March 2018 Pulmonary Case of the Month

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History of Present Illness

The patient was a 62-year-old woman who complained of a sudden severe increase in a three-month history of mild left upper extremity pain.

PMH, SH and FH

The patient had no significant past medical history. She is a non-smoker. Family history is non-contributory.

Physical Examination

- Vital Signs: Pulse 102 beats/min, blood pressure 140/84 mm Hg, respirations 16 breaths/min, Temperature 37.4º C, SpO2 94% on room air.
- Lungs: Clear.
- Heart: Regular rhythm.
- Abdomen: without organomegaly, masses or tendernesses.
- Extremities: Both upper extremities were unremarkable. The left shoulder had a full range of motion. Pulses were intact bilaterally and equal.
- Neurologic: Upper extremity strength was good and equal. Light touch and pin prick were intact. Deep tendon reflexes were well preserved.

Which of the following are indicated in ***management at this time***?

1. Reassurance that the pain will improve
2. Shoulder x-ray
3. Treatment with oxycodone
4. 1 and 3
5. All of the above

Correct!
2. Shoulder x-ray

Although the cause of the pain is not clear from her physical examination, a shoulder x-ray is probably indicated because of her three-month history and severity of the pain. Oxycodone might be indicated to relieve the pain but only after less addicting medications have failed. Reassurance without a diagnosis is not likely to be well-received by the patient especially after 3 months of pain.

The shoulder x-ray is unremarkable. However, the radiologist notes that there is a possibility of bone loss in several thoracic vertebrae. This led to an MRI of the spine (Figure 1).

Figure 1. MRI of the cervical and thoracic spine.

Which of the following are ***indicated***?

1. Chest x-ray
2. Mammography
3. Neurosurgical consultation
4. 1 and 3
5. All of the above

Correct!
5. All of the above

The MRI of the cervical and thoracic spine shows near complete destruction and collapse of T3 (arrow) with boney erosions of T2-7 (Figure 2).

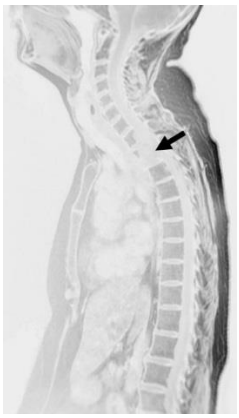

Figure 2. MRI of spine showing the near complete destruction and collapse of T3 (arrow).

The lesions are lytic and the most common cause of a lytic lesion in this patient would be metastatic lung or breast cancer. The neurosurgeon recommends spine stabilization surgery. A mammogram is negative but a chest radiograph showed a question of a left infrahilar mass. A CT scan is performed and a representative image from the CT scan is shown in Figure 3.

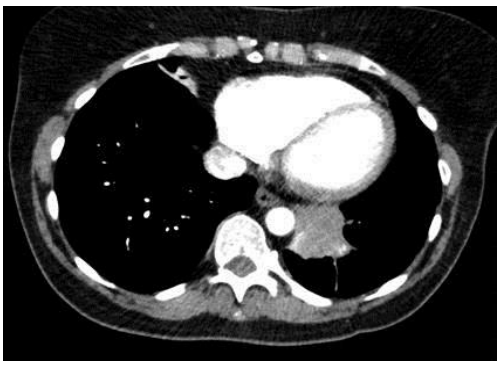

Figure 3. Representative image in soft tissue windows.

Which of the following are ***indicated at this time***?

1. Biopsy of the lesion.
2. Hold spine stabilization surgery until completion of the work-up.
3. CT scan of the brain.
4. 1 and 3
5. All of the above

Correct!
4. 1 and 3

The thoracic CT scan shows a 3.8 cm mass in the left lung (Figure 4).

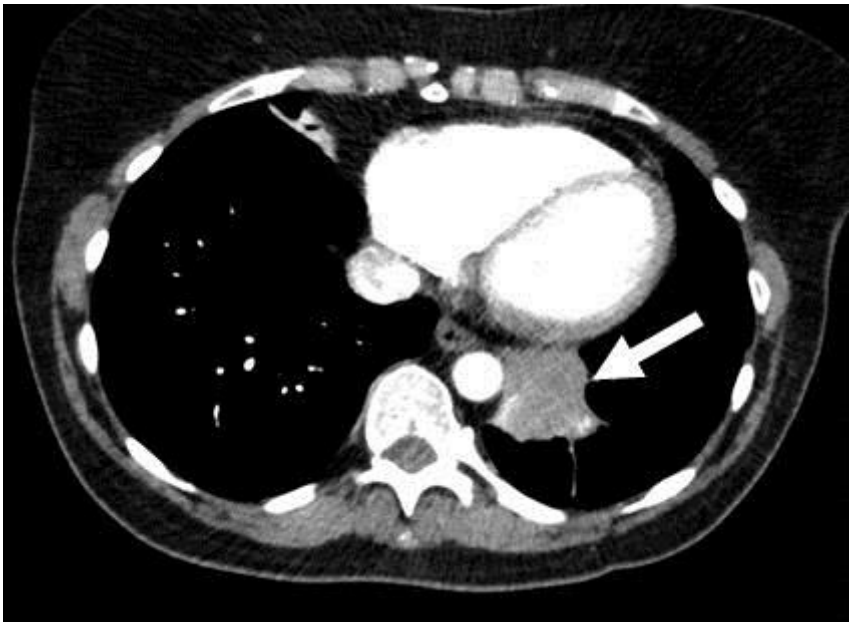

Figure 4. Representative image from thoracic CT scan in soft tissue windows showing a 3.8 cm lung mass (white arrow).

Clinically, the patient likely has lung cancer with metastases to the spine. The spine is unstable and a delay could result in the patient becoming paralyzed from the upper thoracic spine down. Since this likely is a lung cancer both a biopsy to establish the diagnosis and a CT scan of the brain, another common place for metastases, are indicated.

The patient undergoes spine stabilization surgery. Her primary tumor is biopsied and shows an adenocarcinoma with an exon 19 epidermal growth factor receptor (EGFR) mutation. ROS-1, KRAS, and anaplastic lymphoma kinase (ALK) mutations were not detected. Her CT scan of the brain reveals three lesions compatible with brain metastases.

Which of the following should be ***done at this time***?

1. Begin gemcitabine/cisplatin
2. Begin erlotinib and radiotherapy to her brain lesions
3. Begin gamma knife surgery alone for her brain metastases
4. 1 and 3
5. All of the above

Correct!
2. Begin erlotinib and radiotherapy to her brain lesions

Testing for mutations in epidermal growth factor receptor (EGFR), KRAS, and anaplastic lymphoma kinase (ALK) and tailoring therapy accordingly is widely accepted as standard practice (1). EGFR is expressed on the cell surface of a substantial percentage of non-small cell lung cancers (NSCLCs) (2). In general, EGFR mutations are more commonly observed in patients with adenocarcinomas and no prior history of smoking, as well as in women and those of Asian descent (such as our patient). Use of the EGFR-tyrosine kinase inhibitors (EGFR-TKI) such as erlotinib, gefitinib or afatinib is limited to patients with adenocarcinomas who have known EGFR mutations such as the exon 19 EGFR mutation. In these patients, erlotinib has been shown to be superior to gemcitabine/cisplatin in progression free survival (3). Erlotinib does penetrate the blood-brain barrier while traditional chemotherapy generally does not. Although brain metastases can be treated with just radiotherapy such as gamma knife surgery, it leaves the primary tumor and the boney metastases untreated. Therefore, among the selections listed erlotinib and radiotherapy is the best choice.

Erlotinib was begun and gamma knife surgery of the brain metastases were performed. Six months later the lung lesion had shrunk from 3.8 to 1.3 cm. Ten months after beginning therapy her brain MRI was normal, and the bone changes were stable by MRI. However, a new 2.6 cm nodule in the left lower lobe was detected on thoracic CT scan.

What should be ***done at this time?***

1. Biopsy the new metastases
2. Begin another EGFR-tyrosine kinase inhibitor such as gefitinib or afatinib
3. Check cocci serologies
4. 1 and 3
5. All of the above

Correct!
4. 1 and 3

If you realized that the patient is from and was being cared for in Washington state, you can be excused for not ordering cocci serologies. However, many of us practice in the Southwest US where Valley Fever is endemic. Although the new lesion is likely metastatic cancer, a general principle is to biopsy the first metastasis. This is especially important in NSCLC, where the cancer pathobiology can change and tumors can develop resistance to therapy after an initial response. This seems likely in this patient with the development of a new lesion after her good initial response. It seems unlikely that another EGFR-tyrosine kinase inhibitor similar to erlotinib would be successful after it had failed. This new lesion was biopsied and shown to be positive for the T790M mutation which was not seen in the original tumor.

What should be ***done at this time***?

1. Begin osimertinib
2. Begin gemcitabine/cisplatin
3. Begin radiation therapy to the new lesion
4. 1 and 3
5. Any of the above is acceptable

Correct!
4. 1 and 3

In this case it was not entirely clear how to proceed. The new lung lesion was treated with stereotactic body radiation, but erlotinib was continued since the patient was doing reasonably well, and at the time, no targeted therapies were available for the T790M mutation. However, only two months later the original cancer was seen to progress. At that time osimertinib, an irreversible EGFR tyrosine kinase inhibitor that is selective for T790M mutations and has activity in the central nervous system, became available. Osimertinib has been shown to be superior to platinum doublet chemotherapy as a second-line therapy for advanced NSCLC harboring exon T790M following the failure of first or second-generation EGFR-TKI (4). She was begun on osimertinib and has had only mild fatigue as a side effect of the new therapy. Six months later her thoracic scan is devoid of any evidence of parenchymal lung tumor. Her CNS remains clear, and the bone changes are stable as well.

This case illustrates that lung cancer pathobiology can change with time and tumors initially sensitive to a therapy can develop resistance. However, therapy guided by rebiopsy and genetic analysis of the tumor can yield dramatic results.

References

1. Keedy VL, Temin S, Somerfield MR, *et al.* American Society of Clinical Oncology provisional clinical opinion: epidermal growth factor receptor (EGFR) Mutation testing for patients with advanced non-small-cell lung cancer considering first-line EGFR tyrosine kinase inhibitor therapy. J Clin Oncol. 2011 May 20;29(15):2121-7. [CrossRef] [PubMed]
2. Markman M. Genetics of non-small cell lung cancer. Medscape. June 8, 2017. Available at: https://emedicine.medscape.com/article/1689988-overview#a1 (accessed 2/12/18).
3. Wu YL, Zhou C, Liam CK, *et al.* First-line erlotinib versus gemcitabine/cisplatin in patients with advanced EGFR mutation-positive non-small-cell lung cancer: analyses from the phase III, randomized, open-label, ENSURE study. Ann Oncol. 2015 Sep;26(9):1883-9. [CrossRef] [PubMed]
4. Okuma Y, Hosomi Y. Osimertinib for advanced non-small cell lung cancer harboring EGFR mutation exon 20 T790M, acquired resistant mutation for first- or second-generation EGFR-TKI. J Thorac Dis. 2017 Mar; 9(3):470-3. [CrossRef] [PubMed]