Problems in Diagnosis Approach for Carcinoma of Pancreatic Head

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ABSTRACT

Incidences of pancreatic cancer worldwide have been known to be increased. It is the fifth leading cause of death in United State of America. Seventy percent occurs in the head of the pancreas. Major risk factors are related to age, black race, smokers, high-fat diet, chronic pancreatitis, diabetes mellitus and alcohol consumption. Some clinical symptoms such as jaundice, abdominal pain, unexplained weight loss or ascites can occur early or even late in the course of disease.

Diagnosing pancreatic cancer sometimes can be difficult, regarding to discrepancy between clinical symptoms and radiological findings. It is important to take good history of the patient, thorough examination, and combine several modalities in diagnosing tumor of pancreatic head.

In this case report, a 54 year-old female, came to the hospital with abdominal swelling and jaundice. Physical examination revealed liver and spleen enlargement and edema on both lower extremities. The laboratory result showed increment in Carcinoembryonic Antigen (CEA) and carbohydrate antigen 19-9 (CA19-9) level, without marked increase in bilirubin level. Dilatation of the pancreatic duct was found in this patient, without any sign of bile stone. Endoscopic Retrograde Cholangiopancreatography (ERCP) in this patient was failed to have significant result.

Keywords: carcinoma of pancreatic head, papilla vater carcinoma, diagnosis, ERCP, jaundice

INTRODUCTION

Pancreatic cancer is a cancer which mostly arises from the ductal epithelial cells (90%) and most frequently occurs as adenocarcinoma (75%). Until now, there is no effective screening test for the pancreatic cancer. Most cases, i.e. almost 70% occur within the head of the pancreas (caput of pancreas) and it commonly causes obstruction due to its invasion into common bile duct and pancreas duct resulting in clinical jaundice.

The early symptoms of the pancreatic cancer are not specific and often ignored. These initial symptoms last more than 2 months prior to the cancer diagnosis.[1] Patients usually experience clinical symptoms when the tumor has invaded beyond the pancreas. The clinical symptoms include abdominal pain and unexplainable weight loss. Painless jaundice occurs in 10-20% of patients with cancer of pancreatic head. Important clinical manifestations but rarely occur are pancreatitis, migratory thrombophlebitis, hypoglycemia, elevated calcium level, endocarditis and diabetes mellitus.[1,3,7]

Incidence of exocrine pancreatic cancer is 80-90% of all pancreatic tumor. The worldwide incidence of pancreatic cancer is 8-12 cases per 100,000 male patients, and 1.5- 7 case per 100,000 female patients. The male-to-female ratio is 2:1. This cancer is the fifth leading cause of death in United States of America. The median age approximately is 60-80 years

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(in 80 cases). The risks increase in smoker, black race, high-fat diet, alcohol, elderly, diabetes mellitus, and chronic pancreatitis.[1] Pathogenesis of the pancreatic cancer is assumed due to accumulation of various gene mutations. The common gene mutations for pancreatic cancer include K-ras genes, CK-19, depletions and mutations of tumor suppressor genes, such p53, p16, DPC4 and BRCA2.[2]

In simple words, the diagnostic approach for carcinoma of pancreatic head includes complete history taking, thorough physical examination, and workup studies such as tumor markers and imaging studies. Diagnosis frequently deals with difficulties since the symptoms usually arise after the tumor has reached advance stage of disease. Moreover, several modalities that utilized separately frequently fail to detect carcinoma of pancreatic head. Such problems result in delayed diagnosis.

CASE

A 54 year-old female patient was hospitalized with a main symptom of abdominal swelling since three days before admission. The symptom was accompanied with sensation of full-stomach, nausea, and edema on both lower extremities. There was no vomiting and dyspnea, either during activity or at rest. After 2-week hospitalization, the patient experienced subtle intermittent fever and accompanied by dry cough, lightening stools and darkening urine resembling to tea-colored solution. Four months later, the patient noticed yellow colored eyes and skin, and sometimes together with epigastric pain. Previously, the patient had come to other hospital and had undergone an ultrasonography examination, which revealed stone of her bile duct.

The patient had suffered hypertension for a year but she had irregular visit to local primary health care center. She denied any past medical history of diabetes mellitus, blood transfusion, and jaundice. She had not had smoking habits or alcoholic consumption. She usually had high-fat diet and oily food. There was no history of malignancy in her family.

The first physical examination revealed full alert consciousness with moderate illness. The blood pressure was 160/80 mmHg, pulse was regular with the rate of 90 x/minute, body temperature 37ºC, and respiratory rate 22 x/minute. She had active rest position and malnutrition. No deformity on face and head with normal face expression. Her hair was mostly strong and grey with no hair loss. The eye examination revealed pale conjunctiva and jaundice of sclera. There was no lymph node enlargement on the neck region. The chest examination revealed vesicular breath sound and rhonchi on the left lung base, and no wheezing. The left margin of the heart was extend about 1 finger

to the lateral of left mid-clavicle line, there was normal heart sounds (normal $S_1 - S_2$), no murmur or gallop. Abdomen was distended, loose, and there was tenderness on palpation at the right upper quadrant of the abdomen. The liver was detected on palpation at 3 fingers side below the arcus costae, and 3 fingers below the processus xyphoideus. Lien was detected on palpation with lien enlargement until the line of Shuffner 2. There was shifting dullness and normal bowel sound. Extremities were warm and there was pitting edema on pre tibia region.

A preliminary laboratory data showed following results: hemoglobin 8.2 g/dL, hematocrit 26.4%, leukocytes 11,600 cells/uL, and platelets 186,000 cells/uL, alanine aminotransferase (ALT) 141 U/L, aspartate aminotransferase (AST) 38 U/L, with albumin 2.0 g/dL and globulin 4.4 g/dL. The renal function was within normal limits, i.e. ureum 30 mg/dL and creatinine 1.1 mg/dL. The results also revealed direct bilirubin level of 6.1 mg/dL and indirect bilirubin level of 3.0 mg/dL. The blood glucose test revealed normal result (88 g/dL) and the electrolyte level, i.e. sodium level was 138 mEq/L, potassium level was 3.7 mEq/L, and chloride level was 107 mEq/L. The urine test demonstrated positive bilirubin result, while other results were within the normal range

Based on such results, the initial problem of this patient were liver cirrhosis, jaundice, anemia, hypertension grade II, and pneumonia. The diagnosis of liver cirrhosis was established based on physical findings of abdominal distention since 3 days before admission, edema on both lower extremities. Physical examination resulted hepatomegaly, ascites, and pitting edema on pre tibia region. There albumin-to-globulin ratio was inversed and there was increment of aminotransferase enzymes. It was considered as liver cirrhosis with differential diagnosis of bile cirrhosis. Early diagnosis approaches were prepared including seromarker test for hepatitis (HbsAg, anti HCV), abdominal ultrasonography (USG) and endoscopy. As treatment, diuretics were given, e.g. spironolactone 1 x 100 mg, furosemide 1 x 80 mg, and daily negative fluid balance of 500 cc.

The diagnosis of jaundice is established findings of yellowish eyes and body since 4 months before hospital admission, nausea, and alternating pruritus, lightening stools, darkening urine, and increased bilirubin level. Obstructive jaundice caused by cholelithiasis or tumor-induced bile obstruction was pondered. Examinations on a serial bilirubin test, urinalysis, and abdominal USG had been arranged.

The diagnosis of anemia was defined based on evident sign of pale conjunctiva with no bleeding signs. On admission, the patient's hemoglobin level was 8.2 g/dL, Mean Corpuscular Volume (MCV) 98.9 fL

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and Mean Corpuscular Hemoglobine (MCH) 30.7 pg. Normocytic normochrome anemia due to occult blood loss was considered and it was also probably caused by chronic disease. Further tests were planned including reticulocyte count, serum irin (SI), Total Iron Binding Capacity (TIBC), ferritin, and serial peripheral blood test. Treatment was given based on underlying disease. There was no sign of heart failure due to anemia; therefore, blood transfusion could be on delay. The diagnosis of hypertension grade II is established based on history of hypertension and blood pressure data of 160/80 mmHg. Primary hypertension was considered with differential diagnosis of secondary hypertension. Treatment was provided, i.e. captopril 2 x 25 mg.

The diagnosis of pneumonia was evident based on following signs: cough, fever, and leukocytocis 11,600/uL and physical examination findings of coarse rhonchi at the left of lung base. The chest X-ray detected a minimum infiltrate in both lungs. Antibiotic treatment was given, e.g. cefotaxime 3 x 1 gram. Pulmonary tuberculosis as a differential diagnosis was considered and further sputum accumulation for acid fast test (AFT) 3x and the gram-staining test, as well as microorganism test and sputum culture were prepared.

On the third-day of treatment, the patient's condition was evaluated. The patient's rhonchi had been progressively decreased and no more cough. The patient's abdominal circumference was 77.5 cm, and body weight was 40 kg. Examinations of seromarker test on hepatitis HbsAg and anti HCV revealed negative result. Other laboratory result was as follow: hemoglobin 8 g/dL, leukocytes 10,500/uL, platelets 135,000/uL and Erythrocytes Sediment Rate (ESR) was 110 mm, and the differential count was within the normal limit.

Reticulocyte count was 0% and the urinalysis revealed microscopic hematuria (erythrocytes 15-20/hpf and Hb 2+) but no bilirubin was found. The result of cholinesterase test was 1,705 U/L (5,200-12,900). Serum bilirubin remained relatively the same as the previous result, i.e. direct bilirubin level of 6.5 mg/dL and indirect 2.9 mg/dL. Serum iron test showed normal result of 96 ug/dL (60-160), TIBC of 114 ug/dL (250-410) and ferritin level was 775.9 ng/ml (13-150). It represented anemia in chronic disease. Clinically, the patient still had jaundice.

Based on USG result, there was an enlargement of intra-hepatic biliary system, splenomegaly, ascites and enlargement of gall bladder (11.1 x 5 cm), without any enlargement of paraaortic and parailliac lymph nodes (figure 1).

Figure 1. Enlargement of intra-hepatic biliary system on abdominal ultrasonography

At the eighth day care, total bilirubin increased into 12 mg/dL, direct bilirubin was 8.9 mg/dL and indirect was 3.1 mg/dL, alkaline phosphatase test revealed increasing result, i.e. 941 U/L and gamma glutamyl-transpeptidase was 138 U/L, aminotransferase enzymes still increased, i.e. AST 198 U/L and ALT 85 U/L.

Based on the second result of abdominal USG, there was an impression of obstructive jaundice with suspect of a mass at the head of pancreas and differential diagnosis of cholangiocarcinoma. There was a feature of chronic liver disease (non-homogenous echostructure) and splenomegaly. The gall bladder was enlarged with a sludge feature, followed by enlargement of intrahepatic bile duct and Common Bile Duct (CBD).

There was an increase of CEA, i.e. 6.2 (0-4.6) ng/ml, and CA19 -9 of 228.1 (0-39) U/ml. Hemoglobin decreased to 6.7 g/dL, leukocytes 11,200/uL, and platelets 169,000/uL, ESR 140 mm, reticulocyte count 3.6%, and normal differential count. Serum bilirubin decreased, i.e. direct bilirubin of 4.8 mg/dL and indirect bilirubin of 2.4 mg/dL.

There was inversed ratio of albumin 2.3 g/dL to globulin 5.5 g/dL. The serum iron was normal, i.e. 62 ug/dL (60-160), TIBC revealed a result of 145 ug/dL (250-410) and ferritin level was 466.7 ng/ml (13-150). Such results showed a fall compared to previous results. Decreased hemoglobin induced by bleeding has been considered; however, there was no bleeding sign, either in her stools or urine. On the 17th day of treatment, there were decreased of transaminase enzymes with AST 95 U/L and ALT 49 U/L. There was also a decrease of bilirubin, i.e. direct bilirubin of 3.39 mg/dL and indirect bilirubin of 1.6 mg/dL.

On further day care, hemoglobin increased to 7.8 g/dL, leukocytes 6,100/uL, and platelets 186,000/uL. There was more decrease of serum bilirubin level, i.e. direct bilirubin of 3.43 mg/dL and indirect bilirubin of 0.63 mg/dL. The transaminase enzymes result included AST 97 U/L and ALT 50 U/L. The renal function test was within the normal limit with ureum level of 36 mg/dL and creatinine level of 0.8 mg/dL.

Computer tommography (CT) scan of abdomen and pelvis showed an impression of a mass at the head of pancreas (attenuated after contrast), enlargement of pancreatic duct and intra-hepatic bile duct. There was an ascites in lower abdomen up to the pelvis with enlarged lien up to the Shufner 2. Based on CT scan result on pelvic region, there was an impression of ascites on pelvic region without definite enlargement of the left and right inguinal lymph node and intrapelvical mass (figure 2).
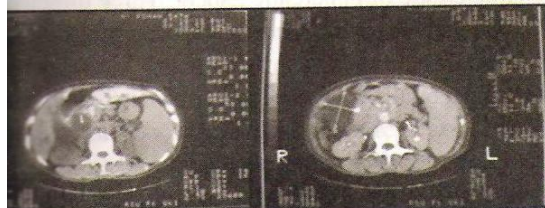

e 2. CT scan of abdomen and pelvis reveals enlargement of reatic duct, intrahepatic bile duct and ascites

There was no erythrocyte found on fecal specimen. Duodenoscopy was performed on this patient and revealed a normal form and measure of papilla vateri, and no mass was found. Based on such result, an Endoscopic Retrograde Cholangiopancreatography (ERCP) was arranged. As preparation, a laboratory test was performed with result of hemoglobin 10.3 g/dL, leukocytes 5,200/uL, and platelets 140,000/u, Prothrombin Time (PT) 1.03 x control, and Activated Partial Thromboplastin Time (APTT) 1.25 x control; direct bilirubin level was 3.7 mg/dL and indirect bilirubin level was 1.3 mg/dL. The aminotransferase enzymes showed AST 114 U/L and ALT 76 U/L. The Ivy bleeding time 3 minutes, and Lee & White clotting time was 11 minutes.

ERCP result found a normal papilla vateri, normal multiple personality disorder (MPD), and no dilatation was found. The CBD was not able to be visualized because deep canulation can not be performed. Pancreatography showed dilatation of pancreatic duct due to the mass of pancreatic, which assumed as total mass obstruction. Afterward, the patient's care was then arranged to be transferred to the division of digestive surgery for operation (figure 3 and 4).
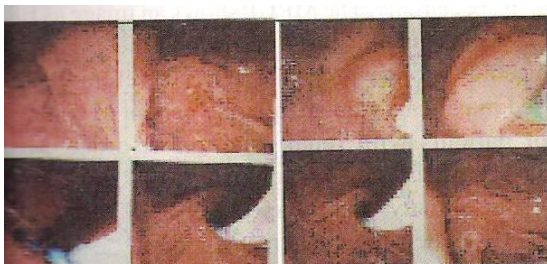

ure 3. The result of ERCP, there is a normal papilla vater, and D cannot be visualized

DISCUSSION

Pancreatic carcinoma together with carcinoma of duodenum, ampulla vater, distal common bile duct is categorized into the same group, i.e. the periampulla carcinoma because they are hard to be differ without evaluating specimen by resection (operation). The pancreatic carcinoma mostly occurs with prevalence of 50-70%, followed by ampulla carcinoma of 15-25%.[3] The pancreatic carcinoma was predominantly located in the head of pancreas, i.e. about 60-70%; while 5-10% occur in the body of pancreas and 10-15% in the tail. Approximately 15-40% cases are multifocal tumor. Histologically, most of pancreatic cancer is adenocarcinoma, with either moderate of good differentiation.

Almost 85% patients have clinical symptoms of obstructive jaundice, pruritus, dark urine, lightening stool, and impression of obstructive bile duct (cholestatic) on liver function test. Symptoms of malignancy are associated with gradual onset, weight loss, and occasionally accompanied with abdominal pain and back pain.

In general, pancreatic carcinoma occurs mostly on age 60-80 years. In this presented case, there is contradiction with epidemiologic evidence, i.e. the patient aged 54 years with symptoms of abdominal distension and jaundice. The history taking revealed symptoms of weight loss, intermittent abdominal pain, and jaundice. The pain was not classified as colic type; therefore it was not appropriate to gall stone disease. In addition, there was a weight loss presenting an initial symptom of malignancy. Some studies reported that 10-20% of pancreatic cancer is identified based on painless jaundice. Data of ascites, pretibial edema, inversed albumin-globulin ratio, and increased of transaminase enzymes leads to a diagnosis of liver cirrhosis. However, the examination of liver seromarker showed negative result. The cirrhosis in this patient probably indicates secondary bile cirrhosis due to obstruction in bile system. Bile obstruction may be caused by stone and tumor, particularly in the head of pancreas. Nevertheless, there were clinical manifestations that did not support the diagnosis of head pancreatic carcinoma, i.e. slight increase of bilirubin level, which spontaneously fall without any intervention. In pancreatic cancer, bilirubin level tends to increase when there is no intervention. Cholinesterase assay in the patient revealed a relatively low result indicating reduced liver function, particularly the function for synthesis. It may be caused by cirrhosis condition.

The abdominal USG showed an impression of dilated intrahepatic bile system, splenomegaly, ascites, and an enlarged gall bladder (11.1 x 5 cm). The USG also revealed normal liver size with homogenous

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structure. No stone was detected in the gall bladder and there was also no enlargement on para-aortic and parailiaca lymph nodes. The first USG examination has found no enlargement or a mass of pancreas and there was also no stone in the gall bladder. Such results can not explain the cause of dilated bile system and jaundice in the patient. On the other hand, the second abdominal USG showed an impression of obstructive jaundice which assumed due to the mass of pancreatic head, impression of chronic liver disease and splenomegaly. This explains that operator has very important role in USG examination. According to literatures, transabdominal USG can detect liver metastasis, ascites, and regional lymphadenopathy. The USG may also reveal dilatation of bile duct and may act as guidance for biopsy of pancreatic mass. However, the USG utilization is limited and it depends on the operator's experiences, and some factors in the patients such as obesity and features of intestinal air. Therefore, USG is not reliable for diagnosing carcinoma of pancreatic head.[3]

During hospitalization, there was increased bilirubin level which indicates an obstruction in bile system. If the condition persisted, then it required an intervention by stent application. However, along with the natural history of illness, the bilirubin level in this patient fell. Therefore, it becomes a rationale of discrepancy with carcinoma of pancreatic head, which usually has a stable or relatively increased serum bilirubin level. Diagnosis of malignancy in papilla vateri has been considered, which usually delicate that may have fluctuating bilirubin level. Other data that supports the diagnosis is the hemoglobin level which gradually decreased during hospitalization. Therefore, duodenoscopy examination to examine the papilla vateri has been taken into account.

Increase CEA level (6.2 ng/ml), and CA19-9 (228.1 U/ml) support the diagnosis of pancreas malignancy. There is no definite examination for tumor seromarker; however, CEA level > 3 ng/ml and CA19-9 > 37 U/ml shows 55 - 95% sensitivity. CEA is usually used for labeling neoplasm of duct, and negative result indicates normal pancreas. Positive result of CA19 - 9 occurs in 80% cases. Other test that can be performed is examination of protein kinase-C and mikroarray.[4,5]

The hemoglobin decreased to 6.7 g/dL and followed by decreased serum bilirubin level in 2 days period. It is assumed that the decreased hemoglobin was caused by bleeding due to a fragile tumor. It may relatively cause bile drainage and hence explains the reason of decreased bilirubin level in the patient. Bleeding sign is not clear in the patient, but it can be demonstrated by occult blood test on fecal specimens.

The abdominal and pelvic CT scan demonstrated a mass on the head of pancreas, dilated pancreatic duct, and intrahepatic bile duct. There was ascites accompanied by enlarged lien up to Schufner II. The enlargement on the left and right side of inguinal lymph node was not clear because it was covered by ascites. The CT scan has a plus point in demonstrating parenchymal disorder or other abnormalities in duct. It can detect hypo and hyper-vascular mass, cysts, inflammation, and calcification.

These are very helpful to find the pathological characteristic of pancreatic cancer. Three dimensional CT scan can also detect a smaller mass in more progressive nature. Its sensitivity to detect liver metastasis with diameter larger than 1.5 cm is almost 100%. CT scan can diagnose ascites and lymphadenopathy, which act as a marker of regional metastasis. CT scan has 90% positive predictive value to determine which tumor that may not be able to be operated by evaluated the expanding mass into mesenteric vessels, particularly to superior mesenteric artery. There was no regional metastasis found in the patient. This has become prognostic factor in defining tumor resectibility.[3]

The duodenoscopy test revealed normal papilla vateri. It excludes earlier suspicion as the differential diagnosis, i.e. carcinoma of papilla vateri. Subsequently, for definite diagnosis, ERCP test was further arranged. ERCP is a diagnostic test to provide a direct visualization on pancreatic and bile ductal by injecting a contrast solution. ERCP may also enable us to perform tissue biopsy on the abnormal site. However, the role of ERCP in determining pre-operative staging is limited because it is unable to determine the metastasis in the liver and lymph node as well as vascular invasion. ERCP is useful in intervention treatment such as stone extraction and stent application.[3]

Another test which is comparable to ERCP is Magnetic Resonance Cholangio Pancreatography (MRCP). This test has more non-invasive characteristic compared to ERCP. The Magnetic Resonance Imaging (MRI) provides a cross-sectional image of parenchyma, bile duct and pancreas duct. It is also able to differentiate benign mass from malignancy with 95% accuracy in predicting the respectability. The MRCP shows an image as ERCP does without any complication due to contrast injection into the pancreatic duct; therefore, it can be used in patients who are allergic patient to contrast or for patients with renal function disorder. MRCP sensitivity is about 84% compared to ERCP which has 70% sensitivity; and the specificity is 97% compared to 94% in detecting pancreatic cancer.[6]

According to a study by Kaltenthaler et al, MRCP is comparable to ERCP in detecting bile obstruction

with 50-100% sensitivity and 83-100% specificity. It has sensitivity of 81-94% and specificity of 92-100% in detecting malignancy.[7] The MRCP is more superior to ERCP for detecting total obstruction of pancreatic duct. However, this advantage will be ineffective when therapeutic intervention is required. ERCP is still the procedure of choice for the patient who is contra-indicated to MRCP and requiring therapeutic procedures.[8]

MRCP sensitivity and specificity in detecting malignancy are 81% and 100%, respectively, which is comparable to ERCP, i.e. 93% and 94%. MRCP may prevent unnecessary invasive exploration on the common bile duct and pancreatic duct.[9] MRCP provides useful staging data for the patient. Georgopoulos et al, reported that the result of MRCP was found in line with operative findings, either on size, location, or related involvement of mesenteric vessel. Moreover, MRCP also provides data of disease distribution, which can not be performed by single ERCP examination.[10]

The role of ultrasonograph endoscopy as diagnostic test includes demonstrating the parenchyma of pancreas, common bile duct, duodenum and ampulla. It can detect a mass sized less than 2 cm. Furthermore, it may also detect the depth of mass invasion with 95% sensitivity, but the specificity is only 53% because it is not quite able to differentiate malignancy from chronic pancreatitis.

Positron Emission Tomography (PET) scan is a modality that may be helpful in diagnosing periampulla neoplasm through altering the function of pancreas cancer cells by using radionucleotide rather than evaluating abnormal structure. It can distinguish neoplasm and chronic pancreatitis with 85-98% sensitivity and 53-93% specificity.[3]

The prognosis of pancreatic cancer depends on some factors. Tumor with poor differentiation has the worst prognosis. Tumor located in the body or tail of pancreas usually has reached more advanced stage. Tumor size also determines the prognosis, particularly if it is > 3 cm. Tumor metastasis usually depends on the fat tissue of peripancreatic retroperitoneum, nerves, blood vessels, and lymph vessel. Lymph nodes which are usually involved are superior and posterior pancreaticoduodenal. The most common distant metastasis is in the liver and peritoneum, and other organs including lung, bone, kidney, brain and skin.

The 2-year survival rate for pancreatic cancer is 28%; while the 5-year survival rate is about 3.5-12%. In the untreated patients, the survival rate is about 3 months, and when the radical resection was performed, the survival rate will increase up to 10-20 months.

The treatment choice for pancreatic cancer includes surgical resection, but only 10-20% cases are selected as candidates for operation. Chemotherapy only brings 10% response with moderate toxic chemotherapy effect.[11] Radiotherapy is usually not effective for pancreatic carcinoma treatment.

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