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Intrahepatic and Extrahepatic Cholestatic Jaundice Caused by Adenocarcinoma Pancreas with Hepatitis B Infection: A Case Report

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ABSTRACT

Background: Cholestasis is defined as the stagnation of biliary duct secretion. Intrahepatic jaundice cholestasis is caused by inflammation that happens intrahepatic from an infection such as hepatitis. Meanwhile, extrahepatic cholestasis is caused by obstruction of the biliary duct outside the liver. Stagnation of the bile flow due to these couple of conditions occurring concurrently has been rarely reported. Biliary duct stagnation that occurs with an infection of hepatocytes will cause more serious and progressive effects. **Case presentation:** A 73 years old woman with extrahepatic and intrahepatic cholestasis caused by pancreatic adenocarcinoma along with chronic hepatitis B. The diagnosis is made based on clinical findings, lab findings, and radiology findings. Quick action is mandatory to prevent complications caused by hyperbilirubinemia and slows the progression of hepatitis B-induced liver fibrosis. A Whipple procedure was performed on this patient to treat the biliary duct obstruction. The patient's condition improved after surgery. The patient is then planned to be given adjuvant chemotherapy, preceded by the administration of antivirals for hepatitis. **Conclusion:** Cholestasis jaundice causes hyperbilirubinemia that presents with clinical complaints such as jaundice, itchy and could cause several complications due to damage to the liver tissue whose clinical manifestations are related to impaired liver function caused by hyperbilirubinemia in the form of hypoalbumin, hypercoagulation, and in advanced stages can end up with liver cirrhosis. The principle management for cholestatic jaundice is bile duct decompression which is expected to rule out the etiology of the blockage. Tenofovir was given before chemotherapy in these patients to prevent hepatitis flare due to hepatitis B.

1. Introduction

Cholestasis is defined as stagnation of secretion from the biliary duct. Cholestasis can be caused by hepatocyte functional disorders on biliary secretion or obstruction on every level of the bile excretory pathway, from the level of liver parenchyma cells on the basolateral membrane (sinusoidal) to the ampulla of Vater in the duodenum.¹

Cholestasis jaundice is classified into intrahepatic cholestasis and extrahepatic cholestasis, depending on the degree of obstruction of the bile ducts, with

clinical manifestations such as jaundice and pruritus due to stagnation of bile flow. Intrahepatic cholestasis or also known as functional cholestasis, can be caused by diseases involving liver parenchyma cells and/or the intrahepatic bile duct, as found in the state of hepatitis virus infection, acute alcoholic hepatitis, intrahepatic atresia (infantile cholangiopathy), and Zellweger's syndrome. While extrahepatic cholestasis or obstructive cholestasis is caused by an excretory blockage at the external part of the liver, along with

extrahepatic bile duct as found in choledocholithiasis, benign bile duct strictures, primary or secondary sclerosis cholangitis, Mirizzi's syndrome, cholangiocarcinoma, pancreatic cancer, and ampullary adenoma/carcinoma.^{1,2,3}

Pancreatic cancer is the second most common malignancy in the gastrointestinal tract and the fourth highest cause of death from cancer in the United States. This type of cancer is rarely found in the population under 45 years of age and is extremely increased in the population aged around 70 years old.¹² It is known that 95% of pancreatic tumors are pancreatic adenocarcinomas and 95% of pancreatic cancer are exocrine type of tumors. Common symptoms found in an individual with pancreatic cancer such as jaundice, pruritus, pale stools, concentrated urine, undesirable weight loss, fatigue, and loss of appetite.¹

Chronic hepatitis B is a chronic necro-inflammatory disease caused by persistent hepatitis B virus infection. Chronic hepatitis B is characterized by a positive result of HBsAg serum test for more than 6 months, high level of HBV DNA, and chronic necro-inflammatory process in the liver. Chronically, hepatitis infection can experience 4 phases of the disease, namely the immune tolerant phase, immune clearance phase, inactive carrier phase, and reactivation phase.⁴

Indication for therapy in chronic HBV infection is determined by the value of HBV DNA, HBeAg status, ALT serum, and liver histology. Indications for therapy in patients with chronic hepatitis B infection accompanied by positive HBeAg are for patients with HBV DNA count $>2 \times 10^4$ IU/ml and ALT score $>2x$ from the normal range. In HBeAg negative patients, therapy can be started if the patient's HBV DNA test results as $>2 \times 10^4$ IU/ml and ALT score are $> 2x$ from the normal range. The therapy initiation can be done if the results are ongoing severe-moderate inflammation or significant fibrosis. The final marker that is often used is the loss of active viral replication markers, which can be seen from the HBeAg and HBV DNA test.⁵

2. Case Presentation

A 73 years-old woman was hospitalized in the internal medicine department of Dr. M. DJamil Province Government Hospital, Padang, with a working diagnosis of intrahepatic and extrahepatic cholestasis. The patient first came to the hospital with a chief complaint of upper right abdominal pain which elevated from 7 days before she was administered. This complaint is accompanied by yellow eyes that patient has felt since 2 weeks ago. The patient also complained of upper right abdominal pain since a month ago, along with other symptoms such as dark-colored urine, loss of appetite, and undesirable weight loss. The eyes started to turn yellow a month ago and have constantly elevated in the last 7 days. Physical examination revealed icteric sclerae, and on abdominal examination, found tenderness along with hepatomegaly and a palpable mass in the epigastric region with a hard consistency, flat surface, and tenderness.

Subsequently, this patient was subjected to several laboratory tests, such as blood test, bilirubin, alanine transferase (ALT), prothrombin time and activated partial prothrombin time (PT/APTT), hepatitis marker test, alkali phosphatase, gamma GT, and due to suspicion of pancreatic tumor, this patient was also examined for tumor marker Ca19-9. From the laboratory result found hemoglobin 8.6gr/dl, leukocytes 5.550/mm³, platelets 204,000/mm³, indirect bilirubin 2.6 ml/dl, direct bilirubin 17.1mg/dl and total bilirubin 19.7mg/dl, serum albumin 2.3gr/dl, Serum globulin 4.9gr/dl, ALT 84 u/l, PT/aPTT 12.9/40.5 (10.9/36.5), alkaline phosphatase 554 u/l, gamma GT 5.6u/l, hepatitis marker showed reactive HBsAg. The result of Ca 19-9 increased by 105.34 U/ml (<37.00).

Based on laboratory tests, it can be concluded that this patient is infected with hepatitis B, resulting in intrahepatic bilirubin stasis, accompanied by stagnation of bilirubin caused by obstruction of extrahepatic biliary ducts along with elevated Ca 19-9 level, and this is explained well that the cause of extrahepatic obstruction on this patient is more likely

the presence of a pancreatic tumor. Furthermore, in order to determine the phase of hepatitis B infection in this patient, an HBeAg examination was performed and carried out with a positive result. HBV DNA test result was 20.000 IU/ml, and to know the degree of fibrosis in this patient, a liver fibroscan examination was carried out with the result of F3. The next examination of the pancreatic tumor by imaging via abdominal ultrasonography (USG) and abdominal CT scan with contrast. The result of abdominal USG showed enlarged liver with a smooth surface, smooth homogenous parenchyma, and sharp edges, along with dilated biliary duct, enlarged gallbladder, thin bile wall, and none of the gallstones were found. A mass appears in the head of the pancreas.

An abdominal CT scan shows an appearance of an enlarged intrahepatic and extrahepatic biliary system and the appearance of a mass in the head of the pancreas with a size of 4,97x3,53x5,2 cm with indistinct borders and irregular edges. The gallbladder enlarged with a diameter of 5,14 cm. the CT scan conclusion for this patient is a pancreatic head tumor that caused dilatation in both intrahepatic and extrahepatic biliary systems with gallbladder hydrops.

The working diagnosis for this case is intrahepatic and extrahepatic cholestasis ec pancreatic head tumor with chronic hepatitis B infection. The most urgent first-line treatment for this patient is immediate biliary decompression by treating the stagnation of bile flow. The static biliary system, together with chronic hepatitis infection, could speed up the damaging process in liver parenchyma and can lead to liver cirrhosis. Besides that, supportive therapy is still given to improve the patient's general condition, such as packed red cells and albumin transfusion. From the clinical and supporting data of this patient, the stadium of the pancreatic tumor was on stadium II, and the tumor was categorized as a resectable tumor which made the patient immediately plan for surgery. The operating procedure used is the Whipple procedure or also known as pancreaticoduodenectomy, which means the surgeon will remove the head of the pancreas, and in some

cases, this procedure also removes the pancreas body, some parts of the stomach and small intestine, several lymph nodes, gallbladder, and bile ducts.

After the Whipple procedure, the patient's clinical condition was monitored within normal limits, and the bilirubin level was decreased to 3.4 ml/dl for direct bilirubin, 1.6 ml/dl for indirect bilirubin, and 5 ml/dl for total bilirubin level. Jaundice in the patient was reduced. The anatomical pathology test on the pancreatic tissue shows pancreatic adenocarcinoma. Subsequently, the patient was treated with analog nucleoside, tenofovir 300 mg once a day, and was planned for adjuvant chemotherapy.

3. Discussion

A 73 years-old female was hospitalized in the internal medicine department of Dr. M. Djamil General Hospital, Padang, with a final diagnosis of intrahepatic and extrahepatic cholestasis et causa adenocarcinoma of caput pancreas with hepatitis B infection.

Diagnosis for this patient was made based on anamnesis, physical examination, laboratory tests, and radiology imaging. From anamnesis, it was well known that the patient was 73 years old. Ashish Sharma, in the Lange Medical Book in 2015, wrote that pancreatic cancer cases are rarely found in the population under the age of 45 years old. The case number increase in the age group around 70 years of age. The chief complaint of this patient is pain in the upper right part of her abdomen and icteric, which was confirmed in the journal about pancreatic cancer diagnosis and management by Frelove R and Walling D back in 2006, which stated that the right-side abdominal pain was found 80% as the chief complaint in patients with pancreatic cancer and was the main reason for the patient to seek for medical treatment. Other references from a journal of cancer of the pancreas and biliary tract in Winawer Sj ed. Management of gastrointestinal disease has stated that 3 of the main complaints found in pancreatic cancer were undesirable weight loss (92%), icteric (82%), and pain (72%).^{5,6}

Clinical investigation of this patient shows a

stagnation of intrahepatic and extrahepatic biliary flows. The indirect bilirubin level was 2,6 mg/dl, direct bilirubin 17.1 mg/dl, and total bilirubin was found at 19.7 mg/dl, accompanied by the increased level of alkali phosphatase (554 u/l), and increase of gamma GT level (5.6 u/l). This patient was also tested reactive for HBsAg, which means that this patient was also infected with the hepatitis B virus. The Ca 19-9 level was also found to increase by a number of 105.34 U/ml (37.000. from the radiology imaging by abdominal CT scan, there was found a mass on the head of the pancreas with a size of 4.97x3.53x5.2 cm with indistinct borders and irregular edges. The increase of Ca 19-9 level, along with the appearance of mass from the CT scan, has confirmed the diagnosis for this patient. To the journal written by C. Haglund in 2010, the Ca19-9 tumor marker (carbohydrate antigen 19-9) is a tumor marker that is most frequently used and recognized as the most relevant for pancreatic cancer diagnosis due to the high sensitivity and specificity (80% and 60-70%). The evaluation of serum Ca19-9 level is used in addition to radiology imaging to determine whether a tumor is resectable or unresectable. High concentrations were usually found in a patient with a tumor size of more than 3 cm, and this was the limit level for tumor resection.⁷

There is a couple of the main pathology found in this patient. First is the hepatitis B infection, and the second is the tumor of the caput pancreas. Both of these conditions can be caused severe injury in the liver parenchyma, and inflammation caused by hepatitis B infection side by side with the stagnation of the biliary system can elevate the disease's progressivity and can lead to progressive liver fibrosis, liver cirrhosis, hepatic failure, and hepatocellular carcinoma with poor prognosis. Hence, immediate treatment is mandatory for this patient. Early treatment performed in this patient was biliary duct decompression to release extrahepatic obstruction caused by the pancreatic head tumor.

Management of pancreatic cancer was based on radiology imaging, surgical findings, and the general

condition of the patient. The best treatment for a pancreatic patient depends on the stadium and the degree of the tumor spread. From the abdominal CT scan, this patient was categorized as stadium II. The principle of treatment for pancreatic cancer was firstly to determine whether this cancer is resectable or unresectable. Resectable pancreatic cancer was found by imaging, which cancer appears to not spread, and the surgeon considered this tumor was able to remove. As found in this patient, the cancer was categorized as resectable. Martin LJ, in 2018 wrote that about 10% of pancreatic cancer was found resectable when an individual was first diagnosed.

The Whipple procedure was one in this patient. From anatomical pathology tests on the pancreatic tissue, there was found an appearance of pancreatic adenocarcinoma, and 95% of pancreatic cancer was an exocrine tumor. Khatri M in 2017 and Louise Chang in 2018 stated in their journal that it was known that 95% of pancreatic tumor is adenocarcinoma and 95% of pancreatic tumor are exocrine tumor.^{2,3} next step, the patient is planned to undergo adjuvant chemotherapy with 5 FU with the aim of clearing the remnants of cancer and prevent recurrence.^{5,6}

After the surgical procedure, the biliary duct obstruction showed improvement that was visible from indirect bilirubin level (1,6 mg/dl), direct bilirubin level (3,4 mg/dl), and total bilirubin level (5 ml/dl). Along with this result, the patient's general condition is also improved. There have not been many reports of cases of obstruction accompanied by chronic hepatitis more than drug-induced hepatitis. The cholestasis form of drug-induced liver damage is immune-allergic appearance, with short incubation time or repetitive drug exposure. If the cholestasis is severe, the disease can be prolonged and may cause biliary duct obstructive syndrome. Cholestasis hepatitis is unlikely to be caused by acute hepatic failure or death caused by liver damage more than acute drug-induced hepatitis. Nonetheless, prolonged cholestasis may worsen the patient's general condition and contribute to multi-organ failure and also death in a patient with

another serious disease along with this condition.⁸

Further management for this patient was intended for the treatment of chronic hepatitis B infection. From the laboratory result, it was known that this patient was declared reactive for the HBsAg test and positive for the HBeAg test. The HBV DNA count was shown as 20.000 IU/ml, and ALT was found at 84 U/L. the fibrosis degree was found in this patient by fibroscan examination, and it was shown as F3. Based on Indonesia's national consensus on Hepatitis B management in 2017, this patient was indicated to undergo antiviral therapy. The patient was given antiviral therapy with analog nucleoside and 300 mg of tenofovir every day. The ultimate goal of chronic hepatitis B treatment is to achieve long-term suppression of viral infection so as to improve quality of life, patient survival, and prevent disease progression.⁹⁻¹²

The next planned step for this patient is to evaluate the pancreatic cancer treatment and evaluate the hepatitis B therapy by Ca 19-9, HBV DNA, anti-HBeAg, and ALT test every 6 months. From the America Cancer Society, 5 years relative survival rate for this patient is 42%. This survival rate number depends on the cancer stage. American Cancer Society used staging from surveillance, epidemiology, and result (SEER) based on evidence of patients with pancreatic adenocarcinoma from the year 2011 to 2017, which pancreatic cancer stages are localized with 5 years survival rate with a percentage of 42%, regional 14% and distant (metastasis) 3%.¹³⁻²⁰

4. Conclusion

Cholestasis jaundice causes hyperbilirubinemia which could lead to clinical symptoms such as icteric sclerae, pruritus, and also the complication of liver tissue injury whose clinical manifestations are related to impaired liver function due to hyperbilirubinemia and could lead to hypoalbuminemia, hypo-coagulation, and in the further lever may lead to hepatic cirrhosis. The management principle of icteric cholestasis is with decompression of biliary ducts by eliminating the etiology of obstruction on the biliary

flow. Chronic hepatitis B in this patient is an indication of antiviral therapy.

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