Intracardiac Involvement by Primary Malignant Mesothelioma: A Report of Two Cases

To the Editor:
Malignant mesothelioma is an aggressive cancer that arises from the mesothelial lining of the pleura, peritoneum, pericardium, and tunica vaginalis. Although mesothelioma commonly infiltrates mediastinal structures, cardiac extension is often limited to the pericardium. In this letter, we describe two patients with malignant peritoneal and pleural mesothelioma with intracardiac tumoral involvement. To our knowledge, cardiac involvement with primary peritoneal mesothelioma has not been previously reported.

Peritoneal mesothelioma was diagnosed in a 45-year-old man in 2006. He underwent several local and systemic therapies (Table 1). Eight years after the initial diagnosis, the patient enrolled in a phase II clinical trial of an investigational agent; routine monitoring echocardiogram showed multiple focal echodensities in the right ventricular apex (Fig. 1A). Follow-up study after 7 weeks showed additional echodensities involving the left ventricle (Fig. 1B). Although the infiltrated segments were hypokinetic, overall left ventricular function was preserved. The echodensities were highly suggestive of intracardiac metastasis given the temporal worsening, which mirrored systemic disease progression. The patient died 5 months after cardiac involvement was detected.

Pleural mesothelioma was diagnosed in a 71-year-old man in 2010. He was treated with pleurectomy and multiple local and systemic therapies (Table 1). He continued to have disease progression and died 3.8 years after diagnosis. An autopsy showed widespread tumor involvement of the right lung, superior mediastinum, mesenteric root, right chest wall, left buttock, liver, and right main stem bronchus, along with a retropericardial mass. Additionally, a 7-mm focus of tumor was detected in the cardiac interventricular septum, with involvement of the endocardium (Fig. 2). Although the patient did not have any overt symptoms attributable to cardiac involvement, he had intermittent atrial fibrillation during the 48 hours preceding death. An echocardiogram 2 days before his death was unremarkable except for abnormal septal motion and a small pericardial effusion.

In this letter, we have described two cases of malignant mesothelioma with metastatic intracardiac involvement. Cardiac involvement was detected in both patients after an unusually long interval subsequent to initial diagnosis. Whereas one patient had biventricular involvement, only the interventricular septum was affected in the second patient. Both patients had symptoms that could be attributed to intracardiac tumor involvement.

Although cardiac involvement of pleural mesothelioma has been previously reported, to our

Table 1. Patient Characteristics and Details of Cardiac Involvement of Mesothelioma

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Patient 1</th>
<th>Patient 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y/sex</td>
<td>45/male</td>
<td>71/male</td>
</tr>
<tr>
<td>Primary tumor location</td>
<td>Peritoneal</td>
<td>Pleural</td>
</tr>
<tr>
<td>Histological type</td>
<td>Epithelioid</td>
<td>Epithelioid</td>
</tr>
<tr>
<td>No. of prior systemic therapies</td>
<td>7</td>
<td>4</td>
</tr>
<tr>
<td>Areas of tumor involvement at presentation</td>
<td>Multiple vertebrae, bilateral lung nodules, sternum, left axilla, right hilum, paravertebral muscles, iliac bones, sacrum</td>
<td>Subcarinal mass, left pleural effusion, chest wall, abdominal wall</td>
</tr>
<tr>
<td>Clinical presentation</td>
<td>Dyspnea, orthopnea, LE edema</td>
<td>Atrial fibrillation</td>
</tr>
<tr>
<td>Mode of diagnosis</td>
<td>Echocardiogram</td>
<td>Autopsy</td>
</tr>
<tr>
<td>Time from diagnosis to detection of cardiac involvement, y</td>
<td>8</td>
<td>3.8</td>
</tr>
<tr>
<td>Part of heart involved</td>
<td>RV apex, LV anterolateral wall, anterior wall and apex</td>
<td>Interventricular septum with endocardial involvement</td>
</tr>
<tr>
<td>Survival after cardiac involvement</td>
<td>5 mo</td>
<td>Not applicable</td>
</tr>
</tbody>
</table>

RV, right ventricle; LV, left ventricle; LE, lower extremity.
**Figure 1.** Echocardiogram findings from the patient with peritoneal mesothelioma with intracardiac metastasis. Yellow arrows indicate (A) focal echodensities in the right ventricular apex (RV). Yellow arrows indicate (B-D) focal echodensities in the anterolateral wall of the left ventricle (LV), anterior wall of the LV, and left ventricular apex.

**Figure 2.** Gross and microscopic findings at autopsy of the patient with pleural mesothelioma with intramyocardial metastasis (A) The white lesion in the anterior portion of the interventricular septum represents a metastatic focus of mesothelioma (gross image). (B) Histological image of the entire metastatic lesion, measuring 0.8 cm in the largest dimension (hematoxylin and eosin; original magnification, ×1). (C and D) Metastatic mesothelioma cells infiltrating myocardial muscle cells (hematoxylin and eosin; original magnifications, ×4 and ×20).
knowledge, this is the first report of primary peritoneal mesothelioma with metastatic involvement of the heart. In the largest series to date of cardiac abnormalities in patients with pleural mesothelioma (n = 64), Wadler et al.4 found arrhythmias, including sinus tachycardia, atrial fibrillation, and conduction blocks, in 60% of patients. Cardiac invasion was found at 14 of 19 autopsies (74%), with more than half to the pericardium and more than a quarter to the myocardium. Our research suggests that intracardiac metastatic involvement is an underrecognized complication of disseminated mesothelioma.

Michel S. Kabbash, BS
Joseph Edmund, MD
Azam Ghafoor, MD
Raffit Hassan, MD
Thoracic and GI Malignancies Branch
National Cancer Institute
Bethesda, Maryland

Douglas Rosing, MD
Cardiovascular Branch Clinical
National Heart Lung and Blood Institute
Bethesda, Maryland

Acknowledgments
This research was supported by the Intramural Research Program of the National Institutes of Health.

References

A Novel Oncogenic RET Fusion Variant in Non-Small Cell Lung Cancer: RELCH-RET

To the Editor:
ret Proto-oncogene gene (RET) fusion is a key driver mutation and therapeutic target in NSCLC. Here we report a new form of oncogenic RET fusion variant retaining the whole kinase domain.

On June 12, 2019, a 60-year-old woman was admitted to our hospital with complaints of irregular coughing and sputum. Computed tomography results revealed a space-occupying lesion in the left lower lobe. Endoscopic biopsy was performed, resulting in a pathological diagnosis of highly differentiated mucinous adenocarcinoma. The patient received a left lower lobectomy by thoracoscopic surgery on June 24, 2019.

To seek potential therapeutic regimens, next-generation sequencing analysis was performed, resulting in identification of a novel RET fusion variant involving RAB11 binding and LisH domain, coiled-coil and HEAT repeat containing gene (RELCH) exons 1 to 10 on chromosome 18 and RET exons 12 to 20 on chromosome 10 (Fig. 1A and B). The fusion was then confirmed by fluorescent in situ hybridization (Fig. 1C). This is the first identification of this novel RELCH-RET fusion variant in NSCLC around the world.

RET fusion had a prevalence around 1% to 2% in patients with NSCLC and was characterized as a key driver mutation for targeted therapy.1 Activated ret proto-oncogene (RET) could promote a series of oncogenic signaling pathways (e.g., the AKT pathway), leading to tumorigenesis and metastasis. Although many RET fusion partner genes have been identified, not all fusion forms were oncogenic. Only fusion variants retain the whole RET kinase domain, and coiled-coiled domains of the partner gene were considered oncogenic by inducing constitutively RET homodimerization and autophosphorylation.2 In