Journal of Infectious Diseases & Preventive Medicine

Liu et al., J Infect Dis Preve Med 2017, 5:2
DOI: 10.4172/2329-8731.1000161

Research Article Open Access

Previous Treatment Failure or Default Increased the Risk of Massive Hemoptysis in PTB Patients

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Received date: February 23, 2017; **Accepted date**: April 10, 2017; **Published date**: April 17, 2017

Abstract

Backgroud: Hemotysis is one of the hallmark symptoms in pulmonary tuberculosis (PTB), which always causes great anxiety and rarely ignored by the patient. Massive hemoptysis is one of the major causes of death in PTB patients.

Objectives: To evaluate the independent association of risk factors with the occurrence of massive hemoptysis in PTB patients.

Methods: Observational retrospective study of PTB patients with hemoptysis hospitalized in the fifth affiliated hospital of Sun Yat-sen University. Patients were categorized into subjects with massive hemoptysis and with mild-moderate hemoptysis. Independent associations of variables with massive hemoptysis were estimated using univariate analysis.

Results: Of 168 subjects with PTB with hemoptysis, 76 (45.23%) reported the presence of massive hemoptysis. In univariate analysis, retreatment cases were more likely to present massive hemoptysis (P=0.020), especially those who had failed or defaulted treatment (P=0.029). Between the two groups, no significant differences were found in the distribution of demographic characteristics and poor radiographic presentations. There were no significant differences in co-morbid diabetes mellitus (DM), lung infection, or bronchiectasis.

Conclusions: Previous treatment failure or default is an independent risk factor for massive hemoptysis in PTB. Poor radiographic presentations could not predict the occurrence of massive hemoptysis.

Keywords: Pulmonary tuberculosis; Massive hemoptysis; Retreatment

Introduction

Tuberculosis (TB) is typically caused by *Mycobacterium tuberculosis* (MTB), with pulmonary TB (PTB) accounting for 70% of cases, although MTB can disseminate to other organs, including lymph nodes. TB is a treatable and curable disease. The vast majority of TB cases can be cured when medicines are provided and taken properly. However, it remains a major global health problem, public health personnel and the governments have not been able to eradicate it especially in developing world. In 2015, there were estimated 10.4 million new TB cases, and 1.8 million TB deaths [1]. Massive hemoptysis is one of the major causes of death in PTB patients [2].

Hemotysis is one of the hallmark symptoms in PTB, which always causes great anxiety and rarely ignored by the patient. Any amount of blood in the sputum is an important and alarming symptom. It can spread MTB in lung and induce a toxic condition in the whole body. It should be noted that while many PTB patients have cavitary lesions, only a proportion of them develop hemoptysis, and a few would evolve into massive hemotysis, for which the risk factors are mostly unknown [3]. Different amounts of hemoptysis are associated with different outcomes. Massive hemotysis is a medical emergency. Without effective and timely rescue, patients might die from hemorrhagic shock or from asphyxiation due to flooding of blood into the tracheobronchial tree.

The objective of this study was to identify if there were some risk factors independently associated with massive hemoptysis in hemoptysis patients with PTB. Identification of such risk factors could provide new clued to predict which kind of hemoptysis in PTB patients might evolve into massive hemoptysis, and lead us timely to take more effective therapies.

Materials and Methods

Design, setting and study population

It was an observational retrospective study conducted between Jan 2010 and Dec 2013 at the Infectious Diseases Department of the fifth affiliated hospital of Sun Yat-sen University, Zhuhai, Guangdong, China. Hospitalized patients diagnosed as PTB with hemoptysis were included in the analysis. Patients were excluded from analysis with the following criteria: (1) combining with any other disease which could disorder the coagulation function, (2) patients were diagnosed with extra-pulmonary TB without microbiologically proven pulmonary TB, (3) information was missing on important variables such as clinical symptoms or documentation status.

The institutional review board of the fifth affiliated hospital of Sun Yat-sen University approved the study. The requirement for informed consent from the patients was waived by the ethical review board.

Definitions

The following definitions were used in this study [4].

Case of pulmonary TB A patient with TB disease involving the lung parenchyma and decided to treat the patient with a full course of anti-TB treatment.

MTB-positive PTB A patients with a positive isolation of MTB (sputum smear or culture).

MTB-negative PTB A patients with a negative MTB culture, but with clinical and radiologic features that prompted empirical treatment for pulmonary tuberculosis.

New case of TB A patient never had treatment for TB or who has taken anti-TB drugs for less than one month.

Retreatment case of TB A patient had received a month or more of anti-TB drugs in the past, and diagnosed as active TB again. There were three types: (i) previous treatment was failed; (ii) previously treatment was defaulted; and (iii) a patient who was previously declared cured or treatment completed and now was diagnosed with MTB-sputum-positive (relapse).

Massive hemoptysis The definition of massive hemoptysis was not completely agreed upon and varies widely in the literature [5]. We defined it as either ≥ 500 mL of expectorated blood over a 24 hour period [6] or bleeding at a rate ≥ 100 mL/hour, regardless of whether abnormal gas exchange or hemodynamic instability exists.

Mild to moderate hemoptysis The amount of blood was less than massive hemoptysis.

Measurements

Subjects of PTB with hemoptysis were categorized into two groups: patients with massive hemoptysis and those with mild to moderate hemoptysis. Information on reported variables was extracted from the patients' medical records. Patients' self-reported symptoms that were recorded as potentially suggestive of PTB included the presence of hemoptysis, cough, fever, night sweats and weight loss over 2 kg. The duration of each symptom was recorded in months prior to hospital evaluation. The longest duration of any one of these symptoms was recorded as the symptom duration [3]. The information on past tuberculosis treatment was reported by the patient themselves. Co-morbid diseases were recored including diabetes, lung infection, and bronchiectasis. Data from the Computed Tomography (CT) were obtained from review of reports dictated by attending radiologists at the time of admission and recorded in the patient records. CT results were recorded as unilobar *vs.* multilobar or miliary infiltrates, as unilateral *vs.* bilateral involvement, with separate counting for the presence of cavitary lesions.

Statistical Analysis

Comparisons of demographic and clinical characteristics were carried out using the chi-squared test or Fisher's exact test for categorical variables.

Variables of asymmetric distributions were represented by median (quartile), [M(QLQU)] using the rank sum test. Odds ratios (ORs), 95% confidence intervals (CIs) and P values were estimated. Significance was defined as $P<0.05$ (two-tailed). Statistical analysis was performed using a statistical software package (SPSS version 13.0; SPSS Inc.Chicago, IL, USA).

Results

There were 591 in-patients with PTB between Jan 2010 and Dec 2013, of whom 169 were complicated by hemoptysis, while 1 was excluded due to coagulation disorders caused by longer-term using of warfarin. Finally, a total of 168 patients were enrolled for analysis. Of these patients, 76 (45.23%) reported the presence of massive hemoptysis. No one was co-infected with HIV.

The demographic characteristics, diagnostic test results and clinical presentations between subjects with massive and mild to moderate hemoptysis were showed in Table 1. In univariate analysis, no significant differences were found in the distribution of demographic characteristics between the two groups. As compared with the mild to moderate hemoptysis patients, PTB patients with massive hemoptysis were more likely to be retreated PTB patients (P=0.020) and presented longer symptom duration (P=0.030). There was no significant difference in co-morbid diabetes mellitus (DM), lung infection, or bronchiectasis. Of all the presenting symptoms and radiological features of patients, there was no significant difference between those who experienced massive hemoptysis and those who did not.

	Total patients (n=168) n(%) or M(QLQU)	**PTB with massive hemoptisis (n=76) n(%) or M (QLQU)**	**PTB with mild-moderate hemoptisis (n=92) n(%) or M (QLQU)**	**P**
Male sex	130 (77.3)	58 (76.3)	72 (78.3)	0.764*
Age	32.5 (23.0,49.0)	33.5 (24,47.75)	31 (21.25,49.75)	0.820§
symptom duration (month)	1.0 (0.0,12.0)	4.5 (0.0,24)	1.0 (0.0,4.75)	0.030§
Smoking habit	50 (29.8)	26 (34.2)	24 (26.1)	0.252*
MTB-positive	79 (47.0)	33 (46.1)	46 (50.0)	0.395*
TB retreatment	39 (23.2)	24 (31.6)	15 (16.3)	0.020*
Co-morbid diseases				
Diabetes	19 (11.3)	7 (9.2)	12 (13.0)	0.435*
Lung infection	16 (9.5)	6 (7.9)	10 (10.9)	0.513*
bronchiectasis	25 (14.9)	14 (18.4)	11 (12.0)	0.241*
Presenting symptoms				
Chronic cough	121 (72.0)	51 (67.1)	70 (76.1)	0.197*
Fever	51 (30.4)	22 (28.9)	29 (31.5)	0.718*
Night sweat	30 (17.9)	11 (14.5)	19 (20.7)	0.298*
Body weight loss	35 (20.8)	14 (18.4)	21 (22.8)	0.484*

Radiographic presentations				
multilobar or miliary infiltrates	118 (70.2)	54 (71.1)	64 (69.6)	0.834*
Bilateral involvement	113 (67.3)	50 (65.8)	63 (68.5)	0.712*
Cavity formation	112 (66.7)	52 (68.4)	60 (65.2)	0.661*
Multi-cavity	46 (27.4)	24 (31.6)	22 (23.9)	
Single-cavity	66 (39.3)	28 (36.8)	38 (41.3)	0.540*
No-cavity	56 (33.3)	24 (31.6)	32 (34.8)	

*χ2 test; §Rank Sum Test; PTB: Pulmonary Tuberculosis; M: Median; Q: Lower Quartile; QU: Upper Quartile.

Table 1: Demographic characteristics and clinical presentations between 168 PTB patients with massive and mild-moderate hemoptisis.

Data from all 39 retreatment cases of TB was analysed and showed in Table 2. Patients with previous treatment failure or default were more likely to have massive hemoptysis (P=0.029). No other significant differences were found in the distribution of demographic characteristics, co-morbid diseases, presenting symptoms and radiological features between patients with mild to moderate hemoptysis and patients with massive hemoptisis.

	PTB with massive hemoptysis (n=24) n(%) or M(QLQU)	**PTB with mild-moderate hemoptysis (n=15)** n(%) or M(QLQU)	**P**
Male sex	22 (91.7)	15 (100)	0.514*
Age	38.5 (29.25,49.5)	49 (41.0,71.0)	0.053§
symptom duration (month)	24.0 (3.02,57.00)	6.0 (0.0, 48.0)	0.357§
Smoking habit	11 (45.8)	11 (73.3)	0.112*
MTB-positive	12 (50)	8 (53.3)	1.000*
Presenting symptoms			
Chronic cough	19 (79.2)	13 (86.7)	0.686*
Fever	12 (50)	4 (26.7)	0.192*
Night sweat	6 (25)	3 (20)	1.000*
Body weight loss	2 (8.3)	1 (6.7)	1.000*
Co-morbid diseases			
Diabetes	4 (16.7)	6 (40)	0.141*
Lung infection	4 (14.7)	4 (26.7)	0.686*
bronchiectasis	10 (41.7)	4 (26.7)	0.496*
Radiographic presentations			
multilobar or miliary infiltrates	21 (87.5)	15 (100)	0.271*
Bilateral involvement	18 (75)	13 (86.7)	0.450*
Cavity formation	18 (75)	13 (86.7)	0.450*
Previous treatment failure or default	18 (75)	6 (40)	0.029*

* Fisher's Exact Test; § Rank Sum Test; PTB: Pulmonary Tuberculosis; M: Median; QL: Lower Quartile; QU: Upper Quartile.

Table 2: Demographic characteristics and clinical presentations between 39 retreated PTB patients with massive and mild-moderate hemoptisis.

Discussion

To our knowledge, this is the first study to demonstrate the risk factors for massive hemoptysis in patients with PTB. Hemoptysis is a common symptom with a good prognosis in lots of pulmonary diseases, such as TB, bronchitis, bronchiectasis, tumor, aspergilloma, lung abscess, emboli, coagulopathy, autoimmune disorders, alveolar hemorrhage, mitral stenosis and pneumonia. Previous reports have suggested that younger age is an independent risk factor for hemoptysis in adults with PTB [3]. There are few reports on the risk factors of PTB with massive hemoptysis. However, patients exhibiting massive bleeding had a poorer prognosis, and need effective and timely rescue.

Our study found an independent association of retreatment with massive hemoptysis in PTB patients (P=0.020). Those who had a failure or default treatment were more likely to get massive hemoptysis. Liang L et al. reported that the top three reasons for failure to complete the TB treatment regimens in China were poor knowledge, financial burden and treatment side effects [7]. Poor knowledge about TB and mild symptoms, many patients tended to delay initiating treatment, prolong the time that patients carry the TB bacteria and allow the disease to progress without proper intervention. It also would increase the risk of massive hemoptysis. We found that there was a significant association of longer symptom duration and massive hemoptysis of PTB patients (P=0.030). Insufficient knowledge about the serious consequences of interrupted and intermittent treatment, some patients would give up treatment when symptoms disappeared, social support was difficult to obtain or side effects kicked in. Some physicians, especially those who worked in rural clinics, also did not have sufficient knowledge of TB, which often resulted in delays in diagnosis and treatment. Although the Chinese government has a policy of free diagnosis and treatment of TB, such a free treatment policy seldom extended to general hospitals and clinics, applies only to the first treatment regimen except ancillary drugs. Even for those who could receive free treatment at institutes for TB control, patients could be out of pocket for extra costs for drugs to combat side effects of the treatment, routine examinations and second-line drugs when needed. A systematic review found that 12.62% of patients with TB in China have side effects from the treatment drugs [8]. some of them might give up their treatment. Irrational prescriptions, poorly formulated medications, insufficient dosage and length of treatment, and inadequate administration of drugs were believed to be the most common practices that might promote drug resistance and induce a failure or default treatment.

This study remains us that proper and complete initial treatment after first diagnosis of TB is the best intervention to prevent massive hemoptysis during retreatment after treatment failure or default, and we should improve the abilities of physicians, strengthen TB education for the whole people. Various interventions have proven effective for

increasing treatment adherence, including reinforced counselling, provision of social support, patient reminder systems and defaulter tracing [9]. Such interventions are essential to minimise treatment interruption and default in new and retreatment TB cases, and they may reduce the risk of TB transmission, massive hemoptysis, drug resistance and death.

There was lack of significance when correlating radiographic presentations used for the prediction of massive hemoptysis. The pathophysiology of hemoptysis in TB may be variable including lung cavitations, residual bronchiectasis, scar carcinoma in old TB, formation of mycetoma in the tuberculous cavity and rupture of Rasmussen's aneurysm, i.e. aneurysm of the pulmonary artery caused by the disease [10]. Brik A et al. reported that the cavity rate of PTB was 37.7%, and massive hemoptysis occurred in 22.2% of cavitary lesions, they suggested that cavitary lesions could be considered one of the dangerous lesions that need rapid surgical interference [11]. In our study, the cavity rate of PTB with hemoptysis was 66.7%, but there was no significant difference in the presence or count of cavitary lesion between massive hemoptysis and mild-moderate hemoptysis PTB patients. We found neither a significant difference in the presence of multilobar or miliary infiltrates between the two groups in univariate analysis, nor a significant association of bilateral involvement with massive hemoptysis. Both surgical treatment and bronchial artery embolization (BAE) can stop bleeding, but they are specialised, expensive and risky procedures. Anuradha C et al. indicate that BAE had no benefit of long-term outcome for hemoptysis in PTB [12]. We could not suggest patients with hemoptysis to take rapid surgical interference or bronchial artery embolization (BAE) only depends on poor radiographic presentations. The time and necessity of surgery and BAE remains a matter of debate.

The association between diabetes mellitus and tuberculosis and their synergistic role in causing human disease has been recognised for centuries [13]. In the previous study, Wang CS et al. showed that PTB co-morbid diabetes patients had higher frequencies of hemoptisis [14]. However, we did not find a significant correlation between DM and massive hemoptysis of TB. Nevertheless, whether increased time to culture conversion in diabetic patients leads to higher risk of relapse has not been adequately studied [13]. Correlation of DM, TB relapse and massive hemoptysis could be addressed in future studies.

In our analysis, we found neither a significant difference in the presence of lung infection between patients with and without massive hemoptysis in univariate analysis, nor a significant association between bronchiectasis and massive hemoptysis. This finding is similar with previous study. Brik A et al. showed that post-tuberculous bronchiectasis (17.7%) and destroyed lung (11.1%) usually presented with minor hemoptysis and there were rare cases presenting with life-threatening hemoptysis [11].

Our study had some limitations. First, as it was a retrospective study, the results should be interpreted with caution; a prospective study is warranted to confirm our findings. Second, this study did not allow us to investigate factors discussed above that may underlie the increased risk of massive hemoptysis among retreated cases, such as the complex retreatment regimen. Third, because some retreated patients could not recall the previous course and could exactly describe the mount if they had hemoptysis before, we were unable to know if patients with massive and mild-moderate hemoptysis had hemoptysis also during previous treatment course. Fourth, we were unable to address the effects of drug resistance, as this information was not routinely collected. Drug resistant cases were difficult to be cured, and more likely to be recurrent. Despite these limitations, this study is valuable as it is the first to examine the risk factor for massive hemoptysis in pulmonary tuberculosis.

Conclusion

In a developing country like China where tuberculosis is endemic, it's imperative for all medical and nursing professionals to be aware of the independent higher risk of life-threatening hemorrhage in PTB patients with a failure or default previous treatment. It remains us that proper and complete initial treatment after first diagnosis of TB is the best intervention to prevent massive hemoptysis during retreatment after treatment failure or default. The poor correlation between the radiographic presentations and massive hemoptysis indicates that a lager randomized prospective study on the time and necessity of surgery and BAE is needed. An effectively functioning tuberculosis control program is clearly essential for good patient outcome, and for reducing the need for a thoracic surgery or BAE with alleviating ecumenical burden.

Acknowledgement

The authors thank the Department of Infectious Diseases, the fifth affiliated hospital of Sun Yat-sen University, for permission to access the TB programme data; the local staff of the TB clinics. The contents of this document are the sole responsibility of the authors and can under no circumstances be regarded as reflecting the positions of the donor.

Funding

This work was funded by the Science and Technology Project of Zhuhai (No. 20161027E030038).

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