse drug reaction (ADR) that may potentially

life threatening. This disease has multiorgan manifestation, including hematologic, hepatic, renal, pulmonary, cardiac, neurologic, gastrointestinal, and endocrine system. Dermatological manifestation in DRESS can be diverse, with morbilliform rash as its common sign. This syndrome have 10% mortality rate, usually derived from fulminant hepatitis with hepatic necrosis.[5]

A systematic review from PubMed-MEDLINE, January 1997 to May 2009 stated that there are 44 drugs that was associated with 172 reported cases. Carbamazepine was the most frequently reported drug and was found in 47 cases (27% from total cases in this series).[6]

DRESS syndrome can manifest 2 months after drug consumption, although its usually happened 2–6 weeks after the patient first exposure to drug. Symptom may appear earlier and heavier to those with repeated exposure to offending drug. Carbamazepine had an onset of 21–28 days.[7] The patient clearly said her medication history with carbamazepine 2 months before, and she became feverish 5 weeks after that.

Usual clinical manifestation for DRESS patient are fever, rash, lymphadenopathy, leukocytosis, and liver function abnormalities. Skin afflictions are explicitly clear, urticaria and maculopapular rash being the most common, though vesicle, bullae, pustule, cheilitis, purpura, target lesion, and erythroderma were also reported.7 Although skin eruption in DRESS is extensive, its morbidity and mortality were caused by systemic involvement. The most common involvement was fever (temperature >38°C) in 95% of cases with visceral organ involvement from lymphatic, hematology, hepatic, followed by renal, pulmonary, and cardiac. Severe and atypical cases can involve neurology, gastrointestinal, or endocrine dysfunction. Certain drugs may have specific organ predilection.[5] The patient was afflicted with extensive skin lesion in the form of erythematous macule and desquamation.

Lymphadenopathy, local or generalized, can be found on 75% of DRESS. The most common lymph node involvement was in cervical, axillary, and inguinal area. Histopathologically, there's 2 main variant, benign and pseudo-lymphomatous type.[8]

Hematological disturbance was frequently encountered and happened 2 weeks after drug eruption onset. Leukocytosis, with high atypical lymphocyte that preceded by leukopenia or lymphopenia, with eosinophilia that may contribute to visceral organ manifestation. There is also thrombocytopenia and anemia.[8]

Hepatic involvement may manifest as hepatocellular or cholestatic liver injury, and on severe cases may become fulminant hepatic failure that require liver transplantation.8 DRESS could be included in one of the phenotypes of drug-induced liver injury (DILI), and some authors recommend the DILI severity index to evaluate the degree of liver injury. It is described that patients with severe acute liver damage may shows an overall survival of 75%, with hepatic encephalopathy, factor V level, prothrombin time were predictors of poor prognosis.[9]

Lung involvement from DRESS may decrease lung capacity as this condition may take form as acute interstitial pneumonitis, lymphocytic interstitial pneumonia, pleuritis, and acute respiratory distress syndrome (ARDS). Lung involvement may also be described by signs such as cough, dyspnea, pleuritic pain and/or radiological findings such as unilateral or bilateral pulmonary infiltrates, lobar infiltrates, and pulmonary nodules.[10]

The patient had many symptoms that formerly thought as several diseases, eventually all those symptoms can be explained as systemic manifestation of DRESS. She had bilateral cervical lymphadenopathy, hematological manifestation in the form of anemia and atypical lymphocyte. She got cholestatic type liver injury with jaundiced sclerae, hepatomegaly that was confirmed by physical exam and ultrasound, increased AST/ALT and conjugated bilirubin. There is no increase in BUN nor creatinine, but we found microscopic hematuria. Lung involvement can be suspected from bilateral infiltrate on her chest x-ray, that was interpreted as bronchopneumonia, in the absence of symptom and sign of infection.

Patient suspected with DRESS must undergo extensive evaluation. Deciding the associated drug oftentimes difficult in polypharmacy or when symptom appeared after long latency period. Clinical examination that was developed to point out DRESS causative agent was not reliable. Regular testing method that was used is skin patch test and lymphocyte transformation test (LTT). Systematic review show that PPV from skin patch test in optimal setting can be as high as 80–100%. For optimal result, patch test must be done 2–6 months after resolution of symptom. Positive LTT result consequential in

diagnosis and determining causative drug in DRESS. Negative LTT result could not rule out drug hypersensitivity.[11] The patient' causative drug can be easily identified so further examination was not required.

Up until this point there's no gold standard diagnostics for DRESS. European Registry of Severe Cutaneous Adverse Reaction Study Group invent scoring system called RegiSCAR, based on the criteria invented by Bocquet et al. Japanese consensus group also used the same criteria with different terminology, which they called Drug Induced Hypersensitivity Syndrome (DIHS).[7] This study was calculated RegiSCAR score on the patient with a total score of four, interpreted as probable DRESS.

Common differential for DRESS is other systemic cutaneous adverse reaction (SCAR), such as Stevens Johnson syndrome/toxic epidermal necrolysis, acute generalized exanthematous pustulosis, and erythroderma which also manifesting skin lesion and visceral involvement. It is important to differentiate DRESS from dermatological findings from exanthem virus (Kawasaki, EBV, viral hepatitis, influenza, CMV, and HIV). DRESS also have to be differentiated from lymphoma, pseudo-lymphoma, collagen vascular disease, serum sickness-like reaction. Other differentials include Kawasaki syndrome, Still's Disease, syphilis, porphyria, and hypereosinophilic syndrome.[12]

In the beginning, this study did not administer any treatment for the patient. The reason was because empirical therapy was not recommended in patient with FUO, as it may cloud disease manifestation and delay diagnosis, thus may hindering proper treatment.[4]

Patient without clear diagnosis and clinical improvement advised to be kept on as minimal medication as possible and wait. Antipyretic can mask patient symptom and can only be given to those who were unable to tolerate their fever. In a certain working diagnosis, empiric therapy is allowed, for example empiric antibiotic is given in bacterial endocarditis even though its blood culture turn out to be negative, antituberculosis drug is given in suspected tuberculosis infection, and glucocorticoid is administered in suspected temporal arteritis with risk of blindness.4 Consultation with subspecialists (infectious disease specialist, rheumatologist, haemato-oncologist) is the correct way to get an insight on working diagnosis.[1]

The biggest challenge in DRESS is early identification of this condition and termination of causative drug. Inability to do so may increase morbidity and mortality.11 All patients must be given adequate supportive measures to stabilize their hemodynamics, given antipyretic for their fever, emolien and topical steroid for their skin condition. Empirical antibiotic must be avoided because it can cross-react with other drugs and may exacerbate the condition.[7] Systemic corticosteroid is the main therapeutic option for DRESS. It was given in prednisone equivalent dose of 1mg/kg/day. Steroid must be tapered slowly in 6-8 weeks, even after clinical resolution is achieved, to prevent relapse. It was done in this fashion because DRESS patient also has higher risk to experience immune reconstitution inflammatory syndrome if steroid is withdrawn recklessly.[7,13] Severe cases or where DRESS is refractory to conventional steroid dose, intravenous methylprednisolone can be given in pulse dose of 30mg/kg/day for 3 days.11 Intravenous immunoglobulin (IVIG) have been tried before in patient unresponsive to steroid or had contraindication to steroid.[14]

Other modalities in DRESS treatment are plasmapheresis and immunosuppressive drug such as cyclophosphamide or cyclosporine. N-acetylcysteine may help to detoxify circulating drug and limit reactive metabolite in anticonvulsant induced DRESS. Valgancyclovir can minimize complication related to HHV-6 reactivation and can be given in combination with prednisone.[15] The patient is given steroid therapy as described, using dexamethasone 7.5 mg intravenously per day (equivalent to 50mg prednisone, based on the patient body weight). Her skin affliction gradually gets better, along with her other systemic symptoms. This study repeat her blood smear, and the atypical lymphocyte is nowhere to be found. Interestingly, her leukocyte and thrombocyte increased significantly on the 5th day since steroid administration (24110/uL and 959,000/uL respectively). This may be caused by high dose steroid effect, because the patient was getting better and there is no sign of infection. Patient who received 40–80 mg prednisone-equivalent may have leukocytosis since a few hours to 2 weeks after administration.[16] Corticosteroid was also known to cause transient thrombocytosis through splenic release of pooled thrombocyte into systemic circulation.[17]

Histopathologically, drug induced lymphadenopathy is flooded with polymorphic cellular infiltrate comprised of lymphocyte, plasma cell, eosinophil, and histiocyte. Some may have focal hemorrhagic necrosis without

fibrosis, with endothelial hyperplasia. On the other hand, tuberculous lymphadenopathy showed epithelioid granuloma with giant Langhans cell accompanied with central necrosis.[18] The patient showed tuberculous characteristic on her right lymph node biopsy, though on her left lymph node it was found to support drug reaction because histopathologically comprised more with lymphocyte and polymorphonuclear cell. Another reason why tuberculosis cannot be excluded completely is that steroid was used. Anti-inflammatory effect from corticosteroid may null the body fever generating mechanism through prostaglandin inhibition from arachidonic acid release blockade. Corticosteroid also able to halt interleukin-1 transcription which is important to augment T-cell proliferation.[19] However, we know that DRESS's mortality and morbidity is caused by its systemic involvement. Fever is manifested in 90% cases and usually very high in DRESS (>38°C), while in tuberculous lymphadenitis, systemic manifestation is uncommon, and fever is reported in HIV coinfection as a low-grade fever. In immunocompetent patient, fever only reported in 20–50% cases.[7]

Therefore, this study conclude from the patient characteristics, that DRESS is the main cause of fever in this patient. Diagnosis of DRESS must be suspected from the symptom of skin rash, liver involvement, fever, and lymphadenopathy in patient with history of drug use. FUO is one of the possible manifestations of DRESS, but thorough investigation still needed to be done, considering the possibility of more than one entity of disease that can cause FUO in one patient. Termination of drug, accurate treatment, supportive measures, wound care, multidisciplinary approach, and early systemic steroid initiation is crucial to reduce mortality and morbidity in DRESS.

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Depression, Anxiety, and Stress due to Changes in Employment Status during COVID-19 Pandemic: A Study in Badung Districts, Bali Indonesia

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Abstract

Objective: To determine the relationship between depression, anxiety, and stress with the employment status of people in Bali during Covid-19 pandemic.

Methods: This study was a cross-sectional analytical study conducted in Bali, Indonesia, in 2021. The instrument used was DASS-21 questionnaire, which was distributed to a total sample size of 96 people. The relationship between variables were analyzed with a p-value of <0.05 as the cut-off for a significant relationship.

Results: Depression symptoms had a significant relationship with gender (p=0.024) while anxiety symptoms had a significant association with the employment status during the pandemic (p=0.027). Similarly, stress symptoms also had a significant relationship with gender (p=0.007) and employment status during COVID-19 pandemic (p=0.007).

Conclusion: There is a relationship between depression, anxiety, and stress due to changes in employment status during the COVID-19 pandemic in Badung Districts, Bali.

Keywords: Anxiety, depression, COVID-19, employment status, stress

Introduction

The novel coronavirus 2019 (COVID-19) is one of the global infections currently a pandemic in 215 countries globally, including Indonesia. Indonesia is currently ranked first as the country with the most COVID-19 cases in ASEAN, with more than 41 thousand total cases and a mortality of 5.5%.[1] As of February 2022, the number of positive cases of COVID-19 in Indonesia reached more than 5,1 million positive cases and more than 146 thousand mortality cases while Bali reached more than 146 thousand positive cases with a mortality of more than 4200 people.[2]

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The COVID-19 pandemic has also had an impact on Indonesia's economic conditions, according to data from the International Labor Organization (ILO), which states that quarantine during the pandemic caused 2.7 billion workers or the equivalent of 81% of the world's workforce, to experience income imbalances.[3] This condition triggers an estimate of an increase in the number of open unemployment in 2020, which will reach 9.35 million workers.[4] Bali is a province in Indonesia that is highly dependent on tourism conditions. The COVID-19 pandemic has certainly caused instability in the tourism sector's growth due to a decrease in tourists visiting Bali. Seventy-five thousand workers have been temporarily fired and laid off, which led to an increase in Bali's unemployment rate by 5.63%.[5]

This situation will undoubtedly impact health conditions such as depression, anxiety, and stress due to decreased income. All

individuals from various groups can feel stress conditions, ranging from school-age students who feel stress due to the distance learning system, productive age who experience stress due to employment termination, to older people who experience anxiety and depression due to limited time to socialize.[6] However, there is no descriptive or analytical data that assess the level of depression, anxiety, and stress in people in Bali and their relationship to work status during the pandemic COVID-19 in Bali, Indonesia. Therefore, this study aims to determine the relationship between depression, anxiety, and stress conditions with the work status of people in Badung Districts Bali during the Covid-19 pandemic.

Methods

This study is an analytical study with-a cross-sectional design carried out during June-August 2020 to determine the relationship between individual characteristics and levels of depression, anxiety, and stress in Bali Province. This research started from proposal preparation, research implementation, data collection, and analysis to prepare a research report that lasted four months. The population in this study were all residents who live in Badung district, Bali Province. Badung was chosen as the sampling location because Badung district is the 3rd with the highest number of confirmed positive cases in Bali, representing the population.[2] There are many tourism-based economic sectors in Badung. Badung district had become the center of tourism activities in Bali, with a portion reaching 60% of the total tourists in Bali. In reviewing this, most of the businesses in Badung certainly ran in the tourism sector. As many as 85% of its citizens made a living by working in the tourism sector, and only 15% work in other sectors. It is quite representative to show changes in economic status and chances of being stressed. Based on calculations using the analytical research formula with the cross-sectional method, the minimum subject was obtained 48 people, and in this study, 96 people were obtained as samples.

The method of selecting samples in this study uses simple random sampling. According to the inclusion criteria, all subjects previously determined are Bali province residents with the latest education, junior high school/equivalent, have reading and writing skills, and are willing to become research respondents by signing informed consent will immediately become research subjects. The data collected in this study were divided into independent and dependent variables. The independent variables are work status during the pandemic, and the dependent variable is depression score, anxiety, and stress. The sample collection was carried out by google form. The questionnaire questions use questions from the Depression Anxiety Stress Scale-21 (DASS-21), consisting of 21 questions. The results of filling out the participant questionnaire will be calculated based on the scoring according to Table 1.

All data collected will be analyzed univariate and bivariate using data analysis software. Data on numerical variables such as age and scores for depression, anxiety, and stress will be tested for normality first with the Kolmogorov-Smirnov test. Univariate data analysis is used to see the distribution description of each dependent and independent variable. Bivariate analysis of categorical data used the chi-square test. Bivariate analysis of numerical variable data with unpaired categorical uses the Mann-Whitney Test and Kruskal Wallis because the data is not normally distributed. A significant value states that there is a relationship between the dependent and independent variables if the p-value is obtained <0.05. Ethical approval for this study has been granted by the Health Research Ethical Committee, Faculty of Medicine, Udayana University, with 1836/UN14.2.2.VII.14/LT/2020.

Results

The characteristics of the research respondents in this study are in Table 2. It was found that

Table 1 Final Score Classification from DASS-21

Classification	Depression Score	Anxiety Score	Stress Score
Normal	0–9	0–7	0–14
Mild	10–13	8–9	15–18
Moderate	14–20	10–14	19–25
Severe	21–27	15–19	26–33
Extremely Severe	>27	>19	>33

Table 2 Characteristics of Research Respondents

Characteristic	Sample (n=96)	
	Frequency (n)	Percentage (%)
Respondent's age		
Mean ± sd	38.41±11.96	
Median (year)	41	
Minimum- maximum (year)	18-64	
Sex		
Male	53	55.2
Female	43	44.8
Marital status		
Not married	25	26
Married	71	74
Living status		
Main family	43	44.8
Big family	53	55.2
Latest education		
Junior high school (jhs)	3	3.1
Senior high school (shs)	66	68.8
Diploma	9	9.4
Bachelor	18	18.8
Job before pandemic		
Civil servant	5	5.2
Private employees	53	55.2
Farmer	3	3.1
Seller	11	11.5
Others	24	25.0
Job after pandemic		
Sent home for a while	24	25
Dismissal	5	5.2
Work from home	56	58.3
Still working	11	11.5
Chronic disease		
Nothing	90	93.8
Diabetes	1	1.0
Hypertension	2	2.1
Asthma	3	3.1
Smoking status		
Yes	16	16.7
Never	74	77.1
Yes before	6	6.3
Depression		
Yes	3	3.1
No	93	96.9
Anxiety		
Yes	8	8.3
No	88	91.7
Stress		
Yes	5	5.2
No	91	94.8

Table 3 Cross-tabulation between Respondent Characteristics and Depression, Anxiety and Stress Levels based on the DASS-21 Score

Characteristics		Depression Level n (%)			Anxiety Level n (%)			Stress Level n (%)	
		Normal	Mild	Moderate	Normal	Mild	Moderate	Normal	Mild
Sex	Male	53 (100)	0 (0)	0	49 (92.5)	1 (1.9)	3 (5.7)	52 (98.1)	1 (1.9)
	Female	40 (93)	2 (4.7)	1 (2.3)	39 (90.7)	1 (2.3)	3 (7.0)	39 (90.7)	4 (9.3)
Age	<39 Years old	39 (97.5)	1 (2.5)	0	36 (90.0)	2 (5.0)	2 (5.0)	39 (97.5)	1 (2.5)
	≥39 Years old	54 (96.4)	1 (1.8)	1 (1.8)	52 (92.9)	0	4 (7.1)	52 (92.9)	4 (7.1)
Marital status	Not married yet	25 (100)	0	0	23 (92.0)	0	2 (8.0)	24 (96.0)	1 (4.0)
	Married	68 (95.8)	2 (2.8)	1 (1.4)	65 (91.5)	2 (2.8)	4 (5.6)	67 (94.4)	4 (5.6)
Living status	Main family	41 (95.3)	1 (2.3)	1 (2.3)	40 (93.0)	1 (2.3)	2 (4.7)	42 (97.7)	1 (2.3)
	Big family	52 (98.1)	1 (1.9)	0	48 (90.6)	1 (1.9)	4 (7.5)	49 (92.5)	4 (7.5)
Level of education	Jhs	3 (100)	0	0	3 (100)	0	0	3 (100)	0
	Shs	69 (97.2)	2 (2.8)	0	60 (90.9)	1 (1.5)	5 (7.6)	61 (92.4)	5 (7.6)
	Diploma	8 (88.9)	0	1 (11.1)	8 (89)	1 (11)	0 (0)	9 (100)	0
	Bachelor	18 (100)	0	0	17 (94.4)	0	1 (5.6)	18 (100)	0
Employment status before pandemic	Government employees	5 (100)	0	0	4 (80)	1 (20)	0	5 (100%)	0
	Private employee	52 (98.1)	1 (1.9)	0	48 (90.6)	1 (1.9)	4 (7.5)	49 (92.5)	4 (7.5)
	Farmer	3 (100)	0	0	3 (100)	0	0	3 (100)	0
	Seller	9 (81.8)	1 (9.1)	1 (9.1)	10 (90.9)	0	1 (9.1)	10 (90.9)	1 (9.1)
	Others	24 (100)	0	0	23 (95.8)	0	1 (4.2)	24 (100)	0
Employment status during pandemic	Temporarily fired	23 (95.8)	1 (4.2)	0	24 (100)	0	0	23 (95.8)	1 (4.2)
	Work from home	55 (98.2)	1 (1.8)	0	52 (92.9)	2 (3.6)	2 (3.6)	55 (98.2)	1 (1.8)
	Laid off	5 (100)	0	0	1 (20)	0	4 (80)	2 (40)	3 (60)
	Still working	10 (90.9)	0	1 (9.1)	11 (100)	0	0	11 (100)	0
Chronic disease	Nothing	87 (96.7)	2 (2.2)	1 (1.1)	82 (91.1)	2 (2.2)	6 (6.7)	85 (94.4)	5 (5.6)
	Diabetes	1 (100)	0	0	1 (100)	0	0	1 (100)	0
	Hypertension	2 (100)	0	0	2 (100)	0	0	2 (100)	0
	Asthma	3 (100)	0	0	3 (100)	0	0	3 (100)	0
Smoking status	Never	72 (97.3)	1 (1.4)	1 (1.4)	67 (90.5)	2 (2.7)	5 (6.8)	70 (94.6)	4 (5.4)
	Stop >6 months	5 (83.3)	1 (16.7)	0	6 (100)	0	0	5 (83.3)	1 (16.7)
	Active	16 (100)	0	0	15 (93.8)	0	1 (6.3)	16 (100)	0

*JHS: Junior High School, SHS: Senior High School

Table 4 The Relationship between Respondents' characteristics and Depression, Anxiety and Stress based on the DASS-21 Score

Variable	Depression Score	P value	Anxiety Score	P value	Stress Score	P value
Gender						
Male	0.55±1.13	0.024*	1.47±2.82	0.077	1.55±3.21	0.007*
Female	1.63±3.25		2.19±3.40		3.07±4.67	
Age						
<39 years old	1.15±2.25	0.220	1.88±3.27	0.569	1.83±3.01	0.883
≥ 39 years old	0.95±2.48		1.73±3.00		2.52±4.56	
Marital status						
Not married yet	0.76±1.02	0.602	1.68±2.96	0.772	1.76±3.20	0.985
Married	1.13±2.70		1.83±3.16		2.39±4.23	
Living status						
Main family	1.23±3.03	0.906	1.74±3.17	0.451	1.84±3.33	0.818
Big family	0.87±1.69		1.83±3.07		2.55±4.45	
Level of education						
Moderate education	1.02±0.16	0.422	1.15±0.53	0.774	1.07±0.26	0.227
High education	1.07±0.38		1.11±0.42		1.00±0.01	
Work status before the pandemic						
Government employees	0.80±1.30	0.885	1.60±3.57	0.507	1.60±1.81	0.791
private Employee	0.70±1.53		1.67±3.02		2.32±4.49	
Farmer	1.67±2.88		1.00±1.73		3.00±5.19	
Seller	2.91±5.54		3.00±4.42		3.36±5.42	
Others	0.88±1.29		1.88±2.67		1.54±1.71	
Work status during the pandemic						
Sent home for a while	1.38±2.24	0.112	1.17±1.52	0.027*	1.96±3.22	0.007**
Work from home	0.73±1.94		1.45±2.84		1.34±2.77	
Dismissal	0.40±0.54		8.60±4.82		11.8±6.79	
Still working	2.09±4.36		1.82±2.75		3.00±3.89	
Chronic disease						
Nothing	1.08±2.45	0.855	1.83±3.17	0.833	2.27±4.09	0.519
Hypertension	0.50±0.70		2.00±2.82		2.50±0.70	
Asthma	0.33±0.57		1.00±1.73		1.67±2.08	
Smoking status						
Never	0.96±2.36	0.491	1.78±3.21	0.471	2.24±4.07	0.151
Stop>6 months	2.17±3.86		2.17±2.13		4.50±5.54	
Active	0.94±1.76		1.69±2.98		1.31±2.60	

the age of the patients was 13-64 years old, with an average age value of 36.46 years. The study's Respondents were dominated by male gender (55.2%) with marital status, married (74%). Based on the residence characteristics, it was found that 55.2% of the respondents lived with their big family. Most of the research respondents had the latest education level at the senior high school level/equivalent (68.8%). The work status of respondents before the COVID-19 pandemic was dominated by private employees (55.2%), while the work status of respondents during the pandemic was dominated by work from home (58.3%). Most of the respondents in this study did not have a history of chronic disease (93.8%) and had no smoking habits (77.1%). Based on the DASS-21 interpretation, it was found that three people (2.9%) had depressive symptoms, nine people (8.6%) had anxiety, and 5 (4.8%) had stress.

Table 3 presents a cross tabulation between data on characteristics and work status with depression, anxiety, and stress conditions during the covid-19 pandemic. Most of the respondents have mild depression and stress levels and have mild to moderate levels of anxiety.

The bivariate test between individual characteristic variables with depression, anxiety and stress score is presented in table 4. This study indicates that depression symptoms significantly correlate with gender (p=0.024). Anxiety symptoms have a significant relationship with work status during the pandemic (p=0.027) and stress symptoms had a significant relationship with gender (p=0.007) and work status during the pandemic (p=0.007).

Discussion

The COVID-19 pandemic caused most countries to implement social restrictions to control the virus's spread, including Indonesia. These social restrictions affect various aspects of life, such as economic conditions and education, and cause psychological impacts such as depression, anxiety, and stress.[7] This study indicates that people in Bali who have depression, anxiety, and stress symptoms are below 50%. It was found that people with depression, anxiety, and stress were 2.9%, 8.6%, 4.8%. These results are in line with Gonzales *et al*., which showed that out of 2530 study respondents, symptoms of depression, anxiety, and stress during the COVID-19 pandemic were experienced by less than 50% of respondents 34.19%; 21.34%; 28.14%.[8] Elbay *et al*. study with 442 participants showed opposite results, there were more than 50% of respondents who experienced symptoms of depression (64.7%) and anxiety (51.6%), but respondents who experienced stress were below 50%. (41.2%).[9]

This study shows a significant relationship between depression, anxiety, and stress scores with gender and work status, but no significant relationship exists between the respondents' marital status. These results are similar to research by Elbay *et al*., that state symptoms of depression, anxiety, and stress have a significant relationship with age (p <0.001), gender (p=0.025), and job position (p= 0.001).[9] The study showed that being married and having children was associated with lower DASS-21, while unmarried and younger had higher DASS-21. Also, respondents who live with their spouses and children have lower scores than those who live alone. Regression analysis shows that female gender, unmarried status, and a history of psychiatric disorders are independent predictors for mental health deterioration.[9] Lai *et al*. also showed similar results that DASS-21 is significantly related to gender. Female respondents have a greater risk of having a risk of psychiatric disorders during the COVID-19 outbreak in China.[10]

The difference in stress response between males and females is caused by the hypothalamic-pituitary-adrenal (HPA) axis and the sympathetic nervous system, which provides negative feedback when an individual experiences stress. The sympathetic nervous system regulates heart rate and blood pressure, while HPA regulates the hormone cortisol regulation. The response of the sympathetic nervous system and HPA in men is higher than in women to influence the individual's attitude in responding to stressors. There are sex hormones in females that affect the sympathetic response and HPA. There is a decrease in negative feedback on the hormone cortisol to the brain, which causes women to have a higher tendency to experience stress.[11,12]

This study indicates that individuals laid off have more symptoms of depression, anxiety, and stress. This result is in line with Volaco *et al*. research that individuals with relatively low economic conditions have a greater chance of experiencing stress, which causes an increase in stress hormones such as cortisol and catecholamines glucagon and growth hormone.[13] Another study evaluating 108 men and 94 women showed that low economic

income individuals experience increased blood pressure and cortisol output during the workday, allowing activation of biological pathways related to stress mechanisms.[14] Worse, several reported suicide-related cases to stress due to COVID-19 are based on job loss, sudden extreme poverty, economic crisis, hunger, and inability to cope with social problems. Traumatic situations must be immediately handled through counseling and counseling to the community appropriately. A study in Bangladesh found that lockdown policies caused mental stress due to COVID-19 without ensuring the community's basic needs.[15]

Several individual characteristics associated with depression, anxiety, and stress were also explored in this study. This study found that individuals who act as students are very few who experience symptoms of depression, anxiety, or stress. This result is contrary to research by Livana *et al*., which shows that most students experience stress during the COVID-19 pandemic, which is caused by learning tasks (70.29%), the boredom of the online learning system (55.8%), and not able to meet peers (40.2%).[16] The cause of stress is reinforced by a study that states that academic stress has a significant relationship with the workload.[17] This condition shows that the COVID-19 pandemic has a negative effect on students' educational process and mental health growth.[8]

This study found that depression, anxiety, and stress symptoms were more common in individuals living with big families. Cao *et al*. show a similar result that living with parents was a factor preventing student anxiety during the pandemic (OR = 0.752, 95% CI = 0.596-0.950).[18] Multivariate analysis in the study of Gonzales *et al*. (2020) also showed that there was a significant relationship between stress scores on DASS-21 and residence status ($p < 0.05$).[8] Individuals who live alone have greater stress symptoms than individuals who live in the same house with 2-4 family members. This condition shows that the COVID-19 pandemic has increased communication relationships and the closeness of individuals with their families so that stress symptoms are decreasing more.[8]

This study concluded that depression symptoms have a significant relationship with gender; anxiety has a significant relationship with work status during the pandemic. In contrast, stress has a significant relationship with gender and work status during the pandemic. This study has limitations in forming a cross-sectional study with a relatively small sample size compared to the total population. Therefore, it is suggested that future research use a longitudinal study design to analyze the long-term impact of the COVID-19 pandemic on an individual's psychological state to conclude the main and accompanying factors that trigger psychological symptoms in individuals. Second, this study only took a sample from Bali province, so large-scale survey with various respondents was still needed to expand and generalize the research results.

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Renal Parameters in Mild, Moderate, and Chronic Cigarette Smokers

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Abstract

Objective: To explore the link between cigarette smoking and kidney function through renal parameter assessment.

Methods: The present study was performed at the Department of Biochemistry Santosh Medical College, Ghaziabad, India, from September 2019 to April 2021. In this study, 140 subjects were included, out of which 35 were non-smokers, 35 smoked <5 cigarette per day, 35 smoked 5–10 cigarette per day, and the remaining 35 smoked more than 10 cigarettes per day.

Results: Blood urea, serum creatinine, urinary albumin, and uACR levels were found to increase significantly ($p<0.001$) in smokers as compared to non-smokers. These increases were higher among chronic cigarette smokers ($p<0.001$) as opposed to mild and moderate smokers. In contrast, serum uric acid, e-GFR, and urinary creatinine levels decreased significantly ($p<0.001$) in smokers when compared to non-smokers, with a higher decrease observed in chronic cigarette smokers ($p<0.001$) as opposed to the mild and moderate cigarette smokers.

Conclusion: Alterations in urinary albumin, serum urea, serum creatinine, urinary creatinine, and e-GFR are associated with the risk of renal dysfunction.

Keywords: Albuminuria, cigarette smokers, e-GFR, kidney function, uACR

Introduction

Cigarette smoking is one of the most serious public health concerns of these days. Worldwide, an estimate of 4 million people is affected by smoking-related disorders every year which is expected to rise to a staggering 10 million a year over the next two decades if the same trend continues.[1] Adolescence is a developmental period that is most affected by emotional and social functions. Tobacco companies use sophisticated marketing campaigns to attract people to begin this practice early. The rate of adolescents getting addicted to smoking is very high in India. It is mostly observed that once an adolescent is initiated into tobacco use, he/she abuse it lifelong, with very low withdrawal rates.2

Cigarette smoking is one of the main causes of preventable fatalities, with cardiovascular disease (CVD) and cancer being the most common.[3] Kidney illness is on the rise in developing countries, owing to a rise in diabetes mellitus (DM) and hypertension.[4] Traditional risk factors for the development of CKD have included advanced age, diabetes, and hypertension.[5]

According to the Global Adult Tobacco

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Survey, more than half of the smokers initiate smoking in their adolescence in India.[1] High-stress jobs also trigger addictive behaviour towards smoking. Tobacco smoke contains more than 4,000 gases and particulate matter, most of which are reported to be damaging and destructive for various organs of the body.

Smoking is highly significant remediable renal risk factors. It not only negatively impacts renal function in subjects without any renal disease but also adversely affects the patients with different types of kidney disease and contributes in increasing the disease severity.[6] Nicotine, tar and some toxic gases (mainly carbon monoxide) are the main hazardous constituents of cigarette smoke. [7] Smoking is known to cause Tachycardia, hypertension and increases, COPD, blood clot formation and triggers fat deposition in the arteries.[8] Urinary albumin is a well-known responsive marker of glomerular injury. This indicates clearly that direct renal damage is induced by tobacco chewing or smoking.[9] The study on Renal Parameters in cigarette smokers is limited in Western Uttar Pradesh, India region; hence the purpose of this study was to evaluate the effect of cigarette smoking on renal parameters in this region.

Methods

The present study was carried out in the Department of Biochemistry Santosh Medical College, Ghaziabad from September 2019 to April 2021. This study was approved from Institutional Ethical Committee F.No. SU/2020/536(48) and informs consent was taken from all the patients prior to the study. All the subjects were divided in to 4 groups. The participants in first groupwere non-smokers, the participants consuming 1–5 cigarettes per days were included in group 2, the participants consuming 5–10 cigarettes per day were grouped as 3 and the participants taking more than 10 cigarettes per day were in group 4.

In this study we included all the subjects who had been smoking for two or more years and all the participants were male and their age was 20–60 years. Patients with Diabetes Mellitus, Subjects with Hypertension, Chronic Diseases, known hepatitis B, C, or HIV/AIDS and Patients consuming Alcohol & other Drugs were excluded from the study.

A 3 ml venous blood sample was collected from medial cubital from each participant, into a plain vial. After centrifugation at 1500 rpm for 3 minutes, the serum was assayed. All the parameters were measured by enzymatic method by using automated analyzer (Beckman Coulter- AU-480).

For the screening of urinary albumin and urinary Creatinine concentration, first morning void (timed) Quantitative midstream urine sample was taken. Urinary albumin (BCG Method) and urinary creatinine (Jaffe's Method) were measures by using fully automated analyzer (Beckman Coulter- AU-480) and eGFR were estimated by MDRD equation.[10]

Statistical analysis was performed using SPSS software, version 16. A two-sided P value <0.05 was considered statistically significant. The statistical differences between the groups were determined by student independent sample t-test.

Results

The mean levels of Blood Urea, Urinary Albumin and uACR were found to be increased significantly (p<0.001) in smokers who were

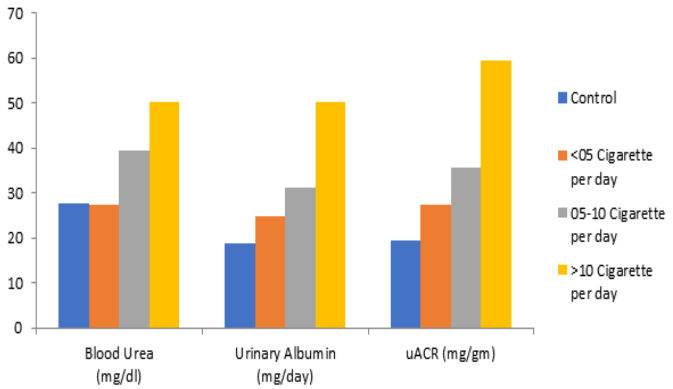

Fig. 1 Comparison of Serum Urea, Urinary Albumin, and uACR in Mild, Moderate and Chronic Smokers

Table Mean and Standard Deviation (S.D) of Biochemical Parameters in Studied Subjects

Variables	Control	Less than 5 Cigarette per day	5–10 Cigarette per day	More than 10 Cigarette per day
Blood Urea (mg/dL)	27.7 ± 5.01	27.54 ± 2.78	39.54 ± 3.17	50.14 ± 5.17
p-Value	-	<0.001	<0.001	<0.001
Serum Creatinine (mg/dL)	0.85 ± 0.13	0.94 ± 0.15	0.97 ± 0.16	1.32 ± 0.16
p-Value	-	0.007	<0.001	<0.001
Serum Uric Acid (mg/dL)	5.05 ± 0.69	4.91 ± 0.72	4.5 ±0.70	3.99 ± 0.76
p-Value	-	0.39	<0.001	<0.001
Urinary Albumin (mg/day)	18.69 ± 2.3	25 ± 4.65	31.2 ± 5.84	50.4 ± 8.96
p-Value	-	<0.001	<0.001	<0.001
Urinary Creatinine (mg/day)	963.83 ± 40.41	907.86 ± 49.03	879.77 ± 44.77	849.26 ± 65.09
p-Value	-	<0.001	<0.001	<0.001
uACR* (mg/gm)	19.36 ± 2.12	27.54 ± 4.91	35.51 ± 6.62	59.61 ± 10.94
p-Value	-	<0.001	<0.001	<0.001
e-GFR** (mL/min/1.72 m^2)	102.28 ± 17.64	90.69 ± 16.30	88.17 ± 17.40	61.0 ± 9.32
p-Value	-	0.005	<0.001	<0.001

consumed 5 to 10 cigarettes per day, as compared to smokers who were consumed less than 5 cigarette. The mean levels of Blood Urea, Urinary Albumin and uACR were found to be increased significantly (p<0.001) in smokers who were consumed more than 10 cigarettes per day, as compared to smokers who were consumed less than 05 cigarettes per day.The mean levels of Blood Urea, Serum Creatinine, Urinary Albumin and uACR were found to be increased significantly ((p<0.001) in smokers who were consumed more than 10 cigarettes per day, as compared to smokers who were consumed 05 to 10 cigarettes per day (Fig. 1).

The level of Serum Uric Acid and Urinary Creatinine were found to be decreased significantly (p<0.001) while the mean level of

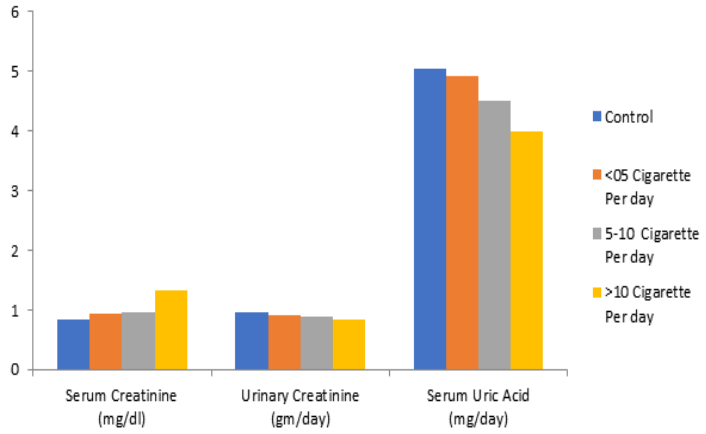

Fig. 2 Comparison of Serum Creatinine, Urinary Creatinin, and Serum Uric Acid in Mild, Moderate and Chronic Smokers

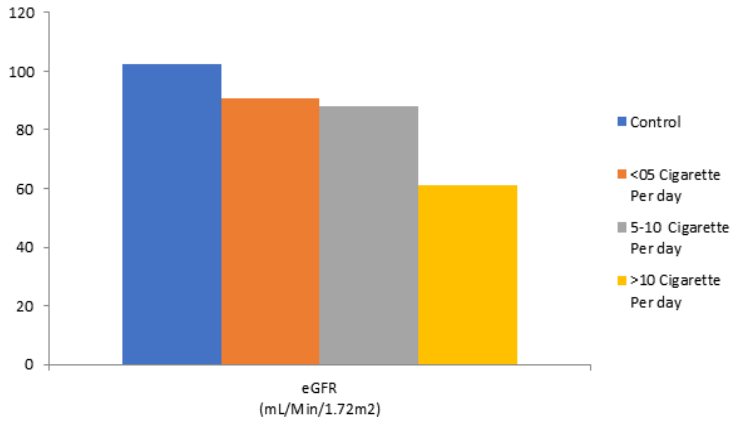

Fig. 3 Comparison of Estimated Glomerular Filtration Rate (eGFR) in Mild, Moderate, and Chronic Smokers

serum creatinine were found to be increased in-significantly (p=0.44) in smokers who were consumed 06 to 10 cigarettes per day, as compared to smokers who were consumed less than 05 cigarette. The level of Serum Uric Acid and Urinary Creatinine were found to be decreased significantly (p<0.001) in smokers who were consumed more than 10 cigarettes per day, as compared to smokers who were consumed less than 5 cigarettes per day.The level of Serum Uric Acid and Urinary Creatinine were found to be decreased significantly (p<0.001) in smokers who were consumed more than 10 cigarettes per day, as compared to smokers who were consumed 05 to 10 cigarettes per day (Fig. 2).

The mean level of e-GFR is decreased in-significantly (p=0.53) in subjects who were consumed 05 to 10 cigarettes per day, as compared to smokers who were consumed less than 05 cigarette. The level of e-GFR were found to be decreased significantly (p=<0.05) in smokers who were consumed more than 10 cigarettes per day, as compared to smokers who were consumed less than 5 & 5 to 10 cigarettes per day (Fig. 3)

Discussion

Among the health risks of tobacco smoking carcinogens, coronary disease and lung disease have got a lot of attention, but the possible influence of smoking on renal function and illness has gotten a lot less attention. Tobacco smoking has lately been shown to play a significant effect in renal disease.[11]

In the present study we found that the mean levels of Blood Urea, Serum Creatinine, uACR and Urinary Albumin were found to be increased significantly in all the study groups as compared to control group and more increase in the parameters in the study subjects who were smoking more than 10 cigarettes per day. In this study, the mean levels of Urinary Creatinine, GFR and Serum Uric Acid were found to be decreased significantly in all the smoking groups as compared to control and the decrease were more in the subjects who were smoking more than 10 cigarettes per day.Mustafa *et al* studied on smokers and found a positive association between number of cigarette per day and uACR and urinary albumin.[12]

This study is in accordance with the previous study Ahmed *et al.*, in which they found that there were an elevated value of Blood Urea and Serum Creatinine in smoker people at (p<0.05) in comparison with the control subjects and the level of Uric Acid in smokers is significantly lower than the non-smokers group (p<0.05).[13]

Metwally *et al.* concluded in their study that there is an insignificant change in Blood Urea, Serum Creatinine, GFR in smokers as compared to non-smokers and Urinary –N-Acetyl glucosaminidase is found to be significantly elevated in smokers as compared to non-smokers.[14]

The higher readings in the participants recruited suggest that tobacco may include some toxic substances that are nephrotoxic, as urea and creatinine are recognized to be indicators of a kidney problem. Previous research has linked increasing kidney

failure to a steady decline in renal and non-renal nicotine elimination, which raises the risk of nephrotoxicity.[15] Another proposed mechanism for cigarette-induced kidney damage is the effects of heavy metals in tobacco, such as Cadmium (Cd) and Lead (Pb).[16] The exact mechanism by which smoking causes kidney damage is unknown, however it could be through an increase in free radical generation that alters glomerular function, as a result, cigarette smokers have increased urea and creatinine levels.[17]

Reduced Renal Plasma Flow and Glomerular Filtration Rate may damage some glomeruli, resulting in hyperfiltration and albumin leakage from capillaries. Urinary albumin has been recognized as a sensitive indicator of glomerular damage, and there is a link between smoking and albuminuria. This suggests that smoking has caused direct or indirect kidney impairment. One of the mechanisms by which smoking leads to albuminuria and renal dysfunction is the production of advanced glycation end products (AGEPs). The non-enzymatic interaction of reducing sugars with the amino groups of plasma proteins, lipids, and nucleic acids produces AGEPs, which are cross-linking moieties.[18] Albuminuria's enhanced vascular permeability effects could be due to AGEPs. A researcher in their study found that both aqueous extracts of tobacco and cigarette smoke include glycotoxins, which are highly reactive glycation products that can cause AGEP production on proteins very quickly.[19] As a result, AGEPs generated by the reaction of cigarette-derived glycotoxins with blood and tissue proteins are expected to have the same effect on renal function.

This study backs up the theory that smoking play a role in the development of renal impairment and subsequent renal diseases. Previous researchers have found a strong link between smoking and renal diseases. In cigarette smokers, we found higher levels of microalbumin, serum urea, and serum creatinine, indicating that smoking is significantly linked to renal impairment, which could lead to future renal function abnormalities.

Cigarette smoking is potentially harmful to the kidneys' function. As a result, now is the moment to educate consumers about the potentially harmful effects of smoking and the resulting health consequences.

The results are in accordance with study done by Desai *et al.* stated that the kidney function is affected adversely in the smoker group, indicated by the elevation of serum creatinine, urea, and a reduction of serum uric acid.[20] The elevation of creatinine and urea almost attributed to a significant fall in glomerular filtration rate (GFR), and a reduction of serum uric acid was attributed to reduced endogenous production by virtue of exposure to toxic cigarette smoke that is a remarkable source of oxidative stress as suggested by the research done by Ahmed *et al.*[13]

The overall tobacco smoking situation in India appears to be very concerning, with an increase in the number of individuals with chronic renal failure in cigarette smoking subjects. Changes in urinary microalbumin, serum urea, serum creatinine, urinary creatinine, and creatinine clearance are linked to an increased risk of renal dysfunction, which can lead to a many renal disorders and using these biochemical parameters as a tool for early detection and reducing the risk of kidney function deterioration could be beneficial. This could be the most reliable approach to renal dysfunction diagnosis, prognosis, and prevention in a tobacco-smoking population.

This study concluded that the smoking is a risk factor for the development and progression of Chronic Kidney Diseases in Western Uttar Pradesh, India. The goal of this study was to evaluate biochemical changes in renal function as a result of smoking. The kidney function of smokers is affected, as seen by an increase in serum creatinine, urea, and a decrease in serum uric acid. The increase in creatinine and urea virtually correlated with a considerable drop in glomerular filtration rate (GFR), whereas the decrease in serum uric acid was linked to decreased endogenous synthesis as a result of cigarette smoking. These findings provide conclusive evidence that, impact of smoking on renal parameters was very high who were taking more cigarettes per day.

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Paraoxonase 1 Activities and Lipid Parameters in Hypertension and Their Association with Chronic Alcoholism

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Abstract

Objective: To determine lipid profile, antioxidant vitamin (E and C), and malondialdehyde (MDA) levels, as well as superoxide dismutase (SOD) levels and paraoxonase 1 (PON 1) activities in alcoholic hypertensive patients.

Methods: Five hundred subjects were selected for this study consisting of 250 normal healthy individuals and 250 alcoholic hypertensive subjects. Total cholesterol, triglyceride, and HDL levels were measured using the enzymatic method while the LDL and VLDL levels were calculated by Friedwald equation. The MDA level were measured using thiobarbiturate (TBA) and the Vitamin E and C were measured using the enzymatic method. The SOD and PON 1 activities were measured using phenyl acetate as the substrate.

Results: Total cholesterol, triglycerides, LDL, VLDL, and MDA levels were found to be significantly high while the HDL and Vitamin E and C levels decreased among the alcoholic hypertensive subjects when compared to the control. Furthermore, significant decreases in SOD and PON 1 activities were also found among the alcoholic hypertensive subjects as compared to control.

Conclusion: Alterations in lipid parameters, antioxidant vitamin levels, MDA level, SOD activities, and PON 1 activities are associated with hypertension that may be enhanced by alcohol intake, which may lead to the development cardiovascular disease.

Keywords: Alcoholism, hypertension, MDA, lipid parameter, antioxidants vitamins (E and C)

Introduction

Alcohol abuse leads to the buildup of fat in the liver. In alcoholics, significant amounts of alcohol disrupt many metabolic processes in the liver, resulting in the formation of reactive oxygen species (ROS). Under mammalian tissue, free radicals are produced in both healthy and pathological situations. In chronic alcoholism, free radicals have an impact and there is oxidative damage, which is a shift in the oxidant-antioxidant balance.[1]

Chronic liver disease is the tenth leading cause of mortality in adults, with alcoholic cirrhosis accounting for over 40% of cirrhosis-related deaths. Three enzymes, Alcohol Dehydrogenase (ADH), Cytochrome P-4502E1 (CYP2E1), and mitochondrial catalase, metabolise alcohol in the liver. Heavy drinkers have steatosis in 90 percent to 100 percent

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of cases, alcoholic hepatitis in 10% to 35% of cases, and alcoholic cirrhosis in 8% to 20% of cases. Alcoholic fatty liver eventually leads to alcoholic hepatitis, cirrhosis, and liver failure.[2]

The enzyme paraoxonase (PON) has both paraoxonase and aryl esterase activity. Aromatic carboxylic acid esters and certain organophosphorus insecticides, particularly paraoxon and nerve gas, are hydrolyzed. PON1, PON2, and PON3 are members of the PON gene family, which are found on chromosome 7q21.3–22.1. PON1 is primarily produced in the liver and is firmly linked to HDL, protecting both LDL and HDL against lipid peroxidation (LPO).[3]

Paraoxonase 1 (PON1) activity varies up to 40-fold between individuals4, and it is regulated by genetic, developmental, environmental, and pathologic factors.5,6 Low PON1 and Arylesterase (AE) activity has been linked to a number of health problems.7 Due to the liver damage produced by high alcohol use, it has been hypothesised that excessive alcohol consumption would result in a decrease in serum PON1 and AE activity, which has been seen in a few studies.[8]

Excess synthesis of peroxides and free radicals causes oxidative stress, which is described as an imbalance between oxidants and reductants within the body. Oxidative stress is linked to an increase in the generation of oxidizing species or a considerable reduction in the efficiency of antioxidants and antioxidant enzymes chemically. LPO is a free radical-related process that can be damaging if it goes unchecked; the self-enhancing process disrupts membranes, lipids, and other cell components.[9] As a result, the presence of LPO in the blood can help determine the prognosis of non-alcoholic fatty liver disease (NAFLD) patients. The study on PON 1 activity in hypertension and its association with chronic alcoholism is limited hence the objective of this study was to evaluate the effect of chronic alcohol intake on lipid parameters, oxidative stress and paraoxonase 1 activity in hypertensive subjects.

Methods

The present cross-sectional study was carried out in the Department of Biochemistry Santosh Medical College and Hospital Ghaziabad, Department of Biochemistry, Muzaffarnagar Medical College and Hospital, Muzaffarnagar. This study was approved by Institutional Ethical Committee and informed consent was taken from the subjects, prior to study. The minimum sample size has been calculated using the appropriate sample size formula:

$n=z^2pq/d^2$
Where z=1.96 at 95 % confidence interval,
p=0.20 and q=1-p=0.80,
d=absolute error 5%
$n= (1.96)^2\times0.20\times0.80/(0.05)^2$
$=245.86\approx246$

In this study, 500 subjects were included out of which, 250 were already diagnosed hypertensive subjects with alcoholism and 250 were normal and healthy controls. All the subjects were male with 30-60 years of age.

Patients with Type 2 diabetes mellitus, hepatic disease, cardiovascular disease, renal disease, Pulmonary tuberculosis, Acute or chronic inflammatory illness, Gout and arthritis, Prolonged illness, Subjects not willing to give consent in the study, Patients receiving medicines known to alter glucose and lipid metabolism were excluded from the study.

The subjects were requested individually for overnight fasting. Blood samples were drawn with the help of disposable syringe and collected in clean vials. The serum was separated and lipid profile was done on fresh serum and remaining serum sample was kept in small fractions at -200C. Total cholesterol and HDL cholesterol were measured by CHOD-PAP method, triglyceride by GPO-PAP method and the level of LDL-c and VLDL-c were calculated by Friedwald Equation. MDA was measured by chemical method by using thiobarbituric acid (TBA). SOD was measured by modified Marklund and Marklund method by using pyrogallol. Vitamin E & C were determined by chemical method. The activity of PON 1 was measured by chemical method by using phenyl acetate as a substrate. Statistical analysis between controls & study subjects were performed by the student's t-test using SPSS package for windows. The data were expressed as mean ± SD. $p<0.05$ was considered as highly significant.

Result

The difference between alcoholic hypertensive subjects and control subjects were statistically significant. Alcoholic hypertensive patients were showed significant increase in CHO, TG, LDL and VLDL ($p<0.001$) and significantly decrease in HDL ($p<0.0001$) as compared to healthy control. The level of antioxidant vitamins (E&C) were found significantly

Table 1 Demographical Parameters in Studied Subjects

Variables	Controls	Hypertensive with Alcoholics	p-Value
Age (Years)	42.93 ± 6.32	42.99 ± 6.53	>0.05 NS
SBP (mm of Hg)	113.86 ± 4.99	160.15 ± 6.47	<0.001 S
DBP (mm of Hg)	81.42 ± 3.82	100.15 ± 3.66	<0.001 S
BMI* (kg/m^2)	24.92 ± 3.29	27.71 ± 3.17	<0.001 S
WHR**	0.80 ± .058	1.08 ± 0.11	<0.001 S

SBP: systolic blood pressure; DBP: diastolic blood pressure; BMI: basic metabolic index; WHR: waist to height ratio; S: statistically significant; NS: statistically non-significant

lower (p<0.001) and MDA (p<0.001) was found significantly higher in alcoholic hypertensive subjects as compared to normal healthy Individuals. Superoxide dismutase and paraoxonase 1 activity were found to be reduced in alcoholic hypertensive subjects as compared to normal healthy controls (Table 2). Upon Correlation analysis, a significant and negative correlation of MDA with SOD & PON 1 and a significant positive correlation of SOD and PON 1 were observed (Table 3).

Discussion

Multiple metabolic abnormalities often accompany essential hypertension. Essential hypertension is associated with increased production of ROS predisposing to increase in lipid peroxidation which is a marker for cellular damage. MDA can exacerbate the actions of superoxide ions by impairing endothelium-dependent relaxation and propagation of lipid peroxidation by a chain reaction in membranes.

In this study, increased BMI and Waist/Hip Ratio (WHR) were observed in hypertensive subjects with alcoholics as compared to controls. As BMI and WHR being the markers of general obesity and central obesity, increased BMI and WHR in hypertensive subjects with alcoholics predispose these subjects to an increased risk for CVD.

Table 2 Biochemical Parameters in Studied Subjects

Variables	Controls	Hypertensive with Alcoholics	p-Value
Total Cholesterol (mg/dL)	197.75 ± 23.21	280.52 ± 31.64	<0.001
Triglycerides (mg/dL)	125.93 ± 18.72	239.18 ± 46.16	<0.001
HDL- Cholesterol (mg/dL)	48.82 ± 7.68	32.24 ± 4.62	<0.001
LDL-Cholesterol (mg/dL)	123.75 ± 21.18	200.45 ± 30.18	<0.001
VLDL-Cholesterol (mg/dL)	25.19 ± 3.74	47.84 ± 9.23	<0.001
MDA (nmol/mL)	2.92 ± 0.45	5.05 ± 1.41	<0.001
PON 1 (U/mL)	67.61 ± 7.45	47.21 ± 13.45	<0.001
SOD (U/mL)	10.88 ± 1.87	7.63 ± 1.65	<0.001
Vitamin-E (mg/dL)	1.76 ± 0.25	1.30 ± 0.12	<0.001
Vitamin-C (mg/dL)	1.57 ± 0.18	1.19 ± 0.092	<0.001

MDA: malondialdehyde; PON 1: paraoxonase 1; SOD: superoxide dismutase

Table 3 Correlation Coefficient Among Parameters in Hypertensive Subjects with Alcoholism

Variable	PON1	SOD	Vitamin E	Vitamin C
MDA	r=-0.740 p<0.001	r=-0.620 p<0.001	r=-0.244 p<0.01	r=-0.512 p<0.001

In this study, significantly increase in CHO, TG, LDL-c, VLDL-c and significantly decrease in HDL-cholesterol were observed in alcoholic hypertensive subjects as compared to normal healthy individuals. A study by Paneri *et al.*[10] concluded that there is rise in MDA level in alcoholic hypertensive individuals as compared to normal controls. Decrease in the serum HDL and TAC is also observed in alcoholic individuals when compared to normal controls. Serum total cholesterol, TG, LDL, VLDL were also found to be elevated in the study group when compared to the normal controls. Chen *et al.*[11] found significant increase in total cholesterol, triglycerides, LDL-c and VLDL-c in heavy alcohol consuming individuals. Consumption greater than 50 g/ day significantly reduced the risk of developing low levels of HDL-c, but elevated the risks of developing high levels of cholesterol.

Increased plasma total cholesterol levels which are known to be associated with decreased LDL receptor gene expression and protein abundance in the liver, may be a factor for the change. Chronic alcohol exposure may activates down-regulating the activation of a signaling enzyme that is known to be associated with decreased LDL receptor expression in hepatocytes, suggesting that multiple mechanisms are involved in alcohol-induced down-regulation of LDL receptor.

This study revealed that there was significantly increase in MDA levels associated with high alcohol consumption as compared to control. Our results are in consistent with Deshpande *et al*.[12] who concluded that increase in MDA levels are related to the alcohol consumption and that may be associated with pathogenesis and progression of liver disease. A study by Tan *et al.*[13] reported the same results. An increased MDA level inactivates the antioxidant enzyme (SOD) in untreated hypertension 14 causing damage to various proteins that may also the cause for reduced enzymatic activity of SOD.[15]

The body produces its own antioxidants as a protective mechanism against oxidative stress. Vitamin-like beta carotene, ascorbic acid, Vitamin E, antioxidants enzyme like glutathione peroxidase, catalase and superoxide dismutase are natural antioxidants, which maintain the balance between oxidants and antioxidants.

As discussed earlier, antioxidant vitamin (E & C) decrease the superoxide anion level in the presence of superoxide dismutase in a healthy individual. In case of hypertension, it was found in the present study that there was a direct correlation between the activity of superoxide dismutase (SOD) and the levels of Vitamin E and ascorbic acid.

The significant rise in the levels of reactive oxygen species and decrease antioxidant enzyme may be explained as the combat mechanism showing a relationship between oxidant and antioxidant that has been further raised in alcoholic with hypertensive subjects.

This study observed a significant decrease in PON 1 activity in hypertensive with alcoholic patients as compared to control. A positive correlation was also observed between antioxidant vitamin (E & C) and PON 1. Individuals carrying low PON 1 activity may have a higher risk for CVD. A case-control study has shown that the reduced PON 1 activity is very common in CHD patients.[16]

Previous studies, including ours, have suggested that the PON1 provides the protection for LDL and HDL oxidation and PON1 confers antioxidant activity on HDL. While the susceptibility of HDL to lipid peroxidation and the antioxidant effect of HDL were not measured in our population, the increased risk of CVD in subjects carrying low PON 1 activity could be attributed to the acceleration of atherosclerotic process in these subjects, i.e., an increased susceptibility of LDL to oxidation, a reduction in the antioxidant effect of HDL, and an alteration of their functionality.[17]

Serum PON 1 levels decline in various types of liver diseases. PON1 in association with HDL in the circulation protects LDL from peroxidation. The lowering of PON 1 may be due to peroxidative changes that occur in the hepatocytes. A fall in serum PON 1 could be taken as a manifestation of the different liver function tests i.e., synthesis, detoxication, and secretion.

Correlation studies have found that MDA was positively and significantly correlated with TC where as it was significantly negatively correlated with HDL, PON1, SOD, Vit E and Vit C. However, PON1 was significantly and negatively correlated with TC and MDA where as it was positively correlated with HDL, SOD, Vit E and C.

Furthermore, SOD was significantly and negatively correlated with TC and MDA. However, it was positively correlated with HDL, PON1, Vit E and C in hypertensive subjects with alcoholism. Moreover, Vitamin E was significantly and negatively correlated with TC and MDA and positively correlated with HDL, PON1, SOD and Vit C. Similarly, Vitamin C was significantly and negatively correlated with TC

and MDA and positively correlated with HDL, PON1, SOD and Vit E in hypertensive subjects with alcoholism.

This study showed a negative correlation between MDA & vitamin C, vitamin-E, SOD, PON1 and positive correlation between PON1 & antioxidants (SOD, Vitamin-E & C). Results of present study demonstrate that serum PON1 activity measurement may add a significant contribution to cardiac marker. Thus the present study concluded that the decreased activity of PON1 and HDL-c levels may be contributed to the risk of atherosclerosis via alteration in oxidized-LDL and oxidative stress.

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Secondary Chronic Immune Thrombocytopenia in Diffuse Large B-cell Lymphoma: A Rare Case Report

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Abstract

Objective: To present a case of rare secondary chronic immune thrombocytopenia in diffuse large B-cell lymphoma.

Methods: A case of secondary ITP associated with diffuse large B-cell lymphoma (DLBCL) in a 58-year-old woman suffering from hemorrhagic tendencies that was refractory to conventional treatments of ITP was reported. This case is a rarity because there are not many cases of secondary chronic ITP due to DLBCL have been reported to date.

Results: A 58-year-old woman was diagnosed with ITP around 11 months before she was admitted to the Emergency Room with bleeding. Previous treatment with steroid and azathioprine was only temporarily effective. During the course of treatment, splenomegaly and lymphadenopathy were identified, but lymph node biopsy was delayed by the thrombocytopenia. The drug was then replaced to the eltrombopag, which showed good response. However, the patient had to undergo splenectomy because of the mechanical effect of splenomegaly, with the biopsy result showed DLBCL. Immune thrombocytopenia then went into a complete remission after splenectomy.

Conclusion: In cases of ITP that are refractory to conventional treatments, a thorough search for secondary ITP might be helpful, even if no underlying disorder is detected at the initial presentation.

Keywords: Diffuse Large B-Cell Lymphoma, refractory, secondary immune thrombocytopenia, splenectomy

Introduction

Immune thrombocytopenia (ITP) is a bleeding disorder characterized by isolated thrombocytopenia (platelet count <100,000/µL), and can be caused by various etiologies.[1] Primary ITP is idiopathic, whereas secondary ITP is linked to an underlying condition.[2] It has been reported that approximately 20% of cases of ITP are associated with underlying factors, such as other autoimmune diseases, drugs, viral infections, or Helicobacter pylori infection. In cases of ITP that are refractory to conventional treatment, a thorough search for secondary ITP might be helpful, even if no underlying disorder is detected at the initial presentation.[3]

This study presented a rare case of secondary ITP associated with Diffuse Large B-Cell Lymphoma (DLBCL) in a 58-year-old woman which was refractory to conventional treatments of immune thrombocytopenia.

Case

A 58-year-old woman was admitted to our hospital Emergency Room (ER) in March 2020 due to oral mucosal bleeding accompanied by a red skin rash, bruised skin, and red-coloured urine that appeared three days prior to the patient's admission.

Eleven months before the ER admission,

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she came to our Hematology outpatient clinic with oral mucosal bleeding. She had been receiving treatment for ITP from another hospital with methylprednisolone for six months. The steroid was then tapered down and azathioprine 50 mg was added. One week later, her platelet count had increased from 34,000/μL to 58,000/μL and Immature Platelet Fraction was 7,9. The diagnosis remained and the treatment of methylprednisolone 4 mg and azathioprine 50 mg were continued.

Two months before the ER admission, the patient came to Hematology outpatient clinic again with left upper quadrant abdominal pain. A physical examination revealed splenomegaly (Schuffner I), and an abdominal ultrasonography examination confirmed a splenomegaly of 8x5x6 cm. We still considered ITP diagnosis even though other causes were still possible, and more examinations were planned to look for secondary causes. The Antinuclear Antibody (ANA) test was negative. She continued methylprednisolone and azathioprine, and 2 weeks later the platelet count increased to 81,000/μL. Methylprednisolone was then stopped, while azathioprine was continued.

A chest Computed Tomography (CT) with contrast that had been done prior to ER admission showed right superior and inferior paratracheal lymphadenopathy and left supraclavicular lymphadenopathy with the largest size ± 1.1 x 1.3 x 1 cm in the left supraclavicle. Lymphoma or tuberculosis was suspected as the underlying disease. She was referred to a surgical oncologist for an excisional biopsy of the lymph node, but by then her platelet count had decreased to 2,000/μL and bleeding occurred, so eventually she was sent to our ER.

A physical examination on the day of hospitalization showed that her vital signs were stable. She was anemic with petechiae on her skin and oral mucosal bleeding was identified. The lymph nodes in the neck were not palpable. An abdominal examination revealed splenomegaly (Schuffner III). Laboratory examinations showed pancytopenia with a hemoglobin level of 8.9 g/dL, a leukocyte count of 2,800/μL, and a platelet count of 2,000/μL. A peripheral blood smear analysis revealed anisocytosis, some polychromasia, a normal leucocyte count without immature cells, and thrombocytopenia without giant platelets. There was microscopic hematuria.

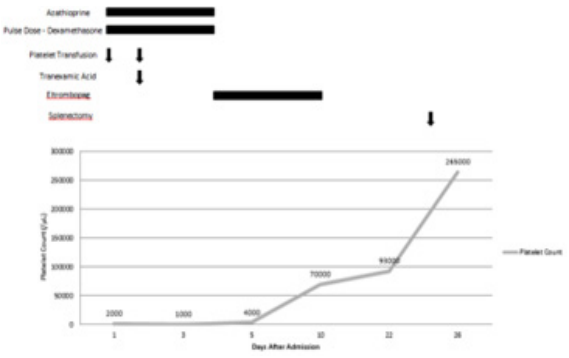

Fig. 1 The Patient's Clinical Course

She was treated with a pulse dose of dexamethasone (40 mg intravenously) daily for four days, 50 mg of azathioprine orally twice daily, and platelet transfusion until the platelet count >50,000/μL or until the bleeding stops. On the third day of hospitalization, the platelet count decreased to 1,000/μL. She underwent another abdominal ultrasonography on the fourth day of hospitalization which revealed a lymphadenopathy in the right para-iliac region with a diameter of ±1.74 cm. On the fifth day of hospitalization the platelet count was 4,000/μL. We stopped azathioprine and started giving her 25 mg of eltrombopag orally once daily. After the seventh day of eltrombopag, the platelet count was 70,000/μL. The patient was discharged on the tenth day of hospitalization and was scheduled to have an abdominal CT with contrast after discharged. The patient's clinical course can be summarised in Fig. 1.

The abdominal CT revealed multiple hypodense lesions, lobulated, conglomerated in paraaorta region and the enlargement of multiple inguinal lymph nodes bilaterally, suggestive of lymphoma and hepatosplenomegaly. The laboratory test twelve days after discharge revealed a platelet count of 93,000/μL.

Two weeks after discharge, the spleen size increased to Schuffner VI so the patient underwent a splenectomy in consideration of mechanical problems caused by the size of the spleen, pursuit of tissue histopathological diagnosis, and possible hypersplenism. Macroscopic and microscopic views of the spleen can be seen in Fig. 2A and 2B. A histopathological examination of the spleen revealed Diffuse large B-cell lymphoma with positive immunohistochemical (IHC) staining for expression of CD20, CD5, and Ki67 (positive >40%) but negative for expression of CD10. The microscopic view shows tumor mass consists of proliferation of small cells with follicular structure, clear cytoplasm and

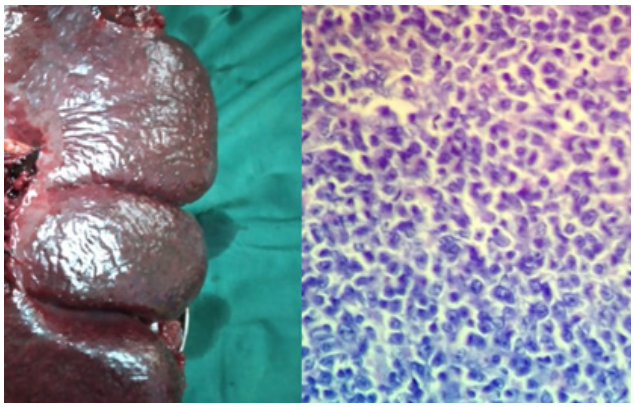

Fig. 2A. Macroscopic View of the Spleen; 2B. Microscopic View of the Spleen Shows Tumor Mass Consists of Proliferation of Small Cells with Follicular Structure, Clear Cytoplasm And Irregular Nucleus. Centrum germinativum infiltrated by small lymphoid cells. Sinuses and cords of Billroth are infiltrated by lymphoid cells

irregular nucleus. Centrum germinativum infiltrated by small lymphoid cells. Sinuses and cords of Billroth are infiltrated by lymphoid cells. Laboratory tests one day after the splenectomy showed a significant increase in the platelet count to 265,000/μL.

Microscopic view of the spleen shows tumor mass consists of proliferation of small cells with follicular structure, clear cytoplasm and irregular nucleus. Centrum germinativum infiltrated by small lymphoid cells. Sinuses and cords of Billroth are infiltrated by lymphoid cells.

The final diagnosis of the patient was stage IV high grade B-cell lymphoma (Diffuse large B-cell lymphoma) and Secondary Immune Thrombocytopenia (Lymphoma-associated).

Discussion

The incidence of ITP is estimated to be 2 to 5 per 100.000 persons in the general population.[4] Immune thrombocytopenia can manifest before, during, or after the diagnosis of lymphoma.5 Immune thrombocytopenia occurring prior to the diagnosis of aggressive DLBCL is rare.6 Ogata *et al*., 2019 revealed only 10 cases of DLBCL, which is the most common type of Non-Hodgkin lymphoma (NHL), complicated by ITP have been reported to date.[7] Tan *et al*. retrieved published papers from 1960 to 2010 and in three reported cases the ITP occurred 4, 18 and 46 months preceding DLBCL. In five cases ITP and DLBCL occurred concurrently.[6, 8]

Our case is ITP in a 58-year old women, slightly older than reported in previous studies which identified a median age of 50–55 years.[9] Our case presented with thrombocytopenia 11 months before her lymphoma diagnosis, similar to cases reported by Tan.6

Primary splenic DLBCL is very rare as it occurs in less than 1% of NHL. It is most commonly found in females and older males.[10] Shi *et al*., revealed that in 1,085 patients, 679 (62.6%) cases were nodal DLBCL (N-DLBCL) with the most common sites being the lymphonodus (64.8%), Waldeyer's ring (19.7%), the mediastinum (12.8%) and the spleen (2.7%).11

In previously untreated DLBCL, chemotherapy of rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisolone (R-CHOP) remain the backbone of therapy, with the total number of cycles and addition of radiation dependent on the stage at presentation and tumour bulk. This approach can achieve durable remission in approximately 60% of patients.[12,13] R-CHOP is most often given in cycles 3 weeks apart.14

Khalid *et al*.[10] revealed that effective treatment options for massive splenomegaly include splenectomy, chemotherapy and/or radiation.A splenectomy not only releases the pressure on adjacent organs and solves the issues of hypersplenism, but it also provides a definitive histopathological diagnosis of the underlying cause. After a splenectomy, cytopenias resolve in most cases. Djokic *et al*.[15] revealed a case of a patient with resolved cytopenias in the weeks after the splenectomy.

The prognosis of DLBCL-associated ITP is still not fully understood because of only 10 cases being reported before. In most of these cases, the DLBCL-associated ITP was refractory to conventional treatments for

ITP, being refractory to steroid therapy in four cases.[16,17] In all ten cases, the patients underwent specific therapy for DLBCL.[3,6,16-18] In seven cases, the ITP went into remission after treatment.[3,19,20] Three patients underwent an additional splenectomy.[18,19,21] The splenectomy rather than the treatments for lymphoma might have been responsible for the remission seen in these cases. This case suggests that controlling the lymphoma can have beneficial effects on DLBCL-associated ITP. Our case develops ITP remission after a splenectomy without specific therapy for DLBCL. Ideally the patient was also given chemotherapy with R-CHOP regimen, which comprises rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisolone.[3] But our patient refused further treatment.

Our case report has some limitations, such as no BMAT carried out to assess the diagnosis of hypersplenism and bone marrow involvement, and no data on LDH level.

Diagnosis of lymphoma should still be considered as one of the underlying diseases for ITP in middle-aged patients, even if lymphoma symptoms are absent in the initial presentation. A thorough search for underlying disorders is important in cases of ITP that are refractory to conventional treatments. The precise pathogenesis of lymphoma-associated ITP needs further investigation.

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Correlation between Serum KL-6 level and Severity of SARD-related ILD

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Abstract

Objective: To understand the correlation between serum KL-6 level and severity of SARD-related ILD in Indonesia.

Methods: This was a cross-sectional study to evaluate the correlation between serum KL-6 level and Interstitial Lung Disease (ILD) severity based on Chest High-Resolution Computed Tomography (Chest HCRT) among patients with Systemic Autoimmune Rheumatic Disorders (SARD) who visited the Rheumatology Clinic of Dr. Hasan Sadikin General Hospital during the period of January 2019 to February 2020. Secondary data were retrieved from a study on the Effects of Ciplukan Herbs on Organ Fibrosis. KL-6 serum concentration was measured from stored biological material and the correlation between the serum KL-6 level and ILD severity was analyzed by Rank Spearman's test.

Results: Thirty-four patients participated in this study with a median age of 37 years-old. Most of the participants were female (94.1%), Sundanese (64.7%), and had systemic sclerosis as an underlying disease (48.5). The median serum KL-6 level was 57.1 U/mL (21.6-444.1). Most participants belonged to severe ILD group (58.8%) with a mean serum KL-6 level of 65.1±48.9 U/mL. The highest mean serum KL-6 level (111.6±121.8) was observed in the moderate ILD group comprising of 32.4% of the participants. The remaining 11.8% participants belonged to mild ILD group with a mean serum KL-6 level of 61.1±24.9 U/mL. Serum KL-6 level was demonstrated to have a weak correlation with ILD severity (r=-0.229, p=0.193).

Conclusion: There is an insignificant weak correlation between serum KL-6 level and ILD severity based on chest HRCT in SARD patients.

Keywords: ILD, KL-6, SARD

Introduction

Systemic autoimmune rheumatic disease (SARD) is a multiorgan systemic inflammatory disease associated with immune system dysregulation and leading to disability, organ failure, and premature death. Systemic autoimmune rheumatic disease, also known as connective tissue disease or collagen vascular disease, consists of antiphospholipid syndrome, microscopic angiitis, granulomatous polyangiitis, cryoglobulinemia, systemic lupus erythematosus, systemic sclerosis, mixed connective tissue disease, and rheumatoid arthritis.[1]

Immune system dysregulation in PRAS leads to intetstital lung disease (ILD).[2] Data showed that 13.9–15% of SARD patients get ILD.[3] The main investigation modalities in establishing the diagnosis of ILD are conventional X-ray and thorax HRCT. Conventional X-rays have relatively low sensitivity.[4] Thorax HRCT is the gold standard of ILD diagnosis with a sensitivity of 95% which can also determine the severity of ILD.[5] HRCT examination is not

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yet widely available, limited to certain health care centers, and relatively expensive.[6] Thorax HRCT also carries a risk of radiation exposure so it is not safe for routine disease monitoring.[7] Krebs von den Lugen-6 (KL-6) serum is a biological marker that has high sensitivity in the diagnosis of ILD, monitoring the course of the disease, assessing therapeutic response, and predicting the prognosis of ILD.[8] Secretion of KL-6 into the bloodstream occurs due to severe damage to the alveolar basement membrane and increased permeability of the blood-air barrier. High serum KL-6 levels were found in more than 70% of SARD associated-ILD cases.[9]. Serum KL-6 level had a strong and significant correlation with the severity of PPI and the area of lung segments involved based on chest HRCT.[10,11]

Lee *et al.* showed that KL-6 levels had a strong and significant correlation with the severity of ILD and the area of the involved lung segment (r=0.561, p <0.001) based on thorax HRCT.[10,11] Yamakawa *et al.* reported a significant correlation between serum KL-6 levels and ILD severity in SARD (r=0.418, p=0.010).[8] Another study by Cho *et al.* concluded that KL-6 correlated with ILD severity based on thorax HRCT for interstitial lung disease (r=0.561).[11]

Serum KL-6 levels were influenced by ethnic differences. Evidence from previous studies in Asia and Europe showed different levels of KL-6. Most of the information regarding the role of serum KL-6 as a biological marker of ILD were obtained from studies in Japan and western countries. The effect of ethnic differences on ILD progression has been reported by Ishikawa *et al.*, Cao *et al.*, and Horimasu *et al.* The difference in KL-6 levels was caused by the polymorphism of the MUC1 gene.[12]

Research regarding the relationship between serum KL-6 levels and ILD severity is important to be carried out to serve as the basis for evaluating the use of serum KL-6 as a modality for regular monitoring of ILD in SARD population. Research regarding SARD-related ILD is still limited and to date there have been no studies regarding the use of serum KL-6 in the diagnosis or monitoring of ILD in Indonesian patient population. In this study, we evaluated the correlation between serum KL-6 levels and ILD severity based on chest HRCT in SARD patients.

Methods

Participants of this study was SARD patients in Rheumatology Clinic of Hasan Sadikin General Hospital Bandung, Indonesia in 2019-2020. Inclusion criteria were aged 18-60 years, diagnosed with SARD whose data was recorded in the research "Effects of *Ciplukan* Herbs on Organ Fibrosis", had been scored and staged for ILD severity based on HRCT thorax, and had stored biological material (less than 2 years) for serum KL-6 examination. Exclusion criteria were pneumonia, tuberculosis, history of tuberculosis, malignancy or history of malignancy, and functional class III-IV cardiac decompensation.

Data collection was initiated by looking for SARD patients with ILD who participated in the research "Effects of Ciplukan Herbs on Organ Fibrosis".[13] Serum KL-6 levels were collected as primary data. Blood samples from all the patients were collected in the same day or in maximum interval of 7 days from thorax HRCT examination. Serum were stored in the refrigerator at -80^{o}C. Serum KL-6 concentrations were measured using an enzyme-linked immunosorbent assay kit (Bioassay Technology Laboratory, China), according to the manufacturer's instructions. The ILD score and severity data were taken from the registry confirmed by two thoracic radiology consultants at the Radiology Department. The scoring system used is the Warrick *et al.* method which combines the severity and extent of the lesion.[14] The severity of the ILD was determined by the method of Mohammadi *et al.* which classifies the scoring results into mild, moderate, or severe degrees.[15]

This was a cross-sectional study with correlation analysis. Sample measurement was determined using the correlation test formula, with a minimum total sample of 32 participants was required. Secondary data for baseline characteristic was obtained from medical records, including age, sex, and medications.

The data that had been collected from research participants who met the inclusion and exclusion criteria were analyzed using the Statistical Package for the Social Science (SPSS) program. The numerical scale was presented with the mean and standard deviation if the distribution is normal or median and the range if the distribution was not normal. Categorical scale data was presented in the form of frequency and percentage.[16] Bivariate analysis was performed to examine the correlation of KL-6 levels with ILD severity based on chest HRCT. The correlation test was carried out using the Spearman's Rank correlation test.
This study had been approved by the Ethics

Committee of Hasan Sadikin General Hospital Bandung with ethical approval number LB.02.01/X.6.5/132/2021. For all patients who were enrolled in this study, the informed consent form was signed by the patient herself/ himself.

Result

A total of 60 medical record of SARD patients with ILD were obtained during the study period. There were 26 patients excluded, consisting of 25 patients with incomplete data and 1 patient with active pulmonary tuberculosis infection. Data analysis was performed on 34 patients who met the inclusion and exclusion criteria. Almost all of this study participants were women. The most common underlying disease is systemic sclerosis. The most common types of therapy are methylprednisolone and methotrexate. Complete baseline characteristics can be seen in Table 1.

The median KL-6 level in this study was 57.1 U/mL (21.6-444.1) and the mean ILD score based on the Warrick *et al.* was 16.8±6.4. The largest proportion of participants were in severe ILD group (Table 2.).

Table 1 Baseline Characteristics

Variable	n=34
Age (years)	
Median (minimum-maximum)	37 (21-64)
Sex, (n (%))	
Female	32(94,1)
Male	2(5,9)
Underlying Disease, (n(%))	
Systemic Sclerosis	16(48,5)
SLE	14(40)
MCTD	3(8,6)
Rheumatoid Arthritis	1(2,9)
Medications, (n(%))*	
Methylprednisolone	33(97,1)
Metothrexate	32(94,1)
Aspilet	26(62,9)
Nifedipin	19(55,9)
Ciplukan herbs	17(50,0)
Diltiazem	13(38,2)
Mycophenolate mofetil	11(32,4)
PPI/ H2 receptor antagonist/ antasida	9(26,5)
Azatioprin	9(26,5)
Cyclophosphamid	9(26,5)
Cyclosporin	6(17,6)

Note: *One patient could get multiple medications; PPI: proton pump inhibitor; MCTD: mixed connective tissue disease; SLE: systemic lupus erythematous

Table 2 Concentration of KL-6, ILD Score, and Severity of ILD

Variable	n=34
KL-6 concentration (U/ml) Median (range)	57.1 (21.6–444.1)
ILD Score Mean ± standard deviation	16.8±6.4
ILD Severity (n(%))	
Mild	3 (11.8)
Moderate	11 (32.4)
Severe	20 (58.8)

Table 3 and Figure showed that most of the participants had a severe ILD while the highest mean serum KL-6 level was found in the moderate ILD severity group. Dosage and duration of therapy could affected the severity of ILD and serum KL-6 levels but the secondary data source in this study did not record the dose and duration of therapy.

Correlation analysis using Rank-Spearman test at 95% confidence level showed that there was a weak correlation in a negative direction (r=-0,229) that was not statistically significant (p=0.193).

Discussion

This was the first study in Indonesia to assess the value of KL-6 in diagnosing and rmonitoring SARD related-ILD in Indonesia. The results of this study showed a weak correlation which is statistically insignificant between KL-6 levels and disease severity

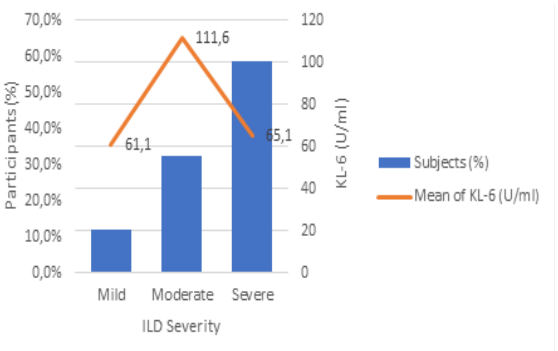

Figure Frequency of ILD Severity and Serum KL-6

Table 3 Serum KL-6 and Medications according to ILD Severity

	Mild	Moderate	Severity	Total
N (%)	3 (11.8)	11 (32.4)	20 (58.8)	34 (100)
Serum KL-6 (U/ml) Mean±Standard deviation	61.1±24.9	111.6±121.8	65.1±48.9	
Medications, n(%)*				
Methylprednisolone	3 (100)	11 (100)	19 (95.0)	33 (97.1)
Methothrexate	3 (100)	11 (100)	18 (90.0)#	32 (94.1)
Ciplukan herbs	1 (33.3)	6 (54.5)	10 (50.0)	17 (50)
MMF	1 (33.3)	2 (18.2)	8 (40.0)	11 (32.4)
Azatioprin	2 (66.7)	4 (36.4)	3 (15.0)	9 (26.5)
Siklofosfamid	3 (100)	3 (27.3)	3 (15.0)	9 (26.5)
Siklosporin	1 (33.3)	1 (9.1)	4 (20.0)	6 (17.6)

Note: *) One patient could get multiple medications; #) Methotrexate was topped once patient received cyclophosphamide or MMF. MMF: mycophenolate mofetil

although based on a literature review, KL-6 was the biological marker with the best diagnostic value in the identification of ILD, followed by surfactant protein-D (SPD) and matrix metalloproteinases 12 (MMP 12).).[17] Spearman's Rank correlation test with a 95% confidence level between serum KL-6 levels and ILD severity showed a weak correlation with a negative direction (r=-0.229) which was not statistically significant (p>0.05). This weak correlation was thought because KL-6 was influenced by many factors apart from the severity of the ILD including genetic factors medications consumed by the patient.

Most of the study participants had a severe ILD while the highest mean KL-6 levels were found in the moderate ILD severity group. The low KL-6 levels in the severe group were thought to be due to medications, hook effect, radiological features that persisted regardless of clinical improvement or discontinued disease progression. The correlation value of KL-6 levels with ILD severity was expected to be better and has a positive direction if KL-6 levels also increase with increasing disease severity.

The ILD treatment strategy is based on stopping or suppressing the inflammatory process. Corticosteroids, immunosuppressants, cytotoxic agents, and antifibrotic agents, either alone or in combination, are used in this disorder.[18] Almost all research participants received methylprednisolone and methotrexate therapy. Mycophenolate mofetil and cyclophosphamide are the treatment of choice for severe ILD according to clinical guidelines our hospital. Mycophenolate mofetil is a drug with tablet preparations that are more practical than cyclophosphamide which given intravenously. This convenience may be the reason that more numbers of severe ILD patients received mycophenolate mofetil therapy (40%) than cyclophosphamide therapy (15%). Dose and duration of therapy were not recorded on the registry so that the precise influence of these factor could not be determined on this study.

KL-6 levels in the moderate-severity group (111.6±121.8 U/mL) were higher than those in the mild-grade group (61.1±24.9 U/mL). These findings were consistent with the relationship between KL-6 levels and the degree of lung tissue damage.[9] The small proportion (18.2%) of moderate ILD participants receiving mycophenolate mofetil therapy was thought to be the reason of the high levels of KL-6 in this group because this drug could inhibit the proliferation of fibroblasts which associated with the secretion of KL-6 into the circulation.[19] Most of the participants were in severe ILD group but the average KL-6 level in this group tended to be lower than the moderate ILD group (65.1±48.9 U/mL vs. 111.6±121.8 U/mL). mL). The combination of the effect of mycophenolate mofetil, the drug most often given in this group, with other therapies (cyclophosphamide, methotrexate, and adjuvant therapy of *ciplukan* herbs extract) could be the reason of low KL-6 levels. Mycophenolate mofetil was most often given to the severe ILD group because this drug is the

treatment of choice for severe ILD according to clinical guidelines at the RSHS Rheumatology Clinic along with cyclophosphamide.

Serum KL-6 levels could be influenced by several other factors, including genetic differences and hook effect. Horimasu *et al.*'s obtained higher KL-6 levels in the patient group in Germany than in the group in Japan. This difference in levels was caused by the polymorphism of the MUC1 gene.[20] There are currently no data regarding the genetic profile of the Indonesian population.

The hook phenomenon that causes lower than expected results had been widely reported. Hook effect has been reported to affect various tests using the ELISA method, including the examination of -HCG, prolactin, calcitonin, aldosterone, and tumor markers (CA 125 and PSA).[21] The sample in this study was not re-examined by dilution when a low KL-6 result was obtained at the initial examination. Dilution would result in higher KL-6 levels if there was a hook effect that interferes with the test results. Duration of sample storage was thought did not influence the concentration of KL-6 since most of the samples for examination of serum KL-6 levels were taken on the same day of examination of HRCT of the thorax, while some examinations were carried out with a maximum length of 1 week.

There is a weak correlation between serum KL-6 levels and ILD severity based on chest HRCT in SARD patients. Serum KL-6 levels in this study is in the low range presumably due to drugs, ethnicity, and hook effects. There is tendency of higher serum KL-6 level on moderate ILD group than mild ILD group while the level tends to lower in severe ILD group compared to moderate ILD group. In conclusion, there is a weak correlation which is statistically insignificant between KL-6 serum and ILD severity found in this study.

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Indications and Complications of Orthopedic Hardware Removal in an Indonesian Tertiary Hospital: A Descriptive Study

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Abstract

Objective: To acquire clinical data regarding indications of implant removal and complications in orthopedic metal implant removal.

Methods: This was a cross-sectional observational descriptive study using patient medical records. The inclusion criterion was all patients who underwent orthopedic metal implant removal during 2018–2020 while the exclusion criterion was unintentional implant removal due to subsequent injury or loosening. Data regarding anatomic regions, indications, and complications were collected and presented in tables.

Results: In 112 patients participated in this study consisting of 75 (67%) men and 37 (33%) women, the implants were mainly located in thigh, lower leg, and ankle (53% combined). The most common indication for metal implant removal was conversion (31%), followed by infection (25%) and patient's request (20%). The only complication observed in orthopedic metal implant removal in this study was disturbed wound healing in a small percentage of the patients (16%). Most patients (84%) did not experience any complication due to metal implant removal.

Conclusions: Indications for metal implant removal may vary, with or without symptoms. Disturbed wound healing is a complication observed in metal implant removal. Despite the advantages of removal, further analysis and guidelines are needed to avoid unnecessary hardware removal considering the risk of complications.

Keywords: Complication, hardware, indication, removal

Introduction

Internal fixation procedures using metallic hardware have been chosen as fracture management in several last decades due to its generally good results.[1,2] After fractures had healed, typically the hardware will be removed from the body.[3,4] Hardware removals are usually done in patients with or without any symptoms such as pain sensation, infection, immobilization, or patient request.[2,4] However, hardware removal procedures are still controversial among orthopedic surgeons because indications of metal implant removal have not been clearly documented.[5,6] In addition, findings of complication from metal implant removal, such as neurovascular injury, refracture, infection, or problems in wound healing have caused indications of metal implant removal still controversial.[7,8,9]

Hardware removal is usually done in lower or upper extremities, such as ankle and wrist, radius, and femur. Based on population based studies in 2009 and 2010 in Germany, metal implant removal procedures were mostly performed in ankle and wrist joints. Besides,

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Indication that was mainly found was due to doctors recommendation as much as 68%, followed by pain (31%) and impaired function (31%).[4] In view of the surgeons, hardware removal is often needed after fractured has united, especially in a weight bearing long bones that risk an local osteoporosis due to prolonged load shielding to the bone structures, although this considerations is still disputable. From a biomaterial view, orthopedic implants is inert that will not result in reactions from the patients' body, but in some cases allergic reactions was reported, as well as implant related microorganism adherence. Based on a research conducted in the Netherlands in 2012, 89% of Dutch surgeons agreed to the metal implant removal procedures with implant infection as the main indication as much as >90%.[10]

Complications of metal implant removal varied based on each patient's condition. Based on a study in Japan from 2010 to 2015, perioperative complications were found after metal implant removal in 11 from 80 patients including arterial injury, blisters, nerve injury, skin necrosis, and infection.[2] In addition, 13 patients (22.4%) had infection with revision surgery based on a different study in Germany in 2014.[11]

To the best of our knowledge, there was no prior study reporting orthopedic hardware removal in Indonesia yet. There is no clear guideline whether patients with metal implant fixation should perform hardware removal or not. The objective of this study was to identify the indication and complication of metal implant removal to provide information for a clinical guideline for hardware removal in orthopedic practice.

Methods

This was a descriptive study with a cross sectional approach that has been approved by Padjadjaran University Ethics Committee (No.694/UN6.KEP/EC/2021) and from Dr. Hasan Sadikin Central General Hospital Bandung (No.7830/UN6.C1/TU.00/2021). Secondary data using patient medical records with history of orthopedic hardware removal from January 2018–December 2020 were collected. Anatomic region of the applied hardware, indications, and complications were gathered. Inclusion criteria was all patients that had orthopedic metal implant removal in Hasan Sadikin Hospital, and exclusion criteria was the patients with unintentionally removed implants due to subsequent injury or loosening.

All data obtained in this study were presented in a table and descriptive calculation was done using software IBM SPSS Statistics for Windows ver. 26.0 (Armonk, NY: IBM Corp.).

Result

As many as 112 patient's data were included to this study. As can be seen in Table 1, hardware removals were mostly performed in lower leg region (25%). Indication of the removal included conversion (31%), infection (25%), patient's request (20%), movement alteration (15%) and pain problems (9%) as shown in table 2.

Types of removed implants was described

Table 1 Distribution of Bone Injuries

Bone Distribution	n=112	%
Upper Extremity		
Upper arm	4	4
Forearm	7	6
Wrist	10	9
Hand	13	12
Shoulder	2	2
Elbow	2	2
Lower Extremity		
Thigh	15	13
Lower leg	28	25
Knee cap	1	1
Ankle	17	15
Foot	8	7
Pelvis	4	4
Spine	1	1

Table 2 Indications/Reasons for Implants Removal

Indication/Reason	n=112	%
Symptomatic		
Pain Sensation	10	9
Motor Function Impairment	17	15
Infection	28	25
Asymptomatic		
Patient's Request	22	20
Conversion	35	31

Table 3 Types of Removed Implants

Types	n=112	%
Plate and screws	45	40
Screw(s)	20	18
Intramedullary nail	19	17
Kirschner wire	16	14
Schanz screw / Steinmann pin	12	10

Table 4 Complication of Implants Removal

Complication	n=112	%
Wound Healing	18	16
No Complications*	94	84

*Complications that were expected but not found in this study including refracture, neurovascular injury, blistering, skin necrosis, and prolonged numbness

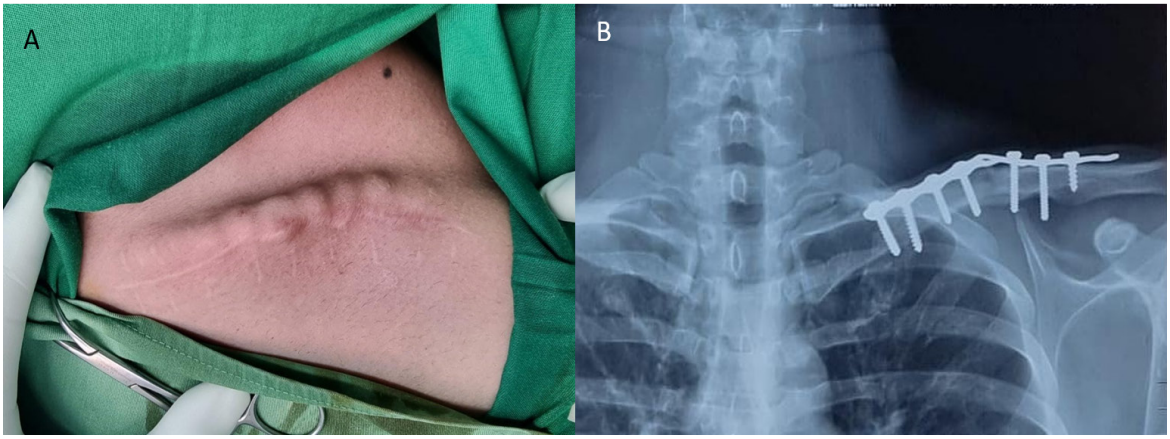

Fig. 1 (A) Preoperative clinical picture depicting a patient complaining pain due to irritation of the hardware to surrounding tissue; (B) Radiograph showing a united fracture with plate and screws applied

in table 3, depicting plate and screws as the most common implant construction to be removed. Table 4 showed the complications of hardware removal procedures. The complications were found in 18 patients (16%) comprised of disturbed wound healing.

Discussion

This was the first study in Indonesian hospitals concerning indications and complications of metal implant removal. It was revealed that the complications and indications were varied

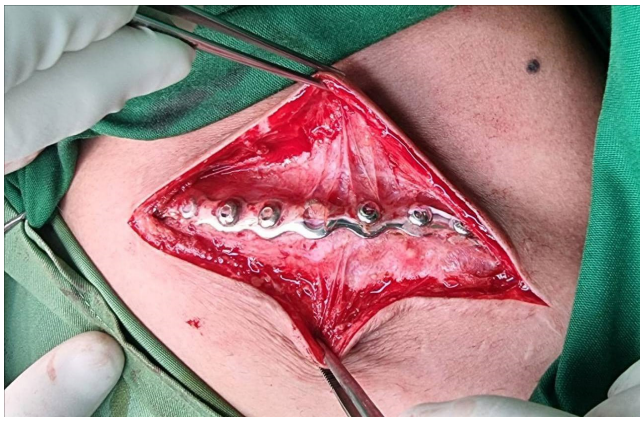

Fig. 2 Intraoperative Finding Showing Bone Formation and Inflamed Tissue

Fig. 3 Extracted Hardware Consisted of One Plate and Seven Screws

among the patients.

Indications of metal implant removal have not been clearly validated and secondly because complications of metal implant removal were found.[5,6] In Indonesia, many patients wanted the hardware to be removed for some religious reasons, e.g. they did not want the foreign material still inside their body when they were deceased. Other irrelevant reason included some false information regarding the danger of the hardware, for example, the fear of the metallic hardware will attract lightning strike.

As shown in Table 1, fractures were mostly found in lower extremity, specifically in lower leg as much as 25%. This result is slightly different from previous research by Georg Reith *et al*. in Germany.[4] Based on their research, fractures were mostly found in the ankle joint (21%) and wrist joint (15%). According to a study in German by Onche *et al*., femoral fractures were the most common findings with 42,6%.[5] The differences between this study and previous studies might be attributable to different injury pattern in different community, such as traffic regulations and people habit regarding daily transportation, housing, or sports activities.

In general, it is widely accepted that orthopedic hardware on lower leg should be removed after fracture healing, due to its weight bearing features. In a weight bearing bones, the internal fixation will induce local osteoporosis because of its load sharing characteristics. As shown in Table 3, most common removed implants are plate and screws construction. This was reasonable due to the extramedullary feature of plate and screws implantation in which they cause attrition and inflammation to surrounding tissues. However, intramedullary nails were also considerably removed despite less risk of tissue attrition. In long bones, especially weight bearing bones, nail can be removed after union to restore the physiological mechanical loading to the bone, also to decrease the pain an insertion site.

There were several indications of metal implant removal found in this study. The main indication was presenting symptoms such as pain (Fig. 1–3), movement system impairment, infection, or surgeon's decision including hardware conversion. Other indications were patient's wishes without any symptoms. The hardware conversion is the changing of implanted metal implant to other type of hardware, due to inefficacy of prior hardware or fixation failures. This procedure was part of the metal implant reconstruction that must be done intentionally by the surgeon. Based on this study, symptomatic indication of metal implant removal that was mostly found in this study was infection as much as 25% cases. This data showed similar result with the study that have been done in Holland which the main indication of metal implant removal was infection with >90%.[10] The infection indication can also be called as infection after fracture fixation (IAFF). IAFF that occurred in patients in this study mostly caused by bacterial growth on metal implant and spread to necrotic bone tissues. Based on time of onset, IAFF was classified into early infection (<2 weeks), delayed infection (2–10 weeks), and late

infection (>10 weeks).[12] As the complication of metal implant fixation, infection can be the most feared and challenging complication in treating patients with musculoskeletal trauma. This is because the complication can be progressive and lead to delay healing, permanent functional loss, or even amputation of the affected limb.[12] Focusing into infection after hardware removal, it is attributable to poor soft tissue due to repeated surgery, especially in regions that muscle pad is so thin that the underlying bone is directly beneath the skin, that will become a *port d'entrée* for subsequent infections.

The other indications were patient's demand (20%), motor function impairment (15%), and pain sensation (9%). There is a little difference between this findings and findings from previous research that mostly had pain as an indication for metal implant removal.[1,4,5] This difference was caused by the variety of indications or reasons which depended on complaints or reactions from implant fixation in patients. A research that was conducted by R Shrestha *et al*. in Nepal showed that 45% of metal implant removal indications were pain.[6] Based on different research by Georg Reith *et al*., surgeons' recommendation (68%) was the most indication, followed by pain (31%) of metal implant removal. In this study, surgeons' recommendation were not included as measurement result because it can be interpreted as presenting symptoms in patients due to metal implant fixation.[4] The pain sensation which felt by patients with implant metal fixation can be caused by varied factors: intrinsic factors and extrinsic factors. The usually occurring intrinsic factors were the malunion or nonunion of the metal implant fixation, thus led to longer period of rehabilitation and might resulted in disability. The external factors were due to poor postoperative pain control which had been explained in a study done in Marshall University of United States. In that study, the difficulty in pain controlling was caused by the high incidence of tolerance to narcotics as analgesics. [13,14]

Based on literature, the findings of complication of metal implant removal vary and differ depending on the type of implant and the anatomic site of the removal. Most of the complications can be subjective depending on patient's complaints such as a larger scar or increased numbness at the anatomic site of removal.[15] Out of 112 samples, 94 samples did not experience complications due to metal implant removal as much as 84% (Table 3). The other 18 samples only experienced wound healing complications by 16% in which inflammatory process did not go as expected. It is known that wound healing is a physiological process of the body that aims to maintain the integrity of the skin after trauma. There were 3 phases of wound healing, that were homeostasis/inflammation, proliferation and remodeling phase.[16,17] This wound healing complication occurs due to trauma caused by open surgery from the metal implant removal. Other complications of metal implant removal such as arterial injury, nerve injury, blistering, skin necrosis, infection and increased numbness were not found in data from patients with metal implant removal.

The results obtained in this study were similar with previous studies, where in previous studies there were various types of complications from metal implant removal. Based on research in Japan from 2010 to 2015 by T Kasai *et al*., perioperative complications were found after metal implant removal in 11 (14%) from 80 patients. Complications that were found such as 1 patient with arterial injury, 3 patient blistering, 3 patient nerve injury, 2 patient skin necrosis, and 2 patient infection.[2]

This study had four main limitations: (1) the specific bones was not described, instead we chose to mention only the region, because there are some region containing too many bones to described one by one; (2) the surgical features including follow-up period were not homogenous so that will complicate the analysis when clinical consideration was taken into account; (3) various first surgeons or hospitals, making it more difficult to investigate the causes and indications of implant removal; and (4) single-centered study origin that might result in lack of external validity and scientific flaw.

As a conclusion, indications for metal implant removal still be vary in different hospital referral level. Considering the risk of developing complications from hardware removal, it is recommended that further research be conducted on the indications and complications of metal implant removal in a larger scale, more understanding to unnecessary hardware removal urge from the patients, and to promote a guideline regarding this matter to be used in orthopaedic practice.

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