Brucellosis and the Respiratory System

Article *in* Clinical Infectious Diseases · November 2003

DOI: 10.1086/378125 · Source: PubMed

6 authors, including:

Georgios Pappas
Institute of Continuing Medical Education of Ioannina
111 PUBLICATIONS **11,352** CITATIONS
SEE PROFILE

Mile Bosilkovski
University Clinic for infectious diseases and febrile conditions
49 PUBLICATIONS **2,357** CITATIONS
SEE PROFILE

MAJOR ARTICLE

Brucellosis and the Respiratory System

Georgios Pappas,[1] Mile Bosilkovski,[3] Nikolaos Akritidis,[2] Maria Mastora,[2] Liliana Krteva,[3] and Epaminondas Tsianos[1]

[1]Department of Internal Medicine, University Hospital of Ioannina, and [2]Department of Internal Medicine, Peripheral General Hospital "G. Hatzikosta," Ioannina, Greece; and [3]Clinic for Infectious Diseases and Febrile Conditions, Medical Faculty, Skopje, Former Yugoslav Republic of Macedonia

Brucellosis is a zoonotic disease that remains endemic worldwide. Its clinical manifestations and focal complications are often troublesome in making a diagnosis. Involvement of the respiratory system in brucellosis is an acknowledged but rare event that is only occasionally described in literature. We describe 37 cases of respiratory involvement during the course of brucellosis that presented as pneumonia, bronchopneumonia, pleural effusion with a predominance of monocytic or lymphocytic infiltrates, and paroxysmal dry cough. We also discuss aspects of the respiratory pathology, radiological characteristics, coexisting complications, and aspects of treatment of respiratory brucellosis.

Brucellosis is a major zoonotic disease that remains endemic in many developing countries and in rural areas of many developed countries around the world [1, 2]. It is commonly implicated in the everyday differential diagnosis in various clinical settings, because the peculiar presentations and complications of the infection are not rare [3]. Transmission is achieved through direct contact with contaminated animals, ingestion of infected dairy products, and inhalation of infectious aerosol particles. The last means of transmission is not only the route by which brucellae achieve direct contact with the respiratory system, but it is a route that has potential for use in biological warfare [4].

Among the most rare complications in the course of brucellosis are those involving the respiratory system. Most large studies of patients with brucellosis have only occasionally focused on the respiratory system, with an estimated rate of involvement of <1%–5% of cases [5]. Here, we review data on respiratory complications in 31 patients with brucellosis—to our knowledge, the largest report ever—from a total of 450 cases of brucellosis diagnosed in 3 hospitals of the Balkan Peninsula during a 3-year period. Moreover, we describe 6 additional patients who presented with respiratory complications of brucellosis in a retrospective study that used data from the archives of one of the participating hospitals.

PATIENTS, MATERIALS, AND METHODS

Brucellosis was diagnosed in 450 patients during the period from 1 October 1999 through 30 September 2002 at 3 reference hospitals on the Balkan Peninsula. The participating hospitals were the University Hospital of Ioannina (specifically, the Internal Medicine Department; Ioannina, Greece), Peripheral General Hospital "G. Hatzikosta" (specifically, the Department of Internal Medicine; Ioannina), and the Clinic for Infectious Diseases and Febrile Conditions (Skopje, Former Yugoslav Republic of Macedonia).

Of these 450 patients, 31 presented with a form of respiratory involvement. Data on 6 more patients with respiratory involvement in the course of brucellosis were retrieved from the archives at one of the participating hospitals (Peripheral General Hospital "G. Hatzikosta") for the years of 1995–1999; these patients were

Received 2 April 2003; accepted 11 June 2003; electronically published 8 September 2003.

Reprints or correspondence: Dr. Georgios Pappas, Dept. of Internal Medicine, University Hospital of Ioannina, 45110, Ioannina, Greece (gpele@otenet.gr).

Clinical Infectious Diseases 2003; 37:e95–9

1058-4838/2003/3707-00E1$15.00

considered to have definitely had pulmonary brucellosis.

For all 450 patients, the diagnosis of brucellosis was based on the following: (1) a positive result of an agglutination test for brucellosis (titers >1:320) with a compatible clinical presentation; (2) a 4-fold increase in the titer, as determined by an agglutination test, during the period of illness; (3) a positive result of a serologic test for brucellosis (i.e., detection of IgM antibodies by ELISA) in the absence of a history of brucellosis during the past year; or (4) isolation of *Brucella* species on culture of blood or pleural fluid specimens. In patients with respiratory involvement, other potential diagnoses and coinfections were excluded (i.e., blood cultures were negative for *Streptococcus pneumoniae;* sputum cultures were negative for common pathogens and mycobacteria; results of Ziehl-Nielsen smears of sputum samples were negative; results of dermal tuberculin tests were negative; results of serologic tests for *Mycoplasma* species, *Chlamydia pneumoniae, Coxiella burnetii,* and *Legionella* species were negative, both for acute- and convalescent-phase specimens; and the results of tests of urine samples for *Legionella pneumophila* antigen were negative). Presence of neoplasia was excluded by cytologic examination of sputum and pleural fluid samples and, in most cases, by resolution of symptoms noted by imaging studies (i.e., lobar pneumonia or pleural fluid noted on radiographs) during posttreatment follow-up.

All 450 patients underwent a thorough clinical examination, provided a chest radiograph, and, when pulmonary pathologic findings were present, underwent additional diagnostic evaluation, as described above. CT of the thorax was performed for 5 patients. Samples of pleural fluid were examined for 2 of the 4 patients with pleural effusion. Thirty-six of 37 patients with respiratory complications were observed throughout the period of treatment and after the resolution of infection, for a minimum observation period of 1 year. All 37 patients underwent additional evaluation for diagnosis of other focal complications of brucellosis.

RESULTS

Of the 450 patients in whom brucellosis was diagnosed, 31 had some respiratory pathologic finding. A retrospective search of the archives for the previous 5 years at one of the participating hospitals revealed 6 more hospitalized patients who had brucellosis with some form of respiratory involvement. The characteristics of patients with symptoms involving the respiratory system, the presenting symptom, the form of the respiratory involvement, and concurrent focal complications of brucellosis are shown in table 1.

Of the 37 patients with respiratory involvement, 25 were men and 12 were women. This 2:1 ratio was similar to the ratio for all patients with brucellosis. The median age of female patients was 53 years (range, 16–85 years). The median age for male patients was also 53 years (range, 29–74 years). The median age for female patients with respiratory involvement was similar to the median age of all female patients with brucellosis, whereas the median age for male patients with respiratory involvement was slightly higher than the median age for all male patients with brucellosis. Thirty-six of the 37 patients with respiratory complications had no previous history of respiratory manifestations of disease, and 1 patient reported that he had tuberculosis a decade before the diagnosis of brucellosis, for which he was adequately treated at that time. Thirty-five (94.5%) of the 37 patients presented with fever; its duration ranged from 7 to 180 days (median, 14 days) before the diagnosis of brucellosis was established.

Cough was reported by 25 patients (67.6%). Ten (27%) of these patients reported productive cough with expectoration, and 15 (40.5%) reported dry cough. One patient presented with paroxysmal, pertussis-like dry cough. Sputum cultures were performed for 7 of a total of 10 patients with expectoration. *Brucella* species were not isolated from any of the cultures. One patient presented with hemoptysis. Dyspnea was reported by 8 (21.6%) of 37 patients. Arterial blood gas values were only randomly determined for these patients, and, thus, the level of dyspnea cannot be adequately evaluated. However, only 1 patient needed respiratory assistance.

Of the 37 patients, 34 (91.9%) were hospitalized, and 3 were treated as outpatients. Chest radiography was performed for all patients at admission or presentation to the emergency department. The patterns of respiratory involvement for each patient are shown in table 1. Twelve (32.4%) of the 37 patients presented with typical lobar pneumonia. The right basal lobe was involved in 7 of the patients, the left basal lobe was involved in 2 of the patients, 1 patient presented with lobar pneumonia of the right middle lobe, and 1 presented with lobar pneumonia of the right upper lobe. One patient exhibited bilateral consolidations. An interstitial pattern was present on the chest radiographs for 15 patients (40.5%) with respiratory symptoms and brucellosis. The interstitial pattern was bilateral in 7 of the patients, involved mainly the right lobe in 7 patients, and involved the left lobe in 1 patient. For patients with unilateral interstitial involvement, paracardial basal infiltration was the usual presentation (5 of 8 patients). A honeycomb pattern was present in 4 patients (10.8%). All 4 of these patients reported extended duration of symptoms before the diagnosis of brucellosis. Four patients (10.8%) presented with pleural effusion. The effusion was bilateral in 1 patient and unilateral in 3 patients (left side in 1 patient and right side in 2 patients).

Sampling of the effusion was performed for 2 of the patients. Culture of pleural fluid specimens yielded *Brucella melitensis* on both occasions. Pleural fluid was characterized as suffusion (i.e., the pleural fluid protein to serum protein quotient was

Table 1. Clinical and epidemiological characteristics of patients with respiratory brucellosis.

Patient	Sex	Age, years	Presenting symptom(s)	Radiographic findings	Other complication(s)
1	M	38	Fever, cough	Interstitial pattern	Hepatitis, spondylitis
2	F	65	Fever, cough, dyspnea	Pleural effusion (right side)	Hepatitis, spondylitis
3	M	35	Fever, dyspnea	Interstitial pattern	Hepatitis, meningitis
4	F	76	Fever, sputum production	Interstitial pattern	Hepatitis, spondylitis
5	M	45	Fever, cough	Interstitial pattern	Hepatitis, spondylitis
6	F	63	Fever	Interstitial pattern	None
7	M	60	Fever, cough	Interstitial pattern	Hepatitis
8	F	16	Fever	Interstitial pattern	Hepatitis
9	M	57	Fever	Interstitial pattern	Hepatitis
10	F	63	Fever	Honeycomb pattern	Hepatitis
11	M	40	Fever	Left-side hilar lymphadenopathy	Hepatitis
12	M	45	Fever, sputum production	Lobar pneumonia (basal left side)	None
13	M	60	Fever, dyspnea	Lobar pneumonia (basal right side)	Spondylitis
14	F	38	Fever, sputum production	Interstitial pattern	None
15	M	62	Fever, cough	Honeycomb pattern	Hepatitis
16	M	29	Fever, cough	Interstitial pattern	Sacroiliitis
17	F	69	Fever, sputum production	Honeycomb pattern	None
18	M	63	Fever, dyspnea	Lobar pneumonia (basal left and right sides)	None
19	M	30	Fever, sputum production	Honeycomb pattern	Hepatitis
20	M	52	Fever, dyspnea	Lobar pneumonia (basal right side)	Hepatitis, spondylitis
21	M	72	Fever, cough	Lobar pneumonia (basal right side)	Hepatitis
22	F	69	Fever, cough	Lobar pneumonia (basal right side)	Spondylitis
23	M	74	Fever, sputum production, dyspnea	Pleural effusion (left side)	Epididymo-orchitis
24	M	71	Fever, cough	Lobar pneumonia (middle right side)	None
25	F	85	Fever, sputum production, dyspnea	Lobar pneumonia (basal right side)	Spondylitis
26	F	33	Lymphadenopathy	Bilateral hilar lymphadenopathy	Generalized lymphadenopathy
27	M	30	Paroxysmal cough	None	None
28	M	65	Fever, cough	Interstitial pattern	Spondylitis
29	M	61	Fever, cough	Interstitial pattern	Hepatitis
30	M	74	Fever, cough	Lobar pneumonia (basal right side)	Spondylitis
31	M	63	Fever, sputum production	Lobar pneumonia (upper right side)	None
32	M	61	Fever, cough	Interstitial pattern	Hepatitis, arthritis
33	F	43	Fever, cough	Interstitial pattern	None
34	M	59	Fever, cough	Interstitial pattern	Spondylitis
35	M	38	Fever, hemoptysis, dyspnea	Lobar pneumonia (basal left side), pleural effusion (left side)	Hepatitis
36	M	48	Fever, sputum production	Pleural effusion (bilateral)	Arthritis, epididymo-orchitis, hepatitis
37	F	59	Fever, sputum production	Lobar pneumonia (basal right side)	Spondylitis

>0.5) in both cases. Samples obtained from the first patient revealed mixed lymphocytes (55%) and mononuclear cells, whereas samples obtained from the other patient revealed predominantly mononuclear cells (95%). Pleural fluid in both patients was not considered suppurative. Two patients (5.4%) presented with hilar lymphadenopathy, as determined by chest radiography and additional CT. One patient presented with bilateral lymphadenopathy, and the other exhibited unilateral, left-side hilar lymphadenopathy. One patient did not exhibit any pathologic findings on chest radiographs. This patient presented with paroxysmal, pertussis-like dry cough. Diagnosis of brucellosis was based on serum agglutination test results for 33 of the 37 patients; the results were in concordance with the entire clinical presentation for the patients. For the remaining 4 patients, the diagnosis was based on conversion of the agglutination test result during hospitalization, positive IgM antibodies (as determined by ELISA), or culture results. Additional diagnostic tests were performed for 24 of the 33 patients

with an initially positive agglutination test result: ELISA was performed for 13 patients, and blood samples were obtained for culture from 21 patients. There were no data available on blood culture results for the 6 patients for whom data were collected from the archives.

Of the 37 patients with respiratory complications, 28 (75.6%) exhibited signs of another form of focal brucellosis. Hepatitis was the most common complication (18 patients [48.6%]); the signs varied from mild elevation of serum aminotransferase levels to profound, sustained cholestatic jaundice. Spondylitis was concomitantly present in 12 patients (32.4%); it mainly involved the lumbar spine in 10 patients, whereas 2 patients presented with dorsal spondylitis. Two patients had polyarthritis. Two patients had epididymo-orchitis. One patient presented with generalized lymphadenopathy, and 1 patient presented with meningitis. Eight (21.6%) of 28 patients exhibited >1 extrapulmonary complication of brucellosis.

Six of the 37 patients (those for whom data were obtained from the archive) were treated with a combination of tetracycline for 42 days and streptomycin for 14 days. Twenty-four patients were treated with a regimen of tetracycline or doxycycline plus rifampin for ⩾42 days. One patient was treated with doxycycline and rifampin for ⩾42 days. Six patients were treated with doxycycline, rifampin, and trimethoprim-sulfamethoxazole for ⩾45 days. The variation in the regimens used reflects the different policies of the institutions involved in this study or different policies of the same institution through time. All patients were considered to have been cured of the respiratory involvement after 6 weeks of treatment. Nevertheless, some patients continued to receive treatment or part of the treatment regimen for a prolonged period (up to 210 days) because of other complications (mainly spondylitis).

DISCUSSION

The aim of this article was to examine the incidence and the modes of involvement of the respiratory system in the course of brucellosis. Although the disease is systemic and exhibits a potential for granuloma formation, the respiratory system is only occasionally involved, which is not the case for other granulomatous diseases. This seems to be the case even in patients in whom airways serve as the presumed or definite entrance of *Brucella* species into the human body.

Pulmonary manifestations of brucellosis are not unknown in our region [6]. As with most infectious diseases, the incidence of the disease—and, thus, the potential for peculiar presentations of it—parallels the interest in the disease shown by medical personnel in the region. Still, even in studies from countries where brucellosis is almost epidemic, the percentage of reported cases with respiratory involvement is extremely low. One has to bear in mind that definitions of "respiratory involvement" vary. It is well known that brucellosis can initially present with atypical symptoms not unlike the symptoms of most mild upper respiratory tract infections. This presentation could be considered the respiratory mononuclear cells' reaction to the invading microbe; it is not considered to truly be "respiratory involvement" by us or by most other specialists, unless it takes a prolonged and paroxysmal course.

In our study, the incidence of respiratory involvement approached 7%, which is, by far, the highest percentage reported. Still, as in most studies, respiratory involvement should be considered a rare focal form of brucellosis, because osteoarticular, genitourinary, and reticuloendothelial system complications are far more common. Moreover, pulmonary complications are rarely serious and readily respond to the usual regimens used for treatment of uncomplicated brucellosis. In our study, none of the patients required prolonged antibiotic therapy for respiratory complications, and none of the patients exhibited serious deterioration of respiratory function.

Of interest is the fact that none of our patients exhibited any previous respiratory manifestations of disease. Brucellosis can often trigger an exacerbation of existing underlying conditions in certain target organs [7], and, thus, one would expect the disease to act, for example, as the trigger of an acute exacerbation of chronic bronchitis or pneumonia in patients with a previous lung condition (e.g., bronchiectasis or neoplasia). Sputum cultures did not yield brucellae for any of our patients. In fact, such isolation has only been rarely reported in the past [8].

Indirect evidence of the pathogenesis of respiratory involvement in brucellosis can be drawn from the characteristics of the pleural fluid obtained from 2 of our patients. One patient presented with pleural effusion characterized by an especially intense mononuclear infiltration. There are other reports linking unusual complications of brucellosis to intense topical mononuclear activation [9]. Still, the exact pathologic characteristics of the process and the reasons for its localization are unclear. One can presume that the same pathway, with a generalized mononuclear activation of the respiratory tree (or part of it), accounts for our patient who presented with a pertussis-like illness.

There are few reports of respiratory involvement in brucellosis, many of which are case reports [10]. Empyema [11–13], pleural effusion [14], granulomas and solitary nodules [15, 16], interstitial pneumonia [17], hilar and paratracheal lymphadenopathy [18], and even pneumothorax [18] have all been reported. Often, respiratory symptoms are the presenting or even the sole symptoms of brucellosis [19]. Military mottling has also been reported [8], thus raising an important issue: it can be difficult to differentiate respiratory brucellosis from tuberculosis [20]. Most regions where there is an increased incidence of brucellosis are also areas where tuberculosis is endemic [21]. Moreover, the clinical presentation of both diseases is often

identical. The burden of empirically and unnecessarily treating a patient who has brucellosis with antituberculous medications, as well as the fact that agents such as rifampin and streptomycin can act against both brucellae and mycobacteria, underlines the need for additional diagnostic evaluation in these cases. In our opinion, it is only in cases in which it is difficult to differentiate respiratory brucellosis from tuberculosis that bronchoscopy would be truly beneficial to the patient.

In conclusion, we should emphasize that—and this is of paramount importance in areas where brucellosis is endemic—the clinician should never forget brucellosis, even the clinician who specializes in respiratory diseases. Prompt recognition and treatment not only is beneficial to the patient, but it also allows the clinician to readily differentiate brucellosis from tuberculosis and neoplasia, thus excluding the need for unnecessary invasive procedures.

References

1. Corbel M. Brucellosis: an overview. Emerg Infect Dis **1997**; 3:213–21.
2. Young E. An overview of human brucellosis. Clin Infect Dis **1995**; 21: 283–9.
3. Colmenero JD, Reguera JM, Martos F, et al. Complications associated with *Brucella melitensis* infection. Medicine (Baltimore) **1996**; 76:195–211.
4. Kaufmann A, Meltzer M, Schmid G. The economic impact of a bioterrorist attack: are prevention and postattack intervention programs justifiable? Emerg Infect Dis **1997**; 3:83–94.
5. Lubani MM, Lulu AR, Araj GF, Khateeb MI, Qurtom MA, Dudin KI. Pulmonary brucellosis. Q J Med **1989**; 71:319–24.
6. Papiris SA, Maniati MA, Haritou A, Constantopoulos SH. *Brucella* haemorrhagic pleural effusion. Eur Respir J **1994**; 7:1369–70.
7. Akritidis N, Pappas G. Ascites caused by brucellosis: a report of two cases. Scand J Gastroenterol **2001**; 36:110–2.
8. Gattas N, Loberant N, Rimon D. Miliary and reticulo-nodular pulmonary brucellosis. Harefuah **1998**; 135:357–9, 407.
9. Noble JT, Mark EJ. Case records of the Massachusetts General Hospital: weekly clinicopathological exercises. Case 22-2002: a 37-year-old man with unexplained fever after a long trip through South America. N Engl J Med **2002**; 347:200–6.
10. Weed LA, Slos PT, Clagett OT. Chronic localized pulmonary brucellosis. JAMA **1956**; 161:1044–7.
11. Garcia-Rodriguez JA, Garcia-Sanchez JE, Munoz Bellido JL, Ortiz de la Tabla V, Bellido Barbero J. Review of pulmonary brucellosis: a case report on brucellar pulmonary empyema. Diagn Microbiol Infect Dis **1988**; 11:53–60.
12. Al-Eissa YA. Unusual suppurative complications of brucellosis in children. Acta Paediatr **1993**; 82:987–92.
13. Mili N, Auckenthaler R, Nicod LP. Chronic brucella empyema. Chest **1993**; 103:620–1.
14. Kerem E, Diav O, Navon P, Branski D. Pleural fluid characteristics in pulmonary brucellosis. Thorax **1994**; 49:89–90.
15. Cobo F, Aliaga L, de Cueto M, Cueto A, de La Rosa M. Solitary lung nodules produced by *Brucella melitensis.* Enferm Infecc Microbiol Clin **2001**; 19:452–3.
16. Webb WA, Thoroughman JC. Solitary pulmonary nodule due to *Brucella suis:* report of a case. Dis Chest **1966**; 49:222–4.
17. Jubber AS, Gunawardana DR, Lulu AR. Acute pulmonary edema in *Brucella* myocarditis and interstitial pneumonitis. Chest **1990**; 97:1008–9.
18. Patel PJ, Suhaibani H, Al-Aska AK, Kolawole TM, Al-Kassimi FA. The chest radiograph in brucellosis. Clin Radiol **1988**; 39:39–41.
19. Abu-Ekteish F, Kakish K. Pneumonia as the sole presentation of brucellosis. Respir Med **2001**; 95:766–7.
20. Takahashi H, Tanaka S, Yoshida K, et al. An unusual case of brucellosis in Japan: difficulties in the differential diagnosis from pulmonary tuberculosis. Intern Med **1996**; 35:310–4.
21. Giner Escobar P, el Amrani A, Corrales Torres AJ, Guijarro Jorge R, Sanchez-Palencia Ramos A, Jimenez-Alonso J. Simultaneous isolation of *Brucella melitensis* and *Mycobacterium tuberculosis* in pleural empyema. Enferm Infecc Microbiol Clin **1990**; 8:595.