The mask of acute bacterial pneumonia may disguise the face of tuberculosis

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Abstract

Introduction: Pulmonary tuberculosis (TB) can present as acute pneumonia. Differentiation of tuberculous from non-tuberculous community-acquired pneumonia (CAP) is an important challenge in endemic areas. The purpose of this study was the comparison between characteristics of tuberculous and non-tuberculous CAP patients.

Methods: In this prospective and observational study, all adult patients (aged ≥16 years) who were admitted to Imam Reza Hospital in Mashhad (Iran) with the diagnosis of CAP, between February 2013 and January 2014, were enrolled. Clinical, radiological, and microbiological data of the patients were collected and reviewed. Statistical analyses were performed using SPSS 14 software and R programming language.

Results: We studied 120 patients with diagnosis of acute CAP including 21 (17.5%) tuberculous and 99 (82.5%) non-tuberculous CAP. The etiologies of CAP in the latter group were as follow: S. pneumoniae 29 (29.3%), followed by S. aureus, polymicrobial including anaerobes, and other agents. The diagnosis of pneumonia remained unknown in 49 (40%) patients. We found approximately equal gender distribution among two study groups (14/21 vs. 61/99, 63.6% vs. 62.9%, p=0.948). Fifty percent of patients with tuberculous CAP had opioid addiction that was more frequent compared with non-tuberculous group (p=0.240). 52.4%, 63.2%, 30%, and 90% of patients with tuberculous CAP had severe presentation based on PSI, IDSA/ATS, CURB-65, and SMART-COP, respectively.

Conclusions: The diagnosis of TB should be considered in all patients who presented with CAP in endemic regions. It could not be differentiated from other causes of pneumonia on clinical and radiological grounds.

Keywords: Pneumonia, Tuberculosis, Community-Acquired Pneumonia

1. Introduction

1.1. Background and study logic

According to the WHO in 2011, there were an estimated 8.7 million new (incident) tuberculosis (TB) cases worldwide, of which 1.4 million people died. In 2009, more than 2 billion people were infected with TB bacilli, and 1 out of 10 of those infected developed active TB (1). Tuberculosis is a major public health problem in Iran. According to the Administration of Tuberculosis and Leprosy Control, a department of the Ministry of Health and Medical Education in Iran, in 2010, a total of 10,485 old and new cases of TB were reported in Iran and of these cases, 326 patients (2.2%) were HIV positive (2). In 2012, the incidence rate of TB was estimated as 21 cases per 100,000 population in Iran (3). As of 2014, the WHO estimates this rate as 22 per 100,000 population with 0.8% multi-drug resistant new cases of TB (1). One of the challenges associated with diagnosis of tuberculosis is

differentiation of pulmonary TB from other common etiologies of community-acquired pneumonia (CAP). Streptococcus pneumoniae is the most common cause of CAP in many countries. However, there are considerable geographic differences in the incidence of other pathogens. Many studies from different parts of the world found that TB is common among patients presenting with CAP. Data show that Mycobacterium tuberculosis is an important cause of CAP in many parts of Asia (4). The classic clinical picture associated with active pulmonary TB is chronic productive cough accompanied by weight loss/anorexia, fever, night sweats, and hemoptysis. However, pulmonary TB sometimes presents as an acute/subacute pneumonia. According to David Schlossberg, "clinicians should err on the side of caution and expand the initial differential diagnosis in patients who presented with the clinical and radiologic manifestations of CAP". He noted that "TB remains a resourceful mimic, and the consequences of missing the diagnosis can be disastrous." (5) Although pulmonary TB is known as a chronic disease, it can present as acute pneumonia. Differentiation of tuberculous from non-tuberculous CAP is an important challenge in endemic areas of TB like Iran. Mashhad, the capital city of the Khorasan Razavi Province, in the northeast of Iran, is the second most populous city in Iran and the second-largest holy city in the world and attracts more than 20 million pilgrims every year. These factors make this city so vulnerable to communicable diseases, especially TB. In 2013, the Iranian Ministry of Health and Medical Education reported an annual incidence rate of 10.59 per 100,000 population for TB in Razavi Khorasan (6). Recently, in a single center study we reported that 17.5% of admitted CAP patients in Mashhad had pulmonary tuberculosis (7). So, it is very important to note that TB should be always kept in mind for decision making and empirical treatment of CAP in endemic regions. It has been suggested that care should be taken with an empirical use of antibiotics with anti-tuberculous activity, such as fluoroquinolones, which may lead to a partial response, mask diagnosis and ultimately promote the development of drug-resistant TB, especially in patients who presented with CAP in TB-endemic regions (4).

1.2. Objectives
The purpose of this study was the comparison between characteristics of tuberculous and non-tuberculous CAP patients. For this reason, we studied hospitalized adult patients with CAP, and performed a comparative analysis on their clinical and para-clinical characteristics. To our knowledge, this is the first study conducted prospectively with the aim of comparing these two groups of CAP patients in our region.

2. Material and Methods
2.1. Research design and setting
This study is the second arm of our previous study on etiologic diagnosis of CAP. The study design was prospective, and observational. We included in this study nearly all adult patients (aged ≥16 years) admitted to Imam Reza Hospital in Mashhad, Iran, between February 2013 and January 2014 with the diagnosis of CAP.

2.2. Selection of participants
To take part in this study, patients were required to have an infiltrate on chest radiograph with fever or clinical signs/symptoms of lower respiratory tract infection, or both. Patients with chronic pneumonia (more than four weeks), pneumonia defined as acute from symptoms lasting less than 4 weeks, recent chemotherapy with or without iatrogenic neutropenia during the previous 3 months, patients with a history of transplantation, pneumonia triggered by hospitalization or during the previous 3 months, and patients with an unsigned informed consent form were excluded from the study. From the original 166 patients with community-acquired lower respiratory tract involvement with chest infiltrates, 140 cases were deemed eligible for this study. Of the patients who were secondarily excluded, there were 20 who had lower respiratory symptoms and infiltrates on chest radiography with an emerging alternative/non-infectious diagnosis during the follow-up (e.g. pulmonary emboli or malignancy). Finally, 120 patients with the diagnosis of acute CAP with infectious etiology including 21 with final diagnosis of pulmonary TB and 99 with non-tuberculous etiologies of CAP were included and statistically analyzed. Elderly was defined for this study as individuals aged 65 years and older. Definition of opium addiction was specified as: lack of control of drug habit, craving, compulsive use, and apathy towards self-harm (8).

2.3. Data collection and methods
Following collection of clinical, radiological, and microbiological data of the patients, sputum specimens were immediately sent to the microbiological laboratory for processing. Except for endotracheal aspiration for patients with early endotracheal intubation, no other special procedures were performed in order to obtain sputum samples if they were unable to obtain them spontaneously. Diagnostic tests which were performed in this study include staining of sputum or other body specimens using Ziehl-Neelsen staining for detecting mycobacteria, Gram staining of the purulent portion of sputum specimens and bacterial culture specimens of acceptable quality, blood inoculation in

standard BACTEC and aerobic/F (Becton Dickinson, Limerick, Ireland), M. tuberculosis DNA extraction from clinical samples using an M. tuberculosis Real-Time PCR Kit [Rotor-Gene^{TM} 3000 (Corbett Life Science)] in the event of negative direct smears, unconcentrated urine sample testing with immunochromatographic assay Binax NOW S. pneumoniae antigen (Binax, Maine, USA) and Binax NOW L. pneumophila antigen (Binax, Maine, USA) for S. pneumonia antigen and L. pneumophila serogroup 1 antigen detection, influenza virus detection and purification using RT-PCR with a QIAGEN Real-Time Detection Kit on respiratory specimens, and establishing PCT level by semi-quantitative solid-phase immunoassay (B.R.A.H.M.S. PCT-Q, B.R.A.H.M.S.-Diagnostica GmbH, Hennigsdorf, Germany) on 200 µl plasma. Serologic and molecular diagnostic tests for Mycoplasma pneumoniae Chlamydophila psittaci, Chlamydophila pneumoniae, and Coxiella burnetii, and viruses were not used in our study, except for PCR for influenza virus. According to the reference scale provided, PCT levels were classified into four groups (< 0.5 µg/l; 0.5-< 2 µg/l; 2-< 10 µg/l; = 10 µg/l). The tests were carried out within the first 12-hour period of the patients' admission. If one or more initial sputum (or other related respiratory or non-respiratory fluids) smear examinations was positive for acid-fast bacilli (AFB) or positive PCR for M. tuberculosis on body fluids was identified, the etiology of the CAP was classified as definite tuberculous CAP. Presumptive diagnosis of tuberculous CAP was defined as clinical, laboratory and radiological findings consistent with pulmonary TB having no response to empirical antibiotic therapy and having other etiological agents ruled out; M. tuberculosis was not isolated in these circumstances. All other patients were defined as non-tuberculous CAP.

2.4. Statistical analysis
Statistical analyses were performed using SPSS 14 software and R programming language. Discrete variables are expressed as counts (percentage) and continuous variables as mean ± standard deviation (SD), unless stated otherwise. Frequency comparison was done by chi-square test or Fisher's exact test for categorical variables and Student's t test or the Mann-Whitney U test for continuous variables. $P < 0.05$ was considered significant.

2.5. Research ethics
Patients gave written informed consent and the study was approved by the Ethics Committee of Mashhad University of Medical Sciences (Code: 900983). There was no deviation from the routine treatment approaches and patients were free to withdraw from the study at any time if they wished.

3. Results
We studied 120 patients with diagnosis of acute CAP including 21 (17.5%) tuberculous and 99 (82.5%) non-tuberculous CAP. The etiologies of CAP in the latter group were as follow: S. pneumoniae 29 (29.3%), followed by S. aureus, polymicrobial including anaerobes, and other agents. The diagnosis of pneumonia remained unknown in 49 (40% of all cases) of patients. We found approximately equal gender distribution among two study groups (14/21 vs. 61/99, 63.6% vs. 62.9%, p=0.948). Patients with tuberculous CAP were younger compared with non-tuberculous patients (46.6±21 vs. 51.2±22.5) but the difference in mean age was not statistically significant (p=0.386) (Table 1). The most common presenting clinical symptoms in both groups were cough and fever, followed by dyspnea, sputum production, chest pain, and hemoptysis. However, cough (90.9% vs. 83.9%), sputum production (75% vs. 50.9%), and weight loss (45.5% vs. 8.6%) were more common in the tuberculous group (90.9% vs. 83.9%), whereas history of fever (84.8% vs. 77.3%), dyspnea (79.6% vs. 72.7%), and chest pain (19.6% vs. 13.6%) were more frequent in the non-tuberculous group. Both groups had approximately equal frequency of hemoptysis (13%). Study groups differed significantly in duration of symptoms before admission (16.5±8.8 vs. 8.1±5.1, p=0.001) that was longer in patients with tuberculous CAP. The frequency of tachypnea, hypotension, and tachycardia were not significantly different between the two groups, however, patients with non-tuberculous CAP were more commonly febrile at the time of hospital admission (85.2% vs. 47.6%, p=0.01). The frequency of high grade fever (temperature > 38.2) was also significantly higher in non-tuberculous group (80.5% vs. 47.6%, p=0.002) (Table 2). Although patients with non-tuberculous CAP were more commonly hypoxic at presentation (76.2% vs. 62.9%) the difference was not statistically significant (p=0.25). The frequency of severe hypoxia (arterial oxygen saturation <85%) was also approximately equal for both groups (47.6% and 43.7%, p=0.744). No significant difference was seen in IVRS requirement between two groups (38.1% vs. 30.5%, p=0.501). In-hospital mortality (IHM) was equal in two groups (22.9% vs. 23.7%; p=0.665). Two (1.6%) patients with CAP were diagnosed to have HIV infection. Fifty percent of patients with tuberculous CAP had opioid addiction that was more frequent compared with non-tuberculous group (p=0.240). Laboratory characteristics on admission were also compared between two groups, including the value of white blood cells count, polymorphonuclear (percent), platelet count, hematocrit level, and PCT level. Hematocrit level<36% (p=0.01) and PCT level >0.5 (p=0.001) were the only parameters that were significantly different between these two groups (Tables 3). Among patients with final diagnosis of pulmonary CAP, 8 (38.1%) cases

received multidrug anti-tuberculous agents empirically in the 1st 24-hour antibiotic treatment regimen. In comparing the two study groups, there were no significant differences in severity of CAP based on pneumonia severity index (PSI) (p=0.378), Infectious Diseases Society of America/American Thoracic Society (IDSA/ATS) (p=0.800), CURB-65 (p=0.478), and SMART-COP (p=0.659) scoring systems. 52.4%, 63.2%, 30%, and 90% of patients with tuberculous CAP had severe presentation based on PSI, IDSA/ATS, CURB-65, and SMART-COP, respectively (Table 4).

Table 1. Comparison between demographic characteristics of patients with pulmonary tuberculosis and other etiologies of community acquired pneumonia.

Demographic characteristics	Non-tuberculosis CAP	Tuberculous CAP	p-value
Age, yrs.	51.2±22.5	46.6±21	0.386
Sex, male	61 (62.9%)	14 (63.6%)	0.948
Opioid Addiction	35 (36.5%)	11 (50%)	0.240

CAP: Community Acquired Pneumonia; Yrs: years old

Table 2. Comparison between symptoms signs of patients with pulmonary tuberculosis and other etiologies of community acquired pneumonia.

Symptoms & Signs	Non-tuberculosis CAP	Tuberculous CAP	p-value
Duration of symptoms, days	8.1±5.1	16.5±8.8	0.001
Cough	78 (83.9%)	20 (90.9%)	0.615
Sputum	27 (50.9%)	9 (75%)	0.130
Fever	78 (84.8%)	17 (77.3%)	0.596
Dyspnea	74 (79.6%)	16 (72.7%)	0.680
Hemoptysis	12 (13%)	3 (13.6%)	1.000
Chest pain	18 (19.6%)	3 (13.6%)	0.735
Weight loss	8 (8.6%)	10 (45.5%)	0.001
Tachypnea	78 (88.6%)	18 (81.8%)	0.617
Hypotension	18 (20.9%)	5 (22.7%)	1.000
Tachycardia (HR>90)	76 (88.4%)	16 (72.7%)	0.132
Fever (Temp>37.9)	75 (85.2%)	12 (57.1%)	0.010
High grade fever (Temp>38.2)	70 (80.5%)	10 (47.6%)	0.002
Parapneumonic effusion	28 (29.5%)	8 (36.4%)	0.528

Table 3. Comparison between laboratory test results of patients with pulmonary tuberculosis and other etiologies of community acquired pneumonia.

Laboratory test		Non-tuberculosis CAP	Tuberculous CAP	p-value
Leukopenia (White blood cell<4000/µl)		12 (17.1%)	2 (12.5%)	0.937
Leukocytosis (White blood cell>12000/µl)		20 (28.6%)	3 (18.8%)	0.626
Polymorphonuclear (%)		81.6±14	84±9.3	0.565
Severe Thrombocytopenia (Platelets<100 000/µl)		18 (18.1 %)	4 (20%)	1.000
Anemia (Hematocrit <36%)		46%	82%	0.01
PCT, ng/mL	>2ng/ml	53 (57.6%)	1* (4.5%)	0.001
	>0.5ng/ml	74 (80.4%)	4 (18.2%)	0.001

PCT: Procalcitonin level.

Table 4. Comparison between severe pneumonia parameters in patients with pulmonary tuberculosis and other etiologies of community acquired pneumonia.

Severe Pneumonia Parameters	Non-tuberculosis CAP	Tuberculous CAP	p-value
Shock requiring vasopressor	8 (8.5%)	2 (9.1%)	0.807
IVRS requirement	29 (30.5%)	8 (38.1%)	0.501
Altered mental status	31 (33.3%)	7 (31.8%)	0.892
Hypoxia (SaO2<92%)	56 (62.9%)	16 (76.2%)	0.250
Severe Hypoxia (SaO2<85%)	38 (43.7%)	10 (47.6%)	0.744
PSI≥ 4	59 (62.8%)	11 (52.4%)	0.378
IDSA/ATS 2007 criteria	54 (59.3%)	12 (63.2%)	0.800
CURB-65≥ 3	35 (38.5%)	6 (30%)	0.478
SMART-COP≥ 3	83 (83%)	18 (90%)	0.659
In-Hospital Mortality	22 (22.9%)	6 (23.7%)	0.665

IVRS: intensive vasopressor or respiratory support; SaO2: arterial oxygen saturation; µl: microliter; ng: nanograms; PSI: Pneumonia Severity Index; IDSA/ATS: Infectious Diseases Society of America/American Thoracic Society; CURB-65: acronym for Confusion, blood Urea level, Respiratory rate, Blood pressure, age≥65 years old; SMART-COP: acronym for Systolic blood pressure, Multilobar chest radiography involvement, low Albumin level, high Respiratory rate, Tachycardia, Confusion, poor Oxygenation.

4. Discussion

M. tuberculosis is an important cause of CAP in developing countries. TB can present as an acute process and mimic classic bacterial pneumonia or masquerade as an atypical pneumonia, with nonproductive cough and systemic symptoms. As such, it should be included in the differential diagnosis of CAP. Both primary and reactivation TB can cause acute manifestations (5). M. tuberculosis is an important cause of lower respiratory infection in many parts of Asia. Peto et al., (4) suggested that decisions about the choice of routine investigations performed for CAP and the choice of empirical treatment should reflect this fact. Although the use of fluoroquinolones as empirical treatment for CAP is appropriate even in regions endemic for TB, indiscriminate use of fluoroquinolones in suspected CAP should be avoided, and critical judgement on the possibility of TB should be considered in patients who present with CAP (5). Missed diagnosis is common as illustrated in a report from Baltimore in which 16 of 33 patients (48%) with culture-confirmed pulmonary TB were initially treated for presumed CAP (9). Of our patients, 17.5% were finally diagnosed as pulmonary TB that demonstrated the important role of M. tuberculosis in the etiology of CAP in our region. The incidence of TB being diagnosed among patients presenting with clinical and radiological signs of a CAP has varied in different series. Previously, studies from China, Japan, Kenya, and Sub Saharan Africa also demonstrated high prevalence of pulmonary TB (9-20.5%) in patients who presented with CAP (10-14). M. tuberculosis was the second most common pathogen (12%) identified in the study performed by Levy et al., (15) in Hong Kong. In the latter study, only patients who presented with features of acute pneumonia were included and those with chronic illness or typical radiologic changes suggestive of TB were excluded. A similar high incidence of TB (10%) among subjects presenting with acute pneumonia had been reported in France (11). In the studies by Nyamande et al., (12) in Sub Saharan Africa and Scott et al., (14) in Kenya, a large number of CAP patients were diagnosed as HIV positive (81.4% and 52%, respectively). However, in our study, only two patients were diagnosed to have HIV infection (1.6%). Of tuberculous CAP patients who were opioid addicted, there were 50%, and 23.8% of them had underlying chronic diseases. In addition to epidemiologic clues, many clinical clues have been suggested that might prompt consideration of a tuberculous etiology. These include duration of symptoms more than 2 weeks prior to admission, upper lobe involvement or cavitary infiltrates on chest radiograph, lymphopenia, total white blood cell count ≤12 × 109/l on admission, night sweats, failure to respond to routine therapy of CAP, relapse following fluoroquinolone administration, relapse following corticosteroid administration, Gram stain with weakly gram-positive or gram-neutral rods (ghosts), signs of healed TB, e.g. fibrocalcific changes, apical capping, Ghon's complex, pneumothorax, and pleural effusion. Identification of these features at presentation, clearly strengthens the diagnostic suspicion of TB (5, 16, 17). According to the literature review performed by Grossman et al., TB is not associated with a rapid response to antimicrobial therapy even when treated with appropriate multidrug regimens. In contrast, some clinical improvement is usually seen within 2 to 3 days of appropriate antimicrobial treatment of patients with non-tuberculous CAP (5). When we compared clinical and laboratory characteristics between patients with tuberculous and non-tuberculous CAP, these two groups differed significantly in the frequency of weight loss, absence of fever on admission, anemia, and duration of symptoms before admission. High grade fever at presentation, was significantly lower among patients with pulmonary TB.

Although the frequency of associated exudative pleural effusion was higher in tuberculous CAP patients, the difference was not statistically significant. PCT level does not appear to be significantly elevated in patients with pulmonary TB, making it an attractive potentially rapid diagnostic method for differentiating pulmonary TB from bacterial CAP. Although there are studies that found PCT level as an unreliable indicator for diagnosis of pulmonary TB (18), most others demonstrated that the PCT level in patients with pulmonary TB is significantly lower than patients with other etiologies of CAP (19, 20). Additionally, several studies showed that high level of PCT among patients with pulmonary TB is an indicator of adverse outcome (19, 20). In the study conducted by Kang et al., (21) the median PCT level was 0.514 ng/mL (range, 0.01 to 27.75) with bacterial CAP and 0.029 ng/mL (range, 0.01 to 0.87) with pulmonary TB. They concluded that the high sensitivity and negative predictive value for differentiating pulmonary TB from bacterial CAP, suggested a supplementary role of PCT in the diagnostic exclusion of pulmonary TB from bacterial CAP in areas with an intermediate prevalence of pulmonary TB. Our study, similarly to most others, demonstrated significantly lower PCT levels in patients with tuberculous CAP compared with the non-tuberculous group however, it was not associated with higher rates of IHM and IVRS requirement among patients with TB. PCT level was significantly associated with poor outcome and IVRS requirement in patients with other etiologies of CAP. In the study performed by Levy et al., (22) the incidence rate of 1.5% has been reported for acute respiratory failure among patients who present with tuberculous hospitalized CAP. In our study, 22.7% and 76.2% of patients with tuberculous CAP developed hypotension and hypoxia, respectively. These rates were not significantly higher compared with non-tuberculous CAP patients. Of patients with tuberculous CAP 38.1% required IVRS. Feng et al., (23) found that higher PSI scores were independently associated with the presence of concomitant pulmonary TB in both health care associated pneumonia (HCAP) and CAP patients. However, severity assessment of CAP based on pneumonia severity index (PSI), Infectious Diseases Society of America/American Thoracic Society (IDSA/ATS), CURB-65, and SMART-COP scoring systems, showed no significant difference between our two study groups. IHM was 23.7% among tuberculous CAP patients which was higher than the non-tuberculous group.

5. Conclusions

Although pulmonary TB is known as a chronic disease, it can present as acute pneumonia. Differentiation of tuberculous from non-tuberculous CAP is an important challenge in endemic areas of TB like Iran. Regarding the fact that M. tuberculosis was the etiologic agent responsible for 17.5% of our acutely presented CAP patients, it seems rational to emphasize that the diagnosis of TB should be considered in all patients who presented with CAP in our region. It could not be differentiated from other causes of pneumonia on clinical and radiologic grounds, although patients with tuberculous CAP had significantly higher frequency of weight loss, anemia, absence of fever on admission, and longer duration of symptoms before presentation. PCT level is significantly lower among the tuberculous CAP group. This study suggested that the severity of illness is also not useful in differentiation of tuberculous from non-tuberculous CAP. Patients with tuberculous CAP had higher IHM, however, it was not statistically significant.

Conflict of Interest:
There is no conflict of interest to be declared.

Authors' contributions:
All authors contributed to this project and article equally. All authors read and approved the final manuscript.

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