Involvement of the pulmonary arteries in patients with Takayasu arteritis

Xiufang Kong
Department of Rheumatology, Zhongshan Hospital affiliated to Fudan University
Lili Ma
Department of Rheumatology, Zhongshan Hospital affiliated to Fudan University
Peng Lv
Department of Radiology, Zhongshan Hospital affiliated to Fudan University
Xiaomeng Cui
Zhongshan Hospital Fudan University
Rongyi Chen
Zhongshan Hospital Fudan University
Zongfei Ji
Zhongshan Hospital Fudan University
Huiyong Chen
Zhongshan Hospital Fudan University
Jiang Lin
Department of Radiology, Zhongshan Hospital Fudan University
Lindi Jiang (zsh-rheum@hotmail.com)
Zhongshan Hospital Fudan University

Research article

Keywords: Takayasu arteritis, pulmonary artery involvement, cardiac function, pulmonary lesions

Posted Date: February 5th, 2020

DOI: https://doi.org/10.21203/rs.2.22686/v1

Version of Record: A version of this preprint was published at Arthritis Research & Therapy on June 5th, 2020. See the published version at https://doi.org/10.1186/s13075-020-02203-1.

Abstract

Background: Takayasu arteritis (TA) is a large-vessel vasculitis that can involve pulmonary arteries (PAs). We studied multiple clinical characteristics related to pulmonary artery involvement (PAI) in TA patients.

Methods: We enrolled 216 patients with TA from a large prospective cohort. PAI was assessed in each patient based on data from magnetic resonance angiography/computed tomography angiography. Pulmonary hypertension, cardiac function, and pulmonary parenchymal abnormalities were evaluated further in patients with PAI based on echocardiography, New York Heart Association Functional Classification and pulmonary computed tomography, respectively. These abnormalities related to PAI were followed up to evaluate treatment effects.

Results: PAI was detected in 56/216 (25.93%) patients, which involved the pulmonary trunk, main PAs and small vessels in the lungs. Among patients with PAI, 28 (50%) patients were accompanied by pulmonary hypertension, which was graded as 'severe' in 9 (16.07%), 'moderate' in 10 (17.86%) and mild in 9 (16.07%). Forty (71.43%) patients had cardiac insufficiency (IV: 6, 10.71%; III: 20, 35.71%; II: 14, 25.00%). Furthermore, 21 (37.50%) patients presented with abnormal parenchymal features in the area corresponding to PAI (e.g., the mosaic sign, infarction, bronchiectasis). During follow-up, two patients died due to abrupt pulmonary thrombosis. In the remaining patients, the abnormalities mentioned above improved partially after routine treatment.

Conclusions: PAI is very common in TA patients. PAI can cause pulmonary hypertension, cardiac insufficiency and pulmonary parenchymal lesions, which worsen the prognosis.

1. Introduction

Takayasu arteritis (TA) is a chronic, granulomatous large-vessel vasculitis. It involves the aorta and its main branches predominantly, and leads to vascular thickness, stenosis and occlusion [1]. In addition, TA occurs preferentially in young (20–40 years) women and has a relatively high prevalence in Asian countries compared with that in the USA and European countries [2].

Besides the aorta and its branches, pulmonary arteries (PAs) are involved in TA. PAs have been reported to be involved in 6.9% to 80% of TA patients from different populations [3-8]. The stenosis, occlusion or embolism of PAs can cause pulmonary hypertension (PH), perfusion defects, or even pulmonary infarction [9-11]. Recently, we also found multiple other parenchymal abnormalities in lung lobes with PA involvement. In addition, right-ventricular function is susceptible to damage in patients with PH due to increased afterload, which has a direct adverse impact on the prognosis [12]. Therefore, PA involvement in patients with TA is life-threatening because it damages cardiopulmonary function.

Multiple imaging modalities can be employed to detect PA abnormalities. These include digital subtraction angiography (DSA), magnetic resonance angiography (MRA), computed tomography angiography (CTA), positron emission tomography–computed tomography (PET–CT) and lung

ventilation/perfusion (VQ) scan [10, 13, 14]. Among them, DSA is applied rarely due to its invasiveness although it is the ‘gold standard’ to assess PA involvement. By contrast, CTA and MRA are undertaken more frequently because they show the structure of, and inflammation in, blood vessels, respectively [15]. PET–CT can also be employed to detect vascular inflammation [16]. Lung VQ scans can display vascular emboli for segmental (or sub-segmental) PAs [10].

We investigated the clinical characteristics, pulmonary parenchymal features and cardiac functions in TA patients with PA involvement by combining multiple imaging modalities (MRA, CTA, PET-CT, lung VQ scan, echocardiography and high-resolution computed tomography (HRCT). Our aim was to elicit better understanding of TA patients with PA involvement to aid rational treatment for these patients and improve their prognosis.

2. Methods And Materials

2.1 Patients

This was an observational study based on a prospective cohort named East China Takayasu arteritis (clinical trial number: NCT03893136). In this cohort, all patients were classified as having TA according to the classification criteria set by the American College of Rheumatology in 1990 [17]. The clinical data of this cohort were recorded using a standardised form and inputted into an electronic database. Patients who visited Zhongshan Hospital regularly from 1 January 2012 to 31 May 2019 were enrolled in the present study. Patients with concurrent disorders that could involve the lungs (e.g., pulmonary infection, asthma, tumours) were excluded. Finally, 216 patients were included in this study (flowchart is shown as Supplementary Fig. 1).

2.2 Disease assessment

At the initial visit, demographic data and clinical features (systemic and ischemic symptoms, physical signs) were recorded. Laboratory workup (routine tests for blood and urine; erythrocyte sedimentation rate (ESR); C-reactive protein (CRP) level; liver-function test; kidney-function test; hepatitis-B/C test; interferon-gamma release assay; antibodies against Mycoplasma species; sputum pathogens) was undertaken.

Vascular involvements were evaluated by whole-body MRA. If MRA was contraindicated, CTA or PET–CT of the thoraco-abdominal region was done. The type of vascular involvement in TA patients was classified according to the imaging classification created by Hata et al. [18]. Echocardiography was also carried out to evaluate cardiopulmonary conditions.

Pulmonary CT was undertaken for each patient. Additional pulmonary CTA or lung VQ scans were carried out for patients in whom a pulmonary embolism was suspected. CT-guided transthoracic lung biopsy was conducted for patients with confusing pulmonary lesions. Histopathology studies using staining (haematoxylin and eosin, immunohistochemical, acid-fast, silver) were done to evaluate vascular

inflammation and detect pulmonary infection. Tissue culture was also carried out to clarify if the pulmonary lesions were caused by infection.

The Kerr criteria [19] were used to assess disease activity: (i) systemic symptoms (infection, tumors, etc. were excluded); (ii) elevated ESR level; (iii) symptoms or signs of vascular ischemia (weakened pulse or pulselessness, vascular bruits, asymmetric blood pressure); (iv) positive imaging results. New onset or worsening of two or more criteria indicated 'active disease'.

2.3 Follow-up

Patients were followed-up each month during the first 6 months and every 2–3 months after that as planned. During follow-up, MRA was repeated every 6 months, whereas other imaging examinations (e.g., pulmonary HRCT, echocardiography) were employed as clinically required.

2.4 Treatment

The therapeutic procedure was divided into induction treatment and maintenance treatment. During the induction phase, prednisone (0.8–1.0 mg/kg/day, p.o.) was administered. After 4 weeks, the prednisone dose was tapered gradually to a maintenance dose of 0.1–0.2 mg/kg/day within the next 5 months. Meanwhile, an immunosuppressant (cyclophosphamide (CYC; 0.6–0.8 g/month, i.v.), methotrexate (MTX; 10–15 mg/week p.o.), azathioprine (AZA; 50–100 mg/d p.o.), leflunomide (LEF; 10–20 mg/d p.o.)) or a biological agent was used according to the discretion of the treating physician.

In the maintenance phase, MTX (10–15 mg/week, p.o.), AZA (25–50 mg/day, p.o.) or LEF (10–20 mg/day, p.o.) was administrated.

For patients suspected of having a pulmonary embolism, anticoagulant therapy (e.g., warfarin) was given. For patients with PH, bosentan, sildenafil, or adempas was also prescribed according to clinical conditions.

2.5 PA involvement

Vascular inflammation, as well as stenosis, dilation, or occlusion of the pulmonary trunk, right/left main PAs or branches of right/left main PAs were identified upon MRA or CTA. Emboli in sub-segmental PAs were confirmed by lung VQ scans combined with CTA. 'Vascular inflammation' was defined as an increased signal intensity of the vascular wall upon MRA compared with that of the back muscle situated beside the vertebral column of the same slice [15] or standard uptake value (SUV) of ^{18}F-fluorodeoxyglucose on PET–CT > 2.5 in the PA [19]. Vascular stenosis was assessed if the vascular diameter of the lesioned segment was less than that of the adjacent normal segment. Vascular dilation was diagnosed if the vascular diameter of the lesioned segment was < 50% greater than the vascular diameter of upper or lower normal segments. A 'vascular aneurysm' was documented if the vascular diameter of the lesioned segment was > 50% of the vascular diameter of upper or lower normal segments.

Imaging results were analysed independently by two experienced radiologists blinded to the clinical data. Discordant interpretations were settled by discussion based on additional clinical information until consensus was reached.

2.6 PH and heart function

PH was considered if patients had typical clinical symptoms (dyspnoea, chest pain, haemoptysis) and satisfied at least one of the following criteria: (i) mean PA pressure ≥ 25 mm, pulmonary artery wedge pressure ≤ 15 mmHg and pulmonary vascular resistance > 3 Wood Units at rest as assessed by right-heart catheterisation (RHC) [20]; (ii) pulmonary arterial systolic pressure (PASP) ≥ 40 mmHg and peak systolic velocity of the tricuspid valve > 3.4 m/s upon echocardiography [21]. Echocardiography was applied in patients with RHC contraindications. PH classes were also analysed in TA patients according to different causes: left-heart disease, lung disease and/or hypoxia, chronic thromboembolism, or unknown multifactorial mechanisms [22].

Given the diagnosis of PH, its severity should be evaluated further. Assessments such as the 6-minute walk test and measurement of biomarkers (e.g., brain natriuretic peptide, cardiac troponin T) were undertaken. According to the PASP upon echocardiography, patients were classified as ‘mild’ (40–54 mmHg), ‘moderate’ (55–64 mmHg) or ‘severe’ (> 65 mmHg) [23].

Impaired right-heart function occurs frequently in patients with chronic pulmonary disorders (especially PH). Cardiac function was also assessed in patients with PA involvement according to the New York Heart Association (NYHA) Functional Classification [24].

2.7 Pulmonary parenchymal abnormalities

Pulmonary parenchymal features within lung segments with PA involvement were analysed by pulmonary CT or PET–CT. Typical pulmonary features due to PA abnormalities (the mosaic sign, pleural effusion, bronchiectasis, pulmonary infarction) were analysed.

2.8 Statistical analyses

Categorical variables are presented as frequencies and percentages. Continuous variables are presented as the mean ± SD. The significance of those parameters among two groups was determined by the chi-squared test, Fisher's exact test or the unpaired Student’s t-test, as appropriate. $P < 0.05$ (two-sided) was deemed significant. SPSS v20.0 (IBM, Armonk, NY, USA) was used for statistical analyses.

3. Results

3.1 Characteristics of the study cohort

The demographic and clinical features of patients are listed in Table 1. Among 216 patients, 118 (54.63%) patients had ‘active’ disease status according to the Kerr score. The most frequent imaging type was type V (94, 43.52%), followed by type I (61, 28.24%). The pulmonary symptoms of chest

pain/distress, cough/expectoration and haemoptysis were present in 51/216 (23.6%), 9/216 (4.17%) and 5/216 (2.31%) patients, respectively. PA involvement was detected in 56/216 (25.93%) patients. Moreover, 34/216 (15.74%) patients were assessed as having PH.

Table 1. Demographic and clinical features

Parameter	Total (n=216)	Patients without PA involvement (n=160)	Patients with PA involvement (n=56)	P*
General information				
Female:male	178:37	130:30	48:7	0.41
Age at diagnosis (years, mean±SD)	35.19±14.75	34.23±15.05	37.96±13.57	0.11
Active status (n, %)	118 (54.63)	91 (56.88)	27 (48.21)	0.63
Clinical symptoms				
Headache/dizziness (n, %)	87 (40.28)	73 (45.63)	14 (25.00)	**0.023**
Weakness (n, %)	64 (29.63)	53 (33.13)	11 (19.64)	0.16
Chest pain/distress	51 (23.61)	27 (16.88)	24 (42.86)	**<0.001**
Fever (n, %)	26 (12.04)	24 (15.00)	2 (3.57)	**0.048**
Amaurosis (n, %)	25 (11.57)	21 (13.13)	4 (7.14)	0.46
Weight loss (n, %)	20 (9.26)	17 (10.63)	3 (5.36)	0.42
Oral ulcer (n, %)	12 (5.56)	6 (3.75)	6 (10.71)	**0.04**
Cough/expectoration (n, %)	9 (4.17)	3 (1.88)	6 (10.71)	**0.008**
Haemoptysis (n, %)	5 (2.31)	2 (1.25)	3 (5.36)	0.092
Clinical signs				
Vascular murmur (n, %)	68 (31.48)	46 (28.75)	22 (39.29)	0.087
Hypertension (n, %)	51 (23.61)	35 (21.88)	16 (28.57)	0.19
Pulselessness/weak pulse (n, %)	46 (21.30)	32 (20)	14 (25.00)	0.34
Neck pain (n, %)	14 (6.48)	11 (6.87)	3 (5.36)	0.21
Claudication (n, %)	13 (6.02)	7 (4.38)	6 (10.71)	0.09
Imaging features				
Aortic regurgitation (n, %)	50 (23.15)	34 (21.25)	16 (28.57)	0.27
Pulmonary hypertension (n, %)	34 (15.74)	9 (5.63)	28 (50.00)	**<0.001**
Type I	61 (28.24)	52 (32.5)	9 (16.07)	**0.001**
Type IIa	12 (5.56)	9 (5.63)	3 (5.36)	
Type IIb	25 (11.57)	**11 (6.88)**	**14 (25.00)**	
Type III	12 (5.56)	12 (7.50)	0 (0)	
Type VI	12 (5.56)	10 (6.25)	2 (3.57)	
Type V	94 (43.52)	66 (41.25)	28 (50)	

Laboratory results				
Haemoglobin (mean±SD, g/L)	117.78±20.18	117.70±20.22	118.04±20.24	0.92
White blood cells (mean±SD, 10^9/L)	9.29±10.27	9.30±11.05	9.24±7.52	0.97
Platelets (mean±SD, 10^9/L)	287.33±110.05	297.33±111.67	256.94±99.98	**0.02**
Erythrocyte sedimentation rate (mmHg)	37.25±33.84	38.66±33.66	33.11±34.33	0.31
C-reactive protein (mg/L)	20.16±31.31	21.40±31.97	18.30±29.41	0.54
Interleukin-6 (pg/L)	10.16±14.19	10.17±13.95	10.11±15.06	0.98

*P-value: comparison between patents with and without pulmonary hypertension

In contrast with patients without PA involvement, patients with PA involvement suffered from more chest pain/chest distress (24 (42.86%) vs. 27 (16.88%), P < 0.001), cough/expectoration (6 (10.71%) vs. 3 (1.88%), P = 0.008), oral ulcer (6 (3.75%) vs. 6 (10.71%), P = 0.04) and PH (28 (50.00%) vs. 9 (5.63%), P < 0.001).

3.2 PA involvement

The PA involvement of 56 patients is listed in Table 2 and representative images are shown as Fig. 1. Among these patients, 105 PAs were involved: pulmonary trunk (34, 32.38%), right PAs (38, 36.19%) and left PAs (33, 31.43%). The most frequent presentation was vascular stenosis (30/105, 28.57%), followed by vascular dilation (25/105, 23.81%) and vascular embolism (17/105, 16.19%). Right or left PAs presented predominantly as vascular stenosis (right: 18/38, 47.37%; left: 11/33, 33.33%) and embolism (right: 7/38, 18.42%; left: 10/33, 30.30%), whereas the pulmonary trunk presented mainly as vascular dilation (22/34, 64.71%) and vascular enhancement/inflammation (10/34, 29.41%). Nine patients with low perfusion upon MRA underwent lung VQ scans (Fig. 1G, I), which demonstrated emboli in multiple sub-segmental arteries, indicating that TA patients with PA involvement can also have small-vessel lesions.

Table 2. Imaging features of involved pulmonary arteries

Imaging feature	PT (n=34)	RPA (n=38)					LPA (n=33)				Total
		Main	U	M	L	Total	Main	U	L	Total	
Thickness (n, %)	1 (2.94)	1	2	0	0	3 (7.89)	0	1	1	2 (6.06)	6 (5.71)
Dilation (n, %)	22 (64.71)	1	0	0	0	1 (2.63)	2	0	0	2 (6.06)	25 (23.81)
Stenosis (n, %)	1 (2.94)	7	12	0	3	22 (57.89)	5	4	4	13 (39.39)	36 (34.29)
Occlusion (n, %)	0 (0)	1	0	0	1	2 (5.26)	2	0	1	3 (9.09)	5 (4.76)
Embolism (n, %)	0 (0)	6	0	1	0	7 (18.42)	8	0	2	10 (30.30)	17 (16.19)
Enhancement (n, %)	10 (29.41)	3	0	0	0	3 (7.89)	3	0	0	3 (9.09)	16 (15.24)
Total	34 (100)	19	14	1	4	38 (100)	20	5	8	33 (100)	105 (100)

PT: pulmonary trunk; RPA: right main pulmonary artery; LPA: left main pulmonary artery; U: upper pulmonary artery; M: middle pulmonary artery; L: lower pulmonary artery.

3.3 PH and cardiac function

Among 56 patients with PA involvement, 28 (50%) patients also had PH, which were graded as severe in 9 (16.07%), moderate in 10 (17.86%), and mild in 9 (16.07%). Based on PH causes, 16 patients belonged to group 2 (due to left-heart disease), 7 patients pertained to group 4 (due to PA involvement), whereas 5 patients had the underlying causes of group 2 and group 4 (PA involvement as well as aortic or left-heart insufficiency).

According to the NYHA classification, 40/56 (71.43%) patients had cardiac insufficiency (IV: 6, 10.71%; III: 20, 35.71%; II: 14, 25.00%), implying that PA involvement reduced cardiac function to a great extent.

3.4 Parenchymal features in the regions corresponding to PA involvement

Low perfusion in PAs can decrease oxygen delivery to tissues and impair cell function, leading to tissue injury. Among 56 patients with PA involvement, 21 (37.50%) patients presented with abnormal parenchymal features, including the mosaic sign in seven patients, infarction in six patients, pleural effusion in four patients, ground-glass opacities in three patients, bronchiectasis in two patients, cavitation in one patient, and atelectasis in one patient. Representative images of low perfusion and corresponding parenchymal lesions are shown in Fig. 2. Lung biopsy was carried out in two of the 56 patients with PA involvement, which indicated haemorrhagic infarction of pulmonary lesions, accompanied by fibrinoid necrosis of small vessels and infiltration of inflammatory cells (Fig. 3). Special stainings such as PAS staining and acid-fast staining were negative, which excluded pulmonary infections (Fig. 3). These results confirmed vasculitis in the parenchymal lesions of TA patients.

3.5 Follow-up of patients with PA involvement

Thirty-six patients completed ≥ 3-month follow-up, and the median duration of follow-up was 12 (interquartile range: 7–31.5) months. At the final visit, 13/36 (36.11%) patients continued to have active

disease or disease relapse; 2/36 (5.26%) patients died due to an acute pulmonary embolism (duration of follow-up as 4 and 12 months, respectively). Stent implantation and balloon dilation intervention was done in one patient respectively with bilateral PA involvement.

During follow-up, we observed that only chemical treatment can't obviously improve pulmonary arterial stenosis, but stent implantation and balloon dilation based on the chemical treatment can improve arterial stenosis and further blood supply in a great extent (Fig. 4A-D). But although their arterial conditions were hard to be reversed, their overall conditions were improved. Cough/expectoration in four cases and haemoptysis in three cases had resolved. In addition, the pulmonary pressure decreased obviously from 62.38 ± 25.84 mmHg to 55.90 ± 25.84 mmHg (n = 19, P = 0.052) (Fig. 4E) for 19 patients with baseline PH. Eleven patients showed improvement in cardiac function (from IV to III in three patients; from III to II in four cases; from II to I in four patients), 20 patients showed no change, and cardiac function worsened in three cases (from II to III in two cases; from I to II in one patient, Fig. 4F).

Nine patients with parenchymal lesions at baseline had repeated pulmonary CT (previously, four cases had pulmonary infarction, two had a pleural effusion, two had the mosaic sign, and one had a pulmonary cavitation). After treatment, pulmonary infarction in 2/4 (50%) patients had dissipated; 2/2 (100%) patients with a pleural effusion had a reduced effusion volume; and 1/1 (100%) patient with pulmonary cavitation has improved. However, no changes were observed regarding other pulmonary lesions upon repeat pulmonary CT.

4. Discussion

We discovered that one-quarter of TA patients can have PA involvement, which presented in the pulmonary trunk, main PA, lobar artery, segmental (or even sub-segmental) arteries. The prevalence of PH was ~ 15% in patients with TA whereas, among TA patients with PA involvement, it was 50%, which contributed to impairment of cardiac function. PA involvement could also cause pulmonary parenchymal lesions (37.5%). Therefore, PA involvement in patients with TA can affect multiple aspects of cardiopulmonary functions, which worsens the prognosis.

One-quarter of patients had PA involvement, a figure similar to that reported in other countries (5–36.7%) [9, 25]. Not all patients presented with symptoms such as cough or haemoptysis, which suggests that PA involvement in TA can be silent [26]. In addition, we did not find an association between PA involvement and disease activity. This finding is in accordance with a report from China [27] but contrary to a study from Korea that discovered PA involvement in a high proportion of patients with clinically active TA [5]. Given that TA is indolent, patients might be diagnosed at different stages of TA. Hence, the relationship between PA involvement and disease activity might differ in different studies.

Stenosis was the most common imaging presentation of the involved PAs, followed by dilation and emboli. Two studies have shown that stenosis or occlusion was the most common presentations of involved PAs in TA [25, 28]. Additional lung VQ scans for patients with low perfusion upon MRA revealed pulmonary emboli to be very common in TA patients, which involved multiple segmental (or

subsegmental) PAs. Therefore, low perfusion upon MRA should not be ignored in patients with TA, and pulmonary VQ scans is valuable for detection of emboli in small arteries.

PH is a direct result of PA involvement. In the present study, half of patients with PA involvement suffered from PH. Among them, the ratio of left heart disease-related PH (group 2) was more than that of pulmonary embolism-related PH (group 4), a finding that is in accordance with a report from Wang and colleagues [28]. This phenomenon can be explained by the higher prevalence of aortic involvement than PA involvement in TA. Moreover, we observed that the PH and cardiac insufficiency were moderate-to-severe in patients with PA involvement, implying cardiopulmonary function was badly damaged in patients with PA involvement.

In TA, PA involvement can also induce parenchymal lesions [29, 30], which was a novel finding of the present study. Various pulmonary lesions (the mosaic sign, infarction, pleural effusion, bronchiectasis, cavitation) were observed in regions corresponding to PA involvement. The mosaic sign and pulmonary infarction are direct pulmonary manifestations on account of hypoperfusion [11, 31, 32]. Recurrence of pleural effusions has been reported to be associated with disease activity [33, 34]. Bilateral effusions are probably induced by cardiac insufficiency, whereas a unilateral effusion might be related to pleural inflammation or small-vessel vasculitis in peripheral pulmonary areas [35]. Bronchiectasis has been reported in one case study of TA [36], which we assumed was the result of involvement of the bronchial arteries in TA. Poor blood perfusion can cause chronic destruction of bronchial tissue and further bronchiectasis. Moreover, cavitation has been reported in TA [37, 38], which can be treated with glucocorticoids combined with immunosuppressants, further confirming that cavitation is mediated by abnormal autoimmune reactions.

Patients with PA involvement should be monitored closely and treated comprehensively. In the present study, two patients died due to a sudden pulmonary embolism even though their disease was assessed to be stable. Besides the usual treatment for TA, PH-targeting agents are necessary for patients with PH (especially group-4 PH). In some cases, surgery is also indicated. Our study demonstrated that symptoms, pulmonary pressure and cardiac function were improved markedly after treatment in most patients, but some patients did not respond well. Hence, ascertaining the factors responsible for such different therapeutic responses must be undertaken. In addition, novel treatment strategies must be explored. These strategies will lay the foundation for future precise treatment for TA.

5. Conclusions

PA involvement is very common in TA patients. Physicians should be alerted to PA involvement even if obvious pulmonary symptoms are absent because they can cause PH, cardiac insufficiency as well as pulmonary parenchymal lesions, which will worsen the prognosis.

Abbreviations

Takayasu arteritis	TA
pulmonary hypertension	PH
digital subtraction angiography	DSA
magnetic resonance angiography	MRA
computed tomography angiography	CTA
positron emission tomography–computed tomography	PET–CT
ventilation/perfusion scan	VQ scan
high-resolution computed tomography	HRCT
erythrocyte sedimentation rate	ESR
C-reactive protein	CRP
cyclophosphamide	CYC
methotrexate	MTX
azathioprine	AZA
leflunomide	LEF
standard uptake value	SUV
right-heart catheterisation	RHC
pulmonary arterial systolic pressure	PASP
New York Heart Association	NYHA

Declarations

Ethics approval and consent to participate

The study protocol conformed to the ethical guidelines set by the 1975 Declaration of Helsinki as reflected in a priori approval (B2016-168) issued by the Ethics Review Board of Zhongshan Hospital (Shanghai, China).

Consent for publication

All patients provided written informed consent for inclusion in this study.

Availability of data and materials

The dataset supporting the conclusions of this article is included within the article and its additional file.

Competing interests

The authors declare that they have no competing interests.

Funding

This work was supported by the National Natural Science Foundation of China (81771730, 81571571), and Shanghai Committee of Science and Technology (17140902000).

Authors' contributions

XFK analyzed the data, while LLM helped in the statistical process. PL and JL were responsible for the pulmonary imaging evaluation. XMC, RYC, ZFJ and HYC contributed to the clinical data collections. LDJ directed the whole process in this study. All authors read and approved the final manuscript.

Acknowledgements

Not applicable

References

[1] E. Seyahi. Takayasu arteritis: an update. Curr Opin Rheumatol. 2017; 29: 51-56.

[2] M.L.F. Zaldivar Villon, J.A.L. de la Rocha, L.R. Espinoza. Takayasu Arteritis: Recent Developments. Curr Rheumatol Rep. 2019; 21: 45.

[3] N. Matsunaga, K. Hayashi, I. Sakamoto, Y Ogawa,T Matsumoto. Takayasu arteritis: protean radiologic manifestations and diagnosis. Radiographics. 1997; 17: 579-594.

[4] M Bicakcigil, K Aksu, S Kamali, Z Ozbalkan, A Ates, O Karadag, H T E Ozer, E Seyahi, S Akar, F Onen, A Cefle, S Z Aydin, N Yilmaz, A M Onat, V Cobankara, E Tunc, M A Ozturk, I Fresko, Y Karaaslan, N Akkoc, A E Yücel, S Kiraz, G Keser, M Inanc, H Direskeneli. Takayasu's arteritis in Turkey - clinical and angiographic features of 248 patients. Clin Exp Rheumatol. 2009; 27: S59-64.

[5] Ga Yeon Lee, Shin Yi Jang, Sung Min Ko, Eun Kyoung Kim, Sung Ho Lee, Hyejin Han, Seung Hyuk Choi, Young-Wook Kim, Yeon Hyeon Choe, Duk-Kyung Kim. Cardiovascular manifestations of Takayasu arteritis and their relationship to the disease activity: analysis of 204 Korean patients at a single center. Int J Cardiol. 2012; 159: 14-20.

[6] David N Brennan, Kenneth J Warrington, Cynthia S Crowson, Jean Schmidt, Matthew J Koster. Cardiopulmonary involvement in Takayasu's arteritis. Clin Exp Rheumatol. 2018; 36 Suppl 111: 46-50.

[7] Wei Jiang, Yuanhua Yang, Xiuzhang Lv, Yidan Li, Zhanhong Ma, Jifeng Li. Echocardiographic characteristics of pulmonary artery involvement in Takayasu arteritis. Echocardiography. 2017; 34: 340-347.

[8] Yanru He, Naqiang Lv, Aimin Dang, Nan Cheng. Pulmonary Artery Involvement in Patients with Takayasu Arteritis. J Rheumatol. 2019; DOI: 10.3899/jrheum.190045

[9] H. Direskeneli. Pulmonary hypertension in Takayasu's arteritis: Should be monitored closely. Int J Cardiol. 2019; 276: 238-239.

[10] M Castellani, M Vanoli, G Calì, G Bacchiani, L Origgi, E Reschini, R Scorza, P Gerundini. Ventilation-perfusion lung scan for the detection of pulmonary involvement in Takayasu's arteritis. Eur J Nucl Med. 2001; 28: 1801-1805.

[11] G Devouassoux, C Pison, P Witmeyer, F Tony, M Coulomb, C Brambilla. Pulmonary infarction revealing pulmonary Takayasu's arteritis. Respir Med. 1998; 92: 969-967.

[12] Xuanqi An, Yechen Han, Bingqing Zhang, Lin Qiao, Yuxing Zhao, Xiaoxiao Guo, Ligang Fang, Wenling Zhu, Quan Fang, Zhujun Shen, Shuyang Zhang. Takayasu arteritis presented with acute heart failure: case report and review of literature. ESC Heart Fail. 2017; 4: 649-654.

[13] Lillian Barra, Tahir Kanji, Jacqueline Malette, Christian Pagnoux. Imaging modalities for the diagnosis and disease activity assessment of Takayasu's arteritis: A systematic review and meta-analysis. Autoimmun Rev. 2018; 17: 175-187.

[14] S Sharma, T Kamalakar, M Rajani, K K Talwar, S Shrivastava. The incidence and patterns of pulmonary artery involvement in Takayasu's arteritis. Clin Radiol. 1990; 42: 177-181.

[15] Lindi Jiang, Dan Li, Fuhua Yan, Xiaomin Dai, Yinliang Li, Lili Ma. Evaluation of Takayasu arteritis activity by delayed contrast-enhanced magnetic resonance imaging. Int J Cardiol. 2012; 155: 262-267.

[16] M. Bardi, A.P. Diamantopoulos. EULAR recommendations for the use of imaging in large vessel vasculitis in clinical practice summary. Radiol Med. 2019.

[17] W P Arend, B A Michel, D A Bloch, G G Hunder, L H Calabrese, S M Edworthy, A S Fauci, R Y Leavitt, J T Lie, R W Lightfoot Jr. The American College of Rheumatology 1990 criteria for the classification of Takayasu arteritis. Arthritis Rheum. 1990; 33: 1129-1134.

[18] A Hata, M Noda, R Moriwaki, F Numano. Angiographic findings of Takayasu arteritis: new classification. Int J Cardiol. 1996; 54 Suppl: S155-163.

[19] Xiaojie Zhang, Jun Zhou, Ying Sun, Hongcheng Shi, Zongfei Ji, Lindi Jiang. (18)F-FDG-PET/CT: an accurate method to assess the activity of Takayasu's arteritis. Clin Rheumatol. 2018; 37: 1927-1935.

[20] Marius M Hoeper, Harm Jan Bogaard, Robin Condliffe, Robert Frantz, Dinesh Khanna, Marcin Kurzyna, David Langleben, Alessandra Manes, Toru Satoh, Fernando Torres, Martin R Wilkins, David B Badesch. Definitions and diagnosis of pulmonary hypertension. J Am Coll Cardiol. 2013; 62: D42-50.

[21] Eduardo Bossone, Antonello D'Andrea, Michele D'Alto, Rodolfo Citro, Paola Argiento, Francesco Ferrara, Antonio Cittadini, Melvyn Rubenfire, Robert Naeije. Echocardiography in pulmonary arterial hypertension: from diagnosis to prognosis. J Am Soc Echocardiogr. 2013; 26: 1-14.

[22] R.J. Oudiz. Classification of Pulmonary Hypertension. Cardiol Clin. 2016; 34: 359-361.

[23] Micah R Fisher, Paul R Forfia, Elzbieta Chamera, Traci Housten-Harris, Hunter C Champion, Reda E Girgis, Mary C Corretti, Paul M Hassoun. Accuracy of Doppler echocardiography in the hemodynamic assessment of pulmonary hypertension. Am J Respir Crit Care Med. 2009; 179: 615- 621.

[24] Jonathan Yap, Fang Yi Lim, Fei Gao, Ling Li Teo, Carolyn Su Ping Lam, Khung Keong Yeo. Correlation of the New York Heart Association Classification and the 6-Minute Walk Distance: A Systematic Review. Clin Cardiol. 2015; 38: 621-628.

[25] Juanni Gong, Yuanhua Yang, Zhanhong Ma , Xiaojuan Guo, Jianfeng Wang, Tuguang Kuang, Suqiao Yang, Jifeng Li, Ran Miao, Kewu Huang Clinical and imaging manifestations of Takayasu's arteritis with pulmonary hypertension: A retrospective cohort study in China. Int J Cardiol. 2019; 276: 224-229.

[26] Arsene Mekinian, Marc Lambert, Damien Huglo, Patrick Devos, Tristan Mirault, Marc Steinling, Eric Hachulla, Pierre-Yves Hatron. Pulmonary perfusion scintigraphy: a tool to detect the presence of pulmonary artery involvement in Takayasu's arteritis. Presse Med. 2012; 41: e37-42.

[27] R Lü, C L Yu, J Li, D D Wen, M W Zheng. [CT findings and clinical features of Takayasu's arteritis with pulmonary artery involvement]. Zhonghua Yi Xue Za Zhi. 2017; 97: 1796-1800.

[28] Xu Wang, Aimin Dang, Bingwei Chen, Naqiang Lv, Qing Liu. Takayasu arteritis-associated pulmonary hypertension. J Rheumatol. 2015; 42: 495-503.

[29] J G Im, S H Kim, M J Chung, J M Koo, M C Han. Lobular low attenuation of the lung parenchyma on CT: evaluation of forty-eight patients. J Comput Assist Tomogr. 1996; 20: 756-762.

[30] K Takahashi, M Honda, M Furuse, M Yanagisawa, K Saitoh. CT findings of pulmonary parenchyma in Takayasu arteritis. J Comput Assist Tomogr. 1996; 20: 742-748.

[31] Tomomi Nakamura, Shinichiro Hayashi, Mami Fukuoka, Naoko Sueoka, Kohei Nagasawa. Pulmonary infarction as the initial manifestation of Takayasu's arteritis. Intern Med. 2006; 45: 725-728.

[32] M A King, C J Bergin, D W Yeung, E E Belezzouli, L K Olson, W L Ashburn, W R Auger, K M Moser. Chronic pulmonary thromboembolism: detection of regional hypoperfusion with CT. Radiology. 1994; 191: 359-363.

[33] T Kawai, Y Yamada, J Tsuneda, T Aoyagi, A Mikata. Pleural effusion associated with aortitis syndrome. Chest. 1975; 68: 826-828.

[34] J B Dou, J N Gong, Z H Ma, T G Kuang, Y H Yang. [The analysis of the clinical records diagnosed as Takayasu's arteritis with pulmonary vascular involvement]. Zhonghua Jie He He Hu Xi Za Zhi. 2016; 39: 603-607.

[35] X H Gui, M Cao, Y Liu, H R Cai, Y L Xiao. [Unilateral pleural effusion as first manifestation in Takayasu arteritis: a case report and review of literature]. Zhonghua Jie He He Hu Xi Za Zhi. 2016; 39: 768-772.

[36] Gamage Nd Perera, Anusha C Jayasinghe, Lalindra D Dias, Aruna Kulatunga. Bronchiectasis and hoarseness of voice in takayasu arteritis: a rare presentation. BMC Res Notes. 2012; 5: 447.

[37] P P Yang , Y H Yang, T G Kuang, M F Yang, J F Wang, Q Huang, S Q Yang, J F Li, X L Diao, K N Zhang, J N Gong. [Pulmonary cavities with Takayasu arteritis: report of 3 cases and literature review]. Zhonghua Jie He He Hu Xi Za Zhi. 2018; 41: 787-792.

[38] S Elsasser, M Solèr, C Bolliger, K Jäger, U Steiger, A P Perruchoud. Takayasu disease with predominant pulmonary involvement. Respiration. 2000; 67: 213-215.

Figures

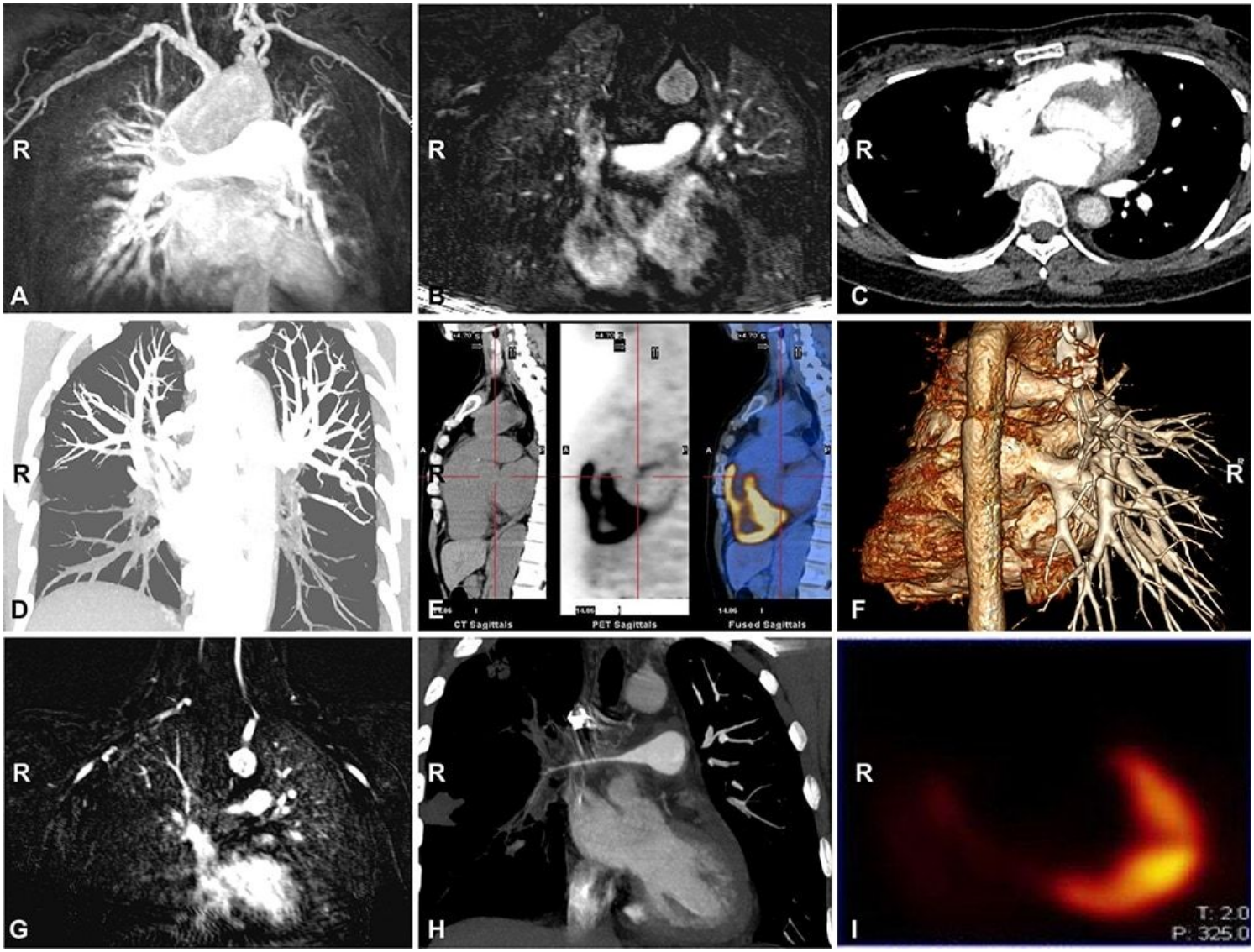

Figure 1

Imaging of PA lesions in TA patients A: Dilation of the pulmonary trunk upon CTA; B: thickness of the pulmonary trunk upon MRA; C: stenosis of the right main PA upon CTA; D: embolism of lower PAs on both sides upon CTA; E: inflammation of the pulmonary-trunk root upon PET–CT (SUV 4.1); F: absence of left PAs and stenosis of the right main PA (reconstructed image of CTA); G–I: pulmonary MRA (G), CTA (H) and VQ scan (I) of a patient with TA. MRA shows a fine right main PA and low perfusion in the right lung (G); CTA demonstrates a fine right main PA and fewer PA branches in the right lung (H); lung VQ scan shows multiple arterial emboli in the right lung and obvious less blood supply to the right lung.

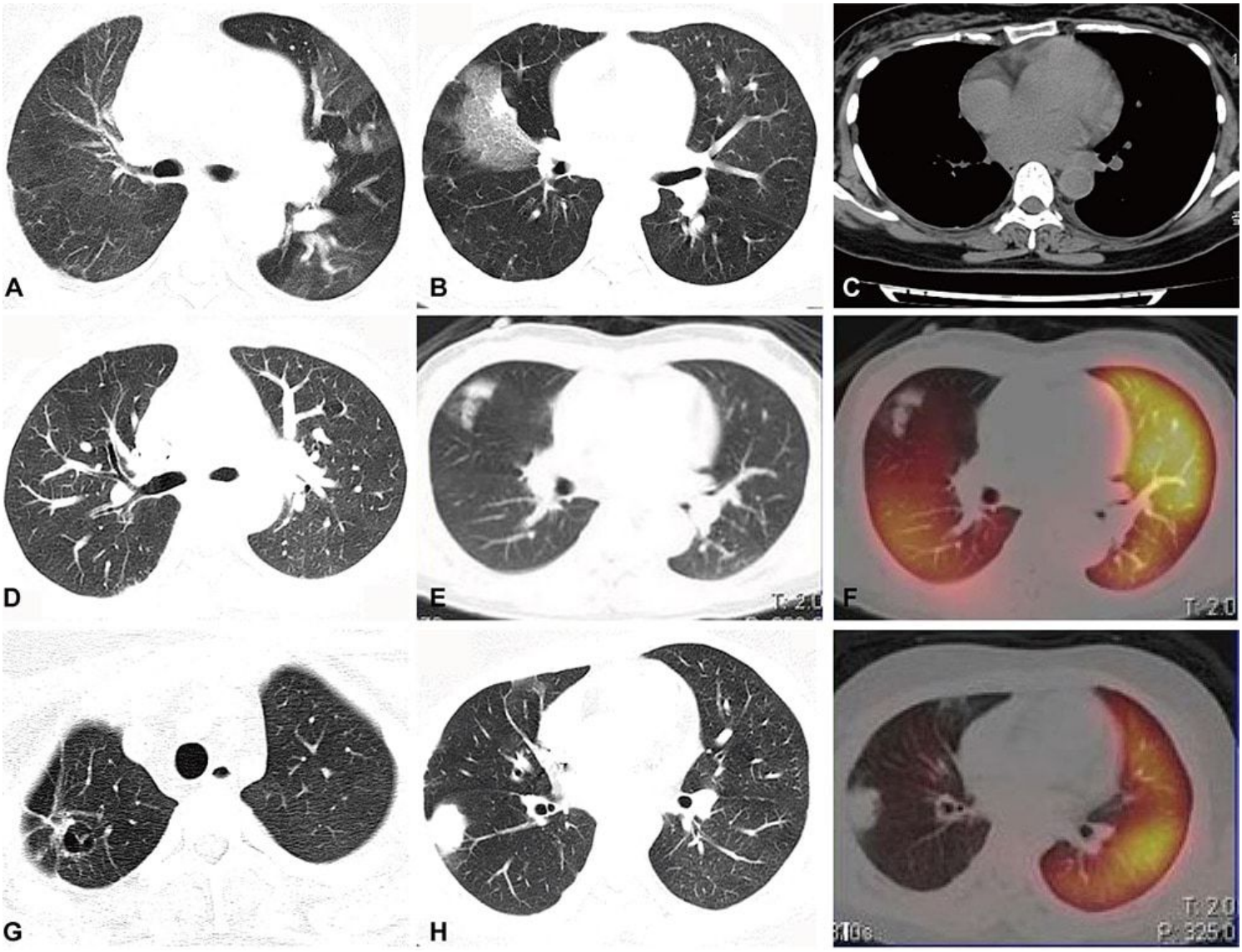

Figure 2

Pulmonary lesions on HRCT A: The mosaic sign in the left lung of a patient with stenosis of the left main PA; B: Pulmonary infarction of the right middle lobe in a patient with severe stenosis of the right main PA; C: Mild pleural effusion on the left side in a patient with pulmonary-trunk dilation and pulmonary hypertension; D: Bronchiectasis in the right lung in a patient with stenosis of the right main PA and its distant branches; E–F: Ground-glass opacity (E) in the right upper lobe of a TA patient with an embolism of the right upper pulmonary branches (F). G–I: Cavitation (G) and mass-like consolidation (H) in the patient with severe stenosis of right main pulmonary artery (I).

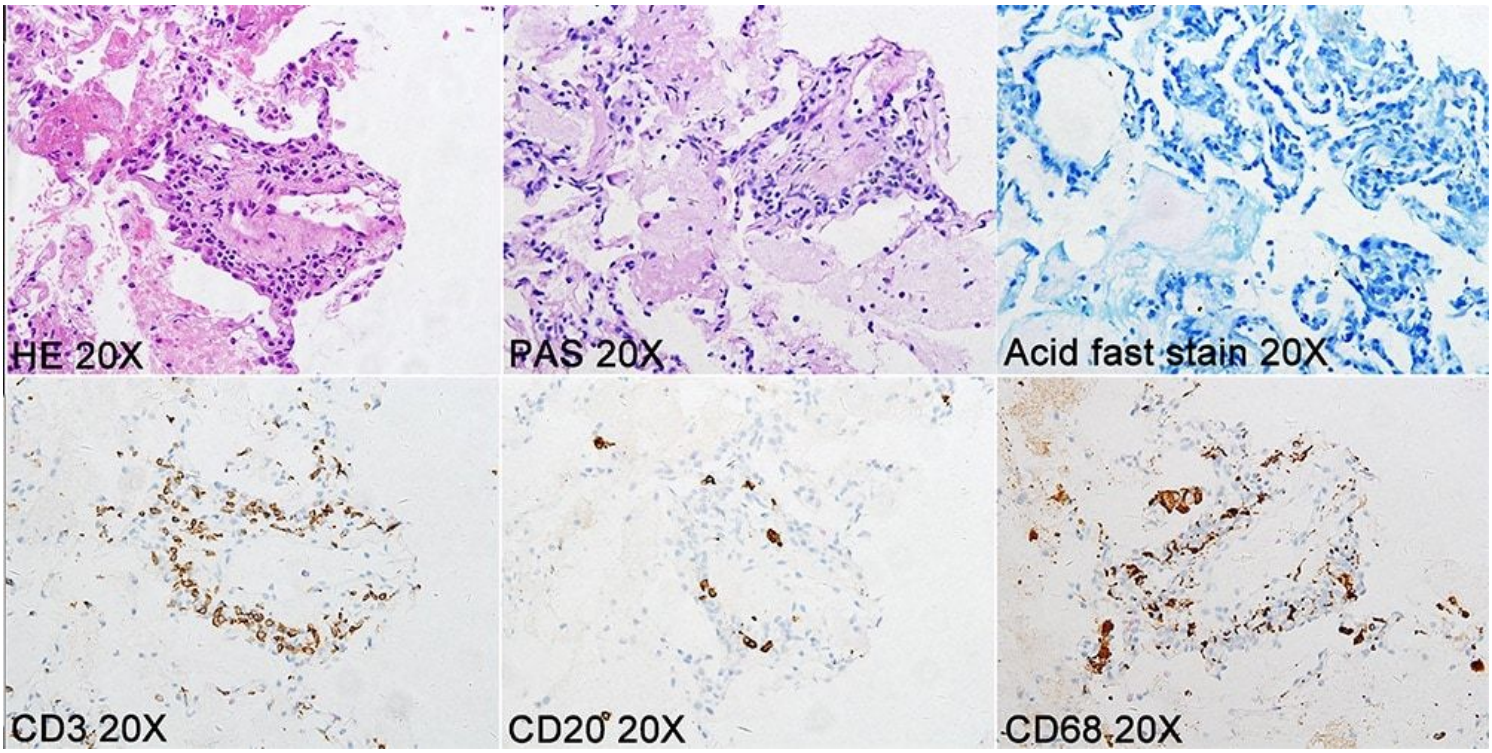

Figure 3

Pathological features of pulmonary parenchymal lesions The pathological of pulmonary lesions indicated vasculitis of pulmonary small vessels with CD3 positive cells, CD68 positive cells infiltration. Special staining (PAS and acid fast stain) didn't find evidence of fungal or tuberculosis Tuberculous bacillus infections.

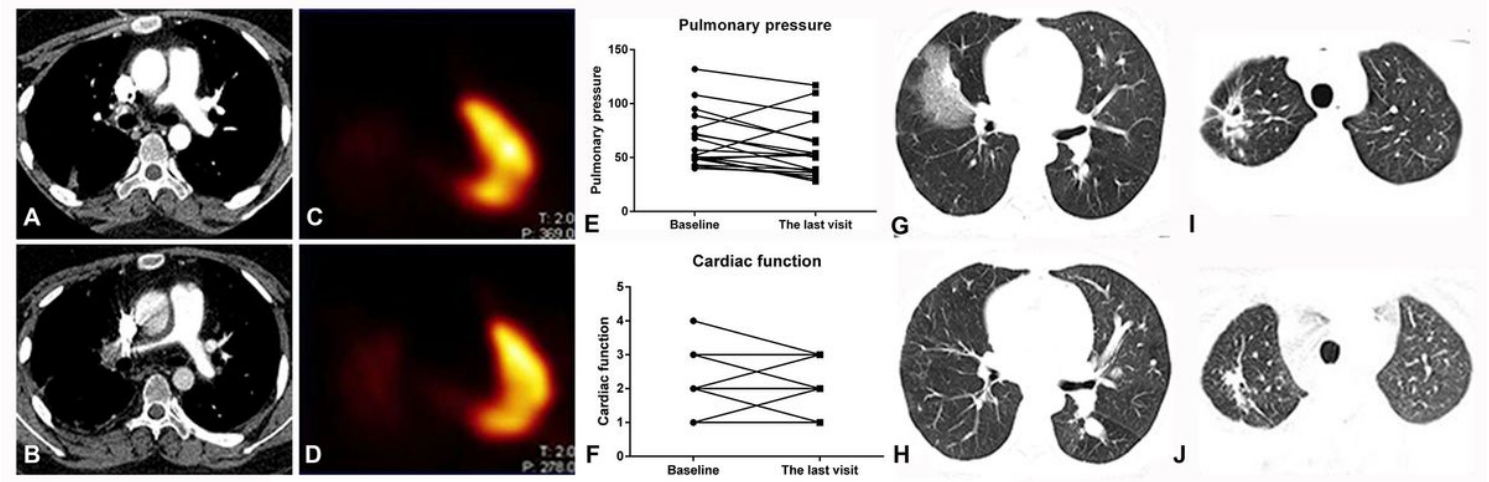

Figure 4

Pulmonary conditions after treatment A-D: The right main pulmonary artery was shown upon CTA after balloon dilation intervention (A-B); correspondingly, the blood supply to the right lung was also increased upon lung VQ scan. E: The pulmonary arterial pressure was decreased significantly (62.38±25.84 to 55.90±25.84 mmHg, n=19, P=0.052); F: After treatment, patients' cardiac function was improved in most

patients. G–H: Infarcted lesions dissipated after treatment. I-J: The cavitation in the right lung apex became smaller after treatment.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- Additionalfile1.doc