Evaluation of Solitary Pulmonary Nodule in Human Immunodeficiency Virus Infected Patients

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BACKGROUND: While the etiologies of solitary pulmonary nodules (SPNs) in immunocompetent patients are well established, common etiology, diagnostic techniques, and guidelines to assess SPNs in patients infected with human immunodeficiency virus (HIV) have not been established. OBJECTIVE: To define the etiology of SPN in HIV-infected patients and to examine efficacy of diagnostic testing for SPN. METHODS: We performed a retrospective chart review of HIV-infected patients admitted to a designated acquired immune deficiency syndrome (AIDS) center. Microbiological and histopathological specimens from sputum, bronchoalveolar lavage, and biopsies were analyzed. Charts were fully analyzed from time of admission until definitive diagnosis or loss to follow-up. RESULTS: During the 10-year observational period, 10 of 5,000 HIV-infected patients admitted to the hospital were diagnosed with SPN via chest radiography or computed tomography (CT). Among these 10 patients, 6 had a definitive diagnosis. Underlying etiologies included infection (5/10) and lung adenocarcinoma (1/10); none were identified in the remaining 4 subjects. Sputum analysis provided no diagnostic value in discovering pathogenesis in any of these cases. Fiberoptic bronchoscopy with bronchoalveolar lavage and transbronchial biopsy were diagnostic in 3 cases, while CT-guided percutaneous transthoracic needle biopsy (PTNB) was diagnostic in 2 cases. One patient required open lung biopsy. CONCLUSIONS: Etiologies of SPN in HIV-infected patients are varied and difficult to diagnose. In our study, SPN was attributable to infectious etiology in 50% of cases. Sputum analysis was of no diagnostic value. Biopsy is necessary for definitive diagnosis and treatment. *Key words: pulmonary nodule; human immunodeficiency virus; acquired immune deficiency syndrome; HIV infection; diagnostic lung testing.* [Respir Care 2012;57(7):1115–1120. © 2012 Daedalus Enterprises]

Introduction

The etiologies of solitary pulmonary nodules (SPN) in immunocompetent patients are well established. Malignancies (most likely primary: 95%), granulomas (most likely infectious), and benign tumors (most likely hamartoma) represent the most common causes. Follow-up in these patients is important in order to differentiate benign from malignant nodules and to inform appropriate clinical follow-up (eg, watchful waiting vs additional clinical evaluation) or appropriate treatment if an infectious origin is suspected. Common etiology, diagnostic techniques, and the guidelines to assess SPN in patients infected with human immunodeficiency virus (HIV) have been rarely reported. We herein present characterization of 10 cases of SPN in HIV-infected patients.

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Methods

Setting

This study was undertaken at Saint Barnabas Hospital, an inner-city community hospital located in Bronx, New York. Saint Barnabas Hospital is a designated acquired immunodeficiency syndrome (AIDS) center, with a census of more than 1,000 HIV-infected patients annually.

Study Design

The study was designed as an observational retrospective analysis of cases meeting inclusion criteria admitted to the hospital from January 1, 2000, through December 31, 2009. Following institutional review board approval, retrospective medical record review was undertaken on all cases that tested positive for SPN.

Subjects

All patients who tested HIV positive and had an SPN, defined as a single discrete pulmonary opacity of < 3 cm, surrounded by normal lung tissue that was not associated with adenopathy, atelectasis, or pleural effusion, were included in the study. Patients admitted between January 1, 2000, and December 31, 2009, were electronically screened for HIV infection, using the International Classification of Diseases, 9th Edition (ICD-9) diagnostic code 042. The data system (UIS version 4.5, Healthcare Association of New York State, Rensselaer, New York) was used to electronically screen the records of the 5,000 HIV-infected patients identified for newly diagnosed SPN admitted within this temporal period using ICD-9 diagnostic code 518.89. Ten HIV-positive patients with newly diagnosed SPN were identified. The medical records of all 10 SPN-positive cases were reviewed for demographics, signs/symptoms, CD4 cell count, chest radiographs, and computed tomography (CT) scans. These data were not collected on the 4,990 patients who did not meet inclusion criteria.

Analysis

All microbiological and histopathological specimens obtained from sputum, bronchoalveolar lavage, and biopsies (transbronchial, CT-guided percutaneous transthoracic needle biopsy [PTNB] and open lung) were analyzed to find the etiology of the SPN. In addition, all other diagnostic studies, including 18-F-2 fludeoxyglucose (FDG) uptake done for the evaluation of SPN, were assessed. The patients' charts were fully analyzed, from admission until diagnosis or loss to follow-up. Nine patients underwent fluoroscopically guided fiberoptic bronchoscopy with bronchoalveolar lavage, while 3 of those patients had transbronchial biopsy. All bronchial washings and transbronchial biopsy specimens were subjected to Gram stain, silver stain, mucicarmine stain, and acid-fast stain, and were sent for bacterial/fungal and mycobacterial cultures. Histopathological examination, using appropriate stains, was done on all the pathological specimens obtained. Two patients had CT-guided PTNB. One patient had an FDG uptake study to rule out the involvement of mediastinal lymph nodes and metastasis before going for open lung biopsy. This patient had an open lung biopsy, as none of the other tests were definitive in diagnosing SPN.

QUICK LOOK

Current knowledge

The etiologies of solitary pulmonary nodules in immunocompetent patients are well established, but common etiologies, diagnostic techniques, and guidelines to assess solitary pulmonary nodules in patients with human immunodeficiency virus (HIV) have not been established.

What this paper contributes to our knowledge

The etiologies of solitary pulmonary nodules in HIV-infected patients are varied and difficult to diagnose. Sputum analysis is of no diagnostic value. Biopsy is necessary for definitive diagnosis and treatment.

Results

Ten HIV-infected patients were found to have SPN (Table 1). The mean age of the SPN-positive subjects was 45 years; 7 subjects were male and 3 were female. The CD4 cell counts ranged from 48 cells/μL to 439 cells/μL (mean 194.6 cells/μL); CD4 counts were < 200 cells/μL in 6 of the 10 index subjects. The most common symptoms were cough, shortness of breath, and chest pain. One patient presented with change in mental status, and one had epistaxis. All 10 patients were either current or past smokers and had smoked an average of one pack per day for 20 years.

Interestingly, 7 of the 10 had normal chest radiographs. Chest CT scans revealed SPNs ranging in size from 3 mm to 3 cm. Six of the 10 nodules were present in the left lung (5 in the upper lobe and one in the lower lobe). Upper lobe localization was noted for 3 of 4 right lung nodules, while one of 4 was centrally localized. The majority of all nodules (8/10) involved the upper lobe.

Sputum analysis was negative in all 10 affected patients. Bronchoscopy with bronchial washing and lavage, including transbronchial biopsy, was done in 9 of 10 patients and

Table 1. Clinical, Radiographic, and Other Diagnostic Profile and Etiology of Our Patients

Patient No.	Age, y	Sex	CD4 Cell Count, cells/μL	Symptoms	Chest Radiograph Findings	Computed Tomography Findings	Sputum Analysis	Other Diagnostic Tests	Etiology
1	44	Male	204	Cough/chest pain	Density overlying in the left upper lobe	1.5 cm left upper lobe nodule	Negative	Open lung biopsy, AFB stain	*Mycobacterium tuberculosis*
2	58	Female	83	Dehydration	2.6 × 2.6 cm well circumscribed nodule in the left lower lobe	2.2 × 2.6 cm well circumscribed nodule in left upper lobe	Negative	PTNB	Adenocarcinoma of the lung
3	70	Male	439	Shortness of breath/cough/ chest pain	Normal	3 mm nodule in the left upper lobe	Negative	Bronchoalveolar lavage, transbronchial biopsy, culture	*Candida albicans*
4	43	Female	137	Shortness of breath/cough/ chest pain	Normal	6 mm nodule in the lingula	Negative	Bronchoalveolar lavage, transbronchial biopsy, culture	*Candida albicans*
5	59	Female	48	Change in mental status	Normal	5 mm nodule in the left lower lobe	Negative	Bronchoalveolar lavage, transbronchial biopsy, culture	*Candida glabrata*
6	49	Male	51	Sore throat	2.8 × 1.8 cm nodule seen in right upper lobe	2.2 × 2.4 cm right upper lobe nodule	Negative	PTNB	*Cryptococcus neoformans*
7	65	Male	83	Fever	Normal	1.7 cm right upper lobe spiculated nodule	Negative	Bronchial washings, cultures for AFB, fungus, bacteria	Unknown
8	42	Male	100	Shortness of breath/cough	Normal	3 mm nodule in right middle lobe	Negative	Bronchial washings, cultures for AFB, fungus, bacteria	Unknown
9	40	Male	400	Cough	Normal	3 cm left lung nodule	Negative	Patient refused	Unknown
10	46	Male	401	Epistaxis	Normal	3 mm nodule in the left apex	Negative	Bronchial washings, cultures for AFB, fungus, bacteria	Unknown

PTNB = percutaneous transthoracic needle biopsy
AFB = acid fast bacillus

was diagnostic in 3 of 9 cases for presence of *Candida*. Two of the 10 cases had PTNB done, resulting in one diagnosis of adenocarcinoma of the lung, while the other case was diagnosed with *C. neoformans*. In one of the subjects an FDG uptake study was done and was inconclusive. This patient later had an open lung biopsy, which resulted in a diagnosis of tuberculosis. Diagnoses were not made in 4 of the 10 patients. Two of these 4 patients refused further work-up and were lost to follow-up. Two of the 4 patients were followed with watchful waiting, with no observation of change over a 2-year period. In summary, etiology was determined in 6 of the 10 patients. The etiology was infectious for 5 of the 10 patients: 3 patients had a *Candida* infection, one had a *C.* infection, and one had tuberculosis. Only one patient presented with a cancer diagnosis, and in 4 of the 10 patients no definitive diagnosis was possible.

Discussion

An SPN is defined as a single, discrete pulmonary opacity that is < 3 cm in diameter, surrounded by normal lung tissue, and not associated with adenopathy or atelectasis. Lesions > 3 cm are considered masses and are treated as malignancies until proven otherwise. In the United States, an estimated 150,000 SPNs are detected annually.[1] The presence of SPN in an HIV-infected person is rare, with a reported prevalence of 7.9 cases per 1,000 HIV-infected patients in one study.[2] In our study, we diagnosed fewer cases of SPN than might be expected, based on this reported prevalence. Between 2000 and 2009 we identified, diagnosed, and treated 10 of 5,000 HIV-infected patients with SPN. When SPN is seen on chest radiograph, the standard of care is to define whether the SPN is malignant

Table 2. Comparison of the Etiologies of Solitary Pulmonary Nodule in Patients Infected With Human Immunodeficiency Virus

Etiology	Martínez-Marcos et al[2]	Jasmer et al[3]	Present Study
Infection	6	3	5
Malignancy	1	2	1
Round atelectasis	1	0	0
Hamartoma	0	1	0
Unknown	2	1	4
Total	10	7	10

or benign, due to the high rate of association (95%) of SPN with malignancy in immunocompetent individuals.

Martínez-Marcos et al[2] studied 10 patients with HIV infection with SPNs. All of these patients underwent further diagnostic evaluation with CT scan, bronchoscopy, transthoracic needle biopsy, or thoracotomy to establish the final diagnosis. In their study, 6 of 10 had an infectious etiology, one was diagnosed with lymphoma, one presented with round atelectasis, and in 2 of the 10 patients the etiology remained unknown. In another study, done by Jasmer et al,[3] of the 7 HIV patients who had SPN, 3 had an infectious etiology, 2 had a malignant etiology, one had a hamartoma, and the etiology in one patient remained unknown. SPN etiology in our study agrees well with the findings of Martínez-Marcos et al[2] and Jasmer et al[3] (Table 2). In non-HIV infected patients, 50% of SPNs are of benign etiology, of which 80% have an infectious etiology.[4]

Infection is the most common cause of SPN in HIV-infected patients. The types of infectious agents reported in other studies include bacteria (*Nocardia*), parasites (*Echinococcus*), viruses (cytomegalovirus), and fungi (*Pneumocystis jiroveci*, *C. neoformans*, and *Mucormycosis*).[2] Our patients presented with fungal infection (*C. neoformans* and *Candida species*) and mycobacterial etiology.

C. neoformans is a life-threatening fungal pathogen, most commonly seen in AIDS patients, usually presenting as disseminated disease.[5-13] In 1996 the National Institutes of Health reported on 3 asymptomatic patients with small SPNs.[5] Each was found by routine surveillance radiographs as part of HIV-related study protocols. The CD4 cell counts of these patients ranged from 116 to 169 cells/μL. The nodules resolved in all 3 patients after 1–6 months of therapy with fluconazole. In our study the patient presented with a sore throat and incidentally was found to have a right upper lobe nodule, which was diagnosed as a cryptococcal nodule on PTNB. This patient's CD4 count was 51 cells/μL and responded to antifungal therapy.

Pulmonary candidiasis is a rare disease, and presentation as an SPN is even rarer. In one study, only 14 of 5,925 HIV-infected patients with pneumonia had *Candida* infection.[14] Three of our patients had candida infections: 2 had CD4 cell counts $<$ 200 cells/μL, and one had a CD4 cell count $>$ 500 cells/μL. Two of our patients presented with respiratory symptoms, while one presented with change in mental status. In all 3 patients the chest radiograph was negative, while CT scans showed SPNs ranging from 3 mm to 6 mm in size. Sputum analyses in these patients were normal, and diagnoses were made by culture of the tissue obtained from transbronchial biopsy. All 3 of these patients were treated with fluconazole, responded to treatment, and had radiological disappearance of the nodule on follow-up. It is interesting to note that all of these patients had sub-centimeter size nodules that were not visualized on chest radiograph. It is difficult to determine whether these patients had true *Candida* infections or whether the isolate represented a contaminant, given the sub-centimeter size of the nodules; however, patient response to antifungal treatment suggests that these represented true fungal infections.

One of our patients was diagnosed with adenocarcinoma of the lung following assessment of biopsy tissue. The risk of non-small-cell lung cancer seems to be greater in HIV-positive patients, especially in those who are smokers. Adenocarcinoma is the most frequent histological type. The prognosis is worse in HIV-infected patients than in the general lung cancer population.[15] Our patient was eventually diagnosed with stage IA non-small-cell lung cancer (adenocarcinoma) and was transferred to the surgical oncology service for further treatment.

In our study, one patient was diagnosed with pulmonary tuberculosis. This patient presented with cough. Chest radiograph revealed a density over the left upper lobe. A 1.5 cm nodule was found on CT scan, and the patient underwent bronchoscopy with bronchoalveolar lavage, which was inconclusive. Due to the peripheral location of the nodule, and because it was localized under a rib, PTNB and CT-guided biopsy were not possible. Open lung biopsy was planned and was preceded by FDG positron emission tomography (PET) to rule out any lymph node involvement in the mediastinum. Open lung biopsy revealed a necrotizing granuloma that was positive for acid-fast bacilli. The patient was treated with anti-tuberculosis therapy and was doing well at 1, 3, and 6 months follow-up.

SPNs larger than one centimeter are detectable by chest radiograph. Sub-centimeter size SPNs are usually not visualized. In our study we found that 7 of the 10 patients with SPN had normal findings on chest radiograph, but all had findings on chest CT scans. Chest CT scanning has many advantages over plain chest radiography, including better resolution of nodules and detection of nodules as small as 3–4 mm.[16] CT scan images also enhance characterization of the morphologic features of various lesions. It is noteworthy that chest radiography findings were nor-

mal in 2 patients with SPNs larger than 1 cm (patients 7 and 9). The location of the 3 cm nodule found in patient 9 in the lower left lobe of the lung may explain why it was not visible by chest radiograph. However, the 1.7 cm nodule in the upper right lobe of patient 7 seems less likely to be missed by chest radiograph. Due to the retrospective nature of this study, we are unable to speculate as to why the chest radiography findings were normal. In patients with normal chest radiography findings, CT scans were generally performed due to the presence of respiratory symptoms, for the purpose of ruling out pulmonary embolism or other interstitial lung disease that can sometimes be missed by chest radiograph. Regardless, our findings suggest that CT scan is considerably more sensitive in the detection of SPN than chest radiography, which was only abnormal in 30% of cases.

FDG-PET scan is one of the noninvasive methods that help differentiate malignant from benign lesions. Because malignant nodules have increased glucose metabolism, compared with benign lesions and healthy lungs, enhanced metabolic activity of the lesion increases the likelihood of malignancy. Metabolic activity of the lesion is assessed by injection of glucose analog 18-F-2 fluorodeoxyglucose. Reported sensitivity, specificity, and accuracy of FDG-PET scanning are $>$ 90%, 75%, and 90%, respectively,[17] and were validated by a meta-analysis of 40 studies evaluating 1,474 focal pulmonary lesions of any size.[18] FDG-PET scanning is an accurate and noninvasive imaging test for the diagnosis of pulmonary nodules and larger masses. FDG-PET should be interpreted with caution in differentiating benign from malignant pulmonary abnormalities, especially in geographic regions reporting a high prevalence of granulomatous lesions. Pulmonary tuberculoma causes an increase in FDG uptake, and this can be confused with malignancy. The role of PET scan in tuberculosis is limited; it may be useful for monitoring responses to anti-tuberculosis treatment.[19]

Sputum analysis is one of the most common tests done worldwide to determine the etiological agent of respiratory infection. The specimen may be either expectorated sputum or suctioned secretions, depending upon whether the patient is ill enough to require endotracheal intubation. The yield of sputum analysis is usually low and was found to be of no value for diagnosis in patients with SPN in the present study, which is supported by similar findings by Martínez-Marcos et al.[2]

Bronchoscopic sampling of the lower airways is a potential diagnostic method in patients with suspected pneumonia. However, for HIV-infected patients with SPN this was found to be of limited diagnostic value, both in the present study and the study reported by Martínez-Marcos et al.[2] Specimens can be obtained by bronchoalveolar lavage, routine brushing, washing, or protected specimen brushing. However, the yield may be limited if the process does not involve the airways and the alveoli.

Fiberoptic bronchoscopy and transbronchial biopsy are of limited use in the evaluation of a SPN located peripherally. Transbronchial biopsy using fiberoptic bronchoscopy has a diagnostic yield of only 14% if the lesions are $\leq$ 2 cm or when located in the peripheral third of the lung. The yield increases to 31% when lesions are located in the inner 2 thirds of the lung.[20] CT-guided percutaneous lung biopsy continues to be a relatively safe and accurate method of establishing tissue diagnosis for lung nodules. Diagnostic accuracy for percutaneous lung biopsies of nodules $\leq$ 1.5 cm was lower than that for nodules $>$ 1.5 cm (69.6% vs 81.3%, respectively). Pneumothorax rate and thoracostomy tube insertion rates were 34.5% and 5%, respectively.[21] Because of the invasive nature of the procedure, open lung biopsy is not usually done, but it should always be considered when other approaches are uninformative.

Endobronchial ultrasound is a newer diagnostic technique used for transbronchial biopsy of peripheral lesions. Kikuchi et al[22] used this technique to biopsy peripheral pulmonary lesions $<$ 30 mm in diameter in 24 patients. Of these 24 patients, diagnoses were made in 14 (58.3%). The diagnostic sensitivity was 53%, suggesting that endobronchial ultrasound is a useful technique for tissue sampling.

Conclusions

Infections and malignancy are the primary etiologies of SPN in HIV-infected patients, but infectious etiology is varied and difficult to predict. In the present study, as well as in other reports, infectious etiology was found to be the most common cause. Biopsy, either transbronchial, CT-guided, or open-lung, is necessary for diagnosis and treatment. Bronchial washings, bronchoalveolar lavage, and sputum analysis appear to have no diagnostic value in the diagnosis of SPN in HIV-infected patients.

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