CASE REPORT
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Gastrointestinal bleeding as a life-threatening complication of liver abnormality in a Turner syndrome patient

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ABSTRACT

Background: Turner syndrome is a rare condition with high morbidity and mortality rates, it leads to multiple organ damage when left untreated. Meanwhile, liver involvement in this condition ranges from asymptomatic to severe such as cirrhosis with massive gastrointestinal bleeding. This study presents a case of gastrointestinal bleeding due to cirrhosis in Turner syndrome where the patient showed third-grade esophageal varices as a sign of portal hypertension.
Case Presentation: A 26-years old female came to the Emergency Department of Dr. Soetomo General Hospital in Surabaya with massive gastrointestinal bleeding. The patient was a Turner syndrome, diagnosed ten years ago. The patient was negative for hepatitis B surface antigen (HbsAg) and anti-hepatitis C virus (anti-HCV). The gastric lavage was performed to reduce active bleeding with blood transfusion. The upper gastrointestinal endoscopy indicated portal hypertension with third-grade esophageal varices, fibro scan indicated cirrhosis hepatic and abdominal CT-scan showed early cirrhosis and splenomegaly supporting the presence of portal hypertension. Since the patient refused to endoscopic varices ligation, hematemesis repeated three times after the first visit resulting death of the patient.
Conclusion: This is a Turner syndrome patient who experienced life-threatening gastrointestinal bleeding as complication of liver abnormality. This case highlights that liver cirrhosis should be evaluated in individuals with Turner syndrome to prevent such complications.

Keywords: Turner syndrome, gastrointestinal bleeding, cirrhosis, esophageal varices.
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INTRODUCTION

Turner syndrome is a rare condition in women caused by complete or partial loss of one X-chromosome.[1] It occurs approximately in 1 out of 2500 women, and is characterized by hypergonadotropic hypogonadism, short stature, ovarian dysgenesis, cardiovascular disease, chronic hepatic dysfunction, and renal dysfunction malformations.[2,3] The management of women with this syndrome requires a multidisciplinary approach because many different organ systems are often affected.[2] Compared to the general population, morbidity and mortality in women are higher due to the diseases associated with Turner syndrome.[1]

Several symptoms are associated with Turner syndrome due to endocrine, gastrointestinal, and hepatic disorders and other phenotypic characteristics. In addition, liver damage appears to be very prevalent in Turner syndrome as indicated by elevated serum biomarkers.[4,5] A study on middle-aged women with Turner syndrome found that abnormal liver function is presented in almost 80% of the cases.[4] The underlying cause is multifactorial, mostly due to increased lipids, but the lack of estradiol in untreated women is also possible. Furthermore, a liver tissue biopsy study showed architectural changes that are probably congenital in origin.[1] Liver involvement is asymptomatic in most cases, but the risk of cirrhosis reportedly increase by five-fold.[5,6]

Cirrhosis is closely related to esophageal varicose veins and gastrointestinal bleeding. The major complication of portal hypertension due to cirrhosis is gastrointestinal bleeding which is often life-threatening. This complication is also associated with substantial morbidity and mortality in the general population as well as Turner syndrome patients although very rarely reported.[7] In this article, we are reporting a patient with massive gastrointestinal bleeding associated with esophageal varices due to liver involvement in Turner syndrome.

CASE PRESENTATION

Ms. A, a 26 years old female reported to the Emergency Department of Dr. Soetomo General Hospital in Surabaya with a chief complaint of gastrointestinal bleeding and vomited up to 500-600 mL blood. The patient also had black, tarry stool two days before being admitted to the hospital and this condition occurred 3-4 times per day. Furthermore, the patient felt nauseated without vomiting, looked pale and frequently experienced fatigue two days before admission. There was no shortness of breath, no complaint of abdominal pain, or any mass around the anus. In addition, the patient complaint about weight loss without loss of appetite in the previous months. There was no complaint of fever, difficulty in urinating,

or other signs such as gum bleeding and petechiae or rash. The history of using analgetic or herbal medicine was denied.

The patient had been hospitalized twice before reporting the similar complaint and had three blood transfusion bags. The patient had been diagnosed with Turner syndrome since 2009 after having menstrual problem at the age of 16. The ultrasound showed a single ovary and the genetic chromosome examination revealed 45,X confirming Turner syndrome. The patient often takes hormonal therapy to induce menstruation but later stopped because the pills increased her body weight. There is no family with a similar disease.

Physical examination indicated general weakness due to anemia. The BMI was 30.8 kg/m^2, classified as class 1 obesity. The head and neck examination showed anemia and a webbed neck, meanwhile, further abdominal examinations showed non-palpable liver and splenomegaly (Schaffner 2 and Hackett 1).

In the Emergency Department, oxygen therapy was given. The gastric lavage was performed to reduce active bleeding and the patient was advised to fast temporarily until the bleeding stopped and 80 mg omeprazole was administered via intravenous bolus with octreotide and saline infusion as maintenance fluid. Initial laboratory investigation showed hyperglycemia, normal liver function, non-reactive for hepatitis B surface antigen (HbsAg) and anti-hepatitis C virus (anti-HCV) (Table 1). The chest X-ray on heart and lungs were within normal limit.

The patient was admitted to the High Care Unit due to active massive bleeding and daily therapy of omeprazole injection 40 mg was given every six hours with two bags of blood transfusion. On the next day of treatment, the melena has stopped and the nasolacrimal tube was cleared. The patient then underwent upper gastrointestinal endoscopy to evaluate the cause of bleeding. The results showed third-grade esophageal varices as a sign of portal hypertension (Figure 1). Furthermore, the transient elastography examination (fibro scan) was performed and the result showed cirrhosis hepatic with the median value was 17.3 kPa (F4). Furthermore, the abdominal CT-scan showed early cirrhosis and splenomegaly, indicating portal hypertension (Figure 2). Based on these results, propranolol 10 mg twice a day was added as treatment of esophageal varices. The patient was advised to continue the treatment and prepare for ligation of varices.

After the first admission, the patient was hospitalized three times with the same massive hematemesis melena complaint. Although all prescribed medications were taken regularly, the patient refused to undergo endoscopic varices ligation. The patient was also offered a liver biopsy but rejected. The patient passed away due to hypovolemic shock caused by massive hematemesis.

DISCUSSION

Turner syndrome is a rare condition in women caused by total or partial loss of X-chromosome.[3] It occurs approximately in 50 per 100.000 women in different populations, meanwhile, the average age at diagnosis is 15 years. Most women with Turner syndrome are diagnosed in adulthood when the complication of certain disorders begin to appear.[1] Liver involvement has also been frequently reported with elevated serum transaminases, gamma-glutamyl, transferase and alkaline phosphatase, with or without increased bilirubin levels.[1,5,8] In a cohort study, the prevalence of

Table 1. Laboratory test results of the patient.

Lab parameters	Result
Hemoglobin	5.0 g/dL
White blood cell	9790/mm^3
Platelet	234000/mm^3
Hematocrit	26.0%
Neutrophile	72.6%
Lymphocyte	19.2%
MCV	92
MCH	27.9
MCHC	30.1
Erythrocyte sedimentation rate	7.0
Blood urea nitrogen	14 mg/dL
Creatinine	0.51 mg/dL
Na	135 mmol/L
Kalium	3.2
Chlorite	104
Albumin	3.7 g/dL
Aspartate transaminase (AST)	25 U/L
Alanine aminotransferase (ALT)	38 U/L
Random blood glucose test RBG	141
Fasting blood glucose	133 mg/dL
2 hours postprandial blood glucose	207 mg/dL
Total cholesterol	163 mg/dL
High-density lipoprotein (HDL)	46 mg/dL
Low-density lipoprotein (LDL)	103 mg/dL
Triglyceride	55 mg/dL
Uric acid	2.2 mg/dL
Viral hepatitis test	
HbsAg	Non-reactive
Anti-HCV	Non-reactive
Hormones	
Growth hormone (GH)	0.724 ng/mL
Luteinizing hormone (LH)	26.32 mIU/mL
Follicle-stimulating hormone (FSH)	60.16 mIU/mL
Thyroxine (FT4)	1.19 ng/dL
Thyroid stimulating hormone (TSH)	0.618 µIU/mL

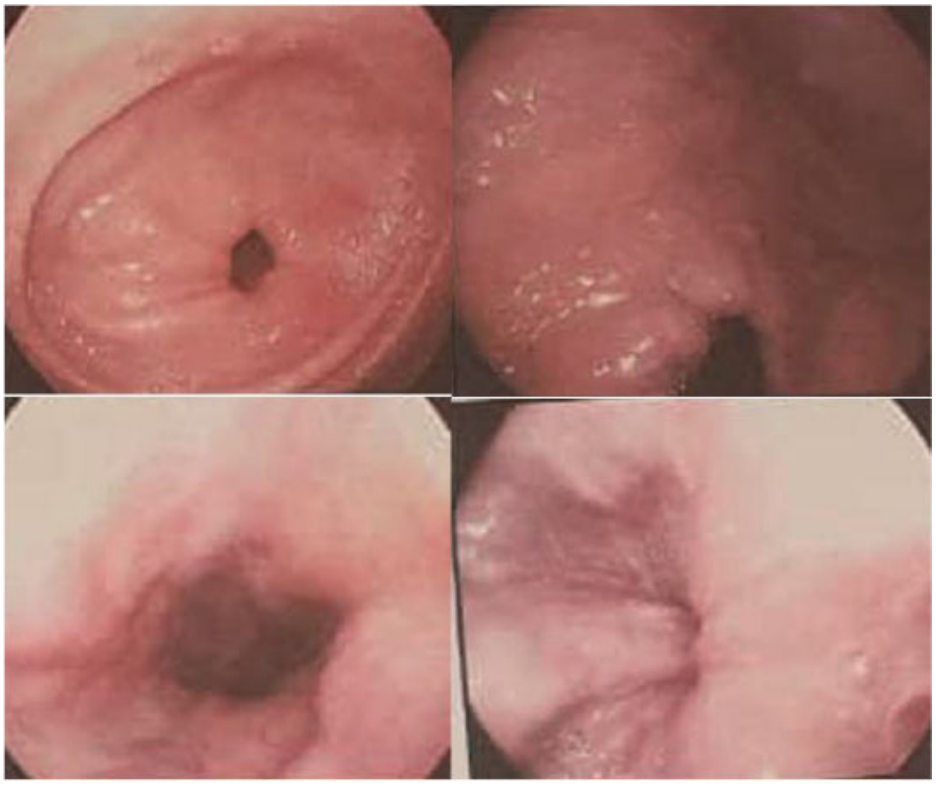

Figure 1. Endoscopy results of the patient suggest third-grade esophageal varices.

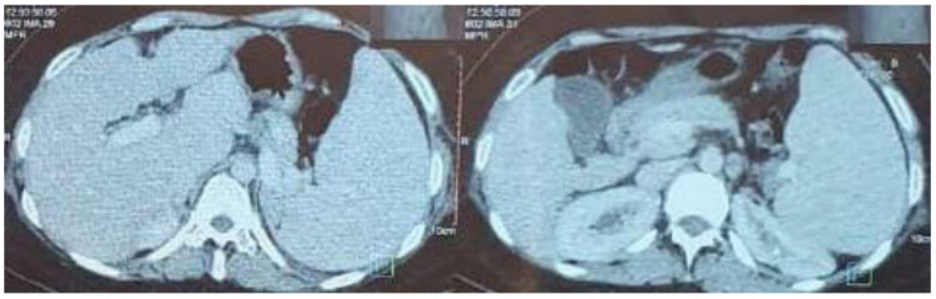

Figure 2. Abdominal computed tomography (CT)-scan of the patient suggests early cirrhosis and splenomegaly.

pathological liver enzymes was 36% at 33 years, increasing 3.4% over 5 years.[9] Meanwhile, the underlying cause of liver function abnormalities in Turner syndrome is multifactorial but is related to elevated lipids, insulin resistance, lack of estradiol, and vascular changes.[1] In addition, autoimmunity has been reported as another related factor.[10,11]

Nevertheless, Turner syndrome with massive gastrointestinal bleeding is rarely reported. In our case, liver abnormality was presented as cirrhosis, the main cause was difficult to evaluate because we did not perform liver biopsy. Several factors that probably contributed to this condition had been discussed. The lipid profile in this patient tends to be within the normal limit without any prior prescription. However, insulin resistance might have a role in the development of cirrhosis as well as vascular changes, but no further evaluation was carried out on the patient.

In most of Turner syndrome cases, early clinical manifestations of liver abnormalities in Turner syndrome are asymptomatic and detected as an increase in serum transaminases during systematic blood testing.[3,5] Furthermore, liver involvement rarely progresses to overt hepatic disease but a few cases develop into end-stage liver disease with several complications and might even require a liver transplant.[3,8] A study on liver abnormalities in Turner syndrome patients reported that a few cases led to severe complications such as refractory ascites and uncontrolled bleeding from esophageal varices.[5] In our case, the patient had a severe complication of uncontrolled bleeding from ruptured esophageal varices. The progression of liver disorder was asymptomatic until massive bleeding occurred as a severe complication.

The pathogenesis of liver dysfunction in Turner syndrome is not yet clear, but various factors are involved such as hyperlipidemia, obesity, vascular changes, autoimmunity, impaired insulin secretion, and the lack of estrogen.[1,3,12] Hepatic changes include minimal abnormalities, steatosis, steatohepatitis, biliary involvement, and cirrhosis.[5] A study reported a fivefold higher risk of cirrhosis in Turner syndrome compared to the general population.[6] In a large cohort study, hepatic vascular lesions were also suggested as the major cause of liver abnormalities followed by steatosis.[5] The vascular changes in Turner syndrome leads to the alteration of hemodynamic state and liver architecture. Vascular abnormalities in Turner syndrome patients with marked architectural changes of the liver, and these abnormalities are probably congenital in origin and are evenly distributed.[3,12]

The liver involvement in Turner syndrome has a wide spectrum, and ranges from asymptomatic to life-threatening conditions such as uncontrolled bleeding due to severe esophageal varices. Therefore, a regular liver function test is needed to detect abnormalities. The initial evaluation of Turner syndrome patients with abnormal liver tests for over six months needs to be carried out in two non-invasive procedures: liver stiffness measurement using transient elastography and abdominal ultrasound. The abdominal ultrasound examination is required once a year to evaluate the liver architectural changes.[8] Liver biopsy is recommended for diagnostic and prognostic purposes in Turner syndrome with persistently abnormal liver function test.[5, 8] However, when liver biopsy is not feasible, stiffness measurement by transient elastography might reflect the severity of liver fibrosis.

This non-invasive procedure enhances the optimal classification of liver damage.[8] The patients with esophageal varices require either long-term beta-blocker treatment or variceal ligation.[12-15] In our case the patient refused to have variceal ligation.

Previous studies showed that hormone replacement therapy with estradiol also has a beneficial effect on liver function.[13,14] Another study also reported that higher doses of estradiol improve liver function.[1] Treatment with ursodeoxycholic acid is commonly recommended when there is a biliary involvement associated with the cholestatic profile. However, this treatment has no beneficial effect on liver enzymes when altered liver architecture.[8] In this case, the patient underwent hormone replacement therapy at 16 years old when she was diagnosed with Turner syndrome for the first time. But she stopped taking hormonal therapy due to weight gain. The cessation of therapy might worsen the progression of any abnormalities in Turner syndrome, particularly in the liver.

CONCLUSION

This study reported the case of a 26-years old woman with massive hematemesis melena caused by third-grade esophageal varices and Turner syndrome. Esophageal varice is a sign of portal hypertension due to liver cirrhosis. The underlying cause of liver cirrhosis was the progression of the untreated Turner syndrome since other causes such as viral hepatitis and alcoholism have been eliminated. In addition, liver biopsy is needed to evaluate the precise cause of liver cirrhosis. Although the patient was given propranolol to control esophageal varices, gastrointestinal bleeding still occurred, therefore, ligation is required to control esophageal varices and the patient refused the procedure.

PATIENT CONSENT

The patient had agreed and signed informed consent regarding publishing this clinical case in an academic journal without exposing the patient's identity.

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DISCLOSURE OF CONFLICTS OF INTEREST

The authors declare that there is no conflict of interest.

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AUTHOR CONTRIBUTION

Both authors contributed equally to the study.

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