BRONCHOGENIC CARCINOMA, LEUKEMOID REACTION, MARANTIC ENDOCARDITIS, AND CONSUMPTIVE THROMBOCYTOPATHY

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This paper details the simultaneous occurrence of a severe leukemoid reaction, nonbacterial thrombotic endocarditis (NBTE) (marantic endocarditis), and a consumptive thrombocytopathy without signs of microangiopathic hemolysis on peripheral blood smear in a patient with terminal metastatic, undifferentiated, large cell bronchogenic carcinoma. The case is presented and the condition is discussed in detail.

Recently Dalal et al[1] described three cases of large cell bronchogenic carcinoma associated with myeloid leukemoid reactions. This association is indeed rare.

The present case report is a detailed clinical description of a large cell bronchogenic carcinoma associated with an unusually severe myeloid leukemoid reaction and fulminant marantic endocarditis with severe thrombocytopenia, mimicking thrombotic thrombocytopenic purpura without schistocytosis on peripheral blood smear. Of further interest, Döhle bodies were quite manifest on peripheral blood smear in the absence of demonstrable infection.[2]

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CASE DESCRIPTION

A 55-year-old woman with a cigarette smoking history of 40 pack-years was seen on February 27, 1980 for evaluation of a chest mass which had been found by her private physician in December 1979 during evaluation for recurrent gross hemoptysis. She was hospitalized at that time, and diagnostic studies were not helpful beyond confirming the presence of a 4- × 5-cm irregular left hilar mass extending into the anterior segment of the left upper lobe. She refused further diagnostic studies, including a recommended diagnostic thoracotomy and was discharged on antibiotics. A follow-up chest x-ray done on January 28, 1980 revealed no change in the mass lesion. When seen by the authors, she was asymptomatic except for a chronic bronchitic cough. She stated that she was being treated for hypertension and that she drank alcohol in moderation.

Physical examination revealed a blood pressure of 180/80 mmHg, pulse rate 90 per minute, respiratory rate 16 per minute, and a temperature 99.6 F. She was found to have three slightly tender and matted left axillary lymph nodes (each measuring 1.0 × 1.5 cm) that were freely movable in the axillary apex superficial to the chest wall.

Two nontender 3-cm nodules were noted in the upper quadrants of the left breast. Bilateral lower lobe inspiratory and expiratory rhonchi were present and cleared with coughing. Persistent forced

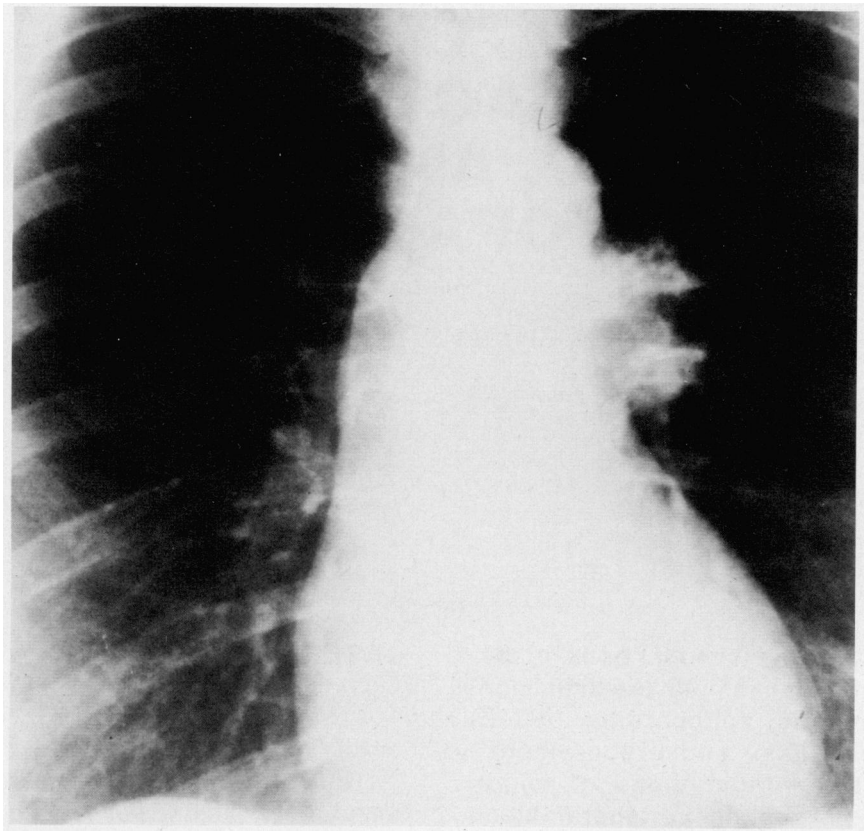

Figure 1. Preadmission chest x-ray demonstrating a lobulated 4- × 5-cm left hilar mass.

expiratory wheezing was noted over the left upper lobe. There was no evidence of edema, cyanosis, clubbing, Horner's sign, loss of triceps' reflex on the left, or phlebitis. Levine's cigarette smoking sign was noted. Otherwise her examination was normal.

A Chem Screen-26 was normal except for a fasting blood glucose of 190 mg/100 ml, alkaline phosphatase of 61 IU (normal, 15-55), magnesium of 1.54 mEq/liter (normal, 1.6-2.3), and a gamma-glutamyl transpeptidase of 63 units/liter (normal, 1-60). A complete blood count revealed hemoglobin of 11.6 gm/100 ml, hematocrit 37.2 percent, red blood cell count 4.59 million/cu mm, and a white blood cell count of 11,700/cu mm with 76.2 percent polymorphonuclears, 16.7 percent lymphocytes, 6.3 percent monocytes, 0.1 percent eosinophils, and 0.7 percent basophils. While attempting to obtain the clinical details, previous chest x-rays and CT chest scan from her previous evaluation, upper and lower gastrointestinal studies were performed and were normal. Angiotensin-I-converting enzyme was 14.5 units/ml (normal, 11-29), carcinoembryonic antigen was 5.5 ng/ml (normal, 0-2.5), and the platelet count was 340,000/cu mm. Complete pulmonary function studies revealed mild resting hypoxemia, mildy reducing lung diffusion capacity, significant reduction in the maximum mid-expiratory flow rate and an elevation of her residual volume; these were suggestive of mild obstructive airways defects predominantly involving small airways. Her chest x-ray is depicted in Figure 1. Xeromammography results were normal, and an M-mode echocardiogram revealed concentric left ventricular hypertrophy with associated decreased left ventricular compliance and calcification of the mitral annulus. She was hospitalized for further evaluation because her left breast masses had enlarged rapidly and coalesced.

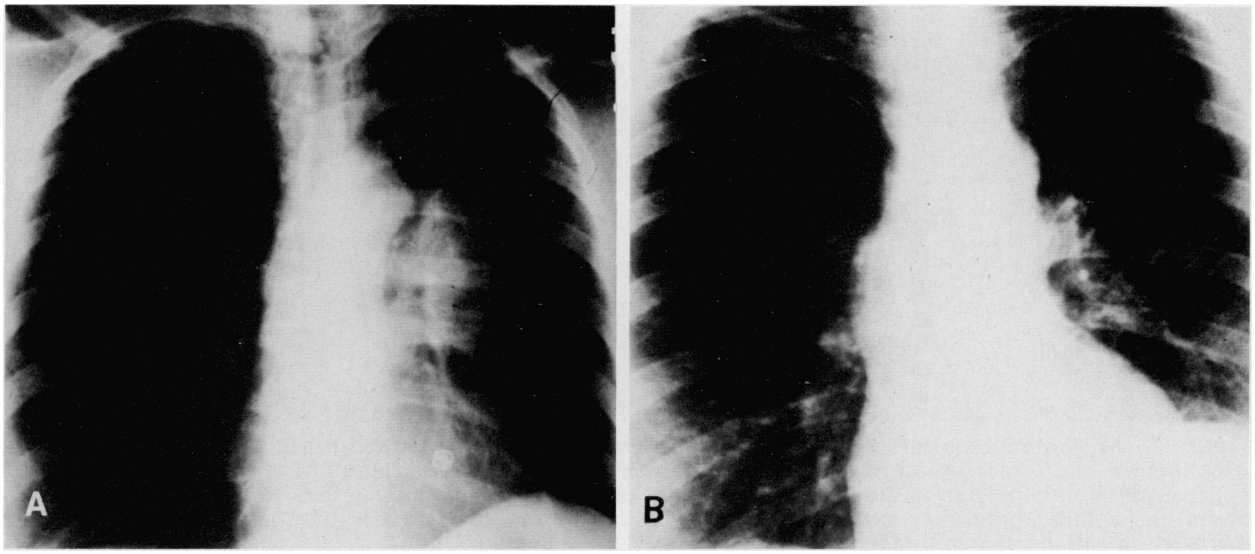

Figure 2. (A) Preoperative chest x-ray. Note the elevation of the left hemidiaphragm and the silhouetting of the left hilar mass by partial atelectasis of the left upper lobe. (B) Chest x-ray taken at the completion of radiotherapy. The left hilar mass is no longer evident because of complete atelectasis of the left upper lobe. Note the marked compensatory elevation of the left hemidiaphragm

Preoperative chest x-ray and full chest tomography revealed a 5-cm irregular left hilar mass and a smaller 1.1-cm nodular lesion in the left upper lobe's perihilar area associated with partial atelectasis of the left upper lobe (Figure 2A). On March 29, 1980, she underwent bronchoscopy (which revealed severe endobronchitis and extrinsic compression of the left upper lobe bronchus), excisional biopsies of the left axillary lymph nodes and of the left breast area mass, and a left anterior mediastinotomy.

Endobronchial biopsy and washings, biopsies of the axillary lymph nodes and breast mass, and multiple biopsies of a large confluent, indurated mass—which was extrinsically compressing the left main stem bronchus and encasing the aorta and left pulmonary artery—revealed bronchogenic undifferentiated large cell carcinoma in all specimens. Her postoperative course was uneventful. Liver, spleen, and bone scans were normal. An anergy panel revealed reactivity only to streptokinase-streptodornase. Preoperative urinary and plasma cortisol studies were normal. Several weeks postoperatively, radiotherapy through opposing fields to a total dose of 5,200 rads was given directly to the mediastinum. After 4,000 rads, the spinal cord was removed from the radioportal, and an additional 3,500 rads were given to the left anterior chest and contiguous left axillary region. The patient tolerated radiotherapy quite well until its completion in early May 1980. A chest x-ray post radiotherapy is shown in Figure 2B.

She did well until August 29, 1980 at which time she complained of right pectoral girdle pain and painful mass swelling of the right axilla of five days' duration.

Examination revealed several tender, 2-cm right axillary lymph nodes. There was gross, edematous, and inflammatory swelling of the muscle forming the right posterior axillary fold. Three nontender right inguinal lymph nodes and two 4- × 5-cm subcutaneous masses of the most proximal area of the right thigh's anteromedial surface were also present. Progression of her symptoms, further enlargement of her mass lesions, fever, and rapidly worsening fatigue convinced the patient that hospitalization for biopsy(ies) was necessary.

She entered the hospital on September 14, 1980 at which time biopsies of all previously described sites were performed without event. The biopsies revealed metastatic bronchogenic large cell carcinoma to lymph nodes (inguinal and axillary), and to skeletal muscle (thigh and posterior axillary muscle groups) as shown in Figure 3.

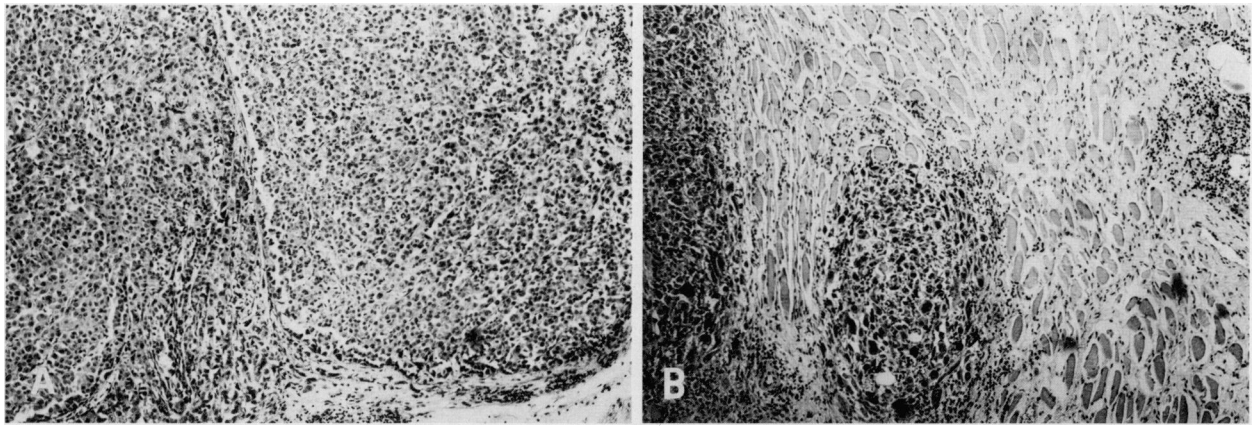

Figure 3. (A) Photomicrograph of a right inguinal lymph node demonstrating loss of normal lymph node architecture and replacement of lymph node elements by massive infiltration of malignant bronchogenic cells. (B) Photomicrograph of the biopsy of the right posterior axillary muscle fold. Note the dramatic carcinomatous cellular infiltration on the left. A similar carcinomatous focus is present in the center of the micrograph within the substance of surrounding skeletal muscle (right)

Postoperatively she rapidly deteriorated, with initial signs of a left cerebral hemispheric lesion as evidenced by dysarthria, right deviation of the tongue, right lower facial paralysis, confusion, and somnolence on the morning of September 17, 1980. A CT head scan with enhancement was done the same day and results were normal. A bone marrow aspirational smear and biopsy were performed on September 19; this procedure was complicated by excessive bleeding at the site of the procedure (left iliac crest).

Microscopic examination of the bone marrow smear and biopsy showed hypercellularity with a myeloid reaction and mild megakaryocytic hyperplasia. Marrow iron stores were markedly decreased. No evidence of metastatic carcinoma was present. Within the next ten hours she was comatose and had developed gross hematuria, fever of 101.6 F, and a systolic pericardial friction rub (Figure 4). Serial pertinent laboratory studies are shown in Table 1; The data were obtained on the patient during her last hospitalization. She received two units of packed red cells on September 18. All peripheral blood smears were reviewed and showed occasional hypersegmented polymorphonuclear cells and toxic granulation with Döhle inclusions, slight anisocytosis and poikilocytosis, no schistocytes, and consistently decreased platelets. A rare nucleated red blood cell was noted on the smear of September 20. Stool and urine were positive for blood from September 18 until death. By September 21, she had cold cyanotic hands with intact radial and ulnar pulses and bilaterally cold cyanotic pulseless feet. She died on September 22, 1980.

NECROPSY

Gross Findings

The right serratus muscle was infiltrated with multiple whitish nodules forming a firm mass. The mesenteric, mediastinal, cervical, inguinal, axillary, and para-aortic lymph nodes were markedly enlarged. Hemorrhagic fluid was present in the pericardial sac. The heart was enlarged with scattered petechiae at the base of the aortic valve. The aortic valvular leaflets' ventricular surfaces were covered with loosely adherent, polypoid, friable vegetations near the line of closure.

The mitral leaflets exhibited fibrous thickening. The coronary arteries were patent and free of atherosclerotic plaque. The right renal vein was completely occluded by a thrombus extending the entire length of the renal vein and extending far into the inferior vena cava, causing partial obstruction of the latter. Both lungs were edematous. The left upper lobe was completely collapsed and exhibited a consolidating pneumonia distal to a firm mass present at the root of the left upper lobe, and left main stem bronchus.

The spleen showed multiple irregular infarcts. The adrenals were markedly enlarged, hemor-

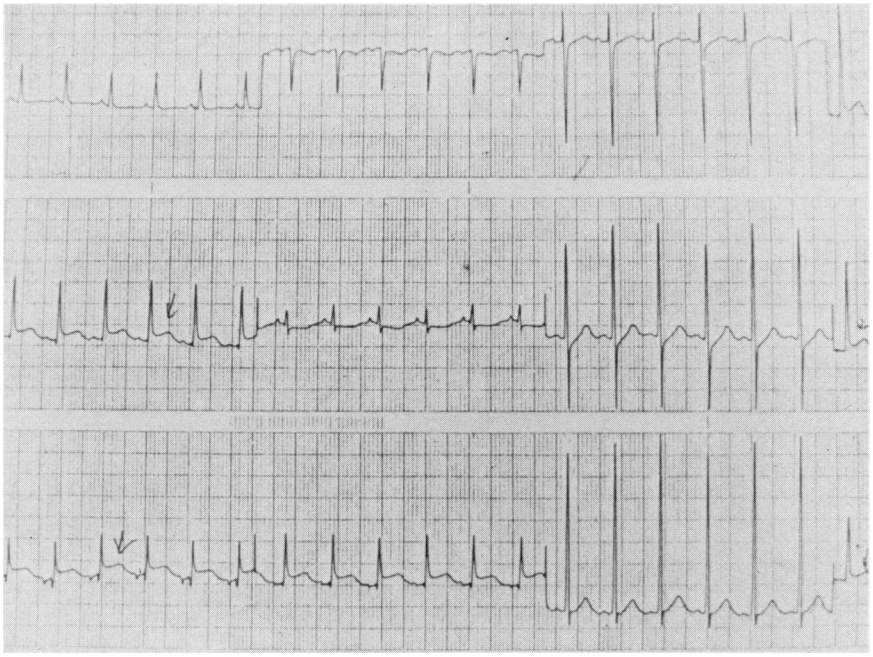

Figure 4. Electrocardiogram consistent with active pericarditis, left ventricular hypertrophy, and sinus tachycardia

TABLE 1. SERIAL LABORATORY STUDIES

Laboratory Study	Normal	3/24/80	9/14/80	9/16/80	9/17/80	9/18/80 (AM)	9/19/80 (PM)	9/19/80	9/20/80
Hematocrit volume (%)	37-47	35.7	33.5	34	34	24.5	24	32.5	30
Hemoglobin (gm/100 ml)	12-16	11.2	11.3	11	11	8	8	10.5	10
Total WBC count (per cu mm)	4,800-10,800	11,000	82,400	123,000	108,000	122,000	128,000	130,000	81,500
% segmented forms	42-81	—	92	98	—	97	99	98	99
Prothrombin time (sec) (control patient)	12	10.6/10.4	10.5/10.0	—	11.4/12.7	11.2/12.3	11.2/13.9	—	—
Partial thromboplastin time (sec) (control/patient)	40	36/38	36/24	—	36/28	36/26	36/26	—	—
Reticulocyte count (%)	0.5-1.5	2	—	—	—	4.2	6.4	—	5
Platelet count (cu mm)	150,000-400,000	435,000	89,000	dec	1,000	10,000-40,000	10,000	dec	5,000
BUN (mg/100 ml)	6-26	12	29	22	30	61	63	83	91
Creatinine (mg/100 ml)	0.7-1.8	0.9	1.4	1.0	1.3	2.7	2.6	3.5	5.2
Fibrinogen (mg/100 ml)	150-400	—	—	—	320	300	—	—	—
Fibrin split products (μg/ml)	Negative	—	—	—	40	10-40	—	—	—
SGOT (IU/liter)	0-41	16	34	—	—	187	—	—	—
SGPT (IU/liter)	0-45	25	28	—	—	128	—	—	—
LDH (IU/liter)	60-250	169	573	—	—	4,660	—	—	—
Alkaline phosphatase (IU/liter)	30-115	137	323	—	—	445	—	—	—

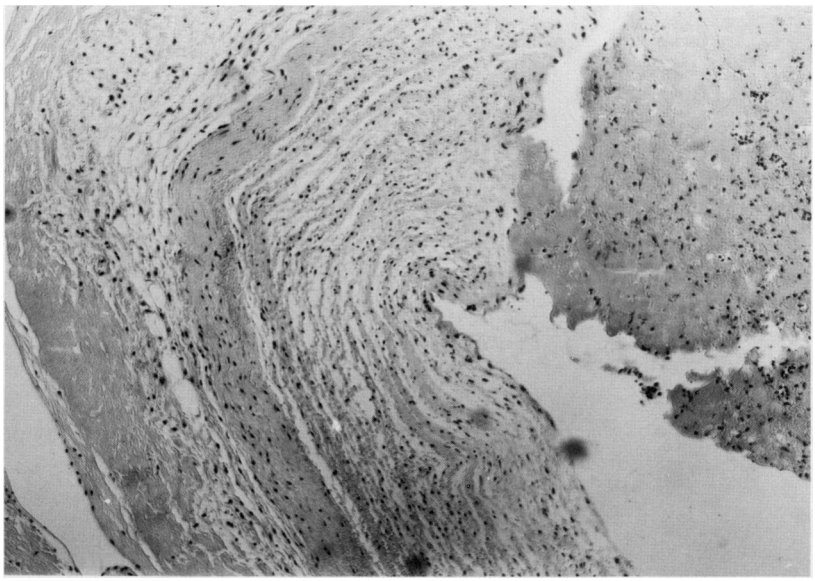

Figure 5. Photomicrograph of the heart demonstrating on the right the fibrinous vegetation adhering to the ventricular surface of the aortic valve

rhagic, and necrotic; they exhibited no remnants of normal adrenal tissue on cut sections. The left kidney was markedly enlarged, hemorrhagic, and infarcted with hemorrhagic thickening of the left ureter in its proximal portion. Bone and leg vein examinations were normal. The brain was edematous with hemorrhagic infarction of the left posterior parietal area. Coronal sections of the brain after fixation revealed multiple, bilateral, hemorrhagic infarctions of the cerebrum and cerebellum. Blood cultures taken from the heart were negative.

Microscopic Findings

Examination of the heart showed marked vascularization and fibrinous thickening of the aortic valve. Loose nonadherent vegetations were noted on the ventricular surface of the aortic valve and consisted of fibrinous material containing a large number of red blood cells (RBCs) and polymorphonuclear cells trapped within (Figure 5). A recent infarction of the papillary muscle and mutliple thrombi of the intramural cardiac vessels were noted. The myofibrils revealed coagulative necrosis and ischemic necrosis with many RBCs and a few polymorphonuclear cells within the myocardial interstitium. Stain results of the aortic valvular vegetations for bacteria were negative. No Aschoff bodies were present. Examination of the left upper lobe revealed atelectasis and thickening of the alveolar septa and blood vessels. Both lungs showed intravenous tumor thrombi and foci of bronchopneumonia. The left bronchus revealed a mucin-negative, poorly differentiated, large cell bronchogenic carcinoma. Metastatic undifferentiated carcinoma was present in the skeletal muscle, lymph nodes (cervical, peribronchial, periaortic, axillary, and inguinal) and almost completely replaced the adrenals' parenchyma. The spleen showed wedge shaped infarctions invaded by polymorphonuclear cells and bordered by RBCs and polymorphonuclear cells. The right kidney revealed coagulation necrosis and hemorrhage, and multiple blood vessel tumor thrombi. Large metastatic undifferentiated tumor infiltrated the right renal vein from the surrounding fibroadipose tissue.

Distal to this a large laminated fibrin platelet thrombus filled the entire right renal vein, and extended without intimal adherence well into the inferior vena cava almost completely obstructing the latter. The left kidney revealed a wedge shaped area of recent coagulation necrosis. The liver showed both coagulative and centrilobular ischemic necrosis. Multiple small biliary hemartomas were noted throughout the liver. The brain re-

vealed multiple hemorrhagic infarcts without evidence of bacterial organisms on special staining. The blood vessels near the areas of infarction were occluded by thrombi composed of a fibrinous material with red blood cells and polymorphonuclears entrapped within. The remaining portions of the necropsy were unremarkable (vertebrae, bone marrow, pituitary, stomach, intestines, pancreas, gallbladder, uterine tract, and ovaries).

FINAL PATHOLOGIC DIAGNOSES

1. Large cell, poorly differentiated, bronchogenic carcinoma with metastases to lymph nodes, skeletal muscle, adrenals (massive), lungs, right kidney, and right renal vein
2. Nonbacterial thrombotic endocarditis with aortic vegetations and embolic infarcts of brain, heart, liver, spleen, and right kidney
3. Tumor and fibrin-platelet thrombus occluding the right renal vein (with secondary infarction of the right kidney) and extending into and partially occluding the inferior vena cava
4. Centrilobular hepatic ischemic necrosis
5. Hepatorenal failure due to 2, 3, and 4
6. Multiple small biliary hemartomas of the liver

DISCUSSION

Leukemoid reactions occur infrequently. Most leukemoid reactions have been recorded as isolated case reports and have been mainly myeloid in type.[3] Leukemoid reaction associated with bronchogenic carcinoma is a distinctly rare event. It is of note that the present case and those of Dalal et al were associated with large cell types of bronchogenic carcinoma. Dalal et al admirably summarized the possible mechanisms causing such leukemoid reactions associated with bronchogenic carcinoma:[1] (1) bone metastasis, (2) pulmonary atelectasis with or without suppuration-necrosis, and (3) tumor production of substances such as altered nucleic acids and their derivatives,[4] or granulocyte colony stimulating factor(s).[5,6]

In addition to these possibilities, the animal model studies of Modama et al[7] studying BALB/cMk mice strains suggest that leukemoid reactions in certain hosts may have a genetic basis, ie, certain hosts have genes permissive to the occurrence of the leukemoid reaction.

Recent clinical studies would tend to support these experimental studies and even suggest that environmental factors may be a variable in the equation explaining leukemoid reactions.[8] In its broadest definition "leukemoid reaction" implies a marked left shift and/or an extremely high neutrophil (myeloid) count. The presence of a leukemoid reaction implies a limited differential diagnosis:[8,9] malignancy with infection, malignancy with or without bone metastases, severe infection, and on rare occasions acutely disseminated caseating tuberculosis. Qualitative changes in neutrophils such as toxic granulation (as occurred in the present case) or Döhle bodies when present strongly favor the presence of bacterial infection.[2,9] Although infection was not documented in the present case, the Döhle bodies may have resulted from clinically missed bacteremia(s) and/ or the absorption of bacterial products from an ischemic intestinal tract secondary to the effects of nonbacterial thrombotic endocarditis (NBTE). It is difficult to explain the presence of these Döhle bodies purely on the basis of the carcinoma alone. The extreme leukemoid reaction was at least in part contributed to by the presence of the terminal NBTE.[10]

Thrombotic thrombocytopenic purpura (TTP) has very recently been reviewed[11-15] and need not be discussed at length in this report. Kwaan's discussion of the pathogenesis of TTP stands as the current classic and authoratative paper on this entity.[13] The hallmark and sine qua non of TTP is platelet consumption and the widespread formation and the histologic finding of hyaline microthrombi in terminal arterioles and capillaries seen most frequently in the heart, brain, kidneys, adrenals, and pancreas.

Inflammatory changes are conspicuous by their absence. These features were not objectively demonstrated in the present case. The pathogenesis of the hyaline microthrombi remains uncertain, but recent studies support the concept that the primary event is capillary endothelial damage by extension of hyaline material intraluminally.

Platelets accumulate over the hyaline material and the endothelial defect caused by the extruding hyaline. Current studies suggest that both fibrin and platelets participate in the formation of hyaline microthrombi. Of importance, TTP differs from disseminated intravascular coagulation (DIC). With TTP there is a failure of compensatory fibrinolysis, coagulation factors are not (or

are minimally) consumed, hemolytic anemia is present in all cases, and there is early, rapid consumption of platelets associated with profound thrombocytopenia and marked bone marrow megakaryocytic hyperplasia. The peripheral blood smear invariably reveals the presence of fragmented red blood cells with helmet shaped, triangular, and other bizarre red blood cell forms being present on review of the peripheral blood smear. The present case showed no signs on peripheral blood smear of the typical microangiopathic red blood cell forms. In many respects this case was clinically suggestive of TTP.

The early rise in fibrin degradation products (indicative of active fibrinolysis) was short lived and yielded to the celerity of the NBTE reaction by quickly returning to the normal range.

The necropsy findings were virtually diagnostic of NBTE, and clinically this case was quite typical for NBTE[10,16,17] exhibiting premortem symptoms and/or signs of infarction of the brain, heart, liver, kidneys, and extremities. Clinically, the most significant emboli were those involving the brain, heart, and right kidney. These findings coincide with those of Bedikian et al[16] but no significant DIC was noted, nor was this patient's malignancy of the mucin producing type as is frequently the case when NBTE occurs in association with solid malignancies.

Since this patient's bone marrow study indicated adequate platelet production, here severe thrombocytopenia was undoubtedly due to an extra bone marrow consumptive mechanism (consumptive thrombocytopathy). Immune mechanisms have been implicated in the pathogenesis of thrombocytopenia in patients with sepsis but without clear laboratory evidence of DIC.[18,19] It is possible that such a mechanism was operative in this case even though sepsis was not objectively documented.

The necropsy findings suggest that her thrombocytopenia was a result of the formation of the large fibrin platelet thrombus occluding the right renal vein, and propagating into the inferior vena cava. If this were indeed the mechanism of the thrombocytopenia, obviously the rate of platelet consumption in the formation of the thrombus far exceeded the ability of the bone marrow to produce new platelets. The absence of schizotocytes on peripheral blood smear exclude TTP and/ or DIC as the cause for this patient's thrombocytopenia.

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