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The Co-Occurrence of Anthracosis with Interstitial Lung Disease

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Abstract. *Objective:* Anthracosis is defined as deposition of black pigments in the bronchial mucosa or lung parenchyma. The aim of this study was to investigate the clinical features of patients with coexisting anthracosis and interstitial lung diseases (ILDs). *Methods:* A total of 335 ILDs patients who underwent bronchoscopy at the affiliated hospital of Qingdao University were included in our study. We enrolled 71 patients who diagnosed with anthracosis by bronchoscopy. The clinical presentations, radiographic features, and bronchoscopic findings of the patients were reviewed. *Results:* Compared with the non-anthracosis group, biomass exposure (48, 67.6% vs. 153, 53.9%, p=0.041), the median pressure of carbon dioxide before six-minute test (42.00 mmHg vs. 40.00 mmHg, P=0.001), the mean peak expiratory flow (115.21±23.55 %predicted vs. 104.20±26.17%predicted, P=0.048), the mean level of triglyceride (1.79±1.27 mmol/L vs. 1.51±0.74 mmol/L, P=0.034) were significantly increased and the mean oxygen saturation after six-minute test (95.49±2.72% vs. 96.56±1.27%, P=0.028), the mean cardiac ejection fraction (61.22±2.07% vs.62.08±2.89%, P=0.019) were significantly decreased in the anthracosis group. However, we didn't find significant difference between the two groups in lymph node calcification (p=0.620) and lymphadenectasis (p=0.440). *Conclusions:* Biomass smoke is a risk factor for anthracosis. Anthracosis produce a bad effect on the oxygenation, cardiac function and lipid metabolism in ILDs patients. The ILDs patients should decrease the exposure of biomass.

Key words: anthracosis, interstitial lung diseases, anthracofibrosis

Introduction

Anthracosis is defined as deposition of black pigments in the bronchial mucosa or lung parenchyma. However, the origin of the black pulmonary matter was a subject of dispute in the early days. In 1813, Pearson first reports that the lungs generally become more dark-colored proportionately to their age. He hypothesizes that the black particles derived from the burning of coal, wood, and other inflammable materials in common life, which deposit in the lungs and are interstitialised. Finally, Pearson proved the carbon nature of the black matter by chemical analyses (1). Although Pearson is the first to describe and explain anthracosis, he did not use the term. The term 'anthracosis' was coined by Thomas Stratton who considered it to be an appropriate term for the blackening of the lungs seen in coalminers (2). The main pathological changes in the transbronchial tissue samples of anthracosis patients were the intracellular and extracellular black particles observed in the macrophages, epithelium, and stroma (3-4). Submucosal fibrosis may also be seen in the bronchial wall and the epithelial lining is usually intact (5-6).

With increasing awareness of anthracosis as a separate entity, the significance of it in the tracheobronchial tree, lung parenchyma, and even non-respiratory organs has been postulated. Studies reported a strong association with certain diseases

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such as tuberculosis (7-8), chronic obstructive pulmonary disease (COPD) (9), and lung cancer (10). But the association between anthracosis and ILDs has not been explained. It is unclear whether the anthracosis will have an impact on ILDs. Further explore may help to provide ideas for the treatment of ILDs. It's well known that fibrosis is also the main characteristic of ILDs. And the pathogenesis of ILDs is not clear now. The study of the co-occurrence of anthracosis with ILDs may provide some hints. However, the association between anthracosis and ILDs is only mentioned in one case report (11). The rarity of such a description in the literature prompted us to investigate the clinical features of patients with coexisting anthracosis and ILDs. In our study, we reported a series of ILD patients with coexisting anthracosis which were confirmed by bronchoscope pathology.

Materials and Methods

Patients

After receiving institutional review board approval, we performed a retrospective search of the medical record system of the affiliated hospital of Qingdao University using the keywords "interstitial lung diseases (ILDs)". Between June 28, 2013, and September 24, 2020, a total of 355 patients with ILDs who underwent bronchoscopy while in hospital were included in the study. The reasons for their hospital admission were ILDs. Among them, 71 patients were identified as having anthracosis by bronchoscopy. All the experiment protocol for involving human data was in accordance to Declaration of Helsinki.

Diagnosis criteria

The diagnosis of anthracosis was based on confirmed pathological characteristics of bluish-black mucosal hyperpigmentation by bronchoscope biopsy. The intracellular or extracellular black particles observed in the macrophages, epithelium, or stroma (Figure 1).

ILD is defined as the inflammatory-fibrotic infiltration of the alveolar walls (septa) resulting in profound effects on the capillary endothelium and the alveolar epithelial lining cells. All subjects had a confirmed multidisciplinary diagnosis of ILD involved contributions from general practice physicians, experienced pulmonologists, radiologists, and pathologists according to evidence-based guidelines (12). ILDs are a group of heterogeneous disorders that occur as idiopathic diseases such as idiopathic pulmonary fibrosis (IPF), be associated with connective tissue diseases (CTD-ILD), or result from exposures to environmental agents and drugs. The patients with pneumoconiosis or sarcoidosis were excluded. Other types of ILDs, specifically IPF, non-specific interstitial pneumonia (NSIP), CTD-ILD, interstitial pneumonia with autoimmune features (IPAF), chronic allergic pneumonia (CHP) and other idiopathic interstitial pneumonia (IIPs), were included in our study.

Infection is defined as presenting fever, sputum, inflammatory lesions in thoracic CT and/or infectious agents identified on microbiologic studies, which is an infectious process requiring both effective antibiotic therapy and hospitalization. Dyspnea is the feeling of patients associated with impaired breathing. And the hyperplasia of fibers is defined as the presence of fibroblastic foci in lung tissue under a microscope. The proliferation of alveolar epithelial is defined as the increase of alveolar epithelial cells under a microscope. Biomass smoke is produced by burning of wood, leaves or manure of farm animals for cooking or heating (13). And the patient history of exposure to factors that may cause pulmonary fibrosis included metal dust (beryllium, cobalt, brass, lead, steel, etc.) and special chemical substance (feather products, several drugs such as amiodarone and chemotherapeutic agents, etc.)

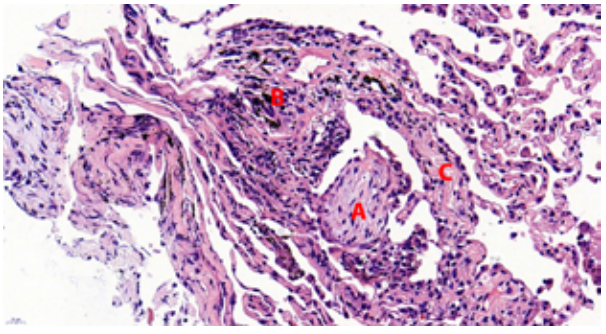

Figure 1. Histopathology of ILD patients with anthracosis
A) Fibroblast foci in the alveolar septum. B) Black particles in the lung tissue C) Collagen deposition in the alveolar septum. (Hematoxylin & Eosin staining in 400x magnification)

Methods

The patients' medical records were then reviewed for demographic characteristics(age, sex, height, weight), clinical symptoms(cough, sputum, hemoptysis, chest pain, dyspnea, fever) and signs(moist rales, velcro lung rales), anamnesis(hypertension, diabetes, coronary heart disease, gastritis, tuberculosis), exposure history(metal dust, special chemical substance, biomass, etc.), smoking and drinking history, laboratory findings (routine blood test, coagulation function, biochemical test, tumor markers, immunoglobulin and complement, fasting blood glucose level, etc.), ultrasonic cardiogram(cardiac ejection fraction and pulmonary arterial systolic pressure, PASP), computed tomography of the chest(emphysema, degree of fibrosis, lymph node calcification, lymphadenectasis, aortic calcification and coronary artery calcification), pulmonary function test(forced vital capacity, FVC; forced expiratory volume in 1 second, FEV1; total lung capacity, TLC; lung diffusion capacity for carbon monoxide, DLCO; peak expiratory flow, PEF; etc.), arterial blood gas analysis, six-minute walk distance, bronchoscopic data (hyperplasia of fibers, proliferation of alveolar epithelial cells, etc.), and outcomes (infection and acute exacerbation of ILDs). The blood samples were collected on empty stomach at early morning after hospitalization. Routine blood tests were measured in whole blood, blood coagulation tests were measured in plasma and other biochemical or immune parameters were measured in serum. Biochemical parameters were measured using the Beckman AU5811 automatic biochemical analyzer (Beckman-Coulter Inc., Germany) with commercially available kits (Leadman Biochemistry Co., Ltd., Beijing, China).

It should be specially explained that the degree of fibrosis was evaluated by semiquantitative image analysis (14-15). Briefly, CT images were scored at five levels (the origin of great vessels, the main carina, the pulmonary venous confluence, halfway between the third and fifth sections, and immediately above the right hemidiaphragm) and the disease extent was estimated in each of the five CT sections (1, subpleural; 2, centrolobular; 3, mixd; 4, diffuse). The total extent of ILD(TEI) was calculated as the mean extent score in the five scored CT sections. What's more, the modified coarseness of reticular disease (MCRD) was also calculated in each of the five sections as follows: 0, normal; 1, ground-glass opacity alone; 2, fine intra-lobular fibrosis; 3, microcystic honeycombing($\leq$4mm); 4, macrocystic honeycombing ($>$ 4 mm). The MCRD was the summed score for all five levels. Finally, the extent of fibrosis was scored by the product of TEI and MCRD. Two observers in consensus who were unaware of the clinical findings or PFT results reviewed all CT images at lung window settings (with a window center of$-$500 to$-$600 HU and a window width of 1600 HU).

Spirometry was performed using JAEGER Medical spirometer using standard guidelines. DLCO was measured by single-breath method. All the parameters were expressed as percent predicted.

This study was approved by the affiliated hospital of Qingdao University Institutional Review Board. Informed consent for publication of the clinical information was obtained from the patient at the time of diagnosis or follow-up.

Statistical analysis

The ILD patient group was divided according to whether the patients had anthracosis, and the two groups were compared in terms of demographic, clinical, pathological, laboratory, and radiologic variables. Descriptive methods were used to analyze measurement data with standard summary statistics. Categorical data were given as numbers and percentages; continuous data as means$\pm$standard deviation and median and 25/75 percentile. The Shapiro-Wilk W test was used for assessing the normality of the data, and appropriate tests were selected accordingly. Categorical variables were processed by the Chi-square test or Fisher's exact tests, as appropriate. Student's t test was used for parametric distribution variables and the Mann-Whitney test for the nonparametric distribution variables. Multi-variate linear regression model was constructed to evaluate the associations between anthracosis and triglyceride or C-reactive protein adjusted by baseline conventional atherosclerotic risk profiles including age, sex, body mass index (BMI), blood pressure, heart rate and medical histories of hypertension, diabetes and coronary heart diseases. To further explore the associations of anthracosis and the acute exacerbation or infection of ILD patients, we further conducted models by using logistic regression analyses. Analysis was performed using SPSS 23.0 (IBM Corporation, Armonk, NY, USA) The significance of difference was set at 0.05.

Results

Patient characteristics

During the study period, we identified 355 consecutive patients with ILDs. Median patient age was 63.00 years. There were 209 men and 146 women. Smokers comprised 167 patients (47.0%) of the study population with median smoking history of 30 pack-years. The numbers of diagnoses were as follows: IPF, 128(36.1%); NSIP, 96(27.0%); IIPs, 10(2.8%); CHP, 2(0.6%); CTD-ILD, 109 (30.7%); and IPAF, 10(2.8%). As for symptoms, 299 patients (84.2%) had cough, 198 patients (55.8%) had sputum, 12 patients (3.4%) had hemoptysis, 40 patients (11.3%) had chest pain, 254 patients (71.5%) had dyspnea, and 68 patients (19.2%) had fever. What's more, 71 patients(20%) had hypertension, 46 patients(13%) had diabetes, 29 patients(8.2%) had coronary heart disease, 38 patients (10.7%) had gastritis and only 5 patients(1.4%) had tuberculosis. There were 82 patients (23.1%) exposed to metal dust and special chemical substance. Biomass exposure was found in 201 patients (56.6%). And velcro lung rales were heard in 223 patients (62.8%). Bronchoscopic features are as follows: 242 patients (68.2%) underwent right bronchoscopy while 113 patients (31.8%) were left. Among all, 71 patients (20.0%) had deposition of black pigments in the bronchial mucosa; 330 patients (93.0%) had chronic inflammation; 259 patients (73.0%) had hyperplasia of fibers; 122 patients (34.4%) had the proliferation of alveolar epithelial cells. Foam cells were seen in the alveolar cavity of 31 patients (8.7%). Lymphocytes were seen in 46 patients (13.0%). The median six-minute walk distance was 480.60m. After the six-minute test, the median oxygen pressure increased from 78.00 to 83.00 mmHg. The median pressure of carbon dioxide remained about the same at 40.00 mmHg. And the mean oxygen saturation increased from 96.0% to 96.6%. The mean(±SD) predicted FVC% was 82.3(±22.7)%. The median predicted DLCO was 63.0%.

Subgroup analysis

In terms of demographic characteristics, age (median 63.00 years vs. 63.00 years, p=0.846) and sex ratios (1.54 male/female vs. 1.41 male/female, p=0.746) were comparable between the anthracosis group(n=71) and the non-anthracosis group (n=284). We also calculated the Body Mass Index (BMI) by height and weight. The average BMI were similar between the two groups (anthracosis group, 25.58±3.63 kg/m^2 vs. non-anthracosis group, 25.39±2.86 kg/m^2; p=0.738).

As for clinical findings, 63 patients (88.7%) complained of cough, 44 patients (62.0%) had sputum, 4 patients (5.6%) had hemoptysis, 11 patients (15.5%) had chest pain, 47 patients (66.2%) had dyspnea, and 9 patients (12.7%) had fever in the anthracosis group. Similar proportion were found in the non-anthracosis group, 236 patients (83.1%) complained of cough, 154 patients (54.2%) had sputum, 8 patients (2.8%) had hemoptysis, 29 patients (10.2%) had chest pain, 207 patients (72.9%) had dyspnea, and 59 patients (20.8%) had fever. The proportion of velcro lung rales was similar between the two groups(p=0.913). On the other hand, we didn't find significant diffidence between the anthracosis and the non-anthracosis group in anamnesis (hypertension, p=0.791; diabetes, p=0.879; coronary heart disease, p=0.923; gastritis, p=0.264, tuberculosis, P=0.260), metal dust or special chemical substance exposure history(p=0.413), smoking history (median 36.00 vs. 30.00 pack years, p=0.596) and drinking history (29, 40.8% vs 82, 28.9%, p=0.052). However, biomass exposure was significantly increased in the anthracosis group compared with the non-anthracosis group (48, 67.6% vs. 153, 53.9%, p=0.041). Results also show that the proportion of IPF (16, 22.5% vs. 112, 39.4%, P=0.008) and NSIP (27, 38.0% vs. 69, 24.3%, P=0.020) is different between the anthracosis group and non-anthracosis group. However, the difference in CTD-ILD (22, 31.0% vs. 87, 30.6%, P=0.954) between the two groups is not significant.

We also compared serum laboratory findings in patients with or without anthracosis. No significant differences were found in routine blood test, coagulation function (D- dimer, p=0.456), tumor markers and fasting blood glucose level(p=0.158). In the biochemical test and complement, significantly higher levels of average albumin (37.52±4.12 g/L vs. 36.33±4.39 g/L, P=0.030), ratio of albumin to globulin (median 1.43 vs. 1.27, P=0.002), mean triglyceride(1.79±1.27 mmol/L vs.1.51±0.74 mmol/L, P=0.034), average complement C3(1.22±0.18 g/L vs. 1.04±0.14 g/L, P=0.050) were observed in those with anthracosis than in those without anthracosis. The level of globulin (median 26.10 g/L vs.

28.54 g/L, P=0.019) was lower in the anthracosis group than that in the non-anthracosis group.

As mentioned above, thoracic computed tomography images were also evaluated. However, we didn't find significant difference between the two groups in emphysema (p=0.796), degree of fibrosis(p=0.936), lymph node calcification(p=0.620), lymphadenectasis(p=0.440), aortic calcification (p=0.319) and coronary artery calcification(0.480).

What's more, we compared the pulmonary function tests to find that the average peak expiratory flow (115.21±23.55%predicted vs. 104.20±26.17%predicted, P=0.048) was significantly increased in the anthracosis group. Other parameters included FVC(p=0.108), FEV1(p=0.277), TLC (p=0.387) and DLCO(p=0.065) were similar between the two groups. On the other hand, the six-minute walk distance (p=0.519) was also similar between the two groups. Compared with the non-anthracosis group, the pressure of carbon dioxide before six-minute test (median 42.00 mmHg vs. 40.00 mmHg, P=0.001) was higher and the average oxygen saturation after six-minute test (95.49±2.72% vs. 96.56±1.27%, P=0.028) was lower in the anthracosis group. We also found that the mean cardiac ejection fraction (61.22±2.07% vs.62.08±2.89%, P=0.019) was significantly decreased in patients with anthracosis. The histopathologic results by bronchoscope biopsy showed that the presence of hyperplasia of fibers (63, 88.7% vs. 196, 69.0%, P=0.001) was increased in anthracosis group. All the characteristics were summarized in Table 1.

In multivariate linear regression analyses, anthracosis was associated with higher level of triglyceride(Coefficient: 0.445 [95% confidence interval{CI}:0.048-0.842], p=0.028). No association

Table 1. Comparison in ILD patients with or without anthracosis

	Anthracosis(n=71)	**Non-anthracosis(n=284)**	**p-value**
Age(years)	63.00(56.00, 69.00)	63.00(56.00, 68.00)	0.846
Sex(M/F)	43/28	166/118	0.746
Height(centimetres)	165.00(159.00,170.00)	165.00(160.00,170.00)	0.560
Weight(kilograms)	68.00(61.00,74.00)	68.00(60.25,76.00)	0.532
BMI(kg/m^2)	25.58±3.63	25.39±2.86	0.738
The pattern of ILDs:			
IPF	16(22.5%)	112(39.4%)	0.008
NSIP	27(38.0%)	69(24.3%)	0.020
CTD-ILD	22(31.0%)	87(30.6%)	0.954
Presenting symptoms			
cough	63(88.7%)	236(83.1%)	0.244
sputum	44(62.0%)	154(54.2%)	0.240
hemoptysis	4(5.6%)	8(2.8%)	0.240
chest pain	11(15.5%)	29(10.2%)	0.208
dyspnea	47(66.2%)	207(72.9%)	0.264
fever	9(12.7%)	59(20.8%)	0.121
Physical signs			
moist rales	3(4.2%)	36(12.7%)	0.042
velcro lung rales	45(63.4%)	178(62.7%)	0.913
Anamnesis			
hypertension	15(21.1%)	56(19.7%)	0.791
diabetes	9(12.7%)	37(13.0%)	0.879
coronary heart disease	6(8.5%)	23(8.1%)	0.923
gastritis	5(7.0%)	33(11.6%)	0.264
tuberculosis	2(2.8%)	3(1.1%)	0.260
Smoker	35(49.3%)	132(46.5%)	0.671
Smoking history (pack years)	36.00(20.00,45.00)	30.00(17.38,45.00)	0.596
Drinking history	29(40.8%)	82(28.9%)	0.052

Table1 continues

Table 1. Comparison in ILD patients with or without anthracosis

	Anthracosis(n=71)	Non-anthracosis(n=284)	p-value
Exposure history			
metal dust or special chemical substance	19(26.8%)	63(22.2%)	0.413
biomass	48(67.6%)	153(53.9%)	0.041
Bronchoscopic features:			
chronic inflammation.	65(91.5%)	265(93.3%)	0.604
hyperplasia of fibers.	63(88.7%)	196(69.0%)	0.001
proliferation of alveolar epithelial cells	27(38.0%)	95(33.5%)	0.468
foam cells	4(5.6%)	27(9.5%)	0.301
lymphocyte	7(9.9%)	39(13.7%)	0.385
Six-minute walk distance(meters)	477.50(399.25,552.50)	480.60(420.00,573.00)	0.519
Before the six-minute walk test			
PaO_2 (mmHg)	77.00(70.00,86.00)	78.00(70.00,86.25)	0.690
$PaCO_2$ (mmHg)	42.00(39.00,44.00)	40.00(37.35,42.00)	0.001
SO_2 (%)	95.75(94.53,96.70)	96.00(94.55,97.00)	0.425
After the six-minute walk test			
PaO_2 (mmHg)	78.00(65.50,88.50)	84.00(77.75,91.25)	0.084
$PaCO_2$ (mmHg)	40.47±3.09	40.00±2.95	0.572
SO_2 (%)	95.49±2.72	96.56±1.27	0.028
Pulmonary function test			
FVC %predicted	87.57±21.40	79.78±23.03	0.108
FEV1%predicted	94.69±18.38	85.80±24.13	0.277
TLC% predicted	75.47±18.63	71.80±19.33	0.387
DLCO %predicted	72.15±23.82	64.02±22.93	0.065
PEF %predicted	115.21±23.55	104.20±26.17	0.048
DLCO/VA %predicted	99.31±20.23	92.20±21.15	0.112
Laboratory data:			
D-dimer(ug/ml)	250.00(170.00,352.50)	270.00(160.00,402.50)	0.456
fasting blood glucose level(mmol/L)	5.03(4.66,5.90)	4.91(4.48,5.70)	0.158
Albumin(g/L)	37.52±4.12	36.33±4.39	0.030
globulin (g/L)	26.10(23.57,31.42)	28.54(25.11,32.22)	0.019
ratio of albumin to globulin	1.43(1.19,1.65)	1.27(1.08,1.50)	0.002
sodium(mmol/L)	141.80(140.30,143.00)	141.00(139.60,142.59)	0.024
creatinine(umol/L)	57.00(51.00,69.00)	66.55(54.00,80.00)	0.003
triglyceride(mmol/L)	1.79±1.27	1.51±0.74	0.034
total cholesterol(mmol/L)	5.02(4.50,5.81)	4.89(4.23,5.71)	0.577
LDL-cholesterol(mmol/L)	3.19(2.51,3.58)	3.01(2.43,3.57)	0.525
HDL-cholesterol(mmol/L)	1.19(1.06,1.41)	1.23(1.01,1.43)	0.767
complement C3(g/L)	1.22±0.18	1.04±0.14	0.050
C-reactive protein(mg/L)	2.36(1.30,3.48)	2.26(1.27,4.96)	0.895
Cardiac ejection fraction(%)	61.22±2.07	62.08±2.89	0.019
PASP*(mmHg)	30.00(27.00,33.75)	30.00(27.00,36.00)	0.213
Thoracic computed tomography			
emphysema	16(22.5%)	60(21.1%)	0.796
degree of fibrosis	22.00(10.80,40.00)	20.20(11.20,39.90)	0.936
lymph node calcification	18(25.4%)	61(21.5%)	0.620
lymphadenectasis	23(32.4%)	106(37.3%)	0.440
aortic calcification	32(45.1%)	152(53.5%)	0.319
coronary artery calcification	22(31.0%)	105(37.0%)	0.480

The data are expressed as mean±standard deviation (parametric distribution) or median 25 and 75 percentiles (non-parametric distribution) or number (%).

BMI, Body Mass Index; IPF, Idiopathic pulmonary fibrosis; NSIP, Non-specific interstitial pneumonia; CTD-ILD, Connective tissue disease-associated interstitial lung disease; FVC, Forced vital capacity; FEV1, Forced expiratory volume in 1 second; TLC, total lung capacity; DLCO, Lung diffusion capacity for carbon monoxide; VA, Alveolar ventilation; PEF, Peak expiratory flow; PASP, Pulmonary arterial systolic pressure; LDL-cholesterol, low density lipoprotein cholesterol; HDL-cholesterol, high density lipoprotein cholesterol.

*PASP was evaluated by echocardiography.

was found between anthracosis and C-reactive protein (p=0.488). We further examined whether anthracosis was a risk factor for acute exacerbation or infection of ILD patients by using logistic regression analyses. However no associations were found between them (both P>0.05).

Discussion

It was reported that: the frequency of simple anthracosis is 3.4-21% (16-17), patients affected with anthracosis was 63±3.8 years (18), the number of affected females in some large series has been equal to males (19-20). Consistently, the occurrence rate is 20% and the median patient age was 63.00 years in our cohort. However, our study shows that males are more than females. It's well known that cigarette smoking is not a risk factor for anthracosis and the risk of tuberculosis increased in anthracosis (7-8 18) with 16.6% incidence. In our cohort, we didn't find that smoking (P=0.671) and tuberculosis (P=0.260) with 2.8% incidence is associated with anthracosis. However, the low prevalence of tuberculosis in our cohort limited the power of our conclusion. We also analyzed the relationship between the exposure history of ILDs and anthracosis. Results show that no significant difference was found in metal dust or special chemical substance exposure history(p=0.413) between the two groups. As summarized in the literature, biomass smoke has been mostly reported as a risk factor for anthracosis (21). In our study, biomass exposure was also significantly increased in the anthracosis group compared with the non-anthracosis group (48, 67.6% vs. 153, 53.9%, p=0.041). We hypothesize that exposure factors between the two diseases may be different. Anthracosis is considered to be associated with prolonged contact with biomass fuel emissions, chronic inflammatory reactions, air pollution, domestic pollution, and chronic infections such as tuberculosis (TB) (22). However, ILDs may associate with inhaling exposures, smoking, drugs, and autoimmune disease (23).

According to reports in the literatures, fibrosis of the bronchi and reactive hyperplasia with black pigmentation were the major histopathological findings in anthracosis (4-6). We also find that the presence of hyperplasia of fibers (63, 88.7% vs. 196, 69.0%, P=0.001) was higher in the anthracosis group than that in the non-anthracosis group. But we couldn't conclude that anthracosis promotes fibrosis in ILD patients in consideration of the fact that the fibrosis is also the main characteristic of ILD patients.

As for clinical manifestations, we also find that cough and dyspnea are the most frequent symptoms of anthracosis as well as most reports(16-17, 19-21). Literatures also reported that the most significant CT finding was lymph node calcification in anthracosis patients (24). However, the proportion of lymph node calcification was similar between the two groups in our study.

On the other hand, some new findings in our study are as follows:

After adjusting for conventional atherosclerotic risk profiles including age, sex, BMI, blood pressure, heart rate (25) and medical histories of hypertension, diabetes and coronary heart diseases, anthracosis was associated with higher level of triglyceride. Anthracosis is found to be a risk factor for cardiovascular diseases realized via lipid metabolism disorders and atherosclerosis development (26). It is well-known that anthracosis is associated with prolonged contact with biomass fuel emissions, air pollution and domestic pollution. A longitudinal study in U.S. demonstrated that people living in polluted areas exhibited an increased risk for developing hypertriglyceridemia(27). A similar situation was reported in a longitudinal study in China, exposures to particulate matter(PM)2.5 and PM10 were associated with elevations in triglycerides(28). Studies carried out in small animals suggest mechanisms, inhalation of PM affected various metabolic pathways and induced inflammation and oxidative stress in the liver, contributing to dyslipidemia(29-31). In addition, the cardiac ejection fraction is lower in anthracosis group compared with non-anthracosis group. It was reported that cooking with biomass exacerbated systemic inflammation and oxidative stress in poor women cooking with biomass fuel and hence, predisposed them to increased risk of cardiovascular diseases(CVD) development(32). Zakharenkov et al. studied the mechanisms of intracellular defense of rat cardiomyocytes in anthracosis development induced by long-term inhalation of coal and rock dust (CRD). They find that the duration of exposure to CRD lead to structural and functional impairments in cardiomyocytes and the activation of free radical oxidation play a role in the process (33). Another animal study observed increased activation of Caspase-8 in the hearts of PM1-treated mice, thus indicating that cardiomyocytes apoptosis

may be involved in the cardiac function impairment triggered by fine PM (34). In my opinion, anthracosis may influence the cardiovascular system in two ways:1. By causing abnormal lipid metabolism. 2. By exerting a direct cytotoxic effect on heart. But we didn't find a relationship between coronary heart disease and anthracosis. Similarly, no significant difference was found in the proportion of coronary artery calcification between the two groups.

What's more, the pressure of carbon dioxide before the six-minute test is higher while the oxygen saturation after six-minute test is lower in the anthracosis group, which may reflect the impairments in ILDs patients caused by anthracosis. It's worth noting that the degree of fibrosis was similar between the two groups. It has also been reported that carbon dioxide partial pressure levels were significantly higher in the biomass smoke exposure than in the cigarette smoke exposure group(35). Another cohort study found that PM2.5 concentrations were associated with reduced oxygen saturation(36).

But what beyond expectation is peak expiratory flow is higher in the anthracosis group. This finding corresponds to the previous report. Some researchers reported that compared with non-bronchial anthracofibrosis COPD, bronchial anthracofibrosis may be associated with milder airflow limitation(9,37). This could not be exactly explained. They also find a relationship between bronchial anthracofibrosis and more common pulmonary hypertension with a greater degree of severity. However, we didn't come to this conclusion in ILDs patients.

Finally, the main pattern of ILDs in the anthracosis group is NSIP, which is higher than IPF. Due to the systemic inflammatory effects of coal and rock dust, anthracosis is associated with the development of various pathologies. The difference in the level of albumin and globulin may also illustrate this point.

Several limitations of the current study should be considered. First, as this study was retrospective, some clinical data were not available. Thus, selection bias could not be avoided. Second, some medical history was taken by an interviewer over the phone. Recall bias should be considered. Finally, the results have the risk of bias due to insufficient sample size.

Conclusion

In conclusion, this is the first detailed description of the concomitant occurrence of anthracosis and ILDs. We firstly evaluated the relationship between these clinical conditions. The findings not only shed light on the association of them but also help to provide ideas for the treatment of ILDs. Biomass smoke is a risk factor for anthracosis. Anthracosis produce a bad effect on the oxygenation, cardiac function and lipid metabolism in ILDs patients. The ILDs patients should decrease the exposure of biomass. Further prospective trials with high statistical power are necessary to be performed.

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