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Henry Ford Hospital Clinicopathological Conference

Hypercoagulable state in cancer of the pancreas in a 57-year-old man

Participants:
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Radiology: Dr. Mark G. Weingarden, Department of Diagnostic Radiology
Pathology: Dr. Chan K. Ma, Department of Pathology

Case Presentation

A 57-year-old unemployed black man was brought to the Emergency Room, lethargic, semi-comatose, and unable to give a medical history. His wife and family stated that he had had many complaints, and hospitalizations since myocardial infarctions, which supposedly took place six and seven years earlier. Several months before this admission to our hospital he had been hospitalized elsewhere for chest and abdominal pain. At that time he signed out against medical advice and was not seen again by his family until three weeks before he was admitted to Henry Ford Hospital. The family stated that the patient was diabetic and had been on tolbutamide for some time, probably for several weeks. When the patient returned to his family, they noted intermittent swelling of his feet. Apparently, in the past he had used a long-acting nitroglycerin preparation, diazepam, and pentazocine for pain.

On physical examination the patient was a thin, elderly black man with dry skin, sunken eyes, stupor state arousal by name, who was unable to obey simple commands. A single, right axillary node was palpable. The chest was clear to percussion and auscultation. Heart examination was unremarkable. Blood pressure was 88/60. Pulse was 120 and irregularly irregular. Examination of the abdomen showed diffuse tenderness to deep palpation. Liver span percussed 9 cm. Spleen was not palpable. Bowel sounds were hypoactive. Examination of the spine and extremities showed 2+ pedal edema and a full range of motion. Genital examination was unremarkable. Rectal examination showed good sphincter tone; stool in the rectal ampulla was guaiac positive.

Laboratory work on admission showed a hemoglobin of 15.9 gm/dl, white count 29,500, sodium 148 mEq/L, potassium 5.8 mEq/L, chloride 102 mEq/L, CO₂ 21 mMol/L, BUN 87 mg/dl, creatinine 2.8 mg/dl, sugar 680 mg/dl, prothrombin time 15.5 seconds with control not specified, lactate 3.9 mMol/L, magnesium 1.3 mEq/L.

The diagnosis of diabetic ketoacidosis was made superimposed on adult diabetes mellitus, maturity onset type. The patient was placed on insulin protocol.

On the following day values showed a CPK of 183 IU/L, LDH 920 IU/L, negative MB band. The next day the patient's sodium after being on protocol was 154 mEq/L, and the following day it was 142. Creatinine subsequently fell to 1.1 mg/dl upon treatment, and the sugar varied between 162 and 381 mg/dl. Calcium and phosphorus values were stabilized and were 8.9 mg/dl and 2.8 mg/dl, respectively, after the acidosis was corrected. Amylase was always within normal limits. Magnesium was low on admission and corrected adequately. Blood gases on admission showed a partial pressure of oxygen of 73 mm Hg, saturation of 96%, a partial pressure of carbon dioxide of 29 mm Hg, pH of 7.47, and a bicarbonate of 20 mEq/L. At the end of treatment, the values returned to normal.

Despite adequate use of the protocol and correction of the laboratory values, the patient became tachypneic, developed a rapid heart beat, and required 300 cc of fluids per hour to maintain his blood pressure despite a good urine output. He gradually responded appropriately to questions and commands. Cerebral spinal fluid examination was noncontributory. Because of the tachypnea and shortness of breath, pulmonary embolism was suspected. Abdominal pain persisted after metabolic disturbances were corrected. Renograms were performed. The patient's white count, which was markedly elevated on admission, returned to 11,700 with 86% PMNs, 6 bands, 5 lymphocytes, and 3 monocytes by the third hospital day; his platelet count was 23,500. Thrombocytopenia persisted throughout. Hepatitis B antigen by radioimmunoassay was negative. By the end of the fourth and fifth hospital days, a surgical consultant suggested anticoagulation because of right calf thrombophlebitis that was confirmed on phlebogram. A hematology consultant recommended a dose of heparin not to exceed 20,000 units in view of the thrombocytopenia. A perfusion scan reported findings indicative of multiple pulmonary emboli bilaterally.

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After the ascites appeared, the patient's condition worsened, characterized by a hyperosmolar coma. The findings and clinical studies were compatible with repeated pulmonary emboli, and the possibility of sepsis on the last day was raised. The patient died quietly 13 days after admission. His death was characterized by shortness of breath, failure to maintain adequate blood gas values, and persistent hypotension.

**Clinical Discussion**

**Dr. Anderson:**
This case revolves around three major problems. The first is hyperosmolar coma. The nonketotic variety of this coma occurs mostly in elderly people with known mild or undiagnosed diabetes, and with one or more of the following precipitating factors: generalized infection; dehydration; cerebro- or cardiovascular accidents; medications such as steroids, dilantin, or potent diuretics; those who are hyperalimented either orally or intravenously or are on dialysis; those being treated for severe burns; or patients with pancreatitis.

The patient was semi-comatose when he was brought to the Emergency Room. Adult-onset diabetes mellitus was present for an unspecified length of time, although his use of an oral hypoglycemic agent (tolbutamide) was suspected to be recent. The urinary incontinence and bed-wetting are most likely the result of the stupor, while the marked osmotic diuresis is due to the hyperosmolar state.

Evidence for the ensuing hypertonic dehydration is found in his dry skin, sunken eyes, hypotension, hemoconcentration, manifested by a marginally high hemoglobin and frankly elevated serum sodium in the 150 mg/dl range, and also by the prerenal azotemia with blood urea nitrogen of 87 mg/dl and creatinine of only 2.8 mg/dl. The blood sugar was 680 mg/dl. Data about acetone in the serum and urine are not given, but the anion gap of 25 suggests that a mild degree of ketosis was present. A small increase in lactic acid was probably due to organ hypoperfusion from the hypotension, although the patient was not frankly acidotic as judged by the elevated blood pH, the nearly normal serum CO₂, and bicarbonate values.

The characteristically large volumes of fluids required to maintain blood pressure were largely due to the depletion of total body water from urinary losses, although recurrent pulmonary embolism may have contributed to the shock and increased fluid requirements (Table I). The amount of insulin administered is not mentioned, but requirements for the control of the diabetic hyperosmolar state vary greatly, and potassium must be administered with caution until the patient's deficit is established. Up to half of the patients with this disorder succumb, as was the case here. The terminal phase of this man's life was marked by refractory hyperosmolar coma.

Lack of appropriate response of the thirst centers (Table I), which occurs in patients with central nervous system disease such as brain tumors or strokes, predisposes to hyperosmolar nonketotic coma and contributes to its course. I believe there was such an underlying brain disorder in this case, and it relates to the next clinical problem, the abdomen, and in particular, the pancreas.

Perhaps we should review the radiographic studies now.

**Radiology Findings**

**Dr. Weingarden:**
A chest radiograph was obtained two days after admission (Fig. 1). There is an area of increased density in the left mid-lung field, a consolidative process. There also appears to be some minimal blunting of the left costophrenic angle. A lung scan (Fig. 2) was done four days after admission, and an area of decreased uptake is seen in the left upper lobe corresponding to the area of consolidation previously described. It is a little more prominent than one would normally expect for that minimal amount of infiltrate. On the posterior view you can see again several areas of diminished uptake on the left lung. Also, in the right lung there is at least one, possibly two, areas of decreased uptake. You will remember that the right lung showed no evidence of an infiltrative process. This entire picture is consistent with multiple pulmonary emboli.

A phlebogram (Fig. 3) was done the day after the lung scan. The left leg is normal. On the right, a great number of collateral vessels have appeared throughout most of the leg. Also notice that you cannot appreciate the deep veins we see on the left because they are occluded. A "railroad track" sign is present in several veins, representing thrombus in the deep venous system. At a higher level (Fig. 3), we
can see a normal popliteal vein on the left. On the right, the popliteal vein is not seen because it is occluded with thrombus, and this process extends to involve the distal two thirds of the femoral vein. A cross-sectional ultrasound image 2 cm below the xiphoid process is shown in Fig. 4. The head of the pancreas is not well outlined here, but the body of the pancreas is in this region and is grossly enlarged. Part of the tail is also visible.

Do you see any evidence of pseudocyst formation in the abdomen?

Dr. Weingarden:
The plain films of the abdomen were negative. That, of course, does not rule out a pseudocyst. Probably the best examination to evaluate the pseudocyst would be ultrasound. We would expect to see an area of diminished echogenicity, a localized area without any echoes, a cystic structure. Since we did not see that, there is no evidence of a pseudocyst.

How about calcifications?

No calcifications were visible on the plain film.

Dr. Anderson:
Thank you, Dr. Weingarden.

This patient was hospitalized for recurrent pain in the abdomen and chest several times during the last four months of his life. Judging from his discontent with his treatment and the prescribed medicines, it appears the pain was refractory and its cause obscure. The absence of elevated serum amylase values works against the presence of acute pancreatitis and, as Dr. Weingarden just told us, there were no calcifications in the abdomen, which occur in 50% of the cases of chronic pancreatitis. Also, there is no history of alcohol abuse.

The finding of the right axillary node may be a clue to some underlying abdominal process, but it is not described well...
enough to make it suspicious. A pancreatic abscess with metastatic abscesses in the liver should be mentioned only for completeness’ sake, especially since the abdomen was tender. But the course was not septic, and at no time is it mentioned that the patient was febrile. The white count fell to 11,700 without antibiotics.

The presence of blood in the stool, a high serum LDH of 920 lu/L, the development of icterus and ascites late in the course, and especially the ultrasound findings of enlargement of the body of the pancreas all point to a diagnosis of a primary pancreatic neoplasm.

Carcinoma of the pancreas is the fourth leading cause of cancer deaths in the United States after lung, colon-rectum, and breast (1). The highest occurrence rate in the world is found in nonwhite American men, like this patient. Incidence in the U.S. has increased threefold since 1930, exactly paralleling the increase in cigarette smoking (2). Indeed, Wynder and his colleagues have proposed that tobacco or other carcinogens are excreted by the liver into the bile, which in turn is refluxed into the pancreas. That cancers most commonly occur in the head of the pancreas may serve as an important lead to the etiology of this disease. The biliary pressure during digestion, at least in dogs, has been shown to periodically exceed pancreatic pressure allowing reflux of the bile into the pancreas, thus setting the stage for local carcinogenesis (1). And that is not too unusual when you consider that everywhere in the gastrointestinal tract where stasis occurs, the incidence of the malignancy is higher: the esophagus, stomach, and the distal colon and, in this case, the pancreatic duct.

In addition, although the incidence of cancer of the pancreas is very strongly correlated with age (in men over 75 it occurs eight to ten times more often than in the general
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Fig. 4

Ultrasound image demonstrating enlarged body of pancreas (arrows).

population), the median age for this malignancy is 10 to 15 years earlier in smokers than in nonsmokers (3), bringing it down to about 60 years of age. This man was 59. It would be interesting to know if this patient smoked cigarettes.

As occurred in this case, diabetes mellitus frequently coexists with pancreatic cancer, which has an incidence in diabetics about twice that of the general population (2). The interval between diagnosis of carcinoma of the pancreas and diabetes mellitus was one year or less in almost 80% of the patients (4). The development of diabetes or difficulties with the control of established diabetes have frequently been observed in early cancer of the pancreas, often before other signs or symptoms appear. The sudden appearance of diabetes in a middle-aged or elderly patient, particularly if associated with weight loss or vague abdominal symptoms, may therefore indicate the presence of a pancreatic malignancy (2). In our patient there is evidence that his diabetes worsened, so that tolbutamide had to be prescribed toward the end of his life. Despite the fact that inflammation of some part of the pancreas is extremely common with carcinoma, there is no evidence that either acute or chronic pancreatitis predisposes to its development (2).

Pain occurs as a presenting symptom in 50-80% of patients and occurs at some time during the disease in 70-90% (2). It is a dull, aching or boring pain in the epigastrium, steadily progressive, often worse at night, often aggravated by food if the cancer is located in the head of the pancreas. With lesions in the body and tail, the pain is worse when the patient lies down but is relieved by sitting forward.

Jaundice occurs at some time in the disease in up to 90% of the patients, often accompanied by pain. It is more common with lesions in the head. The most common symptom is weight loss, which usually precedes other symptoms. It afflicts 70-90% of the patients, who lose an average of 3.1 kg per week (2). Unfortunately, there is no specific diagnostic test for carcinoma of the pancreas. The sedimentation rate is frequently elevated.

Angiography will usually localize the tumor precisely and show metastases. Endoscopic retrograde cholangiopancreatography (ERCP) with injection of radio opaque dye into the ductal system allows a diagnosis of cancer in 75% of the cases, and cytology increases the figure to 90%. Since most pancreatic cancers arise from ductal tissue, ERCP may detect early cancer at a time when resection is possible (2). Likewise, the CT scan of the abdomen is a powerful investigative tool. In view of the false positive and negative results, carcinoembryonic antigen (CEA) at present is not useful in routine screening for pancreatic malignancy in the general population (2).

The mean survival after diagnosis in this disease is six months. Fewer than 10% of the patients survive the first year (2).

The final clinical problem involves the spontaneously elevated prothrombin time, persistent, significant thrombocytopenia, and documented deep venous thrombosis in the right calf, presumably the source of multiple pulmonary emboli with infarction demonstrated on standard chest films and ventilation perfusion lung scan. The most cogent circumstantial evidence that a condition of hypercoagulability exists in medicine is found in this very situation, namely, the increased incidence of venous thrombosis in cancer, especially cancer of the body and tail of the pancreas, in which phlebitis occurs in 50% of the cases (5,6).

Phlebitis is seen predominantly in patients with mucin-producing cancers of whatever organ. The frequency of attacks is proportional to the grade of malignancy, and the presence of jaundice is associated with a decreased incidence of attacks. Phlebitis subsides spontaneously after the cancer has been removed, but in the untreated state resistance to anticoagulation therapy is impressive (5).

An occult cancer must be suspected whenever phlebitis persists or is migratory (phlebitis migrans) despite anticoagulant therapy, in patients of middle age and older, or whenever there is unexplained bleeding with prothrombin times in a therapeutic range (5). Other malignancies associated with phlebitis are shown in Table 11. Carcinoma of the pancreas, lung, ovary, breast, stomach, colon, gallbladder, and prostate gland, even leukemia and lymphoma, all predispose to recurrent phlebitis with thromboembolism, but the hallmark disease is cancer of the pancreas. This man had diabetes that went out of control, suggesting the presence of cancer of the pancreas and evidence for dis-
TABLE II

Thrombotic States with Cancer

Recurrent phlebitis with thromboembolism
- Carcinoma of the pancreas, lung, ovary, breast, stomach, colon, gallbladder and prostate gland

Acute D.I.C.: generalized bleeding
- with consumption coagulopathy
- decreased platelets, clotting factors
- activation of fibrinolysis

Chronic D.I.C.: hypercoagulable state
- clotting factors, fibrinogen may increase
- microangiopathic hemolytic anemia

Non-bacterial (marantic) endocarditis (O.B.S.)

Seminated intravascular coagulation (DIC) (Table II). These cancerous states may induce physical or chemical changes in the blood vessel wall that prevent the normal antithrombotic effect. Also, foreign material from the cancer may enter the bloodstream and activate clotting mechanisms in areas of the circulation where stasis or endothelial damage exists (5).

The rate at which this procoagulant material from neoplastic tissue enters the circulation and consumes labile clotting factors and platelets determines whether bleeding or thrombosis results (7). If consumption is rapid and overwhelming, bleeding will ensue, whereas if thromboplastic material is introduced slowly, as from the breakdown of metastases in a patient with a malignant tumor, a chronic hypercoagulable state occurs (7). Clotting factors and fibrinogen may increase; there may be a microangiopathic hemolytic anemia. Fibrinogen (Table II), therefore, may be increased or decreased, depending on the extent to which it is consumed. If fibrinogen is increased, it accounts for the elevated sedimentation rate that is common in patients with a malignant tumor. Since the patient with a cancer often has thrombocytosis, a low platelet count in this situation and the absence of bone marrow involvement by tumor is evidence for a DIC. Also, the assessment of fibrin degradation products in the blood is a useful screen for its presence, since intravascular coagulation is always accompanied by fibrinolysis (7,8).

In addition, activation of the fibrinolytic system in response to plasminogen activators released from tissue damaged by tumor is a major cause of the hemorrhagic diathesis seen in clinically apparent intravascular coagulation. Thus, consumption of platelets, prothrombin, fibrinogen, and factors V and VIII takes place, and fibrinopeptides and fibrin degradation products (FDP) appear. It is on the basis of the laboratory demonstration of these phenomena that the clinical diagnosis of DIC is confirmed (8).

In a study of 89 patients with DIC at the Memorial Sloan-Kettering Cancer Center (9), all of whom had an increased thrombin time and FDP and diminished fibrinogen, bleeding was encountered in 75% of the patients, thromboembolism in nearly 25%, and an increase in LDH from tissue damage and infarction in 75%. An abnormal prothrombin time of greater than 15-16 seconds was present in 86%, thus enforcing its usefulness as a simple, reliable screening tool for DIC (9). Interestingly, changes in red blood cell morphology suggestive of DIC (schistocytes, helmet cells, and fragmented forms) were present in only one third of the cases examined. The pathogenesis of these bizarre red cell forms is thought to be microangiopathic mechanical damage, as they squeeze through a fibrin network in peripheral vessels (7). In the patient under discussion today, fibrinogen and FDP are not available, but thromboembolism, elevated LDH, and prothrombin time, as well as thrombocytopenia, were present. And I think that's enough to make the diagnosis.

The most direct evidence of intravascular coagulation is the presence of fibrin microthrombi (8), and their suspected presence in the brain of this patient may explain the beginning of his deterioration.

Reagan and Okasaki studied 20 patients who had neurological symptoms associated with thromboembolic disease that affected multiple organs. Sixteen had non-bacterial thrombotic endocarditis (Table II), while all patients had microvascular occlusions and microinfarcts, even those without marantic endocarditis (10). These vegetations on the heart valves are made up of platelets and fibrin. They occur on normal heart valves without any appreciable inflammatory reaction. Because of their sterile, rather friable nature, they tend to embolize. This endocardial lesion may be a dominant feature of an illness, due to an adenocarcinoma of the pancreas, stomach, or lung that has remained clinically silent (11). However, these authors suggest that in situ cerebrovascular microocclusions occur primarily in small leptomeningeal arterioles and cause small cerebral infarcts that lead to more subtle and diffuse signs of cerebral dysfunction than are usually encountered with patients with cerebral emboli emanating from the heart. They describe both abrupt and gradual neurologic changes in the absence of cerebral metastases in patients with other evidence of the hypercoagulable state. A few of their patients experienced insidious, monophasic neurologic illness with changes in the level of consciousness,
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loss of memory, confusion, disorientation, and generalized seizures for which small cerebral infarcts seem to offer the most reasonable explanation (10).

It’s possible that the mental aberrations which punctuated this patient’s behavior during the last two months of his life and predisposed him to a hyperosmolar coma can be ascribed to the deposition of fibrin microthrombi. However, the combination of uncontrolled diabetes with documented vascular disease (i.e., his history of myocardial infarctions) would be sufficient to explain the mental picture.

The final event in this patient, which was characterized by dyspnea, hypoxia, and shock, was probably caused by massive venous embolization to the right heart chambers or lungs. Septic shock or multiple microscopic tumor emboli in the lungs (12) would be less likely explanations.

My impression is that the patient had an adenocarcinoma of the body of the pancreas, metastatic to the liver and perhaps to other organs, which gave rise to a hypercoagulable state. This chronic DIC caused thrombosis in the deep veins of the right leg and perhaps elsewhere, resulting in multiple pulmonary embolization with infarction, which led to the patient’s death. The case was complicated by a diabetic hyperosmolar coma.

Student Diagnosis:
The medical students also believe that the patient had a carcinoma of the body of the pancreas complicated by a hyperosmolar state, mild lactic acidosis, right calf thrombophlebitis, and multiple pulmonary emboli. We felt that the development of ascites and icterus represented metastatic disease and that the patient’s terminal event was due to multiple pulmonary emboli.

Pathology Findings

Dr. Ma:

This patient had cancer of the pancreas involving the entire body and tail. Fig. 5 shows the head of the pancreas with normal lobulation. This is a portion of adjacent duodenum. The bottom arrow indicates a cross-section of the body of the pancreas. There is a loss of normal lobular architecture as a result of replacement by the tumor, which had already metastasized to the lymph nodes of the portal hepatiis, which in turn compress and infiltrate the common bile duct resulting in obstructive jaundice. The middle arrow indicates the proximal portion of the common bile duct, which is dilated as a result of stenosis at the distal site. In addition, the tumor also metastasized to the lung, the stomach, and liver. Another cross-section of the pancreatic carcinoma reveals the portal vein, which was occluded by thrombus. Thromboemboli were also found in a major pulmonary artery, in the peripheral branches of the pulmonary arteries, and in the prostatic veins. Fig. 6 illustrates a section of the portal vein. The lumen is occluded by fresh thrombus, and adjacent liver tissue contains small foci of metastatic carcinoma. A section of the pancreas revealed an adenocarcinoma that showed individual as well as clusters of well-formed, glandular structures with abundant tissue stroma. This is the most common pattern of pancreatic carcinoma. There were residual pancreatic islets. At a higher magnification (Fig. 7), you can see the tumor cells arranged in well-formed, glandular structures. Another section from another area of the pancreatic carcinoma demonstrated tumor involvement in the perineural space.
Fig. 7
Histologic section of pancreatic tumor, demonstrating well-formed glandular structural arrangement of tumor cells.

Now, in answering Dr. Anderson's questions, we didn't see any microthrombi. The brain shows only focal anoxic changes, and there are no microthrombi.

In summary, this is a case of adenocarcinoma involving the body and tail of the pancreas. The accompanying diabetes mellitus, thrombophlebitis of the right leg, and multiple thrombus with pulmonary thromboembolism make this case a good example of pancreatic carcinoma (13).

Cubilla and Fitzgerald reviewed 406 cases of nonendocrine pancreas carcinoma at Memorial Sloan-Kettering Cancer Center, and they found that 308 or 76% were cases of duct cell adenocarcinoma (13). Our patient also had this type of pancreatic carcinoma.

Generally, carcinoma of the pancreas has a very poor prognosis. Most patients die within one year regardless of the histologic type. Nonetheless, there are morphologically distinctive patterns, and their delineation may eventually permit correlation with some genetic, biochemical, endocrinological, clinical, prognostic, or other parameter of significance.

References