Clinical-pathologic conference in general thoracic surgery: Metastatic placental site trophoblastic tumor

G. Alexander Patterson, MD

From the Washington University
School of Medicine, Barnes-Jewish
Hospital, St Louis, Mo.

Participants

From the Washington University
School of Medicine
Barnes-Jewish Hospital
St Louis, Mo.

Thoracic Surgery

Dr G. Alexander Patterson
Dr Joel Cooper
Dr Bryan Meyers
Dr Seth Force

Radiology

Dr David Gierada

Nuclear Medicine

Dr Farrokh Dehdashti

Surgical Pathology

Dr Jon Ritter

Gynecology Oncology

Dr Neil Horowitz

Medical Oncology

Dr Ramaswamy Govindan

Case Presentation

Dr Force: A 35-year-old woman came to an outside hospital 37 weeks' pregnant and reporting shortness of breath. A chest radiograph performed in the emergency department revealed a right pneumothorax. A 12F catheter was placed to drain the pneumothorax. Subsequently, a persistent air leak developed, and the patient was transferred to the obstetric service at our hospital. Three days after admission, she had an uncomplicated vaginal delivery. However, she continued to have a persistent air leak from her chest tube. Several days later, the air leak ceased but a recurrent pneumothorax developed. This required the placement of a larger chest tube, which once again revealed a persistent air leak.

The only significant procedures in the patient's surgical history were a cesarean section and a cholecystectomy. She had a 10 pack-year smoking history and no history of a previous pneumothorax. After the air leak was tracked for 1 week after delivery, the patient was taken for a video-assisted thoracoscopy. A video-assisted thoracoscopic resection of a right lower lobe bleb and mechanical pleurodesis were performed. The patient tolerated the procedure well and was discharged to home on the fourth postoperative day after her chest tube was removed. The case is being presented because of interesting findings in the resected specimen.

Dr Patterson: She had had no imaging other than just a chest radiograph?

Dr Force: She had a computed tomographic (CT) scan as well.

Dr Gierada: On the chest radiograph taken when she was transferred here, you can faintly see the pneumothorax catheter, and there was still a very small right apical pneumothorax. A follow-up radiograph 3 days later showed almost a complete collapse of her right lung (Figure 1). The following day, the lung had come up partly in the morning, and a few hours later it was up almost completely. No obvious lesions were seen in the lungs on images obtained without a pneumothorax present. A CT scan obtained later that same day showed the pneumothorax, and in the right lung base there was a cystic lesion with what looked like perhaps some thin septations with a little thickening of the septations or some vessels running along them. A very thin-walled inferior portion was adhered to it, so that it looked like a thin bleb (Figure 2). This is an unusual location for a bleb as a cause of spontaneous

From the Washington University School of Medicine, Barnes-Jewish Hospital, St Louis, Mo.

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Address for reprints: G. A. Patterson, MD, Washington University School of Medicine, Suite 3108 Queeny Tower, Division of Cardiothoracic Surgery, One Barnes Hospital Plaza, St Louis, MO 63110 (E-mail: pattersona@msnotes.wustl.edu).

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Figure 1. Chest radiograph showing collapse of right lung with pneumothorax catheter in place.

Figure 2. CT scan 4 days after transfer shows pneumothorax and cystic lesion in right lung base.

pneumothorax. Without knowing the pathologic details, the most likely possibility is that this was a result of an old infection or perhaps an old congenital lesion like a small cystic adenomatoid malformation or a sequestration that had cavitated and formed into a cyst.

Dr Cooper: You put in a chest tube here?

Dr Force: She had a pneumothorax catheter from an outside emergency department, and we kept that in initially. That failed, however, so we put in a chest tube.

Dr Cooper: Did the chest tube take care of the problem?

Dr Force: It didn't, she had a persistent air leak and never completely resolved her pneumothorax.

Dr Patterson: Was there a big air leak?

Dr Force: There was a persistent leak.

Dr Cooper: Well, what is a persistent leak?

Dr Force: Longer than a week.

Dr Cooper: Couldn't you put on a Heimlich valve and send her home?

Dr Force: We could have, but she was young and pretty anxious to get the tube out. She was reporting a lot of discomfort with the tube. Furthermore, she is a large woman, and we were having problems with kinking and positioning of the tube. I don't think that she would have tolerated being sent home with a chest tube.

Dr Horowitz: She had a new baby at home as well.

Dr Force: We should discuss the pathologic data on the wedge resection of the bulla.

Dr Ritter: There was a lung wedge biopsy sample $4 \times 1.5 \times 1.0$ cm, and on sectioning it showed a bleb. The tumor had a mixed or mucinous background and was composed of cells that have abundant eosinocytic cytoplasm, with nuclei large and condensed (Figure 3). In a higher view we could see prominent nuclei (Figure 4). Most of these cells were intermediate trophoblastic cells, and this could be confirmed with immunohistochemical testing. The tumor was seen invading blood vessels (Figure 5). Immunostains were performed for human chorionic gonadotropin (HCG), which was weakly positive (Figure 6), and placental alkaline phosphatase, which was strongly positive (Figure 7). On the basis of the cytohistologic features of the cells and the immunostaining results, we believe that this represents a metastatic placental site trophoblastic tumor (PSTT).

Dr Meyers: I think it's worth mentioning that at the initial operation we were operating on a persistent pneumothorax. When you resect a bullous lesion or a bleb what you like to do is have your staple line right in the adjacent normal tissue. The CT scan showed that there were several pulmonary artery branches going to the lower lobe that shared the lateral wall of this bleb. If I had to predict where the staple line ended up, it would be just right along the inner face between the abnormal tissue and the normal lung. We didn't take a rim of normal lung as you would do if you knew you were operating on a malignancy. When the pathologists get the specimen, they sacrifice a few millimeters of tissue. They had no idea that they were looking for any type of malignancy. It was very uncertain as to what the margins were, how close the margins were, or whether they were positive.

Dr Patterson: Could I ask the pathologist to expand on some remarks about the immunohistochemical testing?

Dr Ritter: The differential diagnosis would include various types of trophoblastic tumors. Choriocarcinoma, for example, consists of cells that stain strongly positive for HCG but weaker for placental alkaline phosphatase. In this patient's lesion, the opposite was seen. These tumors are composed of a mixture of syncytial and cytotrophoblast

Figure 3. Tumor shows mixed or mucinous background, composed of cells with abundant eosinophilic cytoplasm, and nuclei that are large and condensed.

Figure 4. Higher-power view than in Figure 4 reveals prominent nuclei.

Figure 5. Evidence of vascular invasion by the tumor.

cells. As stated, the cells of this tumor look like this intermediate form of trophoblast, which is different. Choriocarcinoma also tends to have more hemorrhage, and you will

Figure 6. Weakly positive immunostaining for HCG.

Figure 7. Strongly positive immunostaining for placental alkaline phosphatase.

Figure 8. Fluorodeoxyglucose positron emission tomographic (FDG PET) scan taken January 28, 2002. Nothing is seen in region of right lower lobe lesion. Some uptake in uterus is as expected in postpartum patient.

see hemorrhagic spaces rimmed by trophoblastic cells. These tumors appear to be invading the tissue, and they also tend to invade blood vessels. Once you get HCG positivity

and you've excluded some rare lung cancer that is going to have HCG-positive cells, you are dealing with some sort of trophoblastic tumor.

Dr Cooper: At the margin of the wedge resection, did the lung look normal?

Dr Meyers: Yes. There was no obvious evidence of malignancy.

Dr Force: PSTTs are included in a spectrum of tumors, with molar pregnancy on one end and choriocarcinoma on the other. Women may even embolize normal trophoblastic cells to the lung during pregnancy. The treatment of trophoblastic tumors centers on chemotherapy, but PSTTs are fairly resistant to chemotherapy. After discussing the findings with the gynecologic oncologists, it was decided we should attempt to rule out any possible site of metastatic disease, given that these tumors tend to metastasize to brain, bone, lung, kidney. We concluded that in the absence of other metastatic disease the patient should undergo resection of any possible site in the pelvis as well as the right lower lobe, considering the possibilities of a positive true margin. Before surgery, the patient had a positron emission tomographic scan performed.

Dr Dehdashti: A fluorodeoxyglucose positron emission tomographic scan was taken January 28, 2002 (Figure 8) and was essentially negative. We didn't see anything in the region of the right lower lobe lesion. There was some uptake in the uterus, as would be expected in this postpartum patient.

Dr Force: Subsequently, the patient underwent a right thoracotomy and right lower lobectomy, as well as a hysterectomy and bilateral salpingo-oophorectomy. The lobectomy was a very difficult dissection. The lower lobe was completely fused to the diaphragm and the chest wall and was particularly adherent medially adjacent to the phrenic nerve. This was most likely due to the pleurodesis performed at the first operation.

Dr Meyers: If you look back at her CT scan, she has these calcified Missouri-style granulomatous lymph nodes in her hilum. I think that also made the lobectomy dissection difficult.

Dr Govindan: What did the CT of the abdomen and pelvis show?

Dr Force: The CT of the chest, abdomen, and pelvis was significant only for a breast mass that did not light up on positron emission tomographic scan.

Dr Govindan: Was the breast mass investigated further?

Dr Horowitz: The ultrasonographic appearance of the breast mass was normal breast tissue. We decided that aspiration was not required. This is a very interesting case from our standpoint for two reasons. One, this PSTT is a very rare tumor. There are only about 100 cases reported in the literature, so the fact that this one occurred during the patient's pregnancy and not postpartum sort of makes it a little more interesting. The other reason is that a spontane-

ous pneumothorax in a pregnant patient is also a pretty rare event. Usually spontaneous pneumothoraces in pregnancy occur in women who have previous lung disease or have had a previous spontaneous pneumothorax. The PSTT is a rare variant of gestational trophoblastic disease or gestational trophoblastic neoplasm, which is a continuum that includes invasive moles or persistent molar pregnancies to choriocarcinoma and then this PSTT. Choriocarcinomas and invasive moles have very elevated β -HCG levels, and that is really how we follow up these patients. This is contrasted by the PSTT, which is more of a malignancy of the intermediate cytotrophoblasts that were shown by the pathologists. Unlike the other two gestational trophoblastic neoplasms, the PSTT really doesn't have an elevated HCG level; you see more elevations in the human placental lactogen (HPL), for which this tumor stained very positively. In this patient the initial postpartum HCG level was 22 IU/mL; for the laboratory here, normal or negative would be less than 5 IU/mL. The level of 22 IU/mL is slightly elevated and consistent with her postpartum state, but not as elevated as we would have expected if this would have been a choriocarcinoma or an invasive molar pregnancy.

Dr Cooper: Is that a routine postpartum blood test?

Dr Horowitz: I usually don't check these levels at all. In fact it was only checked after her pathology came back. We had also sent out a laboratory test for HPL, and interestingly that result was negative or in the normal range, so although her tumor stained positively, her serum level of HPL was normal. I don't really know what to make of that, because we have the diagnosis from the pathologic examination of the lung resection. As was already mentioned, the treatment of choice for the PSTT is resection by hysterectomy. Invasive moles and choriocarcinomas, on the other hand, are exquisitely sensitive to chemotherapy, in particular methotrexate or dactinomycin. PSTTs are very chemotherapy insensitive.

Dr Patterson: You mentioned that some of these neoplasms are followed by tracking markers. Is this one of those tumors?

Dr Horowitz: We could have followed this by tracking HPL, if it were a marker for her. Unfortunately, HPL was not elevated in her case. Another marker for PSTTs is inhibin. I don't understand why that is a marker for this particular tumor, but it has been shown to be elevated in some cases. Unfortunately, in her case inhibin also wasn't elevated. She really had no tumor markers with which to follow up.

Dr Gierada: Is there any chance that the lesion could have been present from a previous pregnancy?

Dr Horowitz: That's a very good question. I think it is possible. Perhaps we could review the pathologic examination.

Dr Ritter: In a section of the uterus there were thick-walled vessels indicating the previous implantation site.

None of the specimens that we received showed tumor. We did not find any evidence of the tumor in the uterus. This raises the question about a previous pregnancy. Gestational trophoblastic disease of all kinds will undergo spontaneous involution in the uterus. We often do not find tumor in the uterus, even in patients with metastatic choriocarcinoma. In the section of the lung we could see several hyalinized nodules consistent with typical histoplasmosis. We found nothing residual in the lung itself.

Dr Patterson: Did you section along the staple line? If there was going to be residual tumor, that's probably where you would have found it.

Dr Ritter: Yes we did. There was no evidence of any residual tumor.

Dr Cooper: What's the usual presentation for patients with these tumors?

Dr Horowitz: Most have abnormal bleeding or persistent bleeding postpartum. Most are seen after a normal pregnancy, as in this case, although you may see symptoms after a spontaneous miscarriage or after molar pregnancies as well. Again, most are seen anywhere between 2 weeks up to 2 years after the antecedent pregnancy, although there are cases in the literature in which PSTT was found as long as 8 to 10 years after pregnancy.

Dr Cooper: And when the diagnosis is made, what is the treatment?

Dr Horowitz: In most cases the disease is contained within the uterus. After diagnosis, you do a metastatic workup with a chest, abdominal, and usually head CT. If you don't see any metastatic disease, then a hysterectomy would be your treatment of choice and should be adequate for PSTT. Although PSTT is not a chemotherapy-sensitive tumor when it is metastatic, as in this case, adjuvant chemotherapy would be recommended. Multiagent chemotherapy is used, with etoposide, methotrexate, dactinomycin, and cyclophosphamide (EMICO). EMICO is standard chemotherapy both for PSTTs that are metastatic and for other gestational trophoblastic neoplasms that are widely metastatic and are in what we consider a high-risk group. High-risk patients include those who have undergone previous chemotherapy, have very high HCG levels, or are seen soon after pregnancy.

Dr Patterson: The presumption is that she had a tumor in her placenta that metastasized to the lung. There is no evidence of tumor in her uterus. There isn't any evidence of tumor in the resected lung, so why give her all that chemotherapy?

Dr Horowitz: There is not a lot of experience in the literature to guide treatment for patients with metastatic PSTTs. The largest series is about 15 patients from the New England Trophoblastic Disease Center, and the patients with metastatic disease who were treated with the combi-

nation of hysterectomy and EMICO did the best. In general, women who have metastatic PSTT do very poorly. With a 5-year survival of about 40%, we consider it important to be aggressive, both surgically and with chemotherapy.

Dr Cooper: If in fact aggressive chemotherapy in itself doesn't give a favorable prognosis, maybe that's a good argument not to do anything, because you know you are going to knock the hell out of her with that kind of dose and you don't know if it's needed.

If you had a blood sample from before the time of the pulmonary resection, the initial blebectomy, might you detect the antigen? And if you did and didn't find it now, would you then not treat her and just follow her antigen levels?

Dr Horowitz: We presented this case at our conference earlier this week, and the consensus was that even though the uterus and the lung didn't show persistent residual tumor, all the participants would be aggressive with chemotherapy. She is young and will probably tolerate the chemotherapy regimen therapy well; without it, although we have limited experience, patients do not tend to do very well.

Dr Force: Metastatic cancers to the lung presenting as spontaneous pneumothoraces are rarely seen. Although cases of spontaneous pneumothorax have been reported with metastatic choriocarcinoma, there are no reports in the literature involving metastatic PSTT.^{1,2} These tumors belong to a group of malignancies termed *gestational trophoblastic neoplasms*, a spectrum of tumors that also includes hydatidiform moles, invasive moles, and choriocarcinomas. These malignancies most commonly occur after molar pregnancies but may arise after any gestational event. Histologically, PSTTs are primarily composed of intermediate trophoblasts with extensive vascularization. They produce HPL and, to a lesser degree, HCG. Most of these tumors present with vaginal bleeding, and rarely patients are seen with metastatic disease. Approximately 4% of gestational trophoblastic neoplasms are found to be metastatic at the time of diagnosis; of these, 80% have pulmonary involvement. Staging classifications for PSTTs do not appear to correlate with other gestational trophoblastic neoplasms, but the presence of metastatic disease appears to be the most important prognostic indicator.³ PSTT is a rare tumor, and there have not been any large studies evaluating pulmonary metastasectomy. Two reports in this Journal have recommended resection of isolated pulmonary metastases in choriocarcinoma; however, this tumor behaves differently from PSTT.^{4,5} Unlike choriocarcinoma, PSTT is not usually sensitive to chemotherapy, and despite a few reports showing a significant response to chemotherapy, treatment of PSTT is centered around complete resection if possible.⁶⁻⁸

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