Symptomatic Persistent Post-Coronary Artery Bypass Graft Pleural Effusions Requiring Operative Treatment*

Clinical and Histologic Features

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Background: More than 85% of patients develop pleural effusions after coronary artery bypass grafting (CABG). Although the majority resolve spontaneously, post-CABG effusions can persist. The cause of these persistent effusions is unknown, and the histology of the pleural changes has seldom been reported.

Objectives: To describe the patient characteristics and pathologic condition of the pleural tissues in patients with persistent post-CABG effusions.

Subjects: Eight patients with persistent post-CABG effusions who underwent thoracoscopcy or thoracotomy over a 2-year period by one thoracic surgeon. These eight patients were selected as having undergone CABG > 2 months before their thoracic surgery and had no other identifiable causes of effusion.

Results: The median time from CABG to pleural surgery was 132 days (range, 74 to 2,258 days). The median left ventricular ejection fraction was 57% (range, 15 to 70%). All patients were dyspneic and had large (≥25% of the hemithorax) effusions on chest radiograph. All effusions persisted after two or more thoracenteses. Pleural effusion was left sided in three patients and bilateral in five patients. Pleural fluid was characterized by lymphocytosis (82 to 99%). Four of the eight patients had a visceral peel and trapped lung requiring decortication. Seven of the eight biopsy specimens showed pleural thickening characterized by dense fibrous tissues with associated mononuclear cell infiltration, while the eighth biopsy specimen showed only clotted blood. The degree of inflammation and fibrosis correlated with the interval between CABG and pleural surgery. Early post-CABG patients displayed more inflammation, with abundant lymphocytes in nodular configuration deep in the fibrous tissues away from the surface. Abundant keratin-positive, spindle-shaped cells were present in the fibrous tissues. Late cases showed predominantly mature fibrosis.

Conclusions: Persistent post-CABG effusion can occur. Pleural fluids and pleural tissue in early-stage lesions were characterized by lymphocytosis. With time, the inflammatory changes were replaced by fibrosis that resulted in dyspnea and, at times, trapped lungs requiring surgical intervention.

Key words: coronary artery bypass grafting; pathology; pleural effusion

Abbreviation: CABG = coronary artery bypass grafting

Pleural effusion occurs in up to 89% of patients during the first week after coronary artery bypass grafting (CABG). Most of these effusions are small, self-limiting, and do not require interventions. However, chronic, persistent post-CABG effusions have been reported. The etiology of these persistent effusions remains unknown.

We report the clinical and pleural histologic features of eight patients who had persistent post-CABG pleural effusions and underwent thoracosc-
copy or thoracotomy from 10 weeks to 6 years after their CABG.

**Materials and Methods**

All patients who underwent thoracoscopy or thoracotomy for pleural effusion performed by one thoracic surgeon (J.C.N.) in our institute between October 1, 1997, and October 1, 1999, and who had previous histories of CABG were identified. Their medical records, chest radiographs, laboratory results, and surgical records were reviewed. Post-CABG effusion was defined as a pleural effusion that developed within the first 2 months after CABG where no other causes were identified. Patients were contacted by telephone at the end of October 1999 (2 to 12 months after their thoracoscopy or thoracotomy), regarding whether they had further needs of thoracentesis. This study was approved by the Institutional Review Board of Saint Thomas Hospital.

**Clinical Data**

Eight patients who underwent video-assisted thoracoscopy or thoracotomy for investigation or management of persistent post-CABG pleural effusions were identified. Their pleural tissues from open biopsy were independently examined. The pleural fluid result of one of the patients (patient 7) has been included in a previous publication.7

None of the eight patients had radiologic evidence of pleural effusion before their CABG. Two patients had mild chronic renal impairment (serum creatinine, 1.6 mg/dL and 1.7 mg/dL, respectively) not severe enough to explain their effusions. None of these patients had a history of connective tissue diseases, hepatic cirrhosis, recent pneumonia, significant asbestos exposure, or use of drugs associated with pleural effusions.

**Pathology**

Pleural tissues obtained during thoracoscopy or thoracotomy for investigation or management of persistent post-CABG pleural effusions were identified. Their pleural tissues from open biopsy were independently examined. The pleural fluid result of one of the patients (patient 7) has been included in a previous publication.7

None of the eight patients had radiologic evidence of pleural effusion before their CABG. Two patients had mild chronic renal impairment (serum creatinine, 1.6 mg/dL and 1.7 mg/dL, respectively) not severe enough to explain their effusions. None of these patients had a history of connective tissue diseases, hepatic cirrhosis, recent pneumonia, significant asbestos exposure, or use of drugs associated with pleural effusions.

**Results**

Six male and two female patients was included. Median age was 69 years (range, 47 to 88 years) at the time of thoracoscopy or thoracotomy, with the median interval from CABG to thoracoscopy/thoracotomy being 132 days (range, 74 to 2,255 days). All the patients complained of dyspnea, one had a cough, and two reported weight loss. None of the patients had pleuritic chest pain or fever. Two patients were receiving warfarin (patients 2 and 3), while the remaining six patients were receiving aspirin. Patient 2 also had an aortic valve replacement at the time of CABG. The demographics of these patients, the intervals between CABG and first evidence of pleural effusion as well as between CABG and first thoracentesis, the preoperative left ventricular ejection fractions (measured on echocardiography or during cardiac catheterization), and types of bypass grafts are presented in Table 1.

All patients had large ($\geq 25\%$ of the hemithorax) effusions on chest radiograph. The pleural effusion was left sided in three patients and bilateral in five patients. All effusions persisted after two or more thoracoscopies. Two patients (patients 2 and 7) also underwent tube thoracostomy before their thoracic surgery. The radiographic abnormalities and number of thoracenteses received are reported in Table 2. The thoracentesis results were available in four patients (Table 3). Lymphocytosis (82 to 99%) was a common feature in all these four effusions.

Patient 8 underwent her CABG in June 1992. Bilateral effusions (right side more than left) were diagnosed 4 weeks after CABG, and she received the first thoracentesis at the same time. She underwent a further thoracentesis for symptomatic dyspnea in early 1993, and thereafter two additional right-sided thoracenteses over the following 5 years at times of increasing dyspnea. In August 1998, she was referred for surgical evaluation. No other etiology for the effusions was identified during the 6 years of her disease course. Patient 7 had a CABG operation in October 1996, after which he developed bilateral

<table>
<thead>
<tr>
<th>Patient</th>
<th>Sex/Age</th>
<th>Time When Effusion First Noticed (Days After CABG), No.</th>
<th>Time to First Thoracentesis (Days After CABG), No.</th>
<th>Left Ventricular Ejection Fraction, %</th>
<th>Re-do CABG</th>
<th>IMA Graft, No.</th>
<th>SV Graft, No.</th>
<th>BA Graft, No.</th>
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<td>M/47</td>
<td>5</td>
<td>74</td>
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<td>0</td>
<td>1</td>
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<tr>
<td>2</td>
<td>M/71</td>
<td>3</td>
<td>3</td>
<td>87</td>
<td>55</td>
<td>Yes</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>3</td>
<td>M/88</td>
<td>16</td>
<td>54</td>
<td>95</td>
<td>50</td>
<td>No</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>4</td>
<td>M/67</td>
<td>7</td>
<td>53</td>
<td>115</td>
<td>54</td>
<td>No</td>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td>5</td>
<td>F/74</td>
<td>2</td>
<td>105</td>
<td>148</td>
<td>70</td>
<td>No</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>6</td>
<td>M/76</td>
<td>2</td>
<td>4</td>
<td>227</td>
<td>15</td>
<td>Yes</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>7</td>
<td>M/64</td>
<td>5</td>
<td>79</td>
<td>729</td>
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<tr>
<td>8</td>
<td>F/57</td>
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<td>28</td>
<td>2,258</td>
<td>65</td>
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* M = male; F = female; IMA = internal mammary artery; SV = saphenous vein; RA = radial artery.
(right side more than left) pleural effusions before his hospital discharge. The effusions were rapidly reaccumulating and required frequent thoracentesis for symptomatic relief. Diuretics and a short course of oral corticosteroids offered no apparent benefit.

In February 1997, he received bilateral tube thoracostomy drainage. He underwent unsuccessful chemical pleurodeses with talc slurry to the right pleural space and, later, doxycycline to the left pleural space. In March 1997, he underwent a right thoracoscopy and parietal pleurectomy. Despite that, he continued to suffer from recurrent bilateral effusions (right side more than left). In April 1999, he underwent a right thoracotomy, pleurectomy, and mechanical pleurodesis (under J.C.N.). Extensive investigations did not reveal the etiology of the effusions. The macroscopic and microscopic examinations of the pleura also failed to demonstrate any specific cause for his effusion. Patient 6 had poor left ventricular function with an ejection fraction of 15%, but his effusion was bloody and he had thickened pleura and trapped lung, features not usually associated with effusions because of congestive cardiac failure. It is possible, however, that congestive cardiac failure could be a contributing factor to his pleural effusion.

A summary of the surgical procedures and intraoperative findings of the eight patients are summarized in Table 4. Four of the patients (50%) had trapped lungs requiring decortication. All patients had intraoperative findings suggestive of a chronic inflammatory process, with no macroscopic features of an acute process or of malignancies. None of the patients had further recurrence of their effusions after their thoracoscopic or thoracotomy (follow-up period, 2 to 18 months; median, 12 months).

### Pleural Histology

The pleural biopsy samples showed a spectrum of changes that roughly correlated with the interval between CABG and thoracotomy/thoracoscopy. Cases in which this period was short (<6 months) displayed a predominance of inflammation with dense cellular infiltrates, especially lymphocytes, and relatively little pleural fibrosis (Fig 1). As the interval increased, the biopsy samples showed progressively less inflammation, decreased density of the cellular infiltrate, and increased amounts of fibrosis. The pleura was markedly thickened with the increased amount of dense fibrous tissues (Fig 2). The fibrous component was typically paucicellular, but did contain collections of entrapped cells that were cytokeratin immunoreactive, compatible with mesothelial cells.

In the samples obtained relatively soon after

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### Table 2—Radiographic Appearances and No. of Thoracenteses Prior to Pleural Surgery

<table>
<thead>
<tr>
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<tr>
<td>1</td>
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<td>No</td>
<td>25–50</td>
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<td>0</td>
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<tr>
<td>2</td>
<td>Left more than right</td>
<td>No</td>
<td>No</td>
<td>&gt;50</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>3</td>
<td>Right more than left</td>
<td>Yes</td>
<td>No</td>
<td>25–50</td>
<td>0</td>
<td>4</td>
</tr>
<tr>
<td>4</td>
<td>Left only</td>
<td>No</td>
<td>Yes</td>
<td>25–50</td>
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<td>0</td>
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<tr>
<td>5</td>
<td>Left only</td>
<td>No</td>
<td>No</td>
<td>25–50</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>6</td>
<td>Right more than left</td>
<td>No</td>
<td>Yes</td>
<td>&gt;50</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>7</td>
<td>Right more than left</td>
<td>No</td>
<td>No</td>
<td>25–50</td>
<td>&gt;15</td>
<td>&gt;15</td>
</tr>
<tr>
<td>8</td>
<td>Right more than left</td>
<td>No</td>
<td>No</td>
<td>25–50</td>
<td>0</td>
<td>4</td>
</tr>
</tbody>
</table>

*The size of the effusion indicates the largest size of the effusion on radiographs during the period between CABG and pleural surgery.

### Table 3—Characteristics of the Pleural Fluid of the Four Patients Whose Thoracentesis Results Were Available*

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Side of Thoracentesis</th>
<th>WBC Count, Cells/μL</th>
<th>Lym, %</th>
<th>PMN, %</th>
<th>Mono, %</th>
<th>Eos, %</th>
<th>Baso, %</th>
<th>RBC Count, Cells/μL</th>
<th>LDH, IU/L</th>
<th>Protein, mg/L</th>
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<tbody>
<tr>
<td>5</td>
<td>Left</td>
<td>Nonbloody</td>
<td>1,000</td>
<td>85</td>
<td>2</td>
<td>8</td>
<td>5</td>
<td>0</td>
<td>500</td>
<td>185</td>
</tr>
<tr>
<td>6</td>
<td>Right</td>
<td>Bloody</td>
<td>750</td>
<td>82</td>
<td>13</td>
<td>5</td>
<td>0</td>
<td>0</td>
<td>61,500</td>
<td>460</td>
</tr>
<tr>
<td>7</td>
<td>Right</td>
<td>Nonbloody</td>
<td>2,000</td>
<td>88</td>
<td>5</td>
<td>6</td>
<td>1</td>
<td>0</td>
<td>28,250</td>
<td>324</td>
</tr>
<tr>
<td>8</td>
<td>Right</td>
<td>Nonbloody</td>
<td>225</td>
<td>99</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>6,150</td>
<td>238</td>
</tr>
</tbody>
</table>

*Lym = lymphocytes; PMN = polymorphonuclear leukocytes; Mono = monocytes; Eos = eosinophils; Baso = basophils; LDH = lactate dehydrogenase.*
CABG, the inflammatory cell infiltrate was concentrated deep in the fibrous tissue and away from the mesothelial layer. It consisted predominantly of lymphocytes that focally tended toward a nodular configuration (Fig 3). Immunohistochemical analysis with L26 (pan B-cell-specific marker) and UCHL1 (pan T-cell-specific marker) demonstrated a mixed population of lymphocytes with a predominance of B cells. Small numbers of reactive plasma cells were also present.

One sample of the pleura represented material from a patient with a hemothorax (patient 2) and consisted entirely of blood clots. No granulomata or malignant changes were observed in any of the pleural biopsy specimens.

Discussion

We presented the clinical and pathologic features of eight patients who had persistent post-CABG pleural effusions that failed to resolve with repeated thoracenteses and eventually required surgical intervention. The pleural biopsy samples of these patients demonstrated a spectrum of histologic changes that roughly correlated with the interval between CABG and pleural surgery, and likely represent the temporal evolution of this condition. Inflammation and lymphocytosis were the characteristics in the early phase. With time, these changes were replaced by mature fibrosis, which in some cases resulted in trapped lungs and required decortication.

Pleural effusion is very common after CABG surgery and can be detected in approximately 90% of patients within the first week of operation. While most of these effusions are small and self-limiting, large and persistent pleural effusions have been reported. The etiology of post-CABG effusions and the reasons why some effusions persist while most resolve remain unknown.

None of these patients had other identifiable risk factors for pleural effusion, and the temporal relationship of the onset of effusion and CABG suggested a causal relationship. The lack of pleuritic symptoms or fever and the duration of the effusion virtually excluded post-cardiac injury syndrome. None of the eight patients we described had clinical evidence of pericardial disease or congestive cardiac failure. No other causes were found during the disease course or from thoracoscopy/thoracotomy to explain the effusions. Open pleural biopsy specimens failed to demonstrate any specific cause (eg, malignancy) for these effusions, and there was no recurrence of the effusion after the surgical intervention.

Large post-CABG effusions can be categorized into early- and late-phase effusions. The early ones are usually related with surgical trauma and peak in size within the first month after surgery. These effusions are bloody with associated eosinophilia. The late-phase post-CABG effusions are different in that they usually reach maximum size after the first
The pleural fluids often appear nonbloody and are characterized by significant lymphocytosis. The latter feature has led to the speculation of an immunologic basis of these late-phase post-CABG pleural effusions.

Little is known about the histologic changes of the pleura in patients with persistent post-CABG effusions. Areno et al described the histology of one patient 2 years after CABG. The parietal pleura was thickened and showed evidence of chronic pleuritis with nests of lymphocytes. Kollef described another patient 3 months after CABG who had a closed pleural biopsy specimen showing chronic inflammation and a mesothelial cyst.

Our samples confirmed that lymphocytosis was the key feature on the early biopsy tissues as well as in the pleural fluids. We further defined that the lymphocytes were predominantly B cells and that these lymphocytic infiltrates subsided with time. The trigger for the intense inflammation and lymphocytic infiltration is unknown. The exact etiologic role of these lymphocytes also warrants further evaluation.

All of the patients in our series had symptomatic, large pleural effusions that failed to resolve after at least two thoracenteses. Those with long intervals after CABG were more likely to have evidence of visceral peel and trapped lung that required decortication. This was confirmed by the pleural biopsy samples, which demonstrated that patients with a longer interval after CABG had more pleural fibrosis and thickening. The source of the fibrosis remains unclear. While infiltrating fibroblasts can produce the fibrosis, mesothelial cells have also been shown to produce collagen, which may in part contribute to the fibrotic process.

Four of the patients we described had visceral peel and trapped lungs. Full reexpansion was achieved in three of these four patients after decortication. Of all the cases of persistent post-CABG effusions reported, most resolved with thoracentesis. Only one case of trapped lung from persistent post-CABG effusion had previously been described. In that patient, decortication performed 4 months after CABG was also successful in restoring reexpansion. Cohen and Finch described two patients with loculated post-CABG effusions who were treated successfully with intrapleural urokinase. It was not certain whether they had trapped lungs.

In cases in which fluid reaccumulation continues for >6 months, consideration should be given to more aggressive intervention that may help prevent the eventual development of trapped lungs. Pleurectomy or surgical pleurodesis with talc with or without mechanical abrasion appeared effective in controlling the effusion in the patients we described. None had further recurrence of pleural effusion afterwards.

There are some limitations to this present study. It is a retrospective review, and not all the patients’ pleural fluid analyses were available. Post-CABG pleural effusion is a diagnosis of exclusion. Although there are no other identifiable causes for the effusion in any of our patients, other etiologies cannot be fully excluded. While none of the patients had recurrence of symptoms or required further thoracentesis after thoracoscopy or thoracotomy, no radiographs were obtained. Hence, we cannot fully exclude the possibility of asymptomatic recurrence of the effusions. Also, our method of identifying patients may well have underestimated the true incidence of persistent post-CABG effusions requiring surgical intervention.

Figure 2. Pleural biopsy specimen in a patient who underwent CABG 2 years before the thoracoscopy. The pleura was markedly thickened, with a significantly larger amount of dense fibrous tissue. There were relatively little inflammatory changes (hematoxylin-eosin, original ×40).

Figure 3. Histologic section of the pleura showing the lymphoid aggregates deep in the fibrous tissues away from the mesothelial layer (hematoxylin-eosin, original ×40).
In conclusion, we demonstrated that persistent post-CABG pleural effusion can occur and, in some cases, require surgical intervention. The number of cases of persistent post-CABG effusion may rise as more CABG procedures are performed each year. Increased awareness and recognition of this syndrome is important. If the effusion persists > 6 months, surgical intervention should be considered, as it is effective in decorticating any trapped lung and in preventing reaccumulation of the effusions.

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REFERENCES
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