Case Records of the Massachusetts General Hospital



Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C. CABOT

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Case 31-2002

PRESENTATION OF CASE

A 61-year-old man was admitted to the hospital because of right hemiplegia, aphasia, and obtundation.

According to the patient's family, he had been well at his home in Haiti until about one month earlier, when pain developed in his right leg. Two days later, an ultrasonographic examination of the leg revealed no abnormalities, and a physician advised him to take aspirin. The pain resolved, but three weeks before admission, headache, nausea, and vomiting developed and shortly thereafter disappeared; two days later, the patient had a problem with balance. An ultrasonographic study of the liver raised the possibility of a tumor, and a stool specimen was found to contain Entamoeba histolytica; metronidazole was given for one week. Two weeks before admission, the patient's problem with balance resolved and a computed tomographic (CT) examination of the brain showed no abnormalities. One week before admission, abdominal pain and intermittent headaches developed, and he made plans to travel to the United States. On the morning of departure, a brother who accompanied him on the flight noted that the patient had difficulty signing his name. During the flight he spoke with increasing difficulty and had recurrent headache and weakness of the right leg. Weakness soon developed in the right arm, and he became aphasic. He was brought to this hospital awake and mute, but he quickly became obtunded. The trachea was intubated.

The patient, who resided in a rural area of Haiti, had stopped smoking 18 years earlier and drank a moderate amount of alcohol. There was a history of type 2 diabetes mellitus, for which he took an unknown oral medication. There was a history of diabetes mellitus in several relatives, and a sister had had three later-term spontaneous abortions, without further evaluation. The patient's family reported that to their knowledge he had not had chest pain, dyspnea, fever, chills, night sweats, weight loss, sickle cell disease, recent dental procedures, or exposure to animals or tuberculosis. There was no family history of stroke or clotting disorders.

The temperature was 36.4° C, the pulse was 137, and the respirations were 20. The blood pressure was 165/75 mm Hg.

On physical examination, the patient was obtunded and responded minimally to stimulation. No rash, petechiae, septic lesions, or lymphadenopathy was detected. Scleral icterus was noted. The lungs were clear. A grade 2 systolic apical murmur was present; a third heart sound was not heard. The liver was hard and descended 4 to 5 cm below the right costal margin; the spleen was not felt, and no fluid wave was detected. No bruit was heard. The left carotid pulse was absent; the right carotid, radial, femoral, and popliteal pulses were ++ bilaterally. The lower left leg was pale and cold below the middle of the calf, and the left posterior tibial and dorsalis pedis pulses were absent. The right foot was warm; the right posterior tibial and dorsalis pedis pulses were identified on Doppler examination but were not palpable. No peripheral edema was present.

On neurologic examination, the patient responded to sternal pressure with minimal movement of the left arm and leg; there was infrequent spontaneous movement of the left arm. The pupils were 4 mm in diameter, symmetric, and reactive. No gaze preference was detected. The right arm was flaccid. The deep-tendon reflexes were present bilaterally. The plantar responses were absent.

The urine was orange and was positive for protein (++) and bilirubin (+) and trace-positive for urobilinogen; the sediment contained three to five red cells, up to two white cells, and a few bacteria per high-power field. Hematologic tests and blood chemical studies were performed (Tables 1 and 2). The levels of calcium, amylase, and creatine kinase were normal. While the patient was breathing supplemental oxygen, the partial pressure of oxygen was 189 mm Hg, the partial pressure of carbon dioxide 37 mm Hg, and the pH 7.33. An electrocardiogram showed a sinus tachycardia at a rate of 140, with occasional premature ventricular complexes; there was a pattern of inferior and probably lateral myocardial infarction, which may have been acute. A chest radiograph revealed that the endotra-

TABLE 1. HEMATOLOGIC LABORATORY DATA ON THE DAY OF ADMISSION.

VARIABLE	VALUE
Hematocrit (%)	35.3
White cells (per mm ³)	27,900
Differential count (%)	
Neutrophils	74
Band forms	3
Lymphocytes	17
Atypical lymphocytes	1
Monocytes	4
Metamyelocytes	1
Platelets (per mm ³)	193,000
Erythrocyte sedimentation rate (mm/hr)	39
Mean corpuscular volume (µm³)	81
Prothrombin time (sec)*	14.1
Partial-thromboplastin time (sec)	Normal

*The normal range is 11.1 to 13.1 seconds.

cheal tube was in the appropriate position; there was patchy atelectasis at the base of the left lung; the other regions of the lungs and the cardiac silhouette were normal. CT and magnetic resonance imaging (MRI) of the brain, which showed multiple infarcts, and CT studies of the liver, kidneys, and lower abdomen were performed (Fig. 1, 2, 3, 4, and 5).

The patient was admitted to the intensive care unit. A urine specimen and two blood specimens were obtained for culture. Single doses of ceftriaxone and vancomycin were administered; treatment with aspirin (325 mg daily), minidose heparin, regular insulin, and metoprolol was begun. A transesophageal echocardiogram was obtained (Fig. 6).

On the second hospital day, the patient's temperature did not exceed 37.7°C, and the findings on examination were little changed. Blood chemical studies were performed (Table 2). A test for viral hepatitis B surface antibody was positive; tests for hepatitis B surface antigen, hepatitis C antibody, antibodies to human immunodeficiency virus (HIV) types 1 and 2, antinuclear antibodies, and rheumatoid factor were negative. Another chest radiograph revealed probable atelectasis at both lung bases and a small, linear opacity in the middle zone of the left lung, probably also atelectasis. A renal radioangiographic examination showed that there was virtually no perfusion of the left kidney, except for a small region at the lower pole, and minimal uptake of tracer material, predominantly in the lower pole on delayed images. There was normal perfusion of the right kidney on the initial images, with prompt concentration of tracer material, although clearance of the material was delayed. Another CT study of the brain, performed without the use of intravenous contrast material, revealed no nota-

TABLE 2.	BLOOD	CHEMICAL	VALUES.*

VARIABLE	First Hospital Day	SECOND HOSPITAL DAY
Glucose (mg/dl)	188	142
Conjugated bilirubin (mg/dl)	3.5	
Haptoglobin (mg/dl)†		227
Total bilirubin (mg/dl)	4.9	
Phosphorus (mg/dl)	5.1	
Protein (g/dl)	7.7	
Albumin	2.4	
Globulin	5.3	
Sodium (mmol/liter)	134	
Potassium (mmol/liter)	5.7	
Chloride (mmol/liter)	102	
Carbon dioxide (mmol/liter)	19.9	
Magnesium (mmol/liter)	1.2	
Urea nitrogen (mg/dl)	66	70
Creatinine (mg/dl)	3.9	4.1
Iron (µg/dl)		27
Iron-binding capacity (µg/dl)		124
Creatine kinase (U/liter)		435
Creatine kinase isoenzyme (ng)‡	37.1	12.1
Creatine kinase isoenzyme index (%)§	13.1	3.0
Troponin T (ng/ml)¶	1.27	2.19
Alkaline phosphatase (U/liter)	415	
Aspartate aminotransferase (U/liter)	158	
Alanine aminotransferase (U/liter)	143	
Lactate dehydrogenase (U/liter)		1923
Ferritin (ng/ml)		7705
Lipase (U/liter)**	7.5	

*To convert the values for glucose to millimoles per liter, multiply by 0.05551. To convert the value for total bilirubin to micromoles per liter, multiply by 17.1. To convert the value for phosphorus to millimoles per liter, multiply by 0.3229. To convert the value for magnesium to milliequivalents per liter, divide by 0.5. To convert the values for urea nitrogen to millimoles per liter, multiply by 0.357. To convert the values for creatinine to micromoles per liter, multiply by 88.4. To convert the values for iron and iron-binding capacity to micromoles per liter, multiply by 0.1791.

†The normal range is 16 to 199 mg per deciliter.

[‡]The normal range is 0 to 6.9 ng per milliliter.

\$The normal range is 0 to 3.5 percent.

The normal range is 0 to 0.09 ng per milliliter.

The normal range is 30 to 300 ng per milliliter.

**The normal range is 1.3 to 6.0 U per liter.

ble change in the multiple infarcts and no new infarcts, midline shift, mass effect, bleeding, or hydrocephalus.

All culture specimens were negative, and the results of numerous other laboratory studies were still pending.

DR. PAMELA W. SCHAEFER (Neuroradiology): On the first hospital day, a CT examination of the brain (Fig. 1) was performed without the administration of contrast material. There are areas of hypodensity in the posterior left frontal and left parietal lobes; there is also loss of the normal distinction between

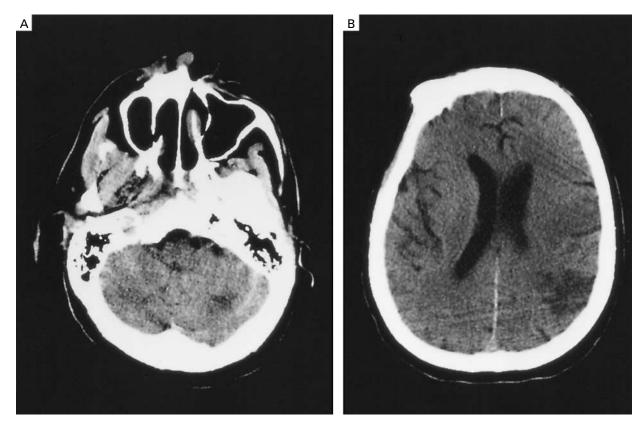


Figure 1. Axial CT Images of the Brain Obtained without the Use of Contrast Material, Showing Bilateral Cerebellar Infarctions (Panel A) and Left Frontal and Parietal Infarctions (Panel B).

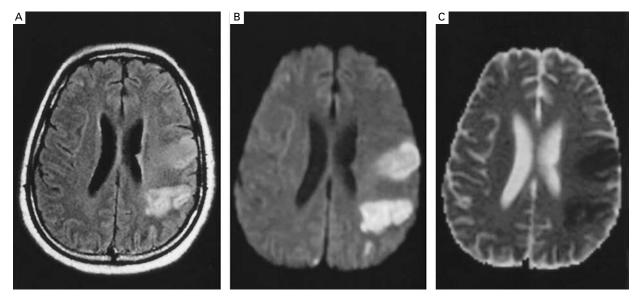


Figure 2. Axial MRI Scans of the Brain.

An image obtained with fluid-attenuated inversion recovery (Panel A) shows infarctions in the left frontal and parietal lobes. The infarcts are hyperintense on diffusion-weighted images (Panel B) and hypointense on apparent-diffusion-coefficient images (Panel C), suggesting that they are acute.



Figure 3. Contrast-Enhanced CT Image of the Liver. Multiple focal, low-attenuation lesions with ill-defined borders (solid arrows) are present. A geographic pattern of low attenuation (open arrow) suggests abnormal perfusion. There is a more discrete, wedge-shaped area of low attenuation that was not enhanced, which indicates that the tissue is infarcted (arrowhead).



Figure 4. Contrast-Enhanced CT Image of the Liver and Kidneys. There is abnormal perfusion of all three organs. There is minimal uptake of contrast material in the left kidney. Contrast material is present in the renal arteries at their origins (arrows).

gray matter and white matter and a local mass effect, as evidenced by effacement of the sulci. These changes are consistent with the presence of acute infarcts in the distribution of the left middle cerebral artery. Bilateral cerebellar infarcts are also present. There was no midline shift or hydrocephalus.

MRI of the brain (Fig. 2), with angiographic examination of the head and neck, showed multiple acute infarcts in several vascular territories. The largest infarcts were in the left middle cerebral artery in the posterior left frontal and left parietal lobes, with exten-



Figure 5. Contrast-Enhanced CT Image of the Lower Abdomen. There is thickening, without dilatation, of the ascending colonic wall (arrows), with an abrupt transition to colonic wall of normal thickness (arrowhead).

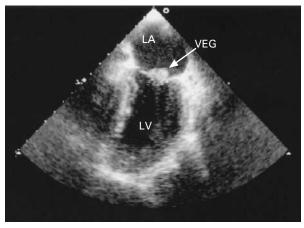


Figure 6. Transesophageal Echocardiogram. A large vegetation is present on the mitral valve. LA denotes left atrium, LV left ventricle, and VEG vegetation.

sion into the left temporal operculum; smaller, focal infarcts were seen elsewhere in the left and right middle cerebral arteries. Small, acute infarcts characterized by hyperintensity on diffusion-weighted imaging and by hypointensity on apparent-diffusion-coefficient imaging were present in both occipital lobes and extended into the temporo-occipital regions. Small, acute infarcts were also present bilaterally within the cerebellum, in the posteroinferior cerebellar arteries. Additional acute infarcts were present bilaterally along the border zones of the middle and posterior cerebral arteries and the middle and anterior cerebral arteries. Subacute infarcts (which were hypointense on diffusion-weighted imaging and hyperintense on apparentdiffusion-coefficient imaging) were seen in the right

superior and right posteroinferior cerebellar arteries. Magnetic resonance angiograms of the neck and the circle of Willis showed no abnormalities.

DR. BRIAN C. LUCEY (Radiology): CT examination of the thorax, abdomen, and pelvis, performed after the intravenous administration of contrast material, disclosed minimal bibasilar atelectasis without pleural effusions, pulmonary masses or nodules, intrathoracic lymphadenopathy, or abnormalities of the thoracic or abdominal aorta or mesenteric vessels. The liver was enlarged, and both lobes contained multiple focal low-attenuation lesions with ill-defined borders, ranging from 2 to 20 mm in diameter. The lesions were so numerous in the right lobe that they appeared to be confluent. After the administration of contrast material, these areas showed heterogeneous enhancement during the portal venous phase. Thus, a diagnosis of hepatic abscess is unlikely. In addition, there were large irregular areas of decreased enhancement in the liver parenchyma, suggesting vascular insufficiency, and a wedge-shaped nonenhancing area, suggesting the presence of infarction (Fig. 3). No dilatation of the intrahepatic or extrahepatic ducts was observed; the hepatic arteries and portal vein were patent. In both kidneys, there were areas of hypoperfusion consistent with the presence of infarcts; the left kidney was more severely affected than the right. The renal arteries were patent at their origins (Fig. 4); the wall of the cecum and ascending colon was thickened, without dilatation, with a pattern of normal enhancement. In the wall of the ascending colon, there was an abrupt transition to normal thickness (Fig. 5) - a finding that is nonspecific but consistent with the presence of colitis. There were nonspecific inflammatory changes in the fat surrounding the ascending colon and inferior aspect of the right hepatic lobe. The findings suggested a focal ischemic colitis.

DR. MARY ETTA KING (Cardiology): After the patient's admission to the intensive care unit on the first hospital day, transthoracic echocardiography was performed because of his history of myocardial infarction and stroke. In the parasternal long-axis view, the anterior mitral leaflet was diffusely thickened. The mitral leaflets showed incomplete coaptation in a pattern consistent with the presence of papillary-muscle dysfunction. There was an eccentrically directed jet of mitral regurgitation. The aortic leaflets were slightly thickened but did not show obvious vegetations. In the parasternal short-axis view, the left ventricular chamber size, wall thickness, and systolic function were normal at the base and at the midventricular level. Apical views of the heart showed segmental dysfunction of the apex and diffuse thickening of the mitral valve, with a moderate degree of mitral regurgitation visible on color Doppler examination. The estimated left ventricular ejection fraction was 52 percent. Mild aortic insufficiency was also present. After the intravenous injection of agitated saline, both while the patient was at rest and while the Valsalva maneuver was being performed, there was dense opacification of the right atrium and right ventricle, with no contrast effect in the left atrium or left ventricle. Contrast material was administered to rule out the possibility that a paradoxical embolus had moved through an interatrial communication; no right-to-left intracardiac shunt was found. Although no discrete vegetations were seen, they could not be ruled out by the transthoracic study.

A diagnostic procedure was performed.

DIFFERENTIAL DIAGNOSIS

DR. MARTIN A. SAMUELS*: Armand Trousseau (1801–1867), professor of clinical medicine at the Faculty of Medicine, Paris, had an enormous impact on 19th-century medicine. His lectures on clinical medicine, which he delivered as physician to the Hotel-Dieu, covered nearly every aspect of internal medicine, including neurology. Two of his most important contributions are the diagnoses in this case.

In a series of landmark articles published in the 1860s,¹⁻⁵ Paul Broca (of the Bicêtre Hospital, Paris) proposed the term "aphemia" for the language disorder that results from a lesion in an area of the left inferior frontal lobe. The observation was important because it suggested that different regions of the cerebral cortex have discrete functions and because it posited the concept of lateralization. Before this time, debate had raged over whether the brain functioned by means of specialized regions (the phrenology of Franz Gall)⁶ or as a homogeneous whole (the argument put forth by Marie-Jean-Pierre Flourens, who refuted phrenology).7 In 1864, Trousseau criticized Broca's term "aphemia" and suggested "aphasia" instead.8 A debate ensued in the Academy of Medicine in which these terms, as well as "alalia" and "aphrasia," vied for dominance.9 Trousseau was correct in that he favored the localization of language disorders (in the frontal lobes) but incorrect in that he did not recognize lateralization, since the left frontal lobe usually controls language. According to Henderson,9 "aphasia" ultimately won, mostly because of Trousseau's power and influence. In the case under discussion, the aphasia, which was due to a left-frontal-lobe infarction, was the first of the patient's two Trousseau's syndromes.

In 1865, in lecture 95 of Trousseau's lecture series on clinical medicine, he described phlegmasia alba dolens (painful white inflammation) due to venous thrombosis in multiple circumstances, including the

^{*}Neurologist-in-chief and chair, Department of Neurology, Brigham and Women's Hospital; co-chief, Partners Neurology; professor of neurology, Harvard Medical School — all in Boston.

period after parturition, and in various cachectic diseases, such as tuberculosis and cancer.¹⁰ This lecture included numerous clinical case presentations, autopsy results, and hypotheses concerning hypercoagulability. The physical findings and probable causes of death included pulmonary embolism, global cerebral ischemia (syncope), and stroke. In this lecture he said the following:

I have long been struck with the frequency with which cancerous patients are affected with painful oedema of the superior or inferior extremities, whether or not either was the seat of cancer. The frequent concurrence of phlegmasia alba dolens with an appreciable cancerous tumor, led me to the inquiry whether a relationship of cause and effect did not exist between the two, and whether the phlegmasia was not the consequence of the cancerous cachexia. I have since that period had an opportunity of observing other cases of painful oedema in which, at autopsy, I found visceral cancer, but in which, during life, there was no appreciable cancerous tumor.¹⁰

About a year and a half after delivering this lecture, Trousseau himself had phlegmasia alba dolens affecting the left leg and predicted, correctly, that he had an occult stomach cancer.¹¹ His friend and colleague, Peter, later recorded the following: "It was on January 1, 1867 when I went to give him my best wishes for the new year that Trousseau told me with resigned sadness — 'I am lost; a phlegmasia which showed itself that night leaves me no doubt about the nature of my affliction.'"¹² This paraneoplastic syndrome, characterized by phlebothrombosis related to a visceral cancer, is one of the few eponymous syndromes that deserves an apostrophe (i.e., the possessive form) because the discoverer both described the disorder and died of it.

In the 137 years since Trousseau's lecture on the subject, many studies have documented the association between venous thromboembolism and cancer.¹³⁻²⁰ Interestingly, treatment of recurrent deep venous thrombosis with warfarin may be associated with a reduced risk of cancer, raising the question of whether warfarin could be acting as an antineoplastic agent.²¹ When cancer is diagnosed within one year after an episode of venous thrombosis, the likelihood of metastatic disease is greatly increased and the survival rate at one year is greatly reduced.²²

Nearly every type of cancer (including gynecologic and urogenital neoplasms, lymphomas, and primary brain tumors) has been reported in association with a hypercoagulable state, but cancer of the gastrointestinal and hepatobiliary tracts, particularly mucinsecreting adenocarcinomas, predominate in this regard. The clinical maxim that pancreatic cancer is especially likely to result in Trousseau's syndrome is probably incorrect, but some patients with Trousseau's syndrome do have this cancer.²³

The precise reason for the hypercoagulable state in some patients with cancer remains unknown, but it is likely that such a state, which resembles chronic disseminated intravascular coagulation, is due to a disruption in the delicate balance between fibrinolysis and inhibition of fibrinolysis. Tumors release substances that interfere with this balance, such as thromboplastin, factor X activator, prothrombinase, plasminogen-activator inhibitor, and plasmin inhibitor. The chronic state of disseminated intravascular coagulation in some patients with cancer has various causes, including genetic predisposition, such as that due to the presence of the factor V Leiden mutation or a mutation in the prothrombin gene. The fact that this patient's sister had had three spontaneous abortions raises the question of whether this family was prone to thrombosis as a result of the primary antiphospholipid-antibody syndrome or some other hypercoagulable state.

Trousseau's syndrome is characterized by microangiopathic changes on peripheral-blood smears and very friable vegetations, often invisible on echocardiograms, on the cardiac valves (nonbacterial thrombotic endocarditis). Visceral organs, including the brain, may thus be damaged by multiple interlocking mechanisms — mainly, venous thrombosis, arterial thrombosis, and cardiac source emboli.

There is little doubt that this patient had Trousseau's syndrome. Infarctions of the kidneys, bowel, heart, and brain followed an episode of pain in the right leg. The multiple small lesions in the liver probably represented metastases from a cancer of the stomach or colon or a cancer of the hepatobiliary system. The diagnostic test was probably a biopsy of the liver. One of the cerebral infarctions involved the left frontal lobe, resulting in a right hemiplegia and aphasia.

DR. ROBERT B. COLVIN (Pathology): Dr. Singhal, what were your thoughts?

DR. ANEESH B. SINGHAL (Neurology): When we first saw this patient, we knew his medical history and the findings on his cranial MRI scans. We considered hypercoagulable states such as the antiphospholipidantibody syndrome, and we thought that vegetations, if present, could be secondarily infected. Since the levels of cardiac enzymes were abnormal, we considered the possibility of a left ventricular thrombus due to a recent myocardial infarction. However, because of the topography of the lesions on diffusion-weighted imaging, we favored a diagnosis of Trousseau's syndrome, with multiple strokes.

CLINICAL DIAGNOSIS

Multiple ischemic strokes, resulting from nonbacterial thrombotic endocarditis due to an underlying cancer (Trousseau's syndrome).

DR. MARTIN A. SAMUELS'S DIAGNOSES

- Trousseau's syndrome (phlegmasia alba dolens as a manifestation of a hypercoagulable paraneoplastic syndrome).
- Aphasia due to a frontal-lobe infarction as described by Trousseau.

PATHOLOGICAL DISCUSSION

DR. COLVIN: Two diagnostic procedures, transesophageal echocardiography and a biopsy of the liver (with a CT-guided core-biopsy needle), were performed.

DR. KING: Since valvular vegetations could not be ruled out by the transthoracic study, a transesophageal echocardiogram was obtained. The midesophageal views revealed a shaggy mass, 1 by 1 cm, attached to the posterior mitral-valve leaflet; in addition, there was a small lesion on the tip of the anterior leaflet (Fig. 6). A video of the transesophageal echocardiogram is available as Supplementary Appendix 1 with

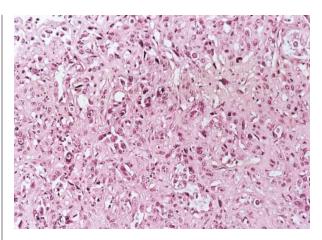


Figure 7. Biopsy Specimen of the Liver, Showing Metastatic Carcinoma (Hematoxylin and Eosin, \times 250).

The hepatic architecture is almost totally effaced and has been replaced by a loosely cohesive, malignant-cell population with focal architectural features suggestive of microglandular formation.

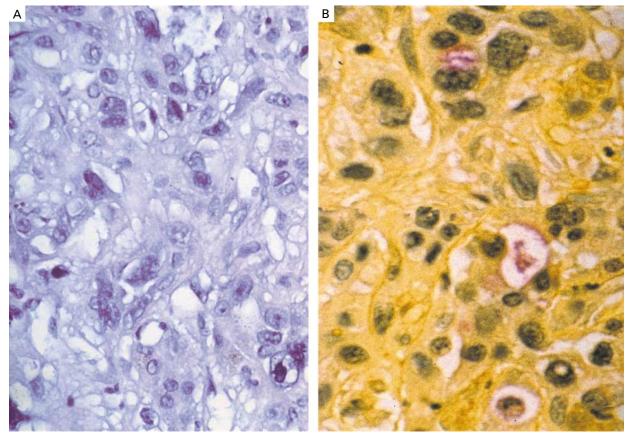


Figure 8. Biopsy Specimens of the Liver.

The findings are consistent with the presence of metastatic, poorly differentiated adenocarcinoma of probable pancreaticobiliary origin. The tumor cells have large, bizarre nuclei (Panel A; hematoxylin and eosin, \times 500). Mucicarmine staining confirms the presence of focal areas of mucin production (Panel B; \times 500).

the full text of this article at http://www.nejm.org. The aortic-valve cusps were diffusely thickened, and there were small, irregular lesions on both aspects of the cusps. On color Doppler examination, eccentrically directed mitral regurgitation was estimated to be moderately severe. Mild aortic insufficiency was present. The tricuspid and pulmonic valves were normal, and the interatrial septum was intact. On the transgastric views, there was segmental dysfunction of the cardiac apex, but no apical thrombus. The valvular findings are consistent with the presence of vegetations, which are due either to infection or to marasmus.

DR. ULYSSES BALIS (Pathology): Specimens from the hepatic biopsy, sectioned and stained with hematoxylin and eosin, reveal an infiltrative cancer with a focal microglandular pattern, consistent with the presence of a poorly differentiated adenocarcinoma (Fig. 7). The presence of pleomorphic nuclei and numerous mitoses indicate a high-grade cancer. There is focal mucin production (Fig. 8). Immunohistochemical studies were positive for cytokeratin 7, suggesting that the neoplasm is of pancreaticobiliary origin.

DR. SINGHAL: The patient died after a cardiac arrest on the seventh hospital day.

ANATOMICAL DIAGNOSIS

Adenocarcinoma, probably of pancreaticobiliary origin and metastatic to the liver, with a hypercoagulable state resulting in thrombophlebitis and nonbacterial thrombotic endocarditis, with multiple embolic infarcts (Trousseau's syndrome).

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35-MILLIMETER SLIDES FOR THE CASE RECORDS

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