CHEST

An Unusual Cause of Pulmonary Nodules After Stem Cell Transplantation

Anna K. Brady, MD; Jonathan R. Fromm, MD, PhD; and Siddhartha G. Kapnadak, MD

A man in his 20s with a history of classical Hodgkin's lymphoma was admitted with fever. His original lymphoma diagnosis was made 3 years prior, when he had presented with lymphadenopathy and a mediastinal mass. He had relapsed disease despite chemotherapy and radiation. As a result, he underwent autologous peripheral blood stem cell transplant (SCT) 6 months prior to current presentation and subsequently allogeneic SCT 2 months prior for added graft vs tumor effect.

CHEST 2017; 151(2):e29-e34

Case Report

One month prior to presentation, surveillance CT scan showed near-resolution of the mediastinal mass and lymph nodes, but detected numerous new 2- to 8-mm lower-lobe pulmonary nodules. The patient was treated empirically with multiple antimicrobials and clinically improved; therefore, bronchoscopy was deferred because of anticipated low yield. The patient was ultimately discharged on voriconazole for suspected pulmonary aspergillosis, along with routine prophylaxis with trimethoprim/sulfamethoxazole and acyclovir. Over the 2 weeks leading up to presentation, he developed fevers and night sweats, without cough, chest pain, dyspnea, or hemoptysis. On admission, his temperature was 37.6°C, and vitals were otherwise normal, including saturation of peripheral oxygen of 96% on ambient air. He appeared thin, with alopecia. He was breathing comfortably, with clear lungs on auscultation. He lacked palpable lymphadenopathy. Abdominal and testicular examinations were normal. His WBC count was normal.

Chest radiograph (Fig 1) showed basilar nodules that had not been apparent previously. Chest CT scan (Fig 2) revealed multiple nodules up to 10 mm, increased in size and number from the previous study. These had smooth borders and were concentrated in the bases and periphery in a vascular distribution, as suggested by the presence of feeding vessels.

Sputum and blood cultures for bacteria and fungi were negative, as were noninvasive fungal markers (urine histoplasma antigen, serum galactomannan, and cryptococcal antigen). Especially given the small and peripheral nature of the nodules, he underwent CT-guided transthoracic core needle biopsy.

Specimens showed a pleomorphic cellular infiltrate comprised of lymphocytes, eosinophils, histiocytes, and large cells with variably prominent nucleoli, moderate amounts of eosinophilic cytoplasm, and occasional atypical cells with bizarre-shaped nuclei embedded in a fibrous stroma (Fig 3). Scattered large atypical mono- and multinuclear cells with prominent nucleoli and abundant cytoplasm were present; these had strong staining for CD30, but lacked CD20 staining. CD15 was focally expressed in the cytoplasm of neoplastic cells. Flow cytometry (Fig 4) revealed an abnormal population comprised of cells with an immunophenotype shown in Table 1.[1] No immunophenotypic evidence of involvement by B- or T-cell non-Hodgkin's lymphoma was present.

AFFILIATIONS: From the Division of Pulmonary and Critical Care Medicine (Drs Brady and Kapnadak) and Department of Laboratory Medicine (Dr Fromm), University of Washington, Seattle, WA.

CORRESPONDENCE TO: Siddhartha G. Kapnadak, MD, Division of Pulmonary and Critical Care, University of Washington Medical Center, 1959 NE Pacific, Campus Box 356522, Seattle, WA 98195-6522; e-mail: skap@uw.edu

DOI: http://dx.doi.org/10.1016/j.chest.2016.11.022

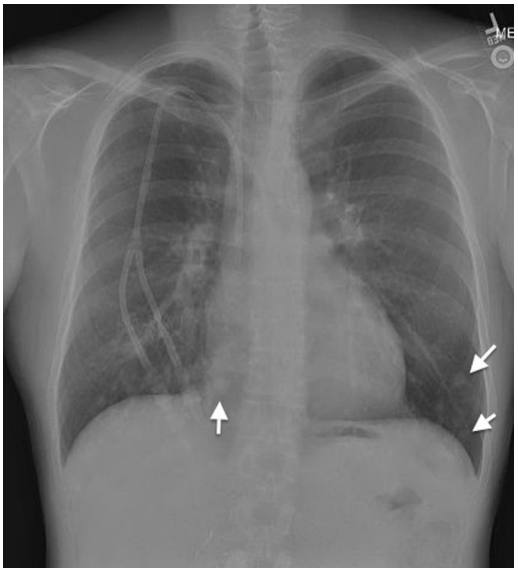

Figure 1 – *Chest radiograph at the time of admission revealed basilar nodules (arrows) which had not been visible on a radiograph obtained 6 weeks prior.*

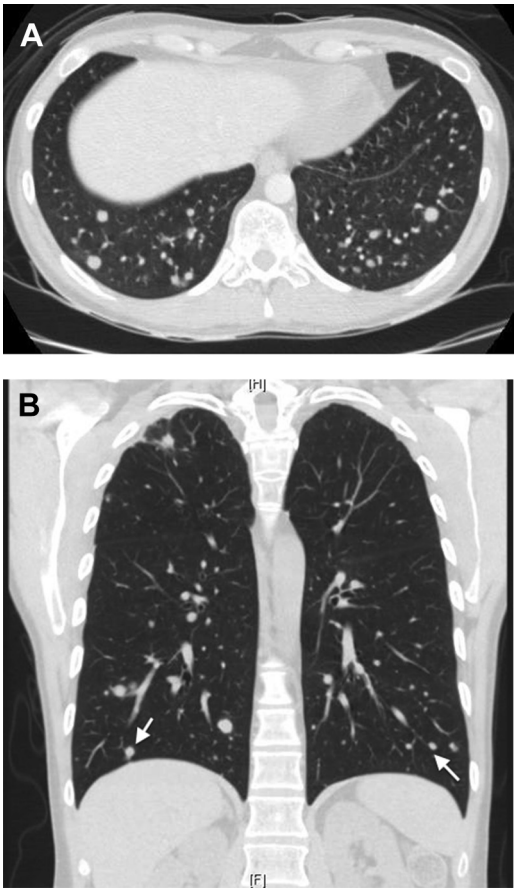

Figure 2 – *A, CT scan of the chest revealed innumerable solid nodules concentrated at the periphery and the bases in a perivascular distribution. B, In the coronal view, feeding vessels (arrows) can clearly be seen at both the right and left lung bases.*

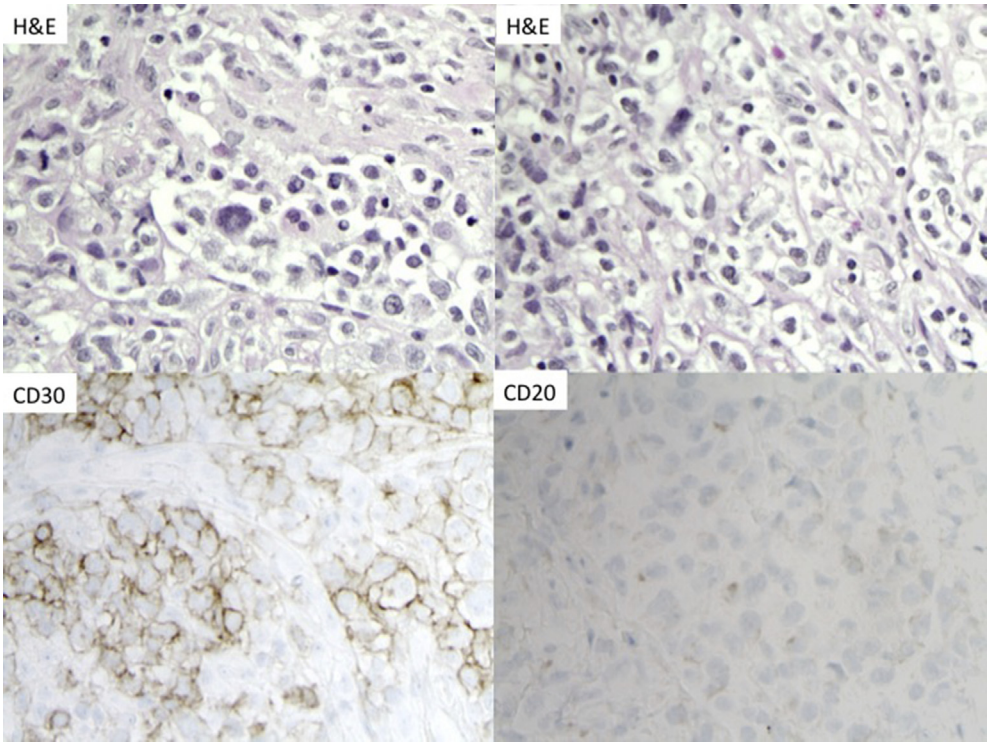

Figure 3 – *H&E staining of the tissue sections (original magnification 320X), with a pleomorphic cellular infiltrate comprised of lymphocytes, eosinophils, histiocytes, and medium to large cells with variably prominent nucleoli, moderate amounts of eosinophilic cytoplasm, and occasional atypical large cells with bizarre-shaped nuclei embedded in a fibrous stroma. The neoplastic cells had strong staining for CD30 but no staining for CD20. H&E = hematoxylin and eosin.*

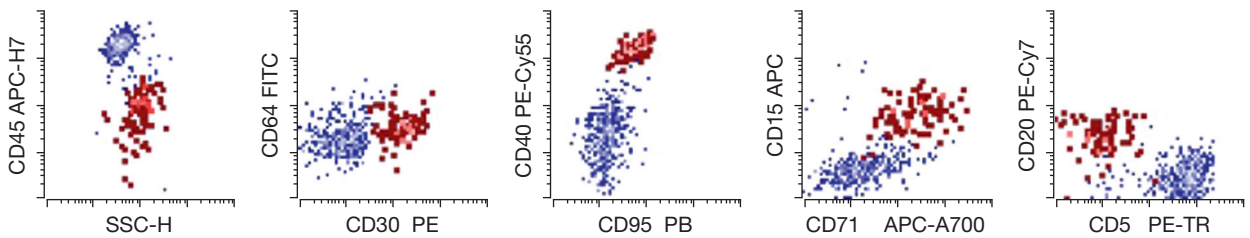

Figure 4 – *Flow cytometry studies of the right lung mass biopsy revealed an abnormal population (in red; all other events in blue) comprised of large cells (as measured by increased forward and side light scatter) with expression of CD15 (low to intermediate), CD30 (intermediate), CD40 (bright), CD45 (low to absent), CD71 (variable), and CD95 (low to intermediate), without expression of CD5, CD20, or CD64. This population represents approximately 5.6% of all WBCs.*

TABLE 1] Immunophenotype of Neoplastic Cells Determined by Flow Cytometry

Antigen	Cell Type Identified	Result in Biopsy
CD5	T cells	Negative
CD15	Granulocytes/Hodgkin's cells	Positive
CD20	B cells	Negative
CD30	Activated lymphocytes/ Hodgkin's cells	Positive
CD40	B cells/macrophage/ Hodgkin's cells	Positive
CD45	Hematopoietic cells	Low positive
CD64	Macrophage/monocytes	Negative
CD71	Activated cells	Positive
CD95	Lineage nonspecific	Positive

What is the diagnosis?

Diagnosis: Relapsed classical Hodgkin's lymphoma.

Discussion

Clinical Discussion

Pulmonary nodules are commonly found during and after stem cell transplant (SCT), with the differential diagnosis divided into infectious and noninfectious etiologies. In the initial post-SCT period, prior to engraftment, infectious etiologies predominate and include septic emboli from bacteria or *Candida* species. The patient had engrafted, and although he had an indwelling central line, his blood cultures were negative.

In the early postengraftment period, infection is still most likely, and opportunistic pathogens become more common causes of nodular pneumonia. These can include atypical bacterial organisms, angioinvasive molds, and endemic mycoses.[2] Patients, particularly those receiving myeloablative conditioning regimens and those with chronic graft vs host disease, remain at risk for infectious etiologies in the late postengraftment period. Other opportunistic pathogens becoming important causes of nodular pneumonias in this period include *Nocardia* species, *Mycobacterium tuberculosis*, and nontuberculous mycobacteria.

The patient presented in the early postengraftement period, at which time angioinvasive molds such as aspergillus often account for infectious pulmonary nodules,[2] usually in the setting of prolonged neutropenia. However, the patient's neutropenia had resolved, and he had developed radiographic progression despite treatment with voriconazole at therapeutic levels. Mucormycosis, another angioinvasive mold, would not respond to voriconazole, but would again be unusual without neutropenia. Among endemic fungi, it is important to consider exposure history; the patient resided in the Pacific Northwest where *Cryptococcus gattii* is endemic, but lacked other relevant exposures. The serum cryptococcal antigen was negative, and although its test characteristics do not completely rule out pulmonary *Cryptococcus* in HIV-negative patients,[3] it did make infection less likely, as did the other noninvasive fungal studies for their respective infections.

Other fungal organisms, such as *Scedosporium* and *Fusarium*, were considered, but the indolent progression of his nodules did not fit with untreated disseminated fungal infection. Nocardia infection was considered less likely for the same reason, in addition to his regimen with prophylactic trimethoprim/sulfamethoxazole.

In the postengraftment period, noninfectious etiologies of lung nodules also become possible. Posttransplant lymphoproliferative disorder after allogeneic SCT occurs early, usually in the first year, and in association with Epstein-Barr virus (EBV) infection; the patient's Hodgkin's lymphoma had been EBV-negative, and whole blood polymerase chain reaction from this presentation was also undetectable, making EBV-associated posttransplant lymphoproliferative disorder unlikely. Pulmonary cytolytic thrombi can occur after SCT: associated with pain and fever, it is diagnosed by biopsy showing basophilic thromboemboli and hemorrhage.[4] Chemotherapeutic agents are associated with several patterns of pulmonary toxicity, but the patient's previous regimen was not associated with nodular pulmonary disease.

Finally, both solid tumors and lymphoproliferative disorders cause pulmonary nodules. The patient's age put him at risk for a germ cell tumor, but his testicular examination was normal.

Radiologic Discussion

The appearance and distribution of pulmonary nodules can help narrow the differential diagnosis. Among infectious causes, typical bacterial pathogens can cause solitary nodular consolidations; septic emboli cause peripheral nodules (often with cavitation). Although invasive pulmonary aspergillosis commonly causes nodular pneumonia, those nodules are often surrounded by ground glass (halo sign) because of angioinvasion and parenchymal hemorrhage; in this case, the nodules had smooth borders without ground glass components, making aspergillus less likely. The radiographic appearance of the nodules, taken together with clinical signs, including the indolent course, absence of cough and dyspnea, progression despite antimicrobial regimen, and absence of neutropenia all supported a noninfectious etiology. Among malignant causes of pulmonary nodules, different radiographic patterns are possible. Primary lung cancer does not usually present as multiple, small pulmonary nodules; however, intrapulmonary metastases can. Renal cell carcinoma and medullary thyroid cancer can cause multiple, small nodules; however, the latter often have a micronodular, miliary pattern.

Among lymphoproliferative disorders involving the pulmonary parenchyma, mucosal-associated lymphoid

tissue lymphoma presents as a solitary consolidation, whereas diffuse large B-cell lymphoma can cause multiple nodules. Lymphomatoid granulomatosis can cause large or small nodules.

Hodgkin's lymphoma commonly involves the thorax, but not the lung parenchyma: studies from the early era of CT scans showed that roughly 74% of patients with Hodgkin's lymphoma had mediastinal adenopathy on CT scan, whereas only 8% to 18% had lung involvement.[5,6] Non-Hodgkin's lymphomas more commonly demonstrate parenchymal involvement.[6]

Pathologic Discussion

Determining the highest yield diagnostic approach for a pulmonary nodule can be challenging, but considering the pretest probability of the diagnoses in question can help choose the best technique. For instance, bronchoscopy with bronchoalveolar lavage has reasonably good yield for pulmonary infections in recipients of SCT, particularly when performed early.[7,8] However, given the clinical and radiographic presentation, infection was considered less likely in this case; therefore bronchoalveolar lavage alone is unlikely to provide a diagnosis. In terms of biopsy techniques, the yield of bronchoscopy with transbronchial biopsy for malignancy varies depending on the location and size of the nodule, with small (< 2 cm) peripheral nodules yielding diagnoses as little as 14% of the time, but larger, more central nodules having higher yields (up to 91% for > 4-cm nodules).[9] Transthoracic core needle biopsy has a higher diagnostic yield for malignancy (70%-80% in nodules ≤ 15 mm and 90% in nodules > 15 mm), but carries an approximately 15% risk of pneumothorax (although only approximately one-half of these will require tube thoracostomy).[10] Characteristics that increase pneumothorax risk include presence of emphysema, small lesion size (< 20 mm), need to cross a fissure to access the lesion, and length of lung traversed by the needle.[11] Indeed, the patient did experience a pneumothorax after biopsy but did not require intervention.

The biopsy demonstrates an immunophenotype consistent with classical Hodgkin's lymphoma (Table 1). However, the imaging findings are unusual. One potential explanation for peripheral, basilar nodules with feeding vessels in Hodgkin's lymphoma is hematogenous dissemination of residual tumor cells (RTCs) during autologous transplantation. RTCs have been found in autologous stem cell collections from patients with a range of solid and hematologic malignancies. Cell reinfusion at the time of autologous SCT has been proposed as a mechanism of relapse. This phenomenon has been reported in leukemias, breast cancer, neuroblastoma, multiple myeloma, and non-Hodgkin's lymphoma.[12] Patients with RTCs have been found to have higher relapse rates; however, consensus is lacking on whether relapse is caused by RTCs themselves or by those patients simply having a higher burden or more aggressive disease (of which RTCs are a marker). Many patients who relapse after autologous SCT do so at their original disease sites, not in new sites that would be consistent with hematogenous spread[13]; however, the patient presented here lacked pulmonary parenchymal disease prior to initial SCT. In fact, his original disease site (the mediastinum) had responded quite well to prior treatments. Accelerated growth of the nodules in this case was likely because of his immunosuppression.

Conclusions

This case of hematogenous spread of Hodgkin's lymphoma to the lung has important implications for practicing pulmonologists. First, the differential diagnosis of pulmonary nodules after SCT is broad and includes both infectious and noninfectious etiologies. Biopsy may be required for diagnosis, and the approach should take into account both patient and procedural factors. Second, Hodgkin's lymphoma should be considered in the differential of nodular pulmonary disease. Finally, tumor cell contamination should be considered as a cause of relapsed disease after SCT.

Acknowledgments

Financial/nonfinancial disclosures: None declared.

Other contributions: *CHEST* worked with the authors to ensure that the Journal policies on patient consent to report information were met.

References

1. Fromm JR, Thomas A, Wood BL. Flow cytometry can diagnose classical hodgkin lymphoma in lymph nodes with high sensitivity and specificity. *Am J Clin Pathol*. 2009;131(3):322-332.
2. Wingard JR, Hiemenz JW, Jantz MA. How I manage pulmonary nodular lesions and nodular infiltrates in patients with hematologic malignancies or undergoing hematopoietic cell transplantation. *Blood*. 2012;120(9):1791-1800.
3. Singh N, Alexander BD, Lortholary O, et al. Pulmonary cryptococcosis in solid organ transplant recipients: clinical relevance of serum cryptococcal antigen. *Clin Infect Dis*. 2008;46(2):e12-e18.
4. Woodard JP, Gulbahce E, Shreve M, et al. Pulmonary cytolytic thrombi: a newly recognized complication of stem cell transplantation. *Bone Marrow Transplant*. 2000;25(3):293-300.
5. Diehl LF, Hopper KD, Giguere J, Granger E, Lesar M. The pattern of intrathoracic hodgkin's disease assessed by computed tomography. *J Clin Oncol*. 1991;9(3):438-443.
6. Romano M, Libshitz HI. Hodgkin disease and non-hodgkin lymphoma: plain chest radiographs and chest computed

tomography of thoracic involvement in previously untreated patients. *Radiol Med*. 1998;95(1-2):49-53.

7. Harris B, Lowy FD, Stover DE, Arcasoy SM. Diagnostic bronchoscopy in solid-organ and hematopoietic stem cell transplantation. *Ann Am Thorac Soc*. 2013;10(1):39-49.
8. Shannon VR, Andersson BS, Lei X, Champlin RE, Kontoyiannis DP. Utility of early versus late fiberoptic bronchoscopy in the evaluation of new pulmonary infiltrates following hematopoietic stem cell transplantation. *Bone Marrow Transplant*. 2010;45(4):647-655.
9. Baaklini WA, Reinoso MA, Gorin AB, Sharafkaneh A, Manian P. Diagnostic yield of fiberoptic bronchoscopy in evaluating solitary pulmonary nodules. *Chest*. 2000;117(4):1049-1054.
10. Gould MK, Donington J, Lynch WR, et al. Evaluation of individuals with pulmonary nodules: When is it lung cancer? Diagnosis and management of lung cancer, 3rd ed: American College of Chest Physicians evidence-based clinical practice guidelines. *Chest*. 2013;143(5 suppl):e93S-e120.
11. Nour-Eldin NA, Alsubhi M, Emam A, et al. Pneumothorax complicating coaxial and non-coaxial CT-guided lung biopsy: comparative analysis of determining risk factors and management of pneumothorax in a retrospective review of 650 patients. *Cardiovasc Intervent Radiol*. 2016;39(2):261-270.
12. DiPersio JF, Ho AD, Hanrahan J, Hsu FJ, Fruehauf S. Relevance and clinical implications of tumor cell mobilization in the autologous transplant setting. *Biol Blood Marrow Transplant*. 2011;17(7):943-955.
13. Shimoni A, Korbling M. Tumor cell contamination in re-infused stem cell autografts: Does it have clinical significance? *Crit Rev Oncol Hematol*. 2002;41(2):241-250.