

Diagnosis and Management of Klatskin Tumor

*Dicky Levenus Tahapary**, *Rudy Hidayat**,
*Achmad Fauzi***, *Marcellus Simadibrata***

* Department of Internal Medicine, Faculty of Medicine, University of Indonesia
Dr. Cipto Mangunkusumo General National Hospital, Jakarta

** Division of Gastroenterology, Department of Internal Medicine, Faculty of Medicine
University of Indonesia/Dr. Cipto Mangunkusumo General National Hospital, Jakarta

ABSTRACT

Klatskin tumor is a cholangiocarcinoma in bifurcation areas and related to poor prognosis. Surgery is the only curative method, but endoscopy also has a role in diagnostic as well as therapeutic measures. This report shall discuss a case of Klatskin tumor in which to establish diagnosis, multimodal imaging using ultrasonography, computed tomography, endoscopic retrograde cholangiopancreatography (ERCP), and tumor markers were used. For palliative therapeutic measures in this case, placement of plastic stents by ERCP was performed. The procedure ERCP with stents placement can be an option in the management of Klatskin tumor, in which surgery is not possible to be conducted.

Keywords: *Klatskin tumor, ERCP, stent, diagnosis, management*

INTRODUCTION

Cholangiocarcinoma is a rare malignancy, consisting of 2% of all cases of malignancy. Nevertheless, this is the second most frequent primary malignancy of the hepatobiliary system after hepatocellular carcinoma.¹ Cholangiocarcinoma which involves bifurcation areas is referred to as Klatskin tumor,^{1,2} and it is the cholangiocarcinoma most commonly found, for about 40-60%.³

Klatskin tumor has a poor prognosis with a five-year survival rate as much as 10% and most patients die within the first year.⁴ Surgery is the only curative measure. However, tumors that have the potential to be treated by surgery consisted of a small percentage, between 5-20%.⁴

Endoscopic retrograde cholangio pancreatography (ERCP), other than being an important diagnostic modality, also plays a role as a therapeutic one. The success rate for stents placement for biliary drainage is varied between 70-90%, although in proximate tumors, especially those involving bifurcation areas, the number is lower.⁴

A case of patient with Klatskin tumor is reported as well as the measures taken to establish the diagnosis and its management. The discussion shall focus on the role of ERCP, both as a diagnostic tool and a therapeutic one.

CASE ILLUSTRATION

A male, 54 years old, presented with the chief complaint of yellowish eyes since three months before admission. At first, yellowish color could only be found in the eyes, but then it started to spread to other parts of the body. The patient was complaining of pale-colored stool, urine with tea-like color, loss of appetite and gradual weight loss + 30 kg in the last three months, as well as itching sensation all over his body. The patient smokes a pack of cigarettes a day for 30 years and drinks traditional herbal medicine.

Since six months before admission, the patient often felt an intermittent upper abdominal pain similar to muscle aching and was nonradiating, his stomach felt easily full, though it has nothing to do with food intake and change of position as well as activity. The patient had sought for hospital care in other private hospital and a computed tomography (CT) was performed. The result of the diagnosis claimed that there was a obstruction of biliary tract and surgery was suggested, but it was not performed due to financial reason. A month before admission, the

Correspondence:

Achmad Fauzi
Division of Gastroenterology, Department of Internal Medicine
Dr. Cipto Mangunkusumo General National Hospital
Jl. Diponegoro No. 71 Jakarta 10430 Indonesia
Phone: +62-21-3153957 Fax: +62-21-3142454
E-mail: ppfauzidr@yahoo.com

patient felt that the upper abdominal pain he had experienced was worsening, accompanied by swelling of the abdomen and legs.

Physical examination showed that the patient looked moderately ill, fully alert, stable hemodynamics, afebrile temperature of 36.6°C, pale conjunctiva, and greenish yellow sclera. Through abdominal examination, hepatomegaly was palpated 5 cm below arcus costae, 15 cm below xyphoid process, blunt sides, smooth surface, jelly-like. Pain on palpation was found in the right hypocondriacal region, no shifting dullness was detected. His skin looked jaundice with slight squama. Laboratory results at admission showed anemia, elevated direct-bilirubin, and elevated transaminase enzyme. Chest X-ray showed no abnormalities. On abdominal CT without contrast from the previous hospital showed dilation of intrahepatic biliary tract, enlargement of liver especially in the right lobe, normal pancreas, sludge and stone in the gallbladder, and did not appear enlarged lymph nodes paraaorta.

From these data, the problem was identified as extrahepatic obstructive jaundice caused by cholangiocarcinoma. Abdominal ultrasonography (USG) examination showed enlargement of the right lobe of liver with flat surface and blunt side. The ecostructures of the right and left lobes were nonhomogenic, an anechoic space occupying lesion (SOL) was found in the left lobe and sludge was found in the gallbladder. The pancreas was normal, both left and right intrahepatic biliary tracts were enlarged, while periaortal lymph nodes were not enlarged.

From the first ERCP in which the stents had not been placed, images of the hilar region showed narrowing of the hepatic duct and filling defect contrast. However, after the procedure, the patient experienced post-acute cholangitis and then given antibiotics cefoperazone, ciprofloxacin, and metronidazole. During the second ERCP, placement of stents was successfully performed, bilirubin level was gradually decreasing, and the patient experienced clinical improvement. From consultation with digestive surgical, an operation was planned, but the patient refused. The patient was then discharged with plastic stents placed and was advised regularly control.

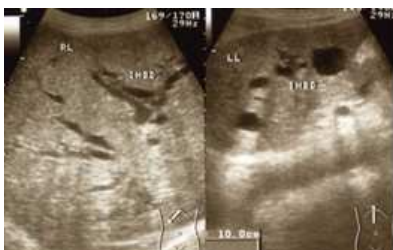


Figure 1. USG result showed dilation of intrahepatic biliary duct in the right and left lobes of the liver

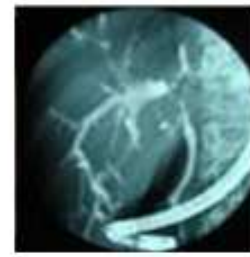


Figure 2. ERCP result showed of hepatic duct stricture in hilar region and filling defect contrast

DISCUSSION

The patient had greenish jaundice, dark urine, pale stool and pruritus, aside from bilirubinuria, elevated gamma GT level and alkaline phosphatase as well as higher level of direct bilirubin in comparison to that of indirect bilirubin, thus a possibility of extrahepatic obstructive jaundice was considered,⁵ with a possibility of a malignancy as the cause.

Biliary tract malignancy is a primary malignancy of the hepatobiliary system which is the second most frequently found after hepatocellular carcinoma.¹ Clinical features frequently found in cholangiocarcinoma are symptoms of obstruction of the biliary tract such as jaundice, pale feces, tea-colored urine, and pruritus.^{2,4} These are consistent with the findings in this patient. About 90-98% of patients present with jaundice, and may be accompanied with other non-specific complaints such as weight loss 29%, abdominal pain 20%) and sometimes fever 9%. Itching sensation is also a fairly common complaint 30%.³ Cholangiocarcinoma is usually identified in an advanced condition with systemic manifestation of malignancy, such as malaise, exhaustion, and weight loss.²

Cholangiocarcinoma is more prevalent in males, and both the existence of stone in biliary tract and smoking are correlated to increased risk of cholangiocarcinoma.^{1,2} The factor of aging is also correlated with increased risk for cholangiocarcinoma, where 2/3 cases of cholangiocarcinoma occurred in individuals > 65 years old and an over ten times increase of risk occurred in those > 80 years old.² Other than that, epidemiological factor should also be taken into consideration. In South East Asia, cases of cholangiocarcinoma are correlated to parasitic infections and chronic typhoid carrier, where cases of chronic typhoid carrier is correlated to a six-times increase of risk for hepatobiliary malignancy.² However, in these cases, adequate diagnostic work up for both risk factors had not been conducted. Risk factors for cholangiocarcinoma in this patient are male, smoking, stone in the biliary tract, and age.

USG is the main modality for cases with suspicion of obstruction bilier.² Initial radiological examination

performed in this patient was USG, and it showed dilation of bilateral intrahepatic biliary ducts without dilation of extrahepatic biliary duct. The diagnosis of hilar cholangiocarcinoma should be considered in cases where dilated of intrahepatic ducts was found without any dilatation in extrahepatic duct.^{2,6} The weakness of USG examination is that it makes it possible to miss perihilar, extrahepatic, and periampullar tumors, and less good for determining the extent of the tumor spread.²

CT can provide a better image for lesions of intrahepatic masses, dilatation of intrahepatic ducts, and local lymphadenopathy, although CT usually can not provide clear image of the spread of the tumor.² In this case, a CT without contrast had been performed six months before, and it showed a dilation of intrahepatic biliary duct and sludge in the gallbladder, no mass or lymph nodes enlargement was found. During hospital stay, other CT was taken, this time using contrast, and it showed dilatation of intrahepatic biliary ducts and cyst in the left lobe of the liver which did not enhance in contrast. There was also no lymph nodes enlargement found.

Cholangiography (MRCP, ERCP) and percutaneous transhepatic cholangiography (PTC) are important in early diagnosis of cholangiocarcinoma and in evaluating resectability.² In this case, selected ERCP performed with a consideration other than as a diagnostic modality can also be as a therapeutic modality and the narrowing of the ductus hepaticus in hilar region as well as a filling defect contrast (see figure 1).

These findings are consistent with Klatskin tumor. Other than making it possible to take bile for cytology, ERCP also allows stent placement in the purpose of palliative care for non-resectable tumors.²

Eventhough positive results in cytology and histology are hard to obtain by ERCP, both are recommended to confirm the diagnosis of cholangiocarcinoma. ERCP allows cytologic samples to be obtained, which resulted positive in approximately 30% cases of cholangiocarcinoma.² A combination of brush cytology and biopsy increased positive results up to 40-70%, although negative result in cytology does not eliminate the possibility of malignancy.² Inadequate samples are the main reason for failure. Brush cytology by endoscopy is usually performed after sphincterotomy.⁷ Sensitivity of brush cytology is largely varied, between 8 and 57%. Type and length of the brush as well as the amount of time it takes to obtain a sample influence cytology result, meanwhile obtaining cytologic samples for three consecutive times increases positive results up to 68%.⁷ Other literature mention that brush cytology is relatively easy to perform and is widely used, with a specificity of 100% while the low

sensitivity of 30-60%.⁴ Forceps biopsy and fine needle biopsy require sphincterotomy, which in turn increases the risk of complications. Fine needle biopsy has a higher sensitivity of 85-90%,⁴ even though other literature reported a lower result of 62%.⁷ Collection of fluid from biliary tract can also be performed, but its sensitivity is so low that it is rarely used.⁴ In this case, a sample should have been obtained at the moment the ERCP was performed, but sample collection could not be conducted due to the stricture being relatively too tight on the brush catheter.

There is no specific tumor marker for cholangiocarcinoma. CA 19-9,⁸ carcinoembryonic antigen (CEA), and CA-125 are the tumor markers most frequently used for cholangiocarcinoma.^{2,8} The CA 19-9 level of this patient was 219.9 U/mL. CA 19-9 increases in 85% of patients with cholangiocarcinoma, it was also reported that a CA19-9 level of over 100 U/mL has a sensitivity and specificity of 75% and 80%, respectively.² Other study mentioned that CA 19-9 has a sensitivity and specificity of 60% and 70% for biliary tract malignancy.⁹ However, CA-19-9 level may increase in obstructive jaundice with no malignancy, but a steadily increasing level even after biliary decompression indicates a malignancy.²

Concentration of CA 19-9 will be influenced with the secretion status of patient's and Lewis genotype, thus these should be taken into consideration in interpreting the result of tumor marker.¹⁰ CA 19-9 level can increase in biliary tract and pancreas malignancies, other than non-malignant conditions such as gallstone, pancreatitis, cirrhosis, and cholecystitis.^{7,11} Other literature mentions that CA 19-9 level before treatment is a prognostic factor where levels of greater than 300 U/mL has a three-times greater risk for early death.¹² Other than that, decreasing level after therapy was correlated with increased survival rate.¹²

In a study involving 55 patients with Klatskin tumor diagnosed by cholangiography and CT scan, 49 among them had had stents placements, of which 28 (57%) patients succeeded in the first effort while 8 (16%) patients succeeded in the second, thus the cumulative number of stents placement success rate was 73%. However, only 20 (41%) patients experienced satisfying biliary drainage.¹³ In resectable cases, placement of biliary endoprosthesis can be conducted instead of surgery, by which biliary drainage can be restored and survival rate can be increased,² as well as increasing the quality of life.¹⁴ Endoscopic stent placement is correlated to high success rate, acceptable morbidity, and low mortality. ERCP is a primary modality for palliative therapy of biliary obstruction caused by cholangio-

carcinoma.¹⁵ To achieve adequate biliary drainage, a previous try on stent placement in this patient had been performed, but it had failed and it was just successful in the second ERCP.

Complications often found in ERCP are pancreatitis, hemorrhage, infection, and perforation.¹⁶ Incidence rate of pancreatitis post-ERCP is 1.9-11.7%.¹⁶ In sphincterotomy, the complications most commonly found are bleeding, pancreatitis, and perforation. The incidence of pancreatitis post-ERCP and sphincterotomy is between 1.3-2.4%.¹⁷ Sphincterotomy by itself is a risk factor for bacterial contamination in biliary tract because it facilitates migration of the bacteria in transpapillary digestive tract.⁸ The risk of cholangitis after ERCP currently is very low, as much as 0.7%.⁸ If diagnostic ERCP was performed without any measure to achieve biliary drainage in the existence of obstruction, the incidence of cholangitis would increase ten times.⁸ This is caused by the gastrointestinal-tract bacterial contaminated the sterile bile.⁸ Biliary obstruction due to hilar stricture and intrahepatic biliary tract obstruction or stones are technically difficult to perform decompression on, thus the risk of cholangitis requires special attention.⁸ In the first ERCP and sphincterotomy on this patient, acute cholangitis occurred caused by the use of contrast without adequate biliary drainage. To patient given a combination of three antibiotics therapy for gram-positive, gram-negative, and anaerobic bacteria, which were ciprofloxacin, cefoperazone, and metronidazole. Second ERCP was then performed with stent placement.

The purpose of acute cholangitis therapy is to control infection and to prevent sepsis. A therapy of broad-spectrum antibiotic was given especially for gram-negative enteric aerobic bacteria (*Escherichia coli*, *Klebsiella* species, *Enterobacter* species), gram-positive, and anaerobic *Enterococcus* (*Bacteroides fragilis*, *Clostridium perfringens*). The therapy is usually administered for short term of 10-14 days.¹⁸ An example of a first-line agent is intravenous ciprofloxacin, which is administered 200-400 mg for every 12 hours. In patients with biliary obstruction, only ciprofloxacin is excreted to the bile in adequate amount, which is 20% of the peak serum level, which is more than enough in comparison to that of the minimum inhibitory concentration (MIC) for gram-negative bacteria.¹⁸ There are several other first-line drugs, such as intravenous metronidazole which is suitable for anaerobic bacteria, ampicillin sulbactam which is appropriate for *enterococcus*, and cephalosporin. The second-line drug is imipenem cilastatin, which has a highly-broad spectrum (gram positive and negative as well as anaerobe).¹⁸ The use of piperacillin as prophylaxis in ERCP is not

correlated with the decreased incidence of post-ERCP acute cholangitis.¹⁹ A meta analysis on the use of prophylaxis antibiotics in ERCP does not show decrease in the risk of cholangitis.⁸ However, failure of adequate biliary drainage is an important risk factor for cholangitis. Hence, prophylactic antibiotic is best be administered in cases where adequate drainage would possibly be failed to achieve, such as in patients with malignancy in the hilar region.⁴ Prophylactic antibiotic is given once before the procedure be performed⁴ and if the procedure involves the use of contrast while adequate drainage is not sufficient, antibiotic therapy should be continued after drainage was achieved.^{4,8} Antibiotic should be bactericidal and has a good penetrating potential in the hepatobiliary system.⁴

Effective ERCP for palliative therapy of the biliary obstruction caused by malignancy, where metal stents have patency duration longer compared to the plastic ones.²⁰ Financial analysis demonstrates that metal stents shall be useful for patients who could survive for over 6 months, while plastic stents for those who are predicted to survive for less than 6 months.² In this patient, plastic stent placement was selected due to limitations in financial capability.

The median of patency duration of plastic stents 10-Fr is between 3-6 months. The incidence of stent occlusion is varied between 20-50%.⁴ The cause of the occlusion begins with the attachment of protein and bacteria in the stent's inner lining. In vitro experiments, administration of antibiotic decreases the attachment of bacteria on the stent. Thus, antibiotic administration seems to be a logical option.⁴ Other than that, there is a study which mention that administering ursodeoxycolic acid may decrease the risk of occlusion.⁴ Hence, this patient was given the antibiotic ciprofloxacin and ursodeoxycolic acid before leaving the hospital. However, a recent study on the use of antibiotic and combination of antibiotic with ursodeoxycolic acid demonstrates no correlation with patency difference in group which was given none.⁴

This case seems to be successful in performing palliative stent placement by ERCP. ERCP procedure without adequate drainage may develop complications such as the occurrence of post-ERCP cholangitis in the patient. However, ERCP procedure with stent placement can be an option in the therapy of Klatskin tumor in which surgery is not possible to be performed.

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