A re-evaluation of ^{18}F -FDG PET/CT for diagnosing relapsing polychondritis and monitoring the therapeutic response to treatment

Jinlin Wang^{1,*}, Minfang Li^{2,*}, Sheng Chen², Shiyue Li¹, Jianxing He^{1,*} and Yunxiang Zeng^{1,*}

¹The State Key Laboratory of Respiratory Disease, China Clinical Research Centre for Respiratory Disease, Guangzhou Institute of Respiratory Disease, First Affiliated Hospital of Guangzhou Medical University, Guangzhou, China

²Department of Respiratory Medicine, Shenzhen Traditional Chinese Medicine Hospital, Shenzhen, China

*These authors contributed equally to this work

Correspondence to: Yunxiang Zeng, email: yunxiangzeng@126.com

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ABSTRACT

Background: Relapsing polychondritis (RP) is a rare degenerative disease and its diagnosis is often delayed and difficult. Although the use of ^{18}F -fluorodeoxyglucose positron emission tomography/computed tomography (^{18}F -FDG PET/CT) for diagnosing RP has been reported previously, its true diagnostic value is uncertain due to the limited number of published case reports. Moreover, its value for biopsy guidance and therapeutic response monitoring remain controversial.

Materials and Methods: Data on 30 patients with a clinical diagnosis of RP who underwent PET/CT scans were retrospectively reviewed. Follow-up scans were performed in 10 patients, and visual scores (VS) and maximal standard uptake (SUV_{max}) values were analysed.

Results: With the initial scan, 83.3% of patients showed lesions in more than one cartilage. Mean VS and SUV_{max} values in the cartilages were 2.92 ± 0.38 and 4.06 ± 0.18 , respectively. In 18 patients with no history of corticosteroid treatment, more cartilages were affected than in patients who previously received corticosteroids (3.89 ± 0.29 vs 2.75 ± 0.63 , respectively; $p = 0.07$). Positive rates for PET/CT-guided biopsy in nasal, auricular and tracheal/bronchial cartilages were 100%, 88.9% and 10.5%, respectively. In comparison, the positive rate for non-PET/CT-guided biopsy of auricular cartilage was 92.3%. Compared with the initial scan, the second scan had significantly lower mean VS (1.41 ± 0.20 vs 2.92 ± 0.38 , respectively; $p < 0.0001$) and SUV_{max} values (2.76 ± 0.14 vs 4.06 ± 0.18 , respectively; $p < 0.001$).

Conclusions: FDG uptake in multiple cartilages suggests a diagnosis of RP, but repeated administration of corticosteroids may undermine the diagnostic value of ^{18}F -FDG PET/CT. Further investigation of its use in locating biopsy sites and in monitoring the response to treatment is required.

INTRODUCTION

Relapsing polychondritis (RP), first described by Jaksch-Wartenhorst in 1923, [1] is a rare autoimmune inflammatory disease characterised by episodic inflammation of cartilaginous tissue and proteoglycan-rich structures throughout the body [2, 3]. Currently, the

diagnosis of RP is mainly based on characteristic clinical findings and is generally made on the basis of a set of clinical criteria established by McAdam et al. in 1976 [4]. However, the initial symptoms are often atypical, and the prognosis is unfavourable when the respiratory tract is involved. Airway involvement is a major cause of morbidity and mortality in affected patients, [5] and this

occurs in up to 50% of RP patients during the course of the illness [4–7].

In 2007, Nishiyama et al. [8] first described a case of RP diagnosed using fluorodeoxyglucose positron emission tomography/computed tomography (FDG PET/CT). Since then, a series of case reports have demonstrated that PET/CT is capable of determining the distribution of all lesions and facilitating their early recognition, locating biopsy sites, and evaluating disease activity and the therapeutic response to treatment [9–16]. However, these were mostly single case reports, and there has been no comprehensive study focusing on the application of PET/CT in RP. In 2014, we retrospectively investigated 6 patients with RP, and found that PET/CT was a valuable tool for diagnosing RP and monitoring the response to treatment [17]. Almost at the same time, Yamashita et al. [18] and Lei et al. [19] analysed a series of RP cases who had undergone PET/CT scans (including their own and others from the literature), and also concluded that PET/CT is a reliable procedure for early diagnosis of RP. Other studies have also suggested that PET/CT is a useful radiological tool for the assisting in the selection of biopsy sites in RP [9, 16, 19]. However, the value of these investigations was limited by relatively heterogeneous populations and small sample sizes. In our previous study, [17] some biopsies of tracheal/bronchial cartilages were negative for RP even though FDG uptake was increased. In this regard, our data contrast with the conclusion of Lei et al. [19] who reported that combining PET/CT with transbronchial needle aspiration (TBNA) was an effective diagnostic approach. There is also controversy as to whether PET/CT is of value for monitoring the therapeutic response to treatment in view of its uncertain accuracy, high cost and radiation exposure.

In this study, we retrospectively investigated the available data on 30 patients with RP, which is largest sample analysed to date, and summarized our experience. We aimed to re-evaluate the value of ^{18}F -FDG PET/CT for diagnosing RP, guiding biopsies, and monitoring the therapeutic response to treatment.

RESULTS

Patient characteristics

The study population comprised 30 patients (17 males, 13 females) of mean age of 44.8 years (range, 25 to 66 years). Their clinical characteristics are shown in Table 1. The main clinical symptom was cough, which was noted in 24 patients (80%); other symptoms included shortness of breath in 15 patients (50%), wheezing in 6 (20%), excessive sputum in 6 (20%), fever in 4 (13.3%), hoarseness in 3 (10%), chest pain in 3 (10%) and pharyngalgia in 1 (3.3%). The duration of these complaints ranged from 6 months to more than 10 years. Eight patients were misdiagnosed as asthma, 3 as chronic obstructive pulmonary disease (COPD), and 1 as tracheal

amyloidosis. Corticosteroids had been administered irregularly to these patients before a definitive diagnosis was made. All the patients received comprehensive treatment with corticosteroids after the definitive diagnosis of RP. Most of them showed improved clinical symptoms, including a complete or partial resolution of cough, easier breathe less sputum and fever, etc. Immune inhibitors (Azathioprine) were plus with in two patients (Nos. 8 and 26) when symptoms were not obviously improved.

Laboratory findings showed the erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) level ranged from normal to markedly increased, with mean levels of 61.9 mm/1 h (range, 10–121 mm/1 h) and 16.64 mg/dL (range, 0.03–34.40 mg/dL). Increased ESR and CRP found in some patients were substantially decreased after regular corticosteroids treatment with mean levels of 41.2 mm/1 h (range, 11–81 mm/1 h) and 10.62 mg/dL (range, 0.04–20.30 mg/dL). Antinuclear antibodies (ANA) were detected in 2 patients (Nos. 16 and 19) but rheumatoid factor (RF) was not detected. Mean fasting blood glucose concentrations before the initial and follow-up scans were 99.23 ± 12.72 mg/dL [5.51 ± 0.71 mmol/L] and 106.1 ± 9.41 mg/dL [5.89 ± 0.52 mmol/L], respectively ($p = 0.126$). Chest CT scans performed prior to the diagnosis showed diffuse thickening and narrowing of the trachea in 26 patients (86.7%) and the main bronchus in 24 (80%), airway wall calcification in 7 (23.3%), and enlargement of the mediastinal lymph node in 2 (6.7%); 1 patient (3.3%) exhibited no abnormal manifestations (Table 1). Lung function measurements indicated that 25 patients (75%) had obstructive ventilatory dysfunction and 5 (25%) had restrictive ventilation dysfunction. The lung function results varied from normal to markedly abnormal.

^{18}F -FDG PET/CT findings in RP (Table 2)

The initial ^{18}F -FDG PET/CT scan was performed in all patients. Twenty-five patients (83.3%) showed lesions in more than one cartilage, and 20 (66.6%) had lesions in three or more cartilages. The most commonly involved cartilages were tracheal/bronchial cartilage (26 patients; 86.7%), nasal cartilage (18 patients; 60%) and auricular cartilage (15 patients; 50%). The mean VS in the cartilages was 2.92 ± 0.38 . The RP lesions demonstrated an increased SUV_{max} in all patients except Patient No. 7, and the mean SUV_{max} value was 4.06 ± 0.18 . Figure 1 shows the affected cartilages or organs in the 30 patients. When patients were classified into 2 groups according to their history of corticosteroid treatment, all 18 patients with no history of corticosteroid therapy were found to have lesions in 2 or more cartilages [Figure 2 shows the PET/CT images for Patient No.12]. In the other 12 patients who had received corticosteroids, fewer cartilages tended to be affected (mean number, 2.75 ± 0.63 vs 3.89 ± 0.29 in those with no history of corticosteroid therapy), although there was no statistical difference between the 2 groups

($p = 0.07$). Among the latter 12 patients, 4 (Nos. 4, 13, 21 and 29) had only 1 cartilage site with intense FDG uptake, and 1 patient (No. 7) did not have intense FDG uptake in any cartilage.

Follow-up PET/CT examinations were performed in 10 patients. In comparison with the initial scan, the second scan had a significantly lower mean VS (1.41 ± 0.20 vs 2.92 ± 0.38 , respectively; $p < 0.0001$), and the mean SUV_{max} value with the second scan was also significantly lower than that with the initial scan (2.76 ± 0.14 vs 4.06 ± 0.18 , respectively; $p < 0.001$). Most of the intense uptake decreased or disappeared during corticosteroid therapy [Figure 3 shows the PET/CT images for Patient No.12 after treatment]. FDG uptakes diminished in most of the affected sites, except in the auricular cartilage of Patient No. 24 who showed symptomatic and inflammatory improvement. However, nasal cartilage FDG uptake was obviously increased in Patient No. 20.

Cartilage biopsy in the RP patients

The results of cartilage biopsies, which were performed at different sites in all patients, are shown in Table 3. Nasal cartilage biopsies were all positive for patients with increased FDG uptake detected by PET/CT-guided nasal cartilage biopsy (5/5, 100%). Fiberoptic bronchoscopy was performed in most of the patients and two-sample paired-proportions test showed significant difference in RP diagnostic performance between ^{18}F -FDG PET/CT and biopsy in tracheal/bronchial cartilage. Biopsies of the tracheal/bronchial cartilage

by bronchoscopy were performed with the aid of PET/CT in 19 patients, but only 2 had positive results (2/19, 10.53%). Biopsies of the tracheal/bronchial cartilage by bronchoscopy were also applied for 4 RP patients negative for PET/CT scan, and none of them showed positive outcomes (0/4, 0%). PET/CT-guided auricular cartilage biopsy was performed in nine patients and eight of them had positive results (8/9, 88.9%) [Figure 4 shows the characteristic RP pathology in Patient No.12]. There were 15 patients in which FDG uptakes at auricular cartilage were negative. Auricular cartilage biopsy was conducted in 13 patients among them. Surprisingly, the biopsy positive rate was as high as 92.31% (12/13). Therefore, no correlation was found between PET/CT and biopsy in RP diagnosis with respect to auricular cartilage.

DISCUSSION

RP is a rare inflammatory chondropathy in multiple cartilages that is not readily diagnosed in the absence of typical clinical findings [2, 17, 25–29]. The diagnosis of RP diagnosis is based on clinical criteria, such as those described by McAdam et al. [4] and on a biopsy of affected cartilage. According to Damiani and Levine, [21] the diagnosis also can be established when one or more of clinical features are present in conjunction with biopsy confirmation. Our previous study revealed that PET/CT is a powerful tool for diagnosing RP as it can detect multisystemic cartilaginous abnormalities via increased FDG uptake. [17] In the study of Yamashita et al. [18]

Figure 1: Affected cartilages or organs in the 30 patients with RP (in descending order).

Table 1: Demographic characteristics of the 30 patients with RP

No.	Age (y)/sex	Chief complaint ^a (duration; mths)	Misdiagnosis	Serum levels			ANAs	Lung function			Chest CT scan ^b	Biopsy site
				ESR (mm/1h)	CRP (mg/dL)	RF (IU/mL)		FEV1 (L)	FVC (L)	FEV1/ FVC (%)		
1	37/M	1 (6)	-	100	22.0	2.1	N	1.68	4.61	36.4	a, b	Tracheal (-)/nasal cartilage (+)
2	38/M	1, 2 (18)	Asthma	115	10.69	3.6	N	1.74	4.69	37.1	a, b	Tracheal (-)/auricular (+)
3	55/M	1, 3 (6)	-	10	0.03	2.4	N	2.57	3.32	77.3	c	Tracheal (-)/nasal cartilage (+)
4	66/F	1, 4 (24)	COPD	105	5.36	4.2	N	1.64	4.56	36.0	e	Tracheal (-)/auricular (+)
5	41/M	1, 4 (9)	-	120	26.41	2.0	N	0.92	1.32	69.7	a, b	Tracheal (-)/auricular (+)
6	55/M	1 (10)	-	112	23.41	2.8	N	1.32	4.19	31.46	a, b	Tracheal (-)/auricular (+)
7	64/M	5 (120)	COPD	11	0.88	4.9	N	0.57	2.37	31.7	a, b	Tracheal (-)/auricular (+)
8	60/M	4 (72)	Amyloidosis	23	1.02	3.4	N	0.49	3.37	92.3	a, b, c	Auricular (+)
9	42/M	1, 4, 6 (4)	-	87	16.2	2.5	N	1.43	4.08	35.0	a, b, c	Tracheal (-)/auricular (+)
10	47/F	1, 4, 7 (1)	-	45	21.0	3.1	N	2.30	4.02	46.5	b	Tracheal (-)/auricular (-)
11	50/F	1 (4); 4 (0.5)	-	34	6.4	3.0	N	1.10	3.67	30.0	b	Tracheal (-)/auricular (+)
12	44/F	1 (4); 4 (1)	Asthma	45	3.4	2.6	N	2.30	4.32	53.2	a, b	Tracheal (-)/auricular (+)
13	44/F	1, 5 (10)	Asthma	68	34.4	3.2	N	1.70	3.89	43.7	a, b	Tracheal (-)/auricular (+)
14	48/F	4 (132)	Asthma	34	10.0	1.0	N	0.67	2.33	28.8	a, b, c	Nasal cartilage (+)
15	25/M	1, 7 (1); 3 (0.5)	-	121	23.0	1.7	N	2.33	4.87	47.8	a, b	Tracheal (-)/auricular (+)
16	26/F	1, 4 (6)	Asthma	56	21.0	2.6	P	1.02	3.24	31.5	a, b	Auricular (+)
17	52/M	1, 5, 7 (60)	Asthma	45	19.3	2.5	N	1.05	3.45	30.4	a, b	Auricular (+)
18	43/F	4 (6); 1, 5 (2)	-	34	12.0	1.3	N	2.00	4.01	49.9	a	Nasal cartilage (+)
19	36/F	1, 8 (12); 4, 7 (6)	-	36	11.7	2.6	P	1.87	3.56	52.5	a, b	Tracheal (-)/auricular (+)
20	36/M	6 (12); 4 (6)	-	110	34.12	2.1	N	1.56	3.67	42.5	a, b, c	Tracheal (+)
21	42/M	1, 7 (60)	Asthma	34	12.8	1.8	N	2.30	4.50	51.1	a, b	Tracheal (-)/auricular (+)
22	45/M	1, 3 (7)	-	22	11.33	2.3	N	1.20	2.05	58.5	a, d	Auricular (+)
23	34/F	2, 4 (8)	-	56	23.0	3.5	N	1.98	2.87	69.0	a, b, d	Tracheal (-)
24	62/M	1, 7 (36)	COPD	45	21.02	2.5	N	1.56	3.45	45.2	a, b	Tracheal (-)/nasal cartilage (+)
25	45/F	1, 5 (17)	-	33	12.34	1.56	N	2.01	4.56	44.1	a	Tracheal (+)
26	34/F	2, 4 (9)	-	98	23.56	2.01	N	1.87	3.45	54.2	a, b	Tracheal (-)/auricular (+)
27	29/M	1, 3 (8)	-	121	26.71	2.76	N	1.23	3.56	34.6	a, c	Auricular (-)
28	45/M	1, 5 (14)	-	56	11.0	2.04	N	1.34	3.21	41.7	a, b, c	Tracheal (-)/auricular (+)
29	64/M	1, 4 (15)	Asthma	45	32.1	2.87	N	2.23	4.67	47.8	a, b	Tracheal (-)/auricular (+)
30	35/F	1, 6 (12)	-	36	23.1	3.45	N	0.97	1.89	51.3	a, b	Tracheal (-)/auricular (+)

^a Chief complaint: 1 = cough; 2 = chest pain; 3 = fever; 4 = shortness of the breath; 5 = wheezing; 6 = hoarseness; 7 = excessive sputum; 8 = pharyngalgia,

^b Chest CT scan: a = diffuse thickening and narrowing of trachea; b = diffuse thickening and narrowing of main bronchus; c = calcification of the trachea; d = enlargement of the mediastinal lymph node; e = no abnormal manifestations.

ANAs, antinuclear antibodies; COPD, chronic obstructive pulmonary disease; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; F, female; FEV₁, forced expiratory volume in 1 second; FVC, forced vital capacity; M, male; N, none; P, present; RF, rheumatoid factor; RP, relapsing polychondritis; y, years.

several specific patterns of PET/CT findings in RP were found, such as FDG uptake in bilateral auricular cartilage, and FDG uptake was noted in various combinations of affected lesions in single patients (for example, auricular and nasal, trachea and unilateral bronchial tree, costal cartilage and joints, etc.). These authors recognised that the specific PET/CT findings may be of high diagnostic value. However, the numbers of patients evaluated in these previous studies were so small that a re-evaluation is necessary. To our knowledge, the current study is the largest series of patients in which the value of PET/CT has been investigated in RP. Significantly, PET/CT scans

in the 30 patients whose data were evaluated showed that 83.3% (25/30) had disease involvement in more than one cartilage. We also found that all 18 patients without a history of prior corticosteroid treatment had involvement in more than one cartilage. Therefore, FDG uptake in multiple cartilages, such as tracheal/bronchial cartilage, nasal cartilage and auricular cartilage, in a single patient suggests the diagnosis of RP and a biopsy might not be necessary. However, the other 12 patients who received irregular corticosteroid treatment previously had fewer affected cartilages detected by PET/CT, and 4 of them (Nos. 4, 13, 21 and 29) had only one site of intense FDG

Table 2: FDG-PET/CT findings of RP in the 30 patients

No.	Initial PET/CT scan				Follow-up PET/CT scan ^a			
	FBG (mg/dL)	Uptake sites ^b	Visual scores	SUVmax ^c	FBG (mg/dL)	Visual scores	SUVmax ^c	Interval (mths)
1	101	1/2//3/4	3/3//3/3	5.8/5.7/3.6/5.1	116	3/3/1/3	3.1/2.7/-/2.7	3
2	89	1/2/3/4/5/6/7	3/3/3/3/3/3/3	3.8/3.7/4.0/3.9/4.0/3.8/3.7	101	2/2/2/0/3/0/0	2.0/2.1/2.1/-/3.1/-/-	3
3	83	2/3/4/6/7/8	3/3/3/3/3/3	4.4/4.2/3.8/3.8/3.8/4.8	98	3/0/3/3/3/3	3.8/-/3.0/3.0/3.0/3.0	2.5
4	93	6	3	3.6				
5	93	1/3/8/9	3/3/3/3	3.3/4.2/4.5/5.0	89	2/0/3/3	2.1/-/3.0/2.8	3
6	115	1/8	3/3	3.5/4.2	108	3/0	2.8/-	4
7	85	-	-	-				
8	116	1/9	3/3	3.9/2.5				
9	88	1/9/10	3/3/3	3.3/4.5/4.3				
10	79	1/10	3/3	3.1/4.3				
11	112	1/8	3/3	3.3/3.8				
12	101	1/3/8/11	3/3/3/3	5.9/2.8/3.2/5.7	121	3/0/0/2	2.8/-/-/2.0	3
13	122	10	3	4.0				
14	99	1/2	3/3	3.4/3.8				
15	87	1/2/8/10	3/3/3/3	3.8/4.9/4.9/3.5				
16	110	1/2/3/9/10	3/3/3/3/3	2.5/2.6/2.2/4.7/2.6				
17	95	1/2/8/12	1/3/3/3	-/6.2/3.2/2.7	113	0/2/0/0	-/3.0/-/-	4
18	123	1/2/8/10	1/2/3/3	-/1.9/3.0/2.2				
19	101	1/2/8/10	3/3/3/3	2.7/3.7/3.0/5.5				
20	111	1/2/4/8/10	3/3/3/3/3	3.2/3.2/4.2/4.0/4.2	110	0/3/0/2/0	-/3.9/-/2.0/-	3
21	121	1	3	2.0				
22	96	1/2/9	3/1/3	3.8/-/6.4				
23	88	1/2/3/8/9/10	3/3/3/3/3/3	3.7/3.0/4.5/3.5/3.5/3.2				
24	99	1/2/3/8/10	3/3/3/3/3	3.8/2.7/8.1/3.6/7.2	103	0/0/0/3/0	-/-/4.2/-	4
25	78	1/2/3/8	3/3/3/3/3	2.2/3.3/4.0/4.3				
26	108	1/2/3/8/10	3/2/3/2/3	4.8/1.8/2.8/1.7/3.8				
27	97	1/2/8/10	3/3/3/3	4.0/2.9/3.9/4.9	102	0/0/1/3	-/-/1.2/2.8	3
28	87	1/2/13	3/3/3	9.1/4.9/17.9				
29	98	1	2	2.0				
30	102	1/2/3/9/10	3/3/3/3/3	4.6/3.2/4.5/4.7/5.0				

^a Results of the second PET/CT scan, even though 3 follow-up scans could be performed.

^b Uptake sites: 1 = tracheal/bronchial cartilage; 2 = nasal cartilage; 3 = costicartilage; 4 = arytenoid cartilage; 5 = hyoid cartilage; 6 = cricoid cartilage; 7 = thyroid cartilage; 8 = auricular cartilage; 9 = lymph node; 10 = auricular cartilage; 11 = vocal cord; 12 = lung; 13 = eye muscle.

^c If the FDG uptakes were in different positions of the same cartilage, SUV_{max} should be representative of the highest one.

FDG-PET/CT, fluorodeoxyglucose positron emission tomography/computed tomography; FBG, fasting blood glucose; SUV_{max}, maximum standardised uptake value.

uptake in cartilages. Patient No. 7 who had received corticosteroid treatment did not exhibit intense FDG uptake in any cartilages. Thus, repeated administration of corticosteroids may undermine the diagnostic value of ¹⁸F-FDG PET/CT.

In our clinical practice, definitive diagnoses of RP are usually made according to both clinical features and biopsy results, especially for patients with atypical symptoms. The main biopsy sites are auricular cartilage and nasal cartilage. In the present study, the positive rate for PET/CT-guided biopsy was relatively high in nasal

cartilage (100%) and auricular cartilage (88.9%), but the positive rate for non-PET/CT-guided biopsy of auricular cartilage in was 92.3%. Thus, while PET/CT was effective for guiding biopsies in nasal and auricular cartilage, a negative PET/CT scan result will not completely exclude RP involvement, especially when auricular cartilage is affected. We consider that there could be a high risk of false-negative results with PET/CT scans of auricular cartilage. A possible explanation is that FDG uptake is consistent with an adequate blood supply which is usually poor in auricular cartilage.

Table 3: Correlation of PET/CT with cartilage biopsy in diagnosing RP

PET/CT ^a	Cartilage biopsy		Total
	Positive	Negative	
Nasal cartilage:			
Positive	5	0	5
Negative	0	0	0
Total	5	0	5
[McNemar's chi-square test: $c^2 = \text{NaN}$; $p = \text{NaN}$]			
Auricular cartilage:			
Positive	8	1	9
Negative	12	1	13
Total	20	2	22
[McNemar's chi-square test: $c^2 = 7.69$; $p = 0.005$]			
Tracheal/bronchial cartilage:			
Positive	2	17	19
Negative	0	4	4
Total	2	21	23
[McNemar's chi-square test: $c^2 = 15.1$; $p = 0.001$]			

^aPET/CT-guided biopsy was performed in affected cartilage when PET/CT showed increased FDG uptake.

PET/CT, positron emission tomography/computed tomography; NaN, not a number; RP, relapsing polychondritis.

The positive rate for PET/CT-guided biopsies was low in tracheal/bronchial cartilage (10.5%) in the present study, even though FDG uptakes were high. Therefore, a positive result in tracheal/bronchial walls with a PET/CT scan is not always consistent with the biopsy result for tracheal/bronchial walls sampled by bronchoscopy. A possible reason for this inconsistency is technical difficulty/challenge in reaching the affected site of tracheal/bronchial cartilage when there is tracheal collapse, fibrosis or stenosis. Bronchoscopy is invasive and consequently may exacerbate mucosal swelling or cartilage inflammation via mechanical stimulation. Serious complications arising from cartilage biopsies of the trachea or bronchus in RP patients have been reported [30]. Thus, the value of PET/CT-guided biopsy may be dependent on the cartilage site affected.

Corticosteroid therapy is the mainstay of treatment for RP, and some researchers have reported that PET/CT is valuable for monitoring the response to treatment. Lei et al. [19] noted that post-treatment PET/CT examinations showed obvious decreases or complete disappearance of high ¹⁸F-FDG-uptake lesions in 10 of 22 cases, which was highly consistent with symptom improvement, and Yamashita et al. [18] reported similar findings. In our research, a follow-up scan performed in 10 of the 30 patients (33%) showed that mean VS and SUV_{max} values were significantly lower with this scan than with the initial scan. These changes were also correlated with clinical symptom improvements and related laboratory data.

These findings suggest that PET/CT is a promising radiological tool for monitoring the treatment response

and disease progress. However, because there is no consensus about the duration of corticosteroid treatment, there is no consensus regarding the use of PET/CT to optimise corticosteroid strategies, although some reports have pointed to its potential value [9–15]. The time interval for PET/CT scans after corticosteroid therapy remains unclear, as it has been reported to range from 1 month to 13 months [9–11, 13, 18]. To our knowledge, there have been no studies that have sought to determine how many and what percentage of patients have had their clinical management altered on the basis of PET/CT results. Therefore, there is no evidence that PET/CT can provide prognostic information in RP patients and could be considered a guide for making treatment decisions. In 2 of our patients, in whom follow-up data indicated symptomatic and inflammatory improvement, FDG uptakes diminished in most of the affected sites but increased in 2 other sites (nasal and auricular cartilage). Thus, in some patients, PET/CT results may differ depending on their symptoms. In some cartilage sites, FDG accumulation after corticosteroid treatment of patients with RP may be correlated with other factors (except inflammatory activity). In the present study, only 33.3% patients (10/30) underwent follow-up PET/CT scans, mainly because of their high cost, and further studies involving larger numbers of patients are necessary to evaluate the role of follow-up PET/CT scans during treatment. In doing so, the cost-effectiveness of repeated PET/CT scans and the resultant radiation exposure must also be taken into account.

Our study has some limitations. Firstly, it was a retrospective study and therefore, the results may not completely translate to clinical practice. Secondly, because all patients included in the study presented with respiratory symptoms, it is possible that we underestimated the value of PET/CT for RP patients without respiratory involvement. Thirdly, although this was the largest dataset studied thus far, the number of patients evaluated was still small reflecting the low incidence of this disease and well-defined patient populations. Thus, a larger, multicentre, prospective, randomised study is needed for further validation of our results.

In conclusion, FDG uptake in multiple involved cartilages suggests the diagnosis of RP, but repeated

application of corticosteroids may undermine the diagnostic value of ^{18}F -FDG PET/CT. Further investigation of ^{18}F -FDG PET/CT is needed confirm its value in guiding biopsies and in monitoring the response to treatment.

MATERIALS AND METHODS

Study design and setting

The clinical characteristics of 30 patients with a diagnosis of RP who were treated at the First Affiliated Hospital of Guangzhou Medical University, Guangzhou between January 2010 and January 2016, were reviewed retrospectively. The patients were admitted to hospital

Figure 2: A 44-year-old female (Patient No. 12) with RP showed multicartilage involvement. (A) A whole-body view showed multiple foci of pathological tracer uptake in cartilages (vocal cord: SUV_{max} 5.8; tracheal/bronchial cartilage: SUV_{max} 5.8; red arrowhead). (B) The SUV_{max} of tracheal cartilage was as high as 5.8 (red arrowhead). (C) Abnormal uptake was detected in costal cartilage and tracheal cartilage (red arrowhead).

Figure 3: The PET/CT image of patient No.12 that significant decrease of FDG uptake after treatment.

due to respiratory symptoms and underwent PET/CT examinations in the Department of Radiology. High-resolution computed tomography (HRCT) revealed diffuse thickening and narrowing of the trachea and/or major bronchi, tracheal calcification, or enlargement of the mediastinal lymph node in all patients except one (Patient No. 4). Patient Nos. 1 and 3 have previously been described in separate case reports, [12, 20] and data on 6 patients (Nos. 1-6) have been retrospectively reviewed in a previous study [17]. PET/CT was performed as a whole-body imaging technique to determine the underlying cause of the disease or to exclude malignant conditions when the diagnosis was difficult to establish on the basis of the available clinical evidence.

All patients were finally diagnosed with RP according to clinical criteria. [4, 21] None had serious underlying diseases such as diabetes or malignant tumours. All patients were treated with corticosteroids following establishment of the diagnosis, initially with prednisolone doses 1 mg/kg/day with subsequent reductions of 5–10 mg per month.

Follow-up ^{18}F -FDG PET/CT scans were performed in 10 patients to assess the therapeutic response and optimise further therapeutic strategies. Six patients had their follow-up PET/CT scans 3 months after beginning corticosteroid therapy, and the other 4 patients had their follow-up PET/CT scans after 2.5 or 4 months. In patient No. 3, follow-up scans were performed at 3, 9 and 15 months during prednisolone treatment. No follow-up scans were performed in the other 20 patients.

Written informed consent was obtained from all patients whose data were analysed and for publication of any accompanying images.

^{18}F -FDG PET/CT scans

As described in a previous report, [17] patient preparation for ^{18}F -FDG PET/CT scans included the following steps: (1) avoidance of strenuous work or

exercise in the preceding 24 hours, fasting for more than 6 hours before the scan, and measurement of fasting blood glucose concentrations prior to the scan (which were required to be under 130 mg/dL [7.2 mmol/L] before ^{18}F -FDG injection); (2) an intravenous injection of ^{18}F -FDG in a dosage of 3.70–5.55 MBq/kg together with 10 mg furosemide to accelerate renal ^{18}F -FDG elimination; (3) a CT scan from the brain to the pelvis using a multidetector spiral CT scanner (3.75 mm slice thickness; pitch 0.875; rotation speed 140 keV; 120 mAs) prior to the PET scan; and (4) acquisition of whole-body PET images using a PET/CT system (GE Discovery ST; GE Medical Systems Inc., WI, USA) 60 min after tracer administration (acquisition time, 2.5 min per bed position for 6 to 7 bed positions).

Data analysis

The PET/CT images were reconstructed using the ordered subset expectation maximisation method (OSEM), with and without attenuation correction. The visual analysis of PET/CT characteristics and pattern was interpreted by at least 2 experienced nuclear medicine physicians who had the patients' clinical information available on a dedicated workstation. When disputes regarding visual interpretation occurred, consensus was reached by discussion. The ^{18}F -FDG PET scans were analysed visually and semi-quantitatively by calculating the SUV_{max} . The intensity of ^{18}F -FDG uptake by cartilages relative to the background and incompatible with normal anatomy/physiology was assessed, and the intensity was scored using a 4-point visual score (VS) scale [22, 23]. A score of 0 on this scale = absence, not visible on the image display; 1 = faint or less intense than mediastinal blood pool activity; 2 = moderate or equal in intensity to mediastinal blood pool activity; and 3 = more intense than mediastinal blood pool activity. A region of interest (ROI) was placed over the entire area of any abnormal uptake (scale 2 or 3) site. The SUV_{max} was calculated (maximum

Figure 4: A biopsy sample obtained from auricular cartilage in Patient No. 12 showed characteristic RP pathology. (A) H&E staining of neutrophils (red arrowhead). (B) H&E staining of normal (a) and necrotic chondrocytes (b).

ROI activity/injected dose per kg body weight), and the highest SUV_{max} was used to evaluate the multiple abnormal uptake sites observed in a given lesion or tissue. As the blood glucose level may affect SUV_{max} results, the SUV_{max} values needed to be corrected for blood glucose (SUV_{glu}) as follows: $SUV_{glu} = SUV_{max} \times \text{blood glucose level}/130$ when the blood glucose level was >130 mg/dL (7.2 mmol/L) [24]. A positive PET/CT result was judged when the VS was ≥ 1 or SUV_{max} was ≥ 2.0 .

Statistical analysis

Continuous variables were presented as the median and range, and qualitative variables as numbers and percentages. Intergroup differences were analysed statistically using SPSS® 17.0 (SPSS Inc, Chicago, IL, USA). Differences in continuous variables between groups were compared using Student's *t*-test. McNemar's test was used to determine the difference between ^{18}F -FDG PET/CT and cartilage biopsy in RP diagnosis. Significance for statistical analyses was set at $p < 0.05$.

Abbreviations

ANA, antinuclear antibody; COPD, chronic obstructive pulmonary disease; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; ^{18}F -FDG PET/CT, ^{18}F -fluorodeoxyglucose positron emission tomography/computed tomography; HRCT, high-resolution computed tomography; OSEM, ordered subset expectation maximisation method; RF, rheumatoid factor; ROI, region of interest; RP, relapsing polychondritis; SUV_{max} , maximal standard uptake value; TBNA, transbronchial needle aspiration; VS, visual score.

Author contributions

JW, ML, JH and YZ were involved in the study concept and design. JW, SC and SL were involved in data acquisition, and ML, SC and SL were involved in the statistical analysis and interpretation of the data. JW, JH and YZ drafted the manuscript. All authors critically reviewed/revised the manuscript and approved the final version. JH and YZ takes responsibility for the integrity of the data and the accuracy of the data analysis.

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CONFLICTS OF INTEREST

None.

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