Clinical-pathologic conference in general thoracic surgery: Cardiac lymphoma

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Case Presentation

Dr Lee: The patient is a 62-year-old man who had a brief episode of substernal chest pressure while lifting a heavy object at home. The pressure was alleviated with a few minutes of rest. Because the patient immediately felt better, he decided to wait to see his primary care physician at an appointment that was previously scheduled. He had asked for the appointment because of symptoms of dizziness and nose bleeding that had occurred during the 3 weeks before the episode of chest pressure.

His medical history is significant for prostate cancer, for which he underwent a prostatectomy in 1995, and new-onset hypertension that is controlled without medication.

On review of systems, he reported a little bit of increased shortness of breath over the past 6 months. He was able to walk a mile on flat ground, but after 2 flights of stairs, he became dyspneic. Also, over the past 6 months, he had a morning cough, with clear, thin mucous production. He reported long-standing reflux and constipation, for which he took stool softeners.

Neurologically, he mentioned having 3 episodes of dizziness over 3 weeks, but he never had syncope. He also had a history of ocular migraines for approximately 2 years.

Social history consisted of working as a serviceman for a heating and air-conditioning company. He had been exposed to asbestos about 35 years prior. He has a 50 pack-year smoking history but stopped smoking 12 years before presentation. He drinks an occasional glass of wine.

His family history is only significant for a heart attack that his father had at the age of 61 years and a mother with dementia. His allergies include tetanus shots made from horse serum and poison ivy.

The results of his physical examination were unremarkable. He had no palpable adenopathy. His neck and head were not edematous. His lungs were clear, and his heart had a regular rate and rhythm. He had no chest wall tenderness. His abdomen was soft without mass, and his extremities had no cyanosis or clubbing.

After the episode of chest pressure, he was fine for the next several days. Eventually, he went to his primary care physician about the nosebleeds and dizzi-

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Figure 1. Thallium scan.

Figure 3. CT scan.

ness. When his primary care physician heard about his chest pressure and his family history of heart disease, he was concerned. Despite a normal electrocardiogram (ECG), the patient underwent a stress test. The stress test showed an ejection fraction of 70% and normal function. However, there was some abnormal uptake of thallium in the base of the heart in the rest images. This was suggestive of some kind of malignancy and led to a computed tomographic (CT) scan. We can now review the radiographic studies.

Dr Gutierrez: The chest radiograph is normal. Now let us examine the thallium scan (Figure 1). These are the left anterior oblique views. Here is the left ventricle; you can see that the uptake is normal. In the area in question, there were some concerns about an area of uptake on top of the right ventricle. That led to the CT scan (Figures 2 and 3). Let me start from the lower mediastinum, and we can work our way down. The superior mediastinum is normal, but as we get into the base of the heart, we can see that there is a soft tissue mass. Here is the right atrial appendage, the aorta, and the pulmonary arteries. There is a soft tissue mass sitting on

top of the atrioventricular groove. As we look lower, we can see the mass encasing the right coronary artery. Fortunately, there is contrast, indicating good flow within the vessels. Therefore, all that tissue around the atrioventricular groove is infiltrated and extends down about this far. There are just a few normal-sized lymph nodes. At the time, we thought that this probably represented some kind of sarcoma, maybe an angiosarcoma or a fibrosarcoma.

Dr Lee: We planned to biopsy this mass, but it was obviously not amenable to a percutaneous approach. Before the biopsy, the patient underwent further cardiac evaluation. This included echocardiography and cardiac catheterization. The echocardiogram showed completely normal cardiac and valve function; however, a large right ventricular mass was seen. After that, he underwent cardiac catheterization, the results of which were completely normal. Unfortunately, after his catheterization, he had transient blindness that lasted about 48 hours.

Dr Govindan: Does he have an atrial septal defect? Was this a paradoxical embolus?

Figure 2. CT scan.

Figure 4. Biopsy, low power.

Figure 5. Biopsy, high power.

Figure 7. CD20 stain.

Dr Lee: No, he does not. A saline contrast study was performed, and its results were normal. After he had this temporary blindness, further workup included normal carotid duplex imaging, a normal head CT scan, and a magnetic resonance angiogram (MRA). The MRA showed no ischemic insult, no cerebral mass, and normal carotid arteries. Fortunately, he recovered from this event and then underwent further preoperative evaluation. Finally, a positron emission tomographic (PET) scan was performed to rule out any other metastatic site.

Dr Patterson: What was the relationship between the cardiac catheterization and the blindness?

Dr Lee: Full visual field bilaterally occurring immediately afterward.

Dr Battafarano: They thought it was a reaction to dye, especially after they did the MRA of the head. There was not anything to suggest an embolic phenomenon, and it did

not look like an infarct. It was a sort of idiosyncratic reaction to the dye and the contrast.

Dr Govindan: Do you know whether this has been reported after routine cardiac catheterizations?

Dr Battafarano: This has happened before. It is not common, but it was not the first time that our cardiologists have seen this. Our cardiologists tell me that this phenomenon occurs once or twice a year at high-volume centers. Now we can review the PET study?

Dr Dehdashti: The PET study on this patient showed an area of increased uptake in the anterior mediastinum superior to the right ventricle. The standardized uptake value was 2.8, which is in the malignant range. However, this degree of uptake is not typical for a high-grade malignant sarcoma. I think a low-grade tumor or even sometimes a benign lesion might have a similar degree of fluorodeoxyglucose uptake. The scan is otherwise unremarkable.

Figure 6. Biopsy, higher power.

Figure 8. CD43 stain.

Dr Lee: This information finally led us to the operating room. Through a median sternotomy, we searched for but did not find any abnormal mediastinal nodes. We then opened the pericardium and found an infiltrating mass on the right ventricle. We performed 2 incisional biopsies, controlled the bleeding with some pressure, and closed.

Dr Battafarano: This was very interesting. The process was not a disease of the para-aortic nodal tissue proper; it really involved the right ventricle. We actually put a flow probe on the mass to find the right coronary artery because we did not want to damage it during any of our biopsies. The mass was infiltrative and very thickened, as predicted by the CT scan. However, as it coursed along the right ventricle, the ventricle became more and more normal. The apex of the ventricle was completely soft and normal. There was a single focus. There were no inflammatory adhesions between the pericardium and the ventricular surface. It was simply a mass in the ventricle that went right up to the base of the heart and involved the lower part of the aorta. That is what we biopsied. It was unclear by means of palpation as to the depth of involvement.

Dr Ritter: This is the low-power view from one of the biopsy specimens (Figure 4). You can see the surface appears to be epicardial. Underneath lies this very dense lymphoid infiltrate. At higher power, there are several germinal centers within the infiltrate (Figure 5). These have macrophages within them. They do appear polarized, which is one of the features that allow us to interpret them as reactive rather than neoplastic follicles. Extending in between them was a fairly diffuse infiltrate of small lymphocytes. On somewhat higher power, you can see that this is a polymorphic mixture. We have lymphocytes, plasma cells, and some eosinophils throughout (Figure 6). You can also see a lot of these endothelial cells from little reactive vascular spaces. This is very vascular, and the lymphoid component itself is very bland. Any of the larger cells that you see here that look a little atypical are actually associated with the vessels. They are the reactive endothelial cells and not the lymphoid component. There were also a series of immunostains done. This is for CD20, which we use as a B-cell marker (Figure 7). You can see these germinal centers here, as well as numerous B cells separating these follicles. A CD3 stain for T cells showed very few T cells within the germinal centers, but more of them were present through the interstitium, for a mixture of B and T cells. A stain for CD43, another T-cell marker, showed many more CD43⁺ cells in between follicles than we found with CD3 (Figure 8). This suggests that there is some aberrant expression of CD43 on these B cells. This aberrant expression is a feature that we see in some B-cell lymphomas.

We also had fresh tissue available for flow cytometry.

There are some atypical features in this specimen, including the density, the location, and this aberrant expres-

sion of CD43 in the B cells. However, this does not meet the diagnostic criteria for lymphoma. This tissue is most consistent with a diagnosis of benign lymphoid infiltrate. I suppose that raises a couple of other possibilities. Taken by itself, this would be consistent with reactive lymphoid tissue around some other lesion. However, from everything else we have seen, it seems like the mass was fairly homogeneous. Therefore, I do not think sampling is going to explain this finding. You can see dense lymphoid infiltrates in severe myocarditis, but again, that does not really seem to fit the clinical picture. I think we are basically left with an atypical lymphoid infiltrate as a diagnosis.

Dr Govindan: Did he travel outside the United States before this developed? You can see myocardial lymphoid infiltrates in some parasitic diseases.

Dr Ritter: I think that is true, but there is no evidence that he has any kind of myocardial disease other than this localized mass. If you transposed this tissue into a lymph node, you would say it was just some kind of reactive lymphoid hyperplasia. If you put it in other sites where you get these kind of extranodal processes (eg, the skin or gastrointestinal tract), that would still come under the heading of lymphoid hyperplasia. It does not have monoclonal expression, and by immunostaining, it shows a mixed pattern. It has reactive germinal centers, and there is no atypical monotonous lymphoid population that you can identify. Our concern is that this is a low-grade marginal-zone lymphoma. Unfortunately, I do not think it meets the diagnostic criteria.

With the vascular proliferation and the number of plasma cells present, Castleman's disease is another possibility. You can find Castleman's disease in unusual locations, and this process does contain some of its features. However, I do not think that is what we have here. I would put it in the broad category of reactive lymphoid hyperplasia. Sometimes the diagnosis is clear if you can identify a primary site, like on the skin if the patient had an insect bite.

Dr Govindan: Castleman's disease spans a wide spectrum from indolent localized disease to extensive multicentric symptomatic disease.

Dr Ritter: Yes, there are both multicentric and isolated forms. He had a PET scan and CT scan. He does not have evidence of adenopathy anywhere else. Even if we said this was involvement of the heart by a lymphoma, we would expect that the heart is not the primary site and that adenopathy would be present elsewhere. I understand there is maybe some question about the inguinal nodes on the PET scan. I think that if he has any adenopathy elsewhere, we should biopsy the nodes to make sure that he does not have a low-grade lymphoma. We just cannot meet the diagnostic criteria for lymphoma.

Dr Govindan: As you know, human herpesvirus 8 (HHV 8) has been associated with Castleman's disease. Do

you think that it is worth looking for HHV 8? I agree that I am going a step ahead. The picture is not all that classic for Castleman's disease.

Dr Ritter: That is a good point. I do not know what tissue we still have left.

Dr Govindan: I want to make the point that typically HHV 8-associated Castleman's disease is often multicentric disease.

Dr Battafarano: There are some gene-rearrangement studies that are currently pending to rule out lymphoma. Clearly this might be benign-looking tissue, but it is in the wrong place. On the basis of its location, we are going to pursue further characterization.

Dr Ritter: The gene-rearrangement studies are still pending and ideally should be done within the next few days. It is unclear whether that alone would be sufficient to make a diagnosis of lymphoma. Again, it is clear that in some reactive conditions, you will detect a clonal rearrangement by using molecular diagnostics.

Dr Govindan: This presentation seems highly unusual for lymphoma.

Dr Battafarano: I think the next step is to obtain another CT scan approximately 6 weeks after surgical intervention and form a new baseline with some of the postoperative changes. Obviously, if this grows or if something else arises in the mediastinum, then we would lean toward treating it or dealing with it in another fashion. If it just stays like this and does not change at all, then we might be willing to follow it. I think the only way to approach future therapy is with a baseline CT scan in about 6 weeks and subsequent serial examinations.

Dr Lee: What about serial PET scans? Would that play a role?

Dr Battafarano: If it is in that low-grade range, I do not think it would help.

Dr Bradley: Is this transmural?

Dr Battafarano: The technologist did not see any heart muscle. We do not really know.

Dr Ritter: I would say that most of what we have obviously infiltrates the epicardial fat, but we do not know how deep it goes.

Dr Bradley: It is just not behaving like something benign. It could be infiltrating heart muscle, right? If it turns out to be a lymphoma and you treat it, what is going to happen? Is it possible that the ventricle could rupture as a result of treatment for lymphoma?

Dr Patterson: He had an echocardiogram, a catheterization, and a stress test. He had several very good functional studies that tell you that his heart is not involved.

Dr Battafarano: Radiographically, his right coronary artery was smooth and open, and therefore this encases it externally. One of the reasons that we did the catheterization was to be sure that there was not either extrinsic compression or even transmural involvement through the arterial wall.

Dr Lee: Postoperatively, he went home on day 3. He was subsequently readmitted for generalized weakness and fatigue, received intravenous hydration, and was discharged again.

Dr Govindan: Did he have a bone marrow biopsy?

Dr Battafarano: Not yet. I think Dr Bartlett plans on doing one.

Dr Patterson: So this was all within the pericardium?

Dr Battafarano: Correct. It did not involve the pericardium at all. In other words, I was thinking that if this was response to some myocarditis or pericarditis, you would expect the pericardium to have adhesions, but there was a free pericardial space with clear fluid, and it just had some reactive cells in it. It did not look like it was myocarditis or a pericarditis.

Dr Govindan: It possibly could be a picture consistent with sarcoid.

Dr Lee: Follow-up gene-rearrangement studies confirmed that this was, in fact, a low-grade lymphoma.