Myocardial Accumulation of Labeled Phosphate in Malignant Pericardial Effusion

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Recognition of the presence of a malignant pericardial effusion is important because of the insidious onset and life-threatening potential. This report presents data on three patients with metastasizing carcinoma of the breast, all admitted with a presumptive clinical diagnosis of malignant pericardial effusion. Two of the three revealed a diffuse concentration of Tc-99m PPi within the myocardium. In these cases the diagnosis was confirmed by identification of malignant cells in the pericardial fluid. We suggest that the use of labeled phosphate agents may allow early recognition of myocardial involvement in patients with disseminated neoplasm that results in malignant pericardial effusion.


It is important to recognize the presence of a malignant pericardial effusion because of its insidious clinical expression and life-threatening potential. Whereas this condition is not encountered as often as other cavitary effusions in patients with disseminated neoplasms, a significant number have impairment of cardiac function because of secondary neoplastic involvement of the heart and pericardium. Some 20% of individuals with disseminated malignant tumors have metastasis to the heart. The incidence varies from 3% in the pericardium alone to 20% in the heart, pericardium, and great vessels (1,2). A particularly high incidence (69%) has been reported in acute leukemia (3) and in malignant melanoma (64%) (4). Other common neoplasms that spread to the heart and pericardium arise in the lung (35%) and breast (35%) (5–7). Thurber reported that 86% of the patients with lesions involving the heart died with this involvement as an immediate or contributory cause. Pericardial effusion was the major cause of cardiac dysfunction in patients with involvement of the heart (8). The fact that pericardium and myocardium are almost always invaded concomitantly suggests a potential causal association (9).

Interest in the possibility of myocardial concentration of labeled phosphate in patients with malignant effusion prompted us to evaluate cancer patients suspected of this condition. Following the report of Bonte et al. (10), demonstrating that technetium-99m stannous pyrophosphate localizes in the dog's heart after experimentally induced myocardial infarction, interest in the imaging of myocardial disorders has flourished.

METHODS

Three patients had disseminated neoplasm and presumptive clinical diagnosis of malignant pericar-
regions, and chemotherapy with Cytoxan, methotrexate 5-FU, and Adriamycin.

EKG evaluation at admission revealed low voltage and nonspecific ST-T changes. Increased heart size and bilateral pulmonary infiltrates were noted on chest radiographs. Physical examination revealed a paradoxical pulse, and echocardiography demonstrated significant pericardial effusion. With the presumptive clinical diagnosis supported by ultrasound, evaluation of the cardiac region with Tc-99m pyrophosphate was undertaken along with a search for skeletal metastasis. Initial blood-pool tracer studies confirmed the finding of pericardial effusion (Fig. 1). Images at 1–2 hr postadministration did not reveal differential myocardial uptake (Fig. 2). Pericardial tap following this study yielded 500 ml of bloody fluid, in which radioassay demonstrated presence of the tracer.

Case B. A 69-year-old white woman presented with chief complaint of shortness of breath and antecedent history of resection of scirrhus carcinoma of the left breast 7 years before the present illness. Therapy included postoperative radiation and a course of androgens followed by a gestational agent. Exercise tolerance at admission was limited to ten steps on the level and no more than four steps climbing stairs. Physical examination revealed a paradoxical pulse and a jugular venous pressure elevated to 8 cm. A significant circumcardiac decrease in tracer activity was seen on the radionuclide blood-pool image, indicating a large pericardial effusion (Fig. 3). Images delayed between 1 and 2 hr revealed a diffuse concentration of the tracer in the myocardium (Fig. 4). Pericardiocentesis yielded bloody fluid, and a repeat study 1 wk later showed cells “suspicious” for malignancy. Before the repeat tap, myocardial images with Tc-99m PPI showed evidence of pericardial effusion on initial blood-pool images, with diffuse myocardial uptake on images delayed 1–2 hr. Ra-

case reports

Case A. A 59-year-old white woman presented with a history of adenocarcinoma of the right breast metastasizing to the right supraclavicular and axillary nodes, diagnosed 1 yr before her current admission. Pre-admission treatment included radiation therapy to the right supraclavicular and axillary

FIG. 1. Equilibrium blood pool following initial administration of Tc-99m PPI. Anterior projection shows evidence of pericardial effusion: the “halo” surrounding the blood-pool image. Dark spot at bottom is radioactive marker on xiphoid.

FIG. 2. Delayed image (1–2 hr postinjection) shows no differential uptake in myocardium, suggesting no myocardial invasion in this patient. (Small arrow denotes sternum; large arrow denotes region of myocardium without tracer concentration.)

FIG. 3. Equilibrium blood-pool image obtained immediately after administration of tracer; demonstrates pericardial effusion.
dioassay of the effusion yielded an activity level less than that of a concurrent whole-blood sample. Centrifugation of both effusion fluid and whole blood to remove the formed elements (primarily RBCs) showed that the activity was not related to labeling of the elements.

Case C. A 54-year-old white woman with a past history of carcinoma of the breast presented with shortness of breath and fatigue. There was marked reduction in exercise tolerance. She had received postoperative radiation therapy as well as systemic chemotherapy (methotrexate and Cytoxan). Physical examination revealed a jugular venous pressure of 12 cm of water at the 45° position. A diagnosis of pericardial effusion was entertained and an immediate pericardial tap was done. Two hundred fifty milliliters of blood-stained fluid were obtained. Myocardial imaging was performed with Tc-99m PPI. On the initial blood-pool images, recurrent pericardial effusion was noted (Fig. 5). Diffuse myocardial uptake of the tracer was seen on delayed imaging (Fig. 6). An additional pericardial tap was performed, yielding bloody fluid that was positive for malignant cells on cell-block study. Radioassay of the effusion fluid showed tracer activity, but less than that in a peripheral blood sample.

RESULTS

Three patients with confirmed pericardial effusion and evidence suggesting a malignant cause were examined for evidence of differential uptake of Tc-99m PPI by the heart. Two patients showed diffuse radioactivity in the cardiac region when imaged 1–2 hr after tracer administration. Subsequent pericardiocentesis revealed malignant cells in the pericardial fluid in two of the three cases. The patients with malignant effusion were those showing differential tracer uptake in the myocardium. The patient without evidence of myocardial uptake did not have cytologic confirmation of malignancy.

To assess the occurrence of myocardial uptake of labeled pyrophosphate agents, a random sample of 100 skeletal radionuclide studies was reviewed independently by three of the authors (MQ, PB, HB). Although accomplished at a standard 4- to 5-hr delay period following administration of the tracer, these studies were assessed for evidence of differential myocardial uptake of the tracer. Of these retrospectively analyzed cases, five patients (5%) showed minimal evidence (1+ on a 1+ to 4+ scale) of uptake. Four of these five had a diffuse pattern, whereas one showed focal deposition. This last patient had a history of myocardial infarction. Of the four patients showing diffuse accumulation of tracer, three had carcinoma of the breast with evidence of metastasis, and one had carcinoma of the lung. Thus, in a random review of studies looking for evidence of skeletal disease in patients with primary neoplasms, 5% showed a pattern of minimal Tc-99m PPI uptake in the heart.

DISCUSSION

Malignant pericardial effusion, although the least frequent of cavitary effusions in patients with neoplastic disease, portends grave consequences in the majority of cases. Early recognition is of particular

FIG. 4. Delayed images (1–2 hr postinjection) in two projections, demonstrating diffuse concentration of Tc-99m PPI in myocardium. (Small arrow indicates sternum; large arrow indicates myocardial uptake.)

FIG. 5. Initial blood-pool image illustrating pericardial effusion in two projections.

FIG. 6. Delayed images in two projections depicting differential uptake of the Tc-99m PPI in myocardium, again in a diffuse pattern. (Small arrow indicates sternum; large arrow indicates myocardial uptake.)
importance because of its insidious symptoms and potential for cardiac tamponade.

Two basic derangements resulting in the production of pericardial effusion have been suggested by Miller (11): first, as a result of tumor implantation on the serosal surface, leading to exudation of fluid; second, the subsequent obstruction of lymphatic flow by mediastinal transudation of fluid into the pericardial sac. Lokich (9), in surveying the management of malignant pericardial effusions, points out that in the experimental model, lymph flow proceeds from the endocardial to the epicardial surface and an effusion is the accumulation of fluid exuded from the visceral pericardium (epicardium). The obstruction of the mediastinal lymphatics draining the heart is not adequate to produce effusion by itself; in the experimental model it is also necessary to ligate the coronary sinus and anterior coronary vein. Thus Lokich's model suggests that mediastinal obstruction by tumor alone will not produce pericardial effusion; both lymphatic and venous obstruction must be present.

Since secondary tumors of the heart and pericardium are often associated with the presence of neoplasm elsewhere in the thorax, metastasis could spread through the lymphatics in retrograde fashion or by contiguous infiltration. Whereas embolic spread remains a possibility, the most common mode of metastasis appears to be through the lymphatic channels. Since pericardial invasion by tumor is nearly always associated with concomitant myocardial involvement, it seems logical to postulate that demonstration of myocardial damage resulting from tumor invasion would be one of the earliest evidences of local involvement. The availability of a sensitive indicator of myocardial damage—i.e., labeled phosphate agents—offers early detection of myocardial injury.

In two of our three cases, diffuse myocardial uptake was found to accompany the pericardial effusion. The malignant origin in these two cases was confirmed by the finding of malignant cells in the fluid. In the patient without differential uptake in the heart, the fluid did not reveal malignant cells. Radioassay of the pericardial fluid demonstrated radioactivity in all three patients. Although normalizing peripheral blood was not available for the patient without myocardial tracer uptake, this patient showed higher radioactivity in the pericardial fluid samples; the two patients with diffuse myocardial uptake showed less. There was no enhancement of radioactivity during passage from blood to pericardial fluid. Although uptake of such tracers has been found in dogs in regions of extensive homogeneous myocardial necrosis at the edge of an infarct, it also occurs in areas of mixed necrosis and ischemia (12). This finding suggests the possibility of differential tracer accumulation in damaged as well as necrotic myocardium. Evidently regional myocardial perfusion after coronary occlusion is a key determinant for the occurrence of necrosis and for radionuclide detection of such infarcts (13). Correlation between the amount of tracer accumulation and the extent of necrosis has varied and may well relate to the available blood flow delivering the radionuclide to the damaged area.

We postulate that neoplastic invasion of the epicardium in patients who subsequently develop malignant pericardial effusion results in myocardial damage, allowing tracer deposition at the site of involvement as well as initiating those mechanisms that result in the effusion. In those patients with pericardial effusion and differential uptake in the myocardium, some contribution to tissue accumulation may have come from the bathing pericardial fluid containing the tracer. This could explain the lower tracer concentration in the effusions of the two patients who showed myocardial uptake, as compared with the one who did not. Moreover, the former two had less activity in the effusion than in the blood.

The foregoing postulated mechanism for the production of pericardial effusion must also be considered in the light of other possible causative agents. In our cases, a number of therapeutic modalities were brought to bear in an attempt to control or palliate the disease. These agents included radiation and a variety of chemotherapeutic protocols administered at times sequentially and at other times concurrently. Radiation portals including the myocardium have been incriminated as a possible cause of diffuse myocardial incorporation of labeled phosphate agents (14). In our cases the site or the time course of radiation therapy does not appear to support this explanation of myocardial uptake. A recent report relative to the role of adriamycin as a cause of abnormal accumulation of Tc-99m pyrophosphate must also be considered (15). We doubt whether adriamycin, in cardiotoxic doses as now defined, was given in any of these cases near the time of imaging and the occurrence of pericardial effusion.

A previous paper (16) reported that during routine bone imaging radioactivity was detected in the noncellular component of malignant pleural effusions. In the two cases reported, tissue deposition was not seen—merely a transfer from plasma to the effusion.

We note that in our random review of 100 radionuclide studies of the skeletal system in patients with primary neoplasms, 5% showed a minimal or
1+ tracer concentration in the myocardium. This percentage is somewhat less than the 9% reported by Soin (14) in his control group. One patient in our series was known to have a history of myocardial infarction, and at autopsy showed severe fibrosis in the region of infarction, which appeared to explain adequately the focal accumulation of tracer at the site of a ventricular aneurysm. Three of the remaining four with diffuse differential uptake had carcinoma of the breast. One must consider the possibility of early myocardial metastasis in these patients resulting in the diffuse incorporation of tracer. The remaining patient, with squamous cell carcinoma of the lung presents a primary lesion with a high probability of contiguous spread, and thus the finding of tracer uptake in the heart may again indicate early involvement in the myocardium.

CONCLUSION

This report presents data on three patients with primary carcinoma of the breast with metastasis, admitted with a presumptive clinical diagnosis of malignant pericardial effusion. These patients were studied with labeled phosphate tracers in a search for skeletal involvement. Two of the three cases revealed a diffuse uptake of tracer within the myocardium and in these cases malignant cells were found in the pericardial fluid; none were found in the patient without tracer uptake in the heart, however. These patients were reviewed in the light of a 5% incidence of minimal myocardial tracer incorporation in a random retrospective review of 100 skeletal images using labeled phosphate agents. Three of the five patients in the "control group" were patients with carcinoma of the breast, and two had squamous cell carcinoma of the lung. It is suggested that invasion of the myocardium by neoplasm is the primary mechanism producing the concentration of tracer while concurrently providing a derangement that resulted in the evolution of pericardial effusion in two of our three case studies. A similar scenario is postulated for those revealed as positive in the "control group" of patients analyzed retrospectively. We suggest that the use of labeled phosphate agents may allow early detection of myocardial involvement in patients with disseminated neoplasm. Since these tracers are commonly used in studies of the skeletal system in such patients, the imaging of the heart sooner after injection than the standard skeletal imaging time may prove valuable in the assessment of cardiac involvement in patients with neoplastic disease.

REFERENCES