Bronchopulmonary Actinomycosis Associated With Hiatal Hernia

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OBJECTIVES: **To describe clinicoradiologic and histopathologic features of bronchopulmonary actinomycosis and to determine whether hiatal hernia (HH) is a potential predisposing factor for bronchopulmonary actinomycosis.**

PATIENTS AND METHODS: **We reviewed the medical charts of 10 patients who had bronchopulmonary actinomycosis between November 1, 2002, and January 31, 2008. Complete clinical data, radiologic studies (chest radiographs and computed tomographic scans), and histopathologic features were assessed to investigate clinical manifestations and predisposing factors related to bronchopulmonary actinomycosis.**

RESULTS: **The series consisted of 6 men and 4 women, with a mean age of 63.5 years; 8 of the patients were smokers. Cough and fever were the most common symptoms. Chest imaging showed mass-like consolidation in 4 patients, bronchial thickening or lung atelectasis with pleural thickening in 2 patients each, and perihilar irregular mass or multiple bilateral nodules in 1 patient each. Primary or metastatic lung cancer was suspected clinically in 8 of the 10 patients. Foreign body–related endobronchial actinomycosis was diagnosed in 6 patients, 5 of whom had HH; only 1 had gastroesophageal reflux–related symptoms. Because of bronchial obstruction, rigid bronchoscopy was performed in 3 patients, lobectomy in 2, and atypical resection in 1. Antibiotic therapy with amoxicillin was given to all patients, with resolution of actinomycosis.**

CONCLUSION: **Bronchopulmonary actinomycosis is a rare condition that mimics pulmonary malignancy on clinical and radiologic grounds. Diagnosis relies on an accurate patient history and histopathologic examination. Although further confirmation is required, esophageal HH appears to be a potential predisposing factor.**

Mayo Clin Proc. **2009;84(2):123-128**

CT = computed tomography; GERD = gastroesophageal reflux disease; HH = hiatal hernia

Actinomycosis is an infectious disease due to anaerobic gram-positive, non-spore–forming bacteria of the genus *Actinomyces* that affects the oropharynx, digestive tract, and genitalia.[1,2] Although ubiquitous, it mainly involves cervicofacial and abdominopelvic regions.[2,3] Thoracic actinomycosis is rare and may affect the upper and lower respiratory tract and the pleura, even extending to the chest wall.[3-6] In the lungs, actinomycosis is generally due to *Actinomyces israelii* or *A meyeri*. More frequently, pulmonary actinomycosis occurs in immunocompetent persons during the fourth and fifth decades of life, with a prevalence in men.[3-6] It is frequently misdiagnosed as primary or metastatic lung cancer or as other more conventional lung infections (eg, tuberculosis), even by experienced clinicians.[3-8] Because laboratory tests and imaging features of thoracic actinomycosis are nonspecific and cultures are generally negative, the correct diagnosis frequently relies on histopathologic examination, so pathologists play a key role.

A widely accepted fact is that pulmonary actinomycosis results from aspiration of bacteria from oropharyngeal or gastrointestinal secretion, and patients with poor oral hygiene or dentition are at increased risk of respiratory tract infection from *Actinomyces* species.[3-6,9-11] In the lungs, actinomycosis may appear as endobronchial or pleuroparenchymal disease, and bronchial foreign bodies (chicken and fish bones, grape seeds, beans, teeth, dental prostheses, alimentary material) or broncholiths may favor secondary colonization by *Actinomyces* spp.[9,10]

In this study, we describe the clinicopathologic, imaging, and histologic features of 10 cases of actinomycosis that primarily involved the bronchi and pulmonary parenchyma and focus on the previously unreported association with hiatal hernia (HH) as a potential predisposing factor for bronchopulmonary actinomycosis.

PATIENTS AND METHODS

Clinical records, imaging studies, and histopathologic biopsy reports of 10 patients with bronchopulmonary actinomycosis were analyzed from the database of the Hospital Azienda Policlinico of Modena (8 patients) and the Hospital St Maria Nuova of Reggio Emilia (2 patients) between November 1, 2002, and January 31, 2008. The collected data include complete medical history, radiologic findings (including chest computed tomography [CT]), treatments, and histopathologic and histochemical findings from the biopsy specimens of all patients.

Hematoxylin-eosin, Gram, Grocott-Gomori methenamine-silver, Ziehl-Neelsen, and periodic acid-Schiff stains were used to analyze biopsy specimens (7 bronchial biopsies, 2 pulmonary lobectomies, and 1 wedge resection). For this descriptive study, all information was used

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TABLE. **Baseline Clinical and Radiologic Features of Bronchopulmonary Actinomycosis in the 10 Study Patients**[a]

Patient No./ age (y)/sex	Smoking status	Presenting symptoms	Associated conditions/events	Hiatal hernia	Chest radiographic findings	Foreign material	Bronchoscopic findings	Treatment[b]
1/68/M	Former	Cough, GERD	Prostatitis, poor dental hygiene	Yes	Opacity in right lobe, mediastinal adenopathy, "bronchial tree-in-bud" pattern	Vegetables	Mass filled with necrotic material obstructing right upper bronchus	Antibiotics
2/73/M	Current	Cough	COPD	Yes	Calcified mass at beginning of bronchus, parenchymal consolidation of middle aspect of lobe	Chicken bone	Granulomatous mass obstructing middle aspect of bronchus	Rigid bronchoscopy to eliminate obstruction, antibiotics
3/68/M	Former	Cough, dyspnea, fever	Stroke, recurrent pneumonia, COPD	No	Complete atelectasis with pleural effusion in base of left lung	No	Extrinsic compression of the left lower lobe	Antibiotics
4/54/F	Never	Fever	Breast neoplasm (14 y before) and kidney neoplasm (5 y before), Tolosa-Hunt syndrome, poor dental hygiene	No	Multiple opacities mimicking pulmonary metastases	No	None of clinical importance	Atypical resection (for diagnostic purposes) and antibiotics
5/54/F	Current	Cough	Edentate, poor dental hygiene, esophagus ectasia	No	Masslike consolidation mimicking a neoplasm in upper lobe of right lung	No	None of clinical importance	Lobectomy and antibiotics
6/41/M	Current	Cough, fever	Recurrent pneumonia, chronic hepatopathy	Yes	Opacity in base and middle aspect of right lung	Fish bone	White, round, and mobile mass obstructing the bronchus intermedium	Rigid bronchosopy to eliminate obstruction, antibiotics
7/74/F	Current	Cough, fever	Diabetes mellitus, HCV-related hepatopathy	Yes	Right hilar adenopathy narrowing right upper bronchus, atelectasis	Chicken bone	Mass obstructing the right upper bronchus	Rigid bronchoscopy to eliminate obstruction, antibiotics
8/66/M	Current	Cough, fever	Lung cancer (left lower lobectomy, radiotherapy, and chemotherapy), recurrent pneumonia, COPD	No	Left hilar hypodense tissue with pleural ipsilateral thickening	Wire suture	Granulomatous tissue in the distal left main bronchus, upper left lobe filled with mucus	Antibiotics
9/54/M	Current	Dyspnea	Splenectomy and left atypical lung resection due to injury in motor vehicle crash, recurrent pneumonia	Yes	Masslike consolidation mimicking a neoplasm in left lower lobe, atelectasis	Wire suture	Extrinsic mass obstructing left lower lobe	Left lower lobectomy, antibiotics
10/83/F	Never	Cough	Asthma	Yes	Masslike consolidation	No	None of clinical importance	Antibiotics

[a] HCV = hepatitis C virus; COPD = chronic obstructive pulmonary disease; GERD = gastroesophageal reflux disease.
[b] Treatment was successful in 8 patients; however, patient No. 3 died of neurologic complications and patient No. 8 died of relapse of lung cancer.

to perform an anonymous and aggregate statistical analysis, and according to Italian laws, approval from a formal ethics committee is not required.

RESULTS

Clinical and Radiographic Findings

The age at diagnosis of the 6 men and 4 women ranged from 41 to 83 years (mean ± SD age, 63.5±12.5 years; median, 67.0 years). Of these 10 patients, 8 had a history of smoking: 6 were current smokers, and 2 were ex-smokers (defined as quitting >3 years before diagnosis). Presenting symptoms were cough (8 patients), fever (5 patients), dyspnea (2 patients), and gastroesophageal reflux disease (GERD; 1 patient) (Table).

Six patients had esophageal HH (Figure 1), but only 1 patient had symptoms related to GERD; 3 patients had dental problems (Table). Two patients had undergone thoracic surgery (patient 8, lobectomy for squamous cell lung cancer; patient 9, wedge resection because of an injury from a vehicle crash). Hiatal hernia, detected by imaging studies after bronchopulmonary actinomycosis had been diagnosed, was subsequently confirmed by endoscopy in 2 patients. Of the 6 cases of HH, 4 were classified as paraesophageal type and 2 as sliding type.

Imaging studies of the chest included standard radiographs and CT scans in all patients; 18–labeled fluorodeoxyglucose positron emission tomography was performed in only 1 patient (No. 5) and showed moderate uptake. Imaging findings suggested primary lung cancer in

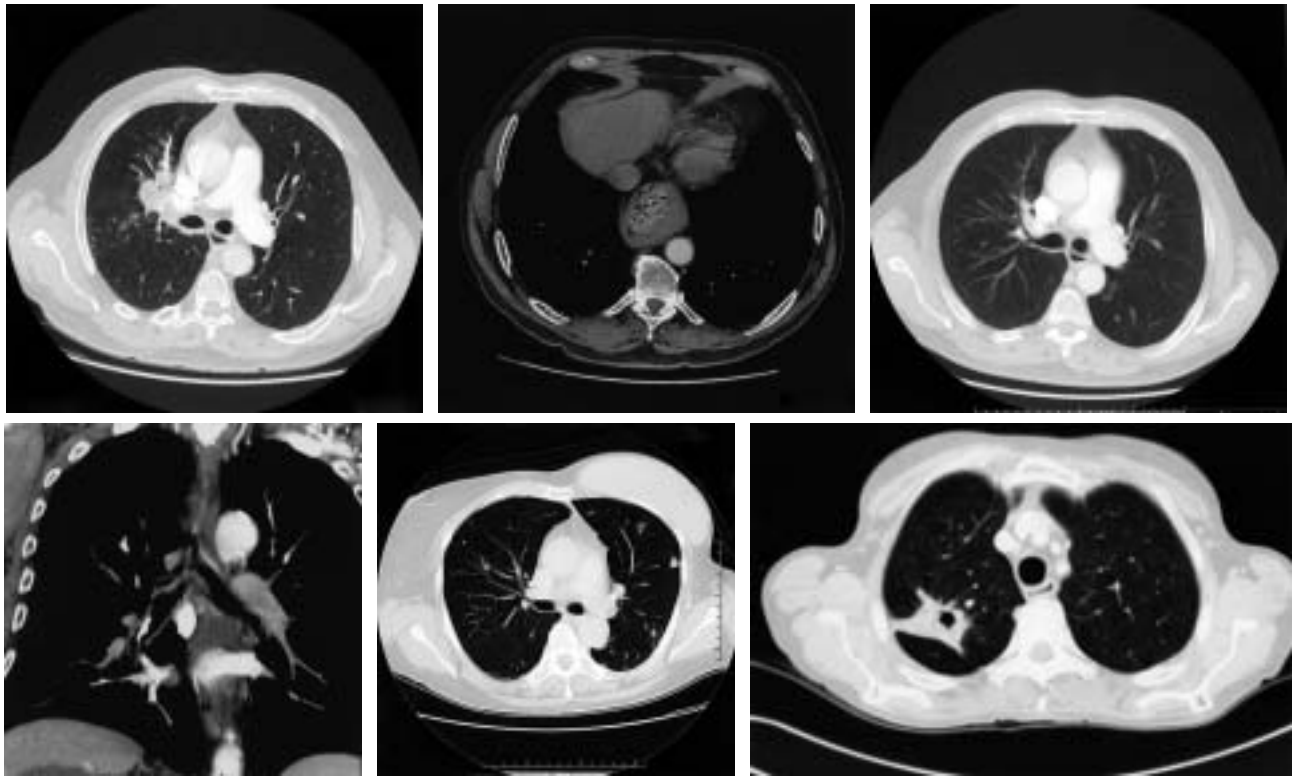

FIGURE 1. Chest computed tomograms. Right perihilar consolidation that is wrapping around the distal portion of the main and right upper bronchi, with mucoid impaction, enlargement of right hilar lymph nodes, and a peripheral "tree-in-bud" pattern (upper left) in patient with a severe hiatal hernia (upper middle). Complete resolution of the bronchopulmonary consolidation after antibiotics (upper right). Coronal reformation of contrast-enhanced chest computed tomogram showing a prominent hiatal hernia in patient 2 with endobronchial actinomycosis due to chicken bone aspiration (lower left). Pulmonary actinomycosis presenting as multiple bilateral nodules and ground-glass opacities in patient 4 with a history of breast and renal cancers (lower middle). Parenchymal actinomycosis appearing as a masslike consolidation with central cavity and associated with moderate esophageal ectasia in patient 5 (lower right).

5 patients (No. 1, 5, 8, 9, 10) and pulmonary metastatic disease in 1 patient (No. 4) (Figure 1).

In patients 2 and 7, imaging studies showed predominantly bronchial involvement with lumen narrowing and the presence of calcified material consistent with a foreign body or bronchioliths into the bronchial tree. Foreign bodies in the other patients with endobronchial actinomycosis (No. 1, 6, 8, and 9) were detected only after histologic examination of the bronchial biopsy specimens. In the remaining 2 patients, CT revealed pleural involvement with effusion in patient 3 and pleural thickening associated with the presence of perihilar hypodense tissue in patient 8.

Overall, fiberoscopic bronchoscopy was informative in 7 (70%) of the 10 patients. It revealed a mass suggestive of a tumor obstructing the bronchial lumen in 5 patients (No. 1, 2, 6, 7, and 9), all of whom had foreign bodies in their bronchi. Of note, in 3 of these patients (No. 2, 6, and 7), the foreign body was observed during the first bronchoscopic examination and removed by rigid bronchoscopy, whereas in the other patients (No. 1 and 9) foreign bodies were not detected and were observed only at histologic examination.

In patient 3, fiberscopic bronchoscopy revealed extrinsic compression of a lobe due to the pleural effusion, and proliferative granulation tissue in the main bronchus was observed in patient 8. In all patients with endobronchial actinomycosis and in patient 3, several bronchial biopsies (from 3 to 8) of exophytic, easily sampled bronchial material were performed to establish the diagnosis. In 2 patients (No. 4 and 5), the diagnosis was determined after examination of lung resections (atypical resection and lobectomy, respectively), whereas a transthoracic biopsy was performed in patient 10. Bronchoalveolar lavage was performed in 8 patients, yielding a nonspecific granulocyte-rich inflammatory picture.

Regarding therapy, 4 patients (No. 1, 3, 8, and 10) were successfully treated with antibiotics (amoxicillin plus clavulanic acid) for 3 to 6 months, and the other patients underwent invasive procedures (3 patients each were man-

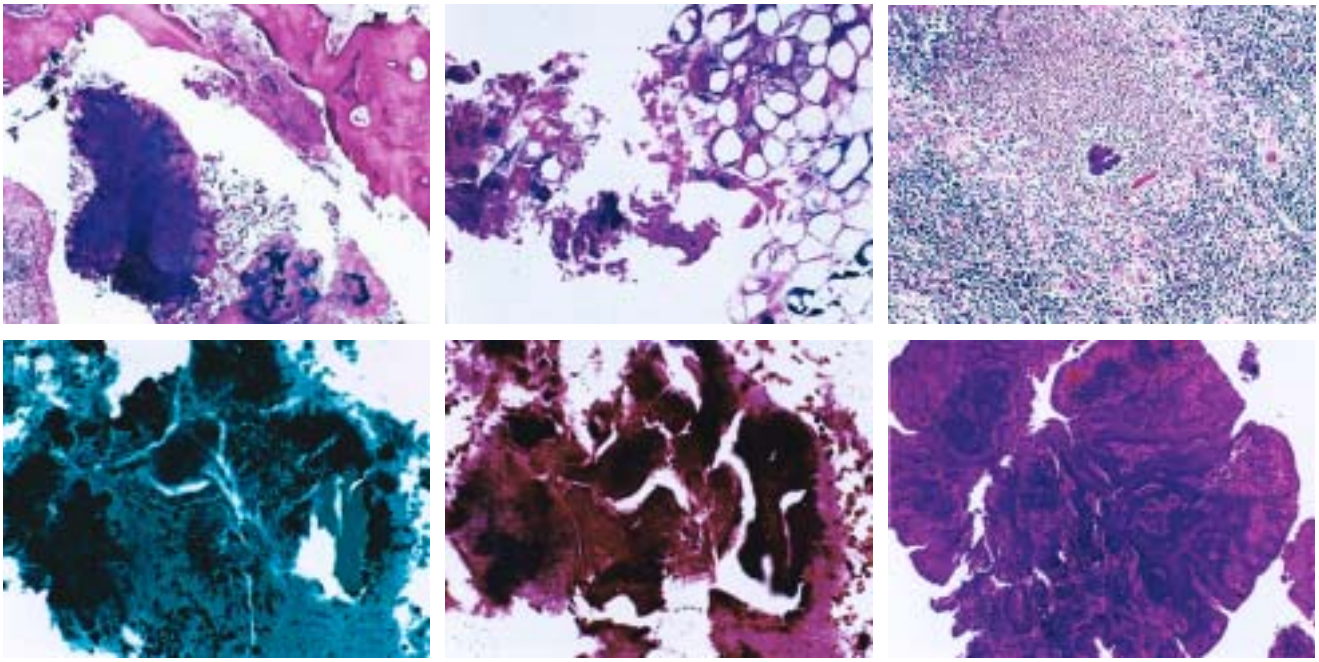

FIGURE 2. Histologic findings of endobronchial foreign body–associated actinomycosis showing sulfur granules around chicken bone (upper left) and digested vegetables (upper middle) (hematoxylin-eosin, original magnification ×150). Pulmonary abscess centered by a sulfur granule in pulmonary actinomycosis (upper right, hematoxylin-eosin, original magnification ×100). Sulfur granules of *Actinomyces* stained with methenamine silver (lower left, histochemical stain Grocott-Gomori, original magnification ×200) and Gram (lower middle, histochemical Gram stain, original magnification ×200). Florid and reactive papillomatous changes of the bronchial mucosa with squamous cell metaplasia and mild cytologic atypia secondary to endobronchial actinomycosis (lower right, hematoxylin-eosin, original magnification ×100).

aged by rigid bronchoscopy or surgery). Among patients with HH, only patient 1 had GERD symptoms and was treated with proton pump inhibitors.

At follow-up, pulmonary actinomycosis had resolved in all 10 patients. Only 2 patients had died: 1 of metastatic lung cancer and 1 of neurologic complications of a previous stroke.

Pathologic Findings

Histologic examination showed a necrotic, suppurative background with a predominance of neutrophils, plasma cells, and histiocytes; granulomatous inflammation with giant cells was observed in only 2 cases. In all cases, "sulfur" granules with clublike, long, thin filamentous branching rods radiating from their periphery (so-called Splendore-Hoeppli phenomenon) were detected within the inflammatory/necrotic tissue.

Foreign material surrounded by granules of *Actinomyces* spp was observed in 6 cases (all bronchial biopsy specimens), including chicken (2 cases) or fish (1 case) bones, wire sutures (2 cases), and digested vegetables (1 case) (Figure 2, upper left and upper middle). In cases of actinomycosis involving lung parenchyma, multiple abscesses with granulation tissue and foamy histiocytes centered by "sulfur" granules of *Actinomyces* spp were observed (Figure 2, upper right). *Actinomyces* spp were positive with Grocott-Gomori methenamine silver stain and Gram stain but were weakly positive with periodic acid-Schiff stain; microorganisms did not appear acid-fast resistant with Ziehl-Neelsen (Figure 2, lower left and lower middle).

DISCUSSION

Bronchopulmonary actinomycosis is a chronic suppurative infectious disease with a protean spectrum of clinical and radiologic presentations. This disease mainly simulates primary or metastatic malignancies and other more common pulmonary infections.[3-8] Thus, the diagnosis can be challenging and is often delayed, with a mean of 6 months from symptom onset; less than 10% of cases are suspected by clinicians.[3] Universally accepted predisposing factors for bronchopulmonary actinomycosis are poor dental hygiene, alcoholism, dental problems and interventions, oral trauma and infections, and various chronic debilitating diseases and other issues (diabetes mellitus, neurologic and psychiatric diseases, virus-related or virus-free hepatitis, malnutrition, radiation, drug abuse, congenital and acquired immunosuppression, and medications).[3-6,11,12] All these factors facilitate aspiration of secretions containing *Actinomyces* spp from the oropharynx into the respiratory tract.

In our series, 8 patients (80%) had some of the aforementioned risk factors, suggesting bronchopulmonary colonization by *Actinomyces* spp. Interestingly, 6 (60%) of our patients had esophageal HH; in 2 of these patients, HH was the only important predisposing factor besides chronic pulmonary obstructive disease or asthma, and only 1 patient had active symptoms related to GERD. To our knowledge, an association between HH and bronchopulmonary actinomycosis has not been previously reported. Because we observed this association in only 10 patients and because further confirmation is needed, the exact mechanism by which HH predisposes to bronchopulmonary colonization by *Actinomyces* spp is not completely clear; however, it is well known that HH is the most important factor associated with GERD.[13] GERD is associated with asthma[14] and is involved in acid regurgitation and choking, thereby promoting the entry of secretions containing *Actinomyces* spp or foreign materials into the bronchial tree. Additionally, foreign bodies offer a conducive environment for *Actinomyces* spp, leading to tissue inflammation and infection.[15] Alternatively, HH may act synergically with other recognized predisposing factors. Of note, previous studies have highlighted the role of esophageal disorders or GERD in causing mycobacterial lung infections and chronic occult aspiration pneumonia.[16,17] In our series of 6 patients with HH, only 1 patient had symptoms of GERD, which were heartburn and nocturnal dysphagia with regurgitations. In addition, our patients with endobronchial foreign body–related actinomycosis reported previous episodes of choking while eating, but they did so only after extensive questioning. In fact, an accurate patient history in combination with the knowledge of risk factors for actinomycosis is necessary in suspecting this uncommon condition. In our patients, HH was diagnosed by imaging studies only after detection of bronchopulmonary actinomycosis. In 2 patients, HH was subsequently confirmed by endoscopy.

Proton pump inhibitors have been associated with an increased risk of pneumonia.[18] However, only 1 patient in our series received treatment with proton pump inhibitors and that was after a bronchial biopsy showed endobronchial actinomycosis and a CT scan revealed an HH.

Six cases of foreign body–related endobronchial actinomycosis can seem high compared with previous series. However, the advent of antibiotics has changed the clinical presentation of pulmonary actinomycosis, which is usually detected by pathologic examination. In fact, because actinomycosis is responsive to penicillin, using antibiotics as the first step in the treatment of pneumonia in patients in whom cultures are negative may obscure the real frequency of pulmonary actinomycosis. By contrast, endobronchial actinomycosis generally requires use of rigid bronchoscopy to eliminate foreign bodies from the bronchus, and use of antibiotics is necessary. In these cases, pathologists can detect the presence of *Actinomyces* spp and then diagnose bronchopulmonary actinomycosis.

The diagnosis of actinomycosis relies primarily on histologic findings, and frequently pathologists are the first to recognize the microorganism. In the current series of patients, the diagnosis was determined on the basis of histologic examination; clinicians had initially suspected primary or metastatic lung cancer in 8 patients, pneumonia due to foreign bodies in the endobronchial tree in 1 patient, and nonspecific pneumonia in 1 patient. Microbiologic culture examination was required in 2 patients in whom cultures were negative. This is not surprising because *Actinomyces* is an anaerobic microorganism that is often associated with aerobic contaminants of the oral flora.[4,6] For therapeutic purposes, it is important to differentiate *Actinomyces* spp from other pulmonary pathogens, particularly *Nocardia* species and botryomycosis.[6] A diagnosis of nocardiosis is mainly based on clinical grounds and histologic examination, including use of special stains. Nocardiosis is a bronchopulmonary infectious disease sustained by *Nocardia* spp and aerobic gram-positive bacilli; it primarily occurs in immunosuppressed patients (especially those with AIDS) and has a tendency for early hematogenous dissemination.[6,17] Histologic examination shows multiple confluent abscesses and long filamentous, thin, and beaded microorganisms arranged in a "Chinese character" pattern.[19] Microorganisms stain positively with Gram and methenamine silver stains and weakly with modified acid-fast stains. Most importantly, *Nocardia* spp often grow in culture in 1 to 2 weeks and do not form sulfur granules.[6,19] Botryomycosis or bacterial pseudomycosis is an uncommon infection caused by nonfilamentous bacteria (generally *Staphylococcus aureus*, *Pseudomonas aeruginosa*, and *Escherichia coli*). Histologic examination reveals aggregates of nonfilamentous, gram-positive cocci or gram-negative bacilli that form sulfur granules and detects Splendore-Hoeppli phenomenon; methenamine silver stains are negative, and cultures are helpful in highlighting the microorganisms.[17]

Our study has several limitations, including its retrospective design, limited number of observations, and lack of a control group.

Finally, endobronchial actinomycosis may be clinically mistaken for centrally located lung cancer, especially squamous cell carcinoma (a histiotype sometimes presenting as calcifications and, if necrotic, commonly associated with synchronous infectious agents). Pathologists should be aware that bronchial mucosa may show prominent reactive changes with proliferative endobronchial papillomatous growth occluding the bronchial lumen and be lined by squamous metaplastic epithelium with some cytologic atypia

(Figure 1, lower right). A thorough histologic examination that shows evidence of maintenance of epithelial maturation, lack of typical or atypical mitoses in the middle or surface epithelial layer, and absence of stromal invasion all argue against a diagnosis of malignancy.

CONCLUSION

Bronchopulmonary actinomycosis is a rare and often unexpected disease that is basically detected only at histologic examination. Most important, HH seems to represent a hitherto unreported potential predisposing condition for bronchopulmonary actinomycosis. This association based on a limited number of cases could simply be due to chance alone and clearly needs further confirmatory studies.

This work is dedicated to the memory of our friend and pneumologist colleague Alberto Fontana, MD.

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