Myocarditis Simulating Myocardial Infarction

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From the case records of Massachusetts General Hospital, Charlestown, Massachusetts

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CLINICAL HISTORY

A 70-yr-old man was admitted for progressive respiratory insufficiency and prolonged substernal discomfort.

He had a 120-pack year history of cigarette smoking and significant exposure to asbestos. In his early fifties, he developed steroid-dependent chronic obstructive pulmonary disease. Multiple recurrent nasal polyps were excised and he eventually exhibited aspirin hypersensitivity. Six years ago he presented with right-sided heart failure, mild-to-moderate hypertension, and electrocardiographic evidence of left bundle branch block. Left ventricular ejection fraction (LVEF) was 61% by gated blood-pool scan. His hypertension and right-sided failure were controlled by medical therapy.

Two weeks prior to admission, the patient stopped his prednisone because of worsening facial acneform eruptions. Subsequently, he became more dyspneic with mild increase in expectoration, nasal congestion, fatigue, myalgias, and brief episodes of substernal discomfort. Two days before admission, the episodes of substernal pressure worsened and were associated with nausea, diaphoresis, and increased dyspnea. He denied orthopnea, paroxysmal nocturnal dyspnea, palpitations, or syncope.

His vital signs on admission were: pulse 140/min; regular; respiratory rate 26/min, labored; blood pressure 160/120; and temperature 37.7°C. Examination of the chest revealed decreased breath sounds at the bases with bilateral basilar rales without wheezes. The heart was normal in size. The second heart sound was paradoxically split with an audible S4 gallop but no S3 or murmur could be heart. The electrocardiogram revealed sinus tachycardia and left bundle branch block with left-axis deviation and left atrial enlargement (Fig. 1). The chest X-ray showed normal heart size and pulmonary venous hypertension with accentuated vascular markings, interstitial edema and Kerley-B lines. Both costophrenic angles were blunted with pleural thickening and some nodularity at the bases which may have been secondary to asbestos exposure. There also was bilateral basal segmental atelectasis without discrete consolidation. The FEV1 had decreased to 0.9 liter from 1.54 liters measured 6 mo earlier. The patient was aggressively treated with bronchodilators and steroids. During the next 24 hr, ST-segment elevations developed in leads II and III, and AVF of his electrocardiogram and his creatine kinase increased from 95 to 150 with 5%–6% MB isoenzyme fraction. The patient was treated with nitrates and dilitiazem and bronchodilators were reduced. On the third day, mild pedal edema appeared and a new apical systolic ejection murmur was heard. The patient remained pain-free and his ST segments returned to baseline. On the fifth day, chest pain recurred accompanied by ST-segment elevation.

Cardiac catheterization was performed for further evaluation. Mean pulmonary artery pressure was 25 mmHg with pulmonary capillary wedge pressure of 15 mmHg. The left ventricle was globally hypokinetic. The coronary arteries were normal. LVEF was 44%. An echocardiogram revealed mild mitral and tricuspid insufficiency in addition to the hypokinetic left ventricle. A right ventricular endomyocardial biopsy showed mild myocyte hypertrophy and focal fibrosis (Fig. 2). Rare leukocyte common antigen-positive cells were present in the interstitium by immunoperoxidase staining. Indirect immunofluorescence revealed antimyofibrillar staining suggesting recent myocyte injury. The changes were considered nonspecific and not indicative of myocarditis. An antimyosin scan performed three days after biopsy demonstrated significant myocardial uptake of antimyosin antibody (Fig. 3) that was diffuse on tomographic reconstructions. The antimyosin scan result was consistent with the presence of acute myocyte necrosis. A diagnosis of myocarditis was strongly suspected, but since left ventricular function was only mildly impaired, a decision regarding repeat endomyocardial biopsy and/or azathioprine therapy was deferred. Anti-anginal medications were gradually tapered. The patient was discharged on digoxin, diuretics, captopril, and prednisone (60 mg daily).

Over the next 2 mo, the patient's general physical

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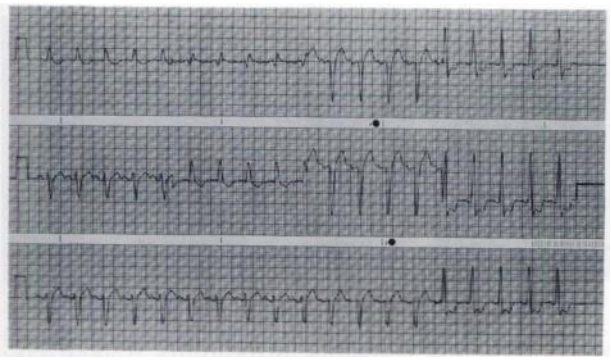

FIGURE 1
Electrocardiogram at first admission showing sinus tachycardia, left atrial enlargement, left bundle branch block with left axis deviation.

status gradually improved. Three months after discharge his dose of prednisone was tapered. He, then began to have recurrent episodes of low-grade fever associated with chills, rigors, nausea, vague abdominal complaints, and morning headaches. He was readmitted for further evaluation.

There were no stigmata of endocarditis, vasculitis, or localizing signs of infection. Physical examination revealed tachycardia, pedal edema, S3 and S4 gallop, bilateral basal crackles, and cerebellar ataxia. The erythrocyte sedimentation rate was markedly elevated (105 mm at 1 hr). An electrocardiogram revealed multiple, multifocal ventricular premature beats. His fever gradually subsided. A gated blood-pool scan showed moderately severe global hypokinesis of the left ventricle with calculated left ventricular ejection fraction of 30%. The right ventricle appeared normal. A repeat antimyosin scan was obtained which revealed increased myocardial antimyosin uptake (Fig. 4A), compared to the initial scan performed 3 mo previously. Tomographic reconstructions confirmed global left ventricular uptake (Fig. 4B). Repeat endomyocardial biopsies from left and right ventricles were characterized by marked myocyte hypertrophy and endocardial, interstitial, and replacement fibrosis. One of the nine left

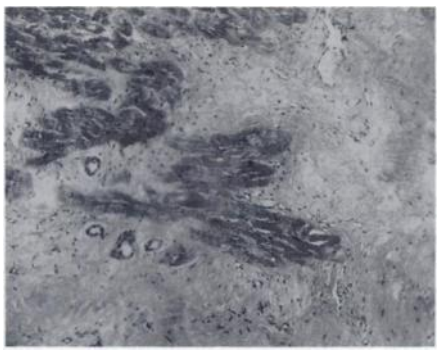

FIGURE 2
Initial right ventricular endomyocardial biopsy was non-diagnostic for myocarditis.

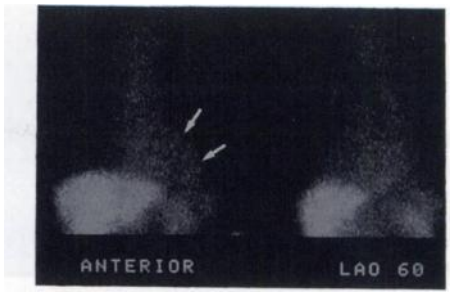

FIGURE 3
Initial antimyosin scan demonstrates significant antimyosin antibody uptake in cardiac region.

ventricular biopsy specimens contained three foci of mixed inflammatory cells including lymphocytes, macrophages, and eosinophils. One of these foci was associated with degenerated and frayed myocytes diagnostic of myocarditis (Fig. 5). Direct immunofluorescence for IgG, IgA, and C3 showed positive staining of scattered myocytes. Indirect immunofluorescence again revealed antimyofibrillar staining. Of the five specimens obtained from the right ventricle, one fragment contained a single aggregate of mixed inflammatory cells without associated myocyte necrosis, i.e., borderline myocarditis. CT scan and MRI of the head revealed atrophic areas in cerebral hemispheres with dilated ventricles without evidence of space-occupying lesion. The patient was discharged on azathioprine (50 mg twice a day) and prednisone (80 mg daily).

His general health continued to deteriorate over the next 5 mo with multiple hospital admissions for worsening congestive heart failure and compression fractures of the lower thoracic spine. During his last admission, the patient suffered from gastric outlet obstruction with pyloric channel and duodenal erosions and gastrointestinal bleeding. A transurethral procedure was performed for bladder obstruction after which he developed a urinary tract infection. He had declining neurologic status with dementia, mental obtundation, hallucinations, tremors of limbs and trunk, and finally developed left-sided hemiparesis. He subsequently succumbed to acute bronchopneumonia.

At autopsy, severe necrotizing pneumonia due to Gram-positive cocci involved all lobes. A healing ulcer crater was present in the pyloric channel. Multiple intracranial infarcts appeared to be embolic. A 5–7-day-old infarct involved a focal area of the right thalamus and internal capsule and small scattered infarcts were present within the pons, medulla, cerebellum, and cervical cord. The left ventricle of the heart was hypertrophied, mildly dilated, and contained diffuse interstitial fibrosis. There was no evidence of ongoing myocarditis. The left anterior decending, circumflex, and right coronary arteries demonstrated focal, proximal plaquing, which was not present when coronary angiography was done 9 mo previously. Scattered subendocardial

without demonstrable coronary artery disease, which may probably be due to transient coronary artery occlusion with subsequent recanalization or coronary arterial spasm (*49*). Viral myocarditis has also been reported to simulate acute MI (*50*). Myocarditis frequently occurs as a focal or multifocal lesion and it is not surprising to eventually find myocarditis when a clinically typical acute MI was diagnosed on the basis of enzyme rises, focal left ventricular wall motion abnormalities, and electrocardiographic ST-T-wave changes and abnormal Q-waves in restricted lead groups (*51–54*). Murine coxsackie virus B1 and B4 infection besides extensive myocardial inflammation may also produce coronary arteritis (*55*), localized myocardial necrosis (*56*), and, occasionally ventricular aneurysms indistinguishable from those following MI induced by epicardial coronary obstruction (*56,57*), and may parallel similar findings in man (*58–60*). Serologic evidence of coxsackie B virus infection in man has been identified in up to 26% of patients with documented MI (*55*) and has been proffered as an evidence of viral myocarditis at least in a subgroup of patients with normal coronary arteries (*54,59*).

The difficulty in associating MI with viral myocarditis is perpetuated by the lack of unequivocal documentation of myocarditis (*61*). Patients with coxsackie virus infection may not always demonstrate a diagnostic rise in neutralization antibody titer, and high static titers merely indicate probable recent infection (*62*). The presence of myocarditis has been reported at autopsy in a patient who had presented with MI with normal coronary arteries and coxsackie B disease (*63*). The occurrence of myocarditis in this setting has only rarely been documented during life (*59,61,64*). In selected patients with clinical, electrocardiographic, and laboratory evidence of MI but normal coronary arteries, presence of diffuse antimyosin antibody uptake in cardiac region offers a strong likelihood of myocarditis. Inflammation-avid isotopic imaging with ^{111}In-labeled autologous leukocytes and/or gallium-67 have also been recommended in similar clinical settings for the detection of myocarditis and therapeutic interventions (*3,61*).

CONCLUSION

Imaging with radiolabeled antimyosin antibodies has been demonstrated to be a safe, reproducible, and highly accurate method for noninvasive visualization of myocyte necrosis. A high sensitivity of antimyosin imaging has been documented for the detection of myocyte necrosis associated with active myocarditis and confirms the utility of antimyosin scintigraphy as a screening method in the initial evaluation of patients with heart failure when myocarditis is clinically suspected. A high negative predictive value may obviate the need for endomyocardial biopsy in patients with negative scans in the clinical setting of dilated cardiomyopathy. A significant myocardial antimyosin uptake, however, occurs in a large proportion of cases of clinical dilated cardiomyopathy. The sub-group of scan-positive, biopsy-negative patients more often shows clinical improvement of their heart failure compared to scan-negative patients. Positive scan results may be due to myocyte necrosis associated with myocarditis, as in the present case which highlights the diagnostic implications of this new methodology.

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SELF-STUDY TEST
Pulmonary Nuclear Medicine
ANSWERS

(continued from p. 203)

ITEM 1: Sarcoidosis

ANSWER: **D**

The gallium image shown in Figure 1 demonstrates increased uptake of tracer in the lungs and parotid regions. There is also a symmetrical pattern of nodal disease involving the cervical, supraclavicular, hilar, paraaortic, inguinal, and femoral nodes. Bronchogenic carcinoma with lymph node involvement may show pulmonary and mediastinal uptake of ^{67}Ga, as well as gallium localization in distant metastases. However, the symmetry of involvement would be highly unlikely for metastatic disease. Lymphoma is a good possibility, given this patient's history, except that patients with Hodgkin's disease often present with intermittent fever or night sweats. Although gallium uptake in nodal chains and in the lungs is consistent with lymphoma, the high degree of symmetry and the parotid involvement make this diagnostic possibility less likely than sarcoidosis, which is the best fit to the clinical and scintigraphic findings. The pattern of gallium uptake with hypersensitivity pneumonitis or with *Pneumocystis carinii* pneumonia in patients with AIDS rarely includes tracer uptake in the lymph nodes. Generally, there is diffuse pulmonary uptake of moderate to high intensity with *P. carinii* pneumonia and of low to moderate intensity in hypersensitivity pneumonitis. In patients with AIDS, hilar and mediastinal nodal ^{67}Ga uptake may be seen with secondary lymphoma or with infection due to *Mycobacterium tuberculosis* or *Mycobacterium avium-intracellulare*. Gallium accumulation associated with the lymphadenopathy of AIDS per se is usually of relatively mild intensity.

ITEM 2: Pulmonary Clearance of Radioaerosols

ANSWER: **D**

Numerous factors are important in determining the clearance rate of a radioaerosol from the lung. Major differences exist between the clearance rates and pathways of soluble and insoluble aerosols. Insoluble aerosols include those of particulate nature, such as ^{99m}Tc-colloids or albumin particles, which must be cleared from the airways and alveoli by either mucociliary action or by lymphatic drainage. Mucociliary clearance requires several hours, even from relatively central airways, and lymphatic clearance of particulates can take days to weeks. On the other hand, soluble radioaerosols are cleared quickly by gaining direct access to the pulmonary blood supply across the alveolar–capillary membrane.

The clearance rates of various soluble aerosols are influenced by a number of factors, including the lipophilicity and polarity of the agent. In general, the more lipophilic and polar compounds are likely to be absorbed more rapidly. The molecular weight of a compound, however, also seems to have an influence. Some relatively high molecular weight lipophilic compounds have slower pulmonary clearances than would be predicted from their lipid solubility alone.

Size is an important factor in radioaerosol clearance, whether the size refers to the molecular weight of a soluble compound, as mentioned above, or whether it refers to the physical size of the inhaled aerosol droplets. Larger aerosol droplets tend to deposit more centrally. From this central location, mucociliary clearance can act more effectively and quickly to clear the particles from the lungs. Conversely, if molecular size is considered, a larger compound may have a slower peripheral clearance. An agent with a combination of physical characteristics leading to the fastest clearance would have a relatively small molecular weight and be a polar, lipophilic compound delivered to the lung as a submicronic aerosol.

Alveolar–capillary membrane permeability appears to be a major factor in determining the clearance rate of soluble radioaerosols from the lung. The clearance of these compounds seems to be related far more closely to the available surface area for absorption across this membrane than to the pulmonary blood flow rate, itself. Total obstruction of pulmonary arterial flow to a lung leads to markedly diminished clearance of soluble radioaerosols, although a small amount of radioaerosol activity still may be absorbed through the bronchial circulation. However, within the typical range of pulmonary blood flow rates encountered in clinical practice, blood flow rate per se has relatively little influence on clearance rates.

Note: For further in-depth information, please refer to the syllabus pages included at the beginning of *Nuclear Medicine Self-Study Program I: Part I.*