Title
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Journal
Annals of the American Thoracic Society, 19(8)

ISSN
2329-6933

Authors
Chen, Annie
Coloma, Melissa
Syed, Bela
et al.

Publication Date
2022-08-01

DOI
10.1513/annalsats.202112-1384cc

Peer reviewed

The Expert Clinician

Section Editors: Danielle Antin-Ozerkis, M.D., and Charlie B. Strange III, M.D.

Dyspnea in a 49-Year-Old Woman with Innumerable Cavitating Pulmonary Nodules

Annie Chen[1], Melissa Coloma[2], Bela Syed[2], and Nader Kamangar[2,3]

[1]Department of Medicine, Olive View–University of California, Los Angeles Medical Center, [2]David Geffen School of Medicine, and [3]Division of Pulmonary and Critical Care Medicine, Department of Medicine, University of California, Los Angeles, Los Angeles, California

ORCID ID: 0000-0002-9206-4954 (N.K.).

Case Vignette

A 49-year-old woman with a medical history of hypertension, type 2 diabetes, and uterine fibroids for which she had undergone abdominal hysterectomy 10 years prior presented with an indolent onset of dyspnea, nonproductive cough, and progressive shortness of breath over 6 months. Her remaining review of systems was unremarkable, denying fevers, chills, chest pain, hemoptysis, night sweats, and weight loss. She was a nonsmoker but had secondhand smoke exposure as a child.

On physical examination, her vital signs and oxygen saturation on room air were normal. Her lungs were clear to auscultation, and the remainder of her examination was unremarkable. A chest radiograph revealed diffuse, bilateral, ill-defined reticulonodular opacities (Figure 1). A computed tomography (CT) scan of the chest showed innumerable randomly distributed subcentimeter pulmonary nodules. Many nodules had central cavitation. In addition, scattered lung cysts and areas of bronchiolar wall thickening were seen (Figure 2). No significant mediastinal, hilar, or axillary adenopathy or pleural effusion was noted. CT of the abdomen and pelvis with intravenous contrast only was notable for posthysterectomy surgical changes.

Results of basic and comprehensive metabolic panels and complete blood count were normal, as were results of urinalysis, with no evidence of proteinuria. Infectious evaluation was negative for human immunodeficiency virus, Mycobacterium tuberculosis by QuantiFERON gold (Qiagen), and fungal serologies. Autoimmune serologies were negative or normal when tested for antinuclear antibody; antineutrophil cytoplasmic antibody; rheumatoid factor; and antibodies against Jo-1, double-stranded deoxyribonucleic acid, Sjögren's syndrome–related antigen A, and Sjögren's syndrome–related antigen B. Angiotensin-converting enzyme concentration was normal.

Pulmonary function testing showed moderate obstruction, with a forced expiratory volume in 1 second of 1.75 L (70% predicted), a forced vital capacity of 2.58 L (88% predicted), and a decrease in the diffusing capacity of the lung for carbon monoxide to 65% predicted.

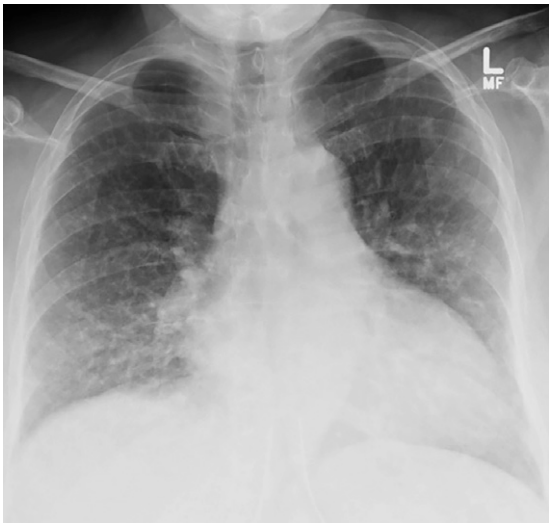

Figure 1. Posteroanterior chest radiograph showing diffuse bilateral ill-defined reticulonodular opacities.

(Received in original form December 30, 2021; accepted in final form May 5, 2022)

Correspondence and requests for reprints should be addressed to Nader Kamangar, M.D., David Geffen School of Medicine at University of California, Los Angeles, Olive View–University of California, Los Angeles Medical Center, 14445 Olive View Drive, Room 2B-182, Sylmar, CA 91342. E-mail: kamangar@ucla.edu.

Ann Am Thorac Soc Vol 19, No 8, pp 1414–1418, Aug 2022

DOI: 10.1513/AnnalsATS.202112-1384CC
Internet address: www.atsjournals.org

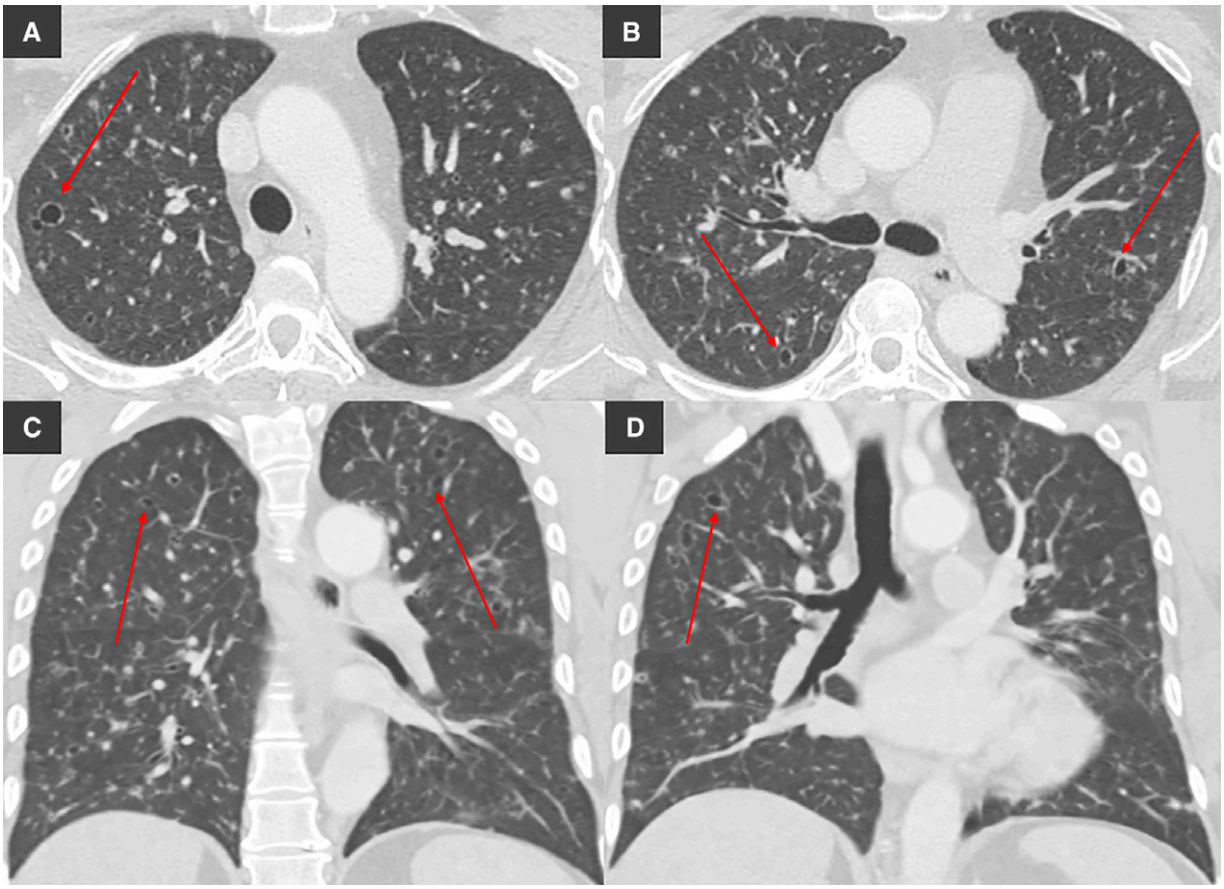

Figure 2. (*A* and *B*) Computed tomography of the chest with contrast (axial, lung window, 1.5 mm); axial cuts of the upper lobes show innumerable bilateral, randomly distributed, subcentimeter pulmonary nodules. Many of the nodules have central cavitation. Also present are scattered lung cysts and areas of bronchiolar wall thickening. (*C* and *D*) Corresponding coronal sections (coronal, lung window, 3 mm) showing the diffuse distribution of pulmonary micronodules with and without cavitation and cystic changes. Arrows depict the bilateral cavitating and cystic nodular opacities.

Questions

1. *What is the differential diagnosis of the diffuse cavitary and cystic micronodular lung disease in this patient?*

2. *What diagnostic approach should be pursued?*

3. *What are the management options for this patient's condition?*

[Continue onto next page for answers]

Clinical Reasoning

The combination of diffuse cavitating and cystic micronodules in this nontoxic patient should result in a relatively narrow differential diagnosis.

Micronodules are the most common parenchymal manifestation of sarcoidosis and are found in a perilymphatic distribution, along the bronchovascular bundles, interlobular septa, major fissures, and subpleural regions. Cavitation occasionally occurs within these nodules. Although the precise mechanism underlying the formation of cavities remains unclear, the histopathology of primary cavitary sarcoidosis is characterized by noncaseating granulomas with minimal fibrosis within the cavity walls. Our patient lacked the clinical and cardinal imaging features of sarcoidosis.

Pulmonary Langerhans cell histiocytosis (PLCH) is a rare sporadic cystic disease of unknown etiology seen in young adult smokers, characterized by the infiltration and destruction of distal bronchiole walls by CD1a (cluster of differentiation 1a)–positive Langerhans-like cells. CT imaging demonstrates ill-defined micronodules in a centrilobular distribution that cavitate with disease progression, creating bizarrely shaped cysts and nodules. PLCH would be unlikely given our patient's distant tobacco exposure during childhood.

Lymphoid interstitial pneumonia (LIP) is an interstitial lung disease characterized by lymphocyte and plasma cell infiltration of the interstitium and alveolar spaces. CT findings include ground-glass opacities, micronodules in a centrilobular distribution, thickening of bronchovascular bundles, and thin-walled cysts in perivascular and subpleural distributions. Histologically, LIP shows extensive infiltration of the alveolar septa with polyclonal lymphocytes and plasma cells. LIP is associated with autoimmune diseases such as Sjogren's syndrome, systemic lupus erythematosus, common variable immune deficiency, or infection with human immunodeficiency virus, none of which was clinically or serologically suspected in our patient.

Amyloidosis is characterized by the abnormal aggregation and deposition of insoluble amyloid proteins. Amyloid-associated cystic lung disease is often associated with amyloid light-chain amyloidosis and underlying connective tissue diseases. CT findings include round or lobulated thin-walled cysts, often accompanied by calcified subpleural or peripheral nodules. Histologically, amyloid appears as a fibrous, eosinophilic substance reactive to Congo red staining. Similarly, light-chain deposition disease (LCDD) is characterized by the deposition of monoclonal light chains in various organs and is histologically similar to amyloid, though it does not reproducibly stain with Congo red. Our patient did not have any of the clinical or laboratory features suggestive of amyloidosis or LCDD.

Because some slow-growing cancers such as spindle-cell carcinoma remained in the differential diagnosis, the patient underwent video-assisted thoracoscopic surgery for an open lung biopsy. Microscopic evaluation of the lung biopsy specimens revealed well-differentiated uterine spindle-shaped cells consistent with smooth muscle differentiation, with low nuclear and cellular variance in size and shape (Figure 3). Immunohistochemical stains were positive for desmin and smooth muscle actin (Figure 4). The absence of increased mitotic activity, cytologic atypia, and necrosis distinguished it from malignant entities such as metastasizing leiomyosarcoma. The patient's history of uterine fibroids together with the histopathologic findings led to the diagnosis of pulmonary benign metastasizing leiomyoma (BML).

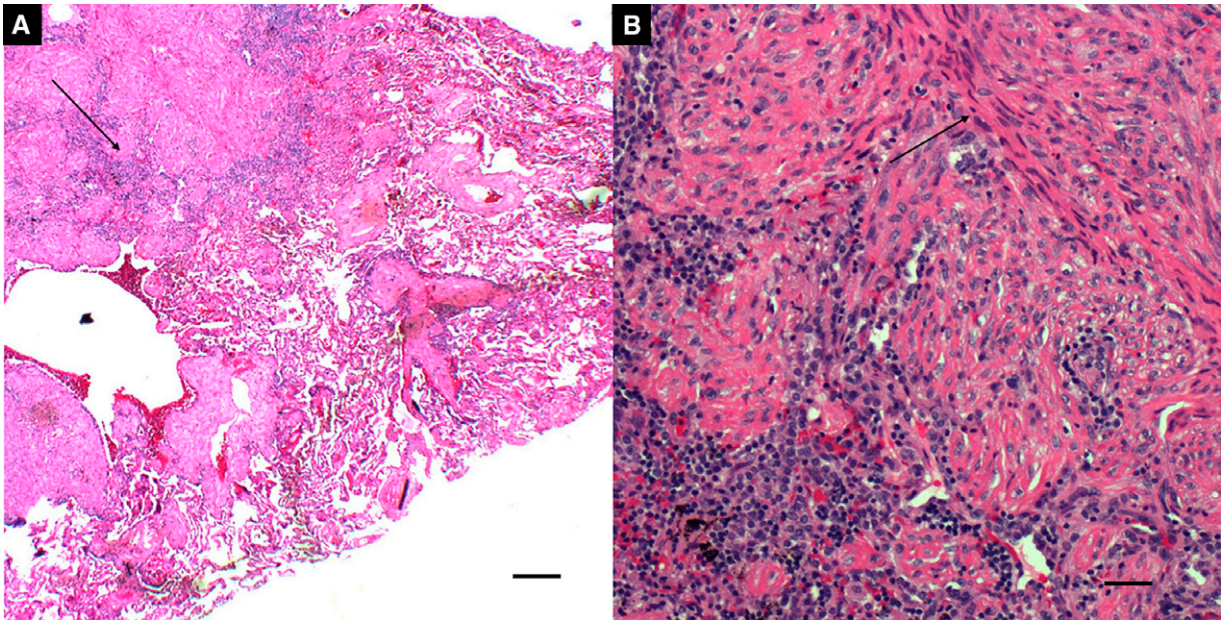

Figure 3. Histopathology from surgical lung biopsy. (*A*) Hematoxylin-eosin stain showing tumor consisting of well-differentiated spindle-shaped cells consistent with smooth muscle differentiation (scale bar, 100 μm; magnification, 20×). (*B*) Hematoxylin-eosin stain showing tumor consisting of well-differentiated spindle-shaped cells with low nuclear and cellular variance in size and shape (scale bar, 40 μm; magnification, 50×). Arrows depict the spindle-shaped cells with smooth muscle differentiation.

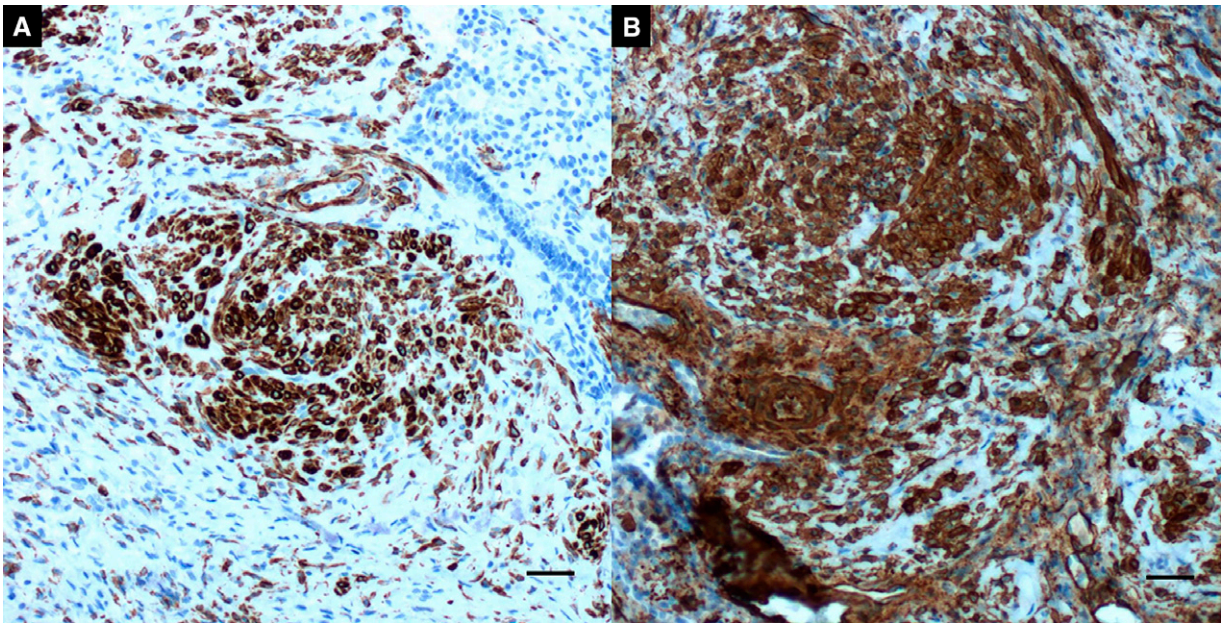

Figure 4. Immunohistochemical staining from surgical lung biopsy. (*A*) Positive desmin stain (scale bar, 40 μm; magnification, 50×). (*B*) Positive smooth muscle actin stain (scale bar, 20 μm; magnification, 100×).

Discussion

BML is a rare condition describing the extrauterine spread of benign tumors histologically identical to uterine leiomyomas. They are seen in premenopausal women with histories of uterine fibroids, often with hysterectomies performed years prior (1–3). Metastatic lesions are found primarily in the lungs, but they have also been observed less commonly in the lymph nodes, bones, retroperitoneum, and heart (4, 5). Although patients are often asymptomatic with lesions incidentally found, they may also present with cough, dyspnea, hemoptysis, chest pain, and pneumothoraces (1, 5).

The pathogenesis of such lesions is unclear. These tumors usually demonstrate strong estrogen and progesterone receptor expression suggestive of a uterine origin. Accordingly, the predominant theories propose a surgically induced hematogenous spread resulting from fragments of benign uterine leiomyomas accidentally left in the peritoneum after laparotomy that subsequently implant and proliferate at distant sites (4, 6). This is not a perfect theory, however, as there have been a number of cases in which BML has been diagnosed in patients who have not previously undergone uterine surgery (4).

Identification of BML can be challenging. Radiographic findings are largely nonspecific and usually reveal multiple bilateral nodules that can have cystic or cavitating characteristics. Diagnosis relies on tissue biopsy, either image guided or surgical, depending on the location of the lesions. By definition, the diagnosis of BML requires the histologic characteristics of uterine leiomyomas to be microscopically observed, with spindle smooth muscle cells that lack any features of malignancy (increased mitotic activity, cytologic atypia, and necrosis). The immunophenotype of BML includes smooth muscle actin, desmin, estrogen receptor, and progesterone receptor positivity (7). The Ki-67 index of the tumor is generally very low, supporting an indolent proliferative state (6, 7). It is important to distinguish BML from malignant diseases such as uterine leiomyosarcoma, which may present similarly. Positron emission tomography/CT can be helpful to make this distinction, as BML nodules have low metabolic activity and should demonstrate minimal uptake (7, 8).

No standard treatment algorithm for BML is established. An individualized treatment strategy depends on the size and location of the tumor(s) and the hormone status. Close observation or curative surgery is recommended in those with single or limited nodule number. In those with more extensive disease, treatment is targeted toward estrogen suppression, as regression has been demonstrated after significant decreases in estrogen concentrations, as occurs after menopause. Historically, bilateral oophorectomy has been considered first-line therapy in those able to tolerate the procedure, followed by antihormonal therapy in those who did not (9). However, given the indolent nature of the disease, there appears to be a move toward conservative management of asymptomatic patients with medical rather than surgical estrogen suppression. Pharmacologic therapy consists of gonadotropin-releasing hormone analogues such as leuprolide, selective estrogen receptor modifiers such as tamoxifen and raloxifene, or aromatase inhibitors such as anastrozole, all of which have been documented to reduce the size of tumors and improve pulmonary function (2, 10, 11). Progesterone therapy has also been used to suppress the hypothalamic–pituitary–gonadal axis and ovarian estrogen production as a result. Furthermore, progesterone also acts to increase the rate of enzymatic inactivation of estradiol and to reduce aromatase activity by up to 30% (10). Regression of BML tumors has been seen after progesterone alone. All patients with BML should undergo long-term surveillance with CT imaging, as disease progression is indolent and can resurface with complications several years later (1).

Outcomes of patients with BML can vary widely depending on the extrauterine site of tumors. Although lesions may be clinically silent in many cases, small tumors manifesting at crucial sites can induce cardiac or pulmonary failure. Overall, the prognosis for patients with BML appears good. Case series demonstrate a median survival time of 94 months after excision of intrapulmonary lesions. In addition, most patients do not die of this disease, even without receiving hormonal therapy (12).

Answers

1. *What is the differential diagnosis of the diffuse cavitary and cystic micronodular lung disease in this patient?*

The differential diagnosis included sarcoidosis, PLCH, lymphocytic interstitial pneumonitis (LIP), LCDD, amyloidosis, and BML. BML was believed to be most likely given this patient's indolent clinical presentation and history of uterine fibroids and abdominal hysterectomy.

2. *What diagnostic approach should be pursued?*

A definitive diagnosis of BML relies on tissue biopsy, either image guided or surgical, depending on the location of the lesions.

3. *What are the management options for this patient's condition?*

Surgical intervention, such as oophorectomy, or the use of agents that decrease estrogen or progestins can result in tumor regression. Expectant management is an option for those with asymptomatic disease.

Follow-Up

After the diagnosis of BML, bilateral salpingooophorectomy was recommended to this patient, as she was premenopausal. She decided against surgical intervention and started a gonadotropin-releasing hormone agonist. With persistent dyspnea and progression to a postmenopausal state, an aromatase inhibitor was added to reduce peripheral estrogen conversion. Surveillance CT imaging shows decreased disease burden.

Insights

- Pulmonary BML is a condition that most often manifests as cystic/cavitary pulmonary nodules in patients with histories of uterine fibroids and hysterectomy.
- The diagnosis of BML needs to be differentiated from malignant processes such as uterine leiomyosarcoma that may present similarly on radiographic and histologic studies.
- Immunohistochemical stains for BML demonstrate smooth muscle actin, desmin, estrogen receptor, and progesterone receptor positivity.
- Optimal management of BML is individualized on a case-by-case basis. Management recommendations include close observation in asymptomatic individuals, surgical resection for those with solitary or limited pulmonary lesions, and the use of drugs or surgery that decreases estrogen or progestins for those with more extensive disease. ■

Author disclosures are available with the text of this article at www.atsjournals.org.

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