A 48-year-old woman presented for evaluation of a 1-week history of progressive dyspnea and chest pain. She had a history of Burkitt lymphoma, treated with chemoradiation therapy, at the age of 6. She was a never smoker. She was not on any prescription medications until 3 weeks before this presentation, when she was diagnosed with unprovoked bilateral pulmonary emboli and was initiated on apixaban. The computed tomography (CT) angiogram of the chest also noted new bilateral subcentimeter pulmonary nodules. She was discharged from the hospital on 3 to 4 liters of oxygen via nasal cannula.

At her outpatient follow-up visit 2 weeks later, she described a 1-week history of progressive dyspnea with exertion and associated pleuritic, left-sided chest pain. She also noted a 2-month history of fatigue and an unintentional weight loss of 5 pounds over the previous month. A chest CT was attempted. However, on the scout x-ray, the patient was noted to have a large effusion throughout her entire left hemithorax, with shift of mediastinal structures toward the right. The patient was immediately transferred to the emergency department. Initial vitals revealed a temperature of 37.1 °C, blood pressure 133/84, heart rate 90, and saturating 92% on 2 liters nasal cannula. Physical examination was notable for normal work of breathing but complete absence of breath sounds over the left lung field. Laboratory findings were revealing of white blood cell 10.6 x 10^9/L (ref 3.4 to 9.6 x 10^9/L), stable hemoglobin 12.7 g/dL (previously 12.5 g/dL, ref 11.6 to 15.0 g/dL), international normalized ratio 1.4 (ref 0.9 to 1.1), creatinine 0.9 mg/dL (ref 0.59 to 1.04 mg/dL), and N-terminal pro B-type natriuretic peptide (NT-proBNP) 122 pg/mL (ref <144 pg/mL). The patient was subsequently admitted to the hospital for further evaluation and management.

1. Which is the best next diagnostic test in this patient?
   a. Serial hemoglobin checks
   b. Blood cultures
   c. Thoracentesis with pleural fluid cultures and cytology
   d. Bronchoscopy with alveolar lavage and endobronchial ultrasound
   e. Transthoracic echocardiogram

The differential diagnosis for this patient’s initial presentation with a large unilateral pleural effusion includes hemothorax, recent pleural effusion, malignant effusion, empyema-parapneumonic effusion, and heart failure. Hemothorax must be considered, given her acuity of presentation, recent pulmonary embolism, and anticoagulated status. However, she is normotensive, without tachycardia, and her hemoglobin appears stable from previous baseline; thus, there is no indication for increased frequency of hemoglobin checks. Blood cultures would be reasonable to obtain, given the possibility of infection causing a unilateral pleural effusion, but clinical suspicion for sepsis is low, as the patient is afebrile, hemodynamically stable, and only has a mild leukocytosis. The next best therapeutic and diagnostic test would be thoracentesis. This would help to characterize the effusion as transudative or exudative, further narrowing the differential. Without evidence of an accessible lesion on imaging, a bronchoscopy would provide little diagnostic yield. A transthoracic echocardiogram could be performed to assess for evidence of heart failure or valve dysfunction, which can lead to pulmonary edema and bilateral pleural effusion.
effusion and rarely can lead to unilateral pleural effusions. However, the patient does not have signs of heart failure (lower extremity edema, elevated jugular venous pressure, gallops, etc) on physical examination, and her NT-proBNP is not elevated.

The patient’s anticoagulation was held on admission. A thoracentesis was performed, with immediate removal of 2.5 L of serosanguinous fluid. A chest tube was placed for continued drainage. Pleural fluid studies were notable for pH 7.33, total nucleated cells 572 (56% lymphocytes) with atypical cells noted, lactate dehydrogenase (LDH) 399 U/L, total protein 4.5 g/dL, and triglycerides 51 mg/dL. Gram stain was negative. Pleural fluid cultures and cytology were obtained, with results pending. Serum total protein was 7.4 g/dL (ref 6.3 to 7.9 g/dL). Of note, serum LDH levels were not obtained, but the upper limit of normal of serum LDH was 222 U/L. A repeat chest CT scan demonstrated improvement in the left pleural effusion and again noted multiple bilateral subcentimeter pulmonary nodules.

2. Which one of the following is the most likely etiology of the patient’s pleural effusion?
   a. Malignancy
   b. Empyema
   c. Chylothorax
   d. Heart failure
   e. Nephrotic syndrome

Using Light criteria, a pleural effusion is classified as exudative if 1 or more of the following criteria are met: pleural fluid protein to serum protein ratio >0.5, pleural fluid LDH to serum LDH ratio >0.6, or pleural fluid LDH > two-thirds the serum LDH upper limit of normal. Given the patient’s high pleural fluid LDH, her effusion is best characterized as exudative. In the setting of a hemorrhagic lymphocytic exudate, recent pulmonary embolism with unintentional weight loss, and multiple pulmonary nodules on imaging, the most likely etiology of the patient’s pleural effusion is malignancy. Empyema is another cause of an exudative pleural effusion. However, a negative Gram stain, pH greater than 7.2, and lack of frank pus on thoracentesis make this diagnosis less likely. A chylothorax is a rare cause of an exudative pleural effusion that results from disruption of the thoracic duct most commonly caused by trauma. However, a low triglyceride level in this patient’s pleural fluid makes this diagnosis less likely. Heart failure and nephrotic syndrome are causes of transudative pleural effusions and unlikely to be a cause of this patient’s presentation.

After the initial thoracentesis, there was minimal drainage from the patient’s chest. Pleural fluid cytology revealed a diagnosis of adenocarcinoma, with immunohistochemistry (IHC) findings consistent with primary lung origin. The patient was discharged from the hospital with close follow-up in the oncology clinic to determine next steps in management.

3. Which one of the following tests is most important to guide therapeutic management in this patient?
   a. Transbronchial biopsy of largest lung lesion
   b. Molecular testing and immunohistochemistry staining of pleural fluid
c. Positron emission tomography-computed tomography (PET-CT) scan
d. Brain magnetic resonance imaging (MRI) scan
e. Flow cytometry of peripheral blood

As a cytology-proven diagnosis of lung adenocarcinoma was already obtained from pleural fluid, obtaining a diagnosis from a primary lung lesion is not necessary. The identification of oncogenic mutations, such as epidermal growth factor receptor (EGFR) and anaplastic lymphoma kinase (ALK), and subsequent development of a rapidly growing list of approved small-molecule inhibitors (SMIs) targeting these oncogenes has vastly changed the therapeutic landscape of lung malignancies. In addition, expression levels of programmed death-ligand 1 (PD-L1) carries treatment-predictive implications and would directly affect choice of initial therapeutic agents in
cases of tumors without a targetable mutation. Thus, molecular testing for genetic mutations and IHC staining for PD-L1 is routinely performed in newly diagnosed lung malignancies and is the most important next step for this patient. Additional imaging studies, including PET-CT and brain MRI, would be important to obtain to determine baseline disease burden and subsequent response to treatment. However, in this patient with known metastatic disease, molecular testing and IHC analysis would have the highest impact on determining appropriate initial therapies. Flow cytometry would have utility in the diagnosis of leukemia and certain lymphomas. Although the patient has a remote history of Burkitt lymphoma, this was definitively treated. Remote recurrence several decades after initial treatment would be extremely unlikely.

Expression of PD-L1 was identified in 95% of tumor cells from the pleural fluid. There was, unfortunately, not enough pleural fluid for assessment of genetic mutations. Evaluation of circulating tumor DNA with next-generation sequencing did not identify any genomic alterations. A PET-CT and brain MRI were also obtained, which showed no evidence of extrathoracic metastasis.

4. Which one of the following is the best treatment option for this patient?
   a. Alectinib (ALK inhibitor)
   b. Osimertinib (EGFR inhibitor)
   c. Pembrolizumab monotherapy
   d. Carboplatin + pemetrexed + pembrolizumab
   e. Carboplatin + paclitaxel + pembrolizumab

   Over the last several years, the discovery of targetable genetic driver mutations has greatly altered the way advanced non—small-cell lung cancer (NSCLC) is treated. Alectinib is a SMI of ALK used to treat tumors with ALK mutations. Osimertinib is a SMI of EGFR used to treat tumors with EGFR mutations. Neither would be an appropriate treatment for our patient without an identified genetic mutation. Pembrolizumab is first-line treatment for NSCLC with PD-L1 expression >50% and without evidence of high tumor burden or rapidly progressive disease. In this patient’s case, her presentation with a large pleural effusion demonstrates high likelihood of rapidly progressive disease, so pembrolizumab monotherapy would not be appropriate. Carboplatin and pemetrexed plus pembrolizumab is used in cases of tumors with PD-L1 expression <50% or in cases of tumors with PD-L1 expression >50% and evidence of high tumor burden or rapidly progressive disease, as in our patient. Carboplatin and paclitaxel with pembrolizumab is the preferred regimen in advanced squamous cell carcinoma of the lung with PD-L1 expression <50%.

   The patient’s tumor PD-L1 expression was 95%, so pembrolizumab monotherapy was considered. However, as mentioned, the patient presented with a significant pleural effusion over the span of 2 to 3 weeks, indicating high likelihood of rapidly progressive disease. In addition, in never smokers—as with our patient—immunotherapy alone has been shown to be inferior compared with combination immunotherapy with chemotherapy. Therefore, it was determined to treat with palliative intent with carboplatin, pemetrexed, and pembrolizumab. After 2 cycles of therapy, the patient was noted to have persistent sinus tachycardia, with heart rates of 110 to 120 seconds. Laboratory evaluation revealed newly decreased thyroid-stimulating hormone (TSH) 0.1 mIU/L (ref 0.3 to 4.2 mIU/L), free thyroxine (T4) 1.7 ng/dL (ref 0.9 to 1.7 ng/dL), and an undetectable thyrotropin receptor antibody (TRAb).

5. What is the most likely cause of the patient’s abnormal thyroid function cascade?
   a. Graves disease
   b. Toxic thyroid adenoma
   c. Radiation thyroiditis
   d. Paraneoplastic hyperthyroidism
   e. Immunotherapy-induced thyroiditis
Graves disease is the most prevalent cause of hyperthyroidism in the general population. However, this patient’s TRAb levels were low, making a diagnosis of Graves disease unlikely. Toxic thyroid adenomas are the second most prevalent cause of hyperthyroidism in the general population. Although a thyroid ultrasound would be reasonable to evaluate for presence of thyroid nodules, the following alternative diagnosis explained here was more likely. Thyroiditis, secondary to radiation therapy, is a well-described entity; however, our patient received radiation therapy more than 4 decades earlier for Burkitt lymphoma, and it would be extremely unlikely to develop this complication far removed from previous exposure. Paraneoplastic hyperthyroidism is a rare phenomenon that has been described in case reports and is primarily associated with germ-cell tumors, not lung adenocarcinoma. Furthermore, paraneoplastic syndromes in lung malignancies are more commonly associated with squamous NSCLC and small-cell lung cancer. Among the various documented immune-related adverse events (irAEs) associated with pembrolizumab, thyroid abnormalities are some of the most common. Given the temporal association of onset of decreased TSH with initiation of immunotherapy, this is the most likely etiology of the patient’s thyroiditis.

The patient was referred to the endocrinology clinic, where a presumptive diagnosis of immunotherapy-induced hyperthyroidism was made. The patient was initiated on propranolol 20 mg 3 times daily, with normalization of her heart rates. A chest CT scan was obtained after 3 cycles of combination chemotherapy with pembrolizumab and showed overall stable disease with significantly improved left-sided pleural effusion. The patient continues on carboplatin, pemetrexed, and pembrolizumab, with plans for repeat CT scan after 6 cycles of therapy.

**DISCUSSION**

Unilateral pleural effusions can develop as a result of many different cardiac, pulmonary, and systemic disease processes. Identification of an underlying cause in cases without clear etiology from clinical history can be facilitated by pleural fluid sampling via thoracentesis. Routine pleural fluid studies performed include total protein, LDH, pH, cell count and differential, and glucose. Other tests including Gram stain, cultures, triglycerides, amylase, and cytology can be obtained to identify a specific diagnosis but are not routinely performed unless clinical suspicion is high. For example, in our case, there was elevated clinical suspicion for malignancy, given the patient’s fatigue, unintentional weight loss, recent diagnosis of unprovoked pulmonary embolism, and remote history of previous radiation therapy. Therefore, cytology was obtained with her initial thoracentesis. Pleural fluid cytology has an overall sensitivity of only 60% in detecting malignancy; thus, many guidelines recommend repeat testing, which increases sensitivity to approximately 75%.1 If a diagnosis of NSCLC is made on pleural-fluid cytology, this automatically upstages the malignancy to stage IV and indicates incurable disease.2

A number of factors have been shown to increase the risk of developing lung cancer. The most significant of these is tobacco use, with other risk factors including environmental exposures (ie, heavy metals), previous radiation therapy, and underlying lung disease.3 It is interesting that our patient was a never smoker and lacked other significant modifiable risk factors for developing lung malignancy. However, she likely had multiple unmodifiable risk factors stemming from her history of childhood Burkitt lymphoma that can be categorized into 3 groups: genetic susceptibility, previous radiation therapy, and previous chemotherapy. Given our patient’s previous diagnosis of Burkitt lymphoma, the patient may have an elevated risk of malignancy at baseline compared with the general population. In addition, radiation therapy is a well-known risk factor for developing secondary malignancies, particularly in women who received radiation therapy at a young age.4 Many chemotherapy regimens, including ones commonly used in childhood lymphoma, are most associated with
increased risk for myelodyplastic syndrome and acute myeloid leukemia. However, chemotherapy has also been shown to increase the risk of various solid malignancies including sarcoma, lung, thyroid, gastrointestinal, and bladder cancers. 

Given the increased survival and significant risk of secondary malignancy in patients with childhood cancer who underwent chemoradiation therapy, investigation of more stringent screening in this population has been considered. This is best demonstrated by national guidelines recommending initiation of screening for breast cancer in patients who have undergone thoracic radiation therapy at age 25 to 30 or 8 years after completion of treatment. 

Screening recommendations for other secondary malignancies, including lung cancer, have yet to be defined in this population.

The management of advanced NSCLC has rapidly evolved over the past several years, owing to the advent of targeted therapies against oncogenic drivers and the success of immune checkpoint inhibitors (CPIs) such as pembrolizumab. Previously, standard of care for advanced NSCLC was cytotoxic platinum-based chemotherapy, which demonstrated a median survival of approximately 12 months. 

An improved understanding of aberrant molecular pathways that drive tumor-cell survival and proliferation has led to the development of therapies that specifically target oncogenic drivers such as osimertinib (EGFR inhibitor) and alectinib (ALK inhibitor). However, a targetable oncogenic driver is not identified in approximately 40% to 50% of advanced NSCLC. 

In these cases, the standard of care is now centered upon the programmed cell death protein 1 (PD-1) inhibitor, pembrolizumab. The KEYNOTE clinical trials have shown significant efficacy of pembrolizumab in patients with advanced NSCLC expressing PD-L1, with the greatest survival benefit demonstrated in PD-L1 expression >50%. Thus, current first-line therapy in patients with advanced NSCLC with PD-L1 expression >50% and no evidence of rapidly progressive disease is pembrolizumab monotherapy. Otherwise, guidelines recommend treating advanced NSCLC with combination platinum-based chemotherapy and pembrolizumab.

As the number of indications for CPI use increase, the number of reported immu

related irAEs has also increased. Our patient developed a decreased TSH level with high-normal free T4 levels after starting pembrolizumab, suggestive of CPI-induced hyperthyroidism. A recent meta-analysis found an incidence rate for hyperthyroidism of approximately 0.6%, indicating that this is a relatively rare irAE. Hypothyroidism typically follows hyperthyroidism as an irAE caused by immune-related destruction of the thyroid gland. Management of most irAEs is based on severity of the event. Temporary holding of the CPI and monitoring are used for low-grade events, whereas glucocorticoids and cessation of the CPI are used for high-grade events. However, for endocrine-related side effects, including thyroid dysfunction, immunotherapy does not need to be held. If CPI-induced hyperthyroidism becomes clinically significant, management is similar to primary hyperthyroidism and can include beta-blockers for control of symptoms and antithyroid drugs such as methimazole.

In conclusion, we present a patient with a unilateral pleural effusion, leading to a new diagnosis of advanced lung adenocarcinoma. This presentation was in the setting of receiving previous chemoradiation therapy for a childhood diagnosis of Burkitt lymphoma, likely elevating her risk of developing a secondary malignancy. The patient is now receiving appropriate therapy with combination immunotherapy and chemotherapy, which was complicated by the development of CPI-induced hyperthyroidism.

Potential Competing Interests: The authors report no competing interests.

Correspondence: Address to Adam P. Sawatsky, MD, MS, Division of General Internal Medicine, Mayo Clinic, 200 First Street SW, Rochester, MN 55905 (sawatsky.adam@mayo.edu; Twitter: @APSawatskyMD).

REFERENCES


CORRECT ANSWERS: 1. c. 2. a. 3. b. 4. d. 5. e