

FDG PET-CT combined with TBNA for the diagnosis of atypical relapsing polychondritis: report of 2 cases and a literature review

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Objective: To explore the value of ^{18}F -fluorodeoxyglucose positron emission tomography-computed tomography (FDG PET-CT) combined with transbronchial needle aspiration (TBNA) in diagnosing atypical relapsing polychondritis (RP).

Methods: Data from two patients with atypical RP, which had been diagnosed in our hospital using FDG PET-CT combined with TBNA, were retrospectively analyzed. A review of the relevant literature was also performed.

Results: Consistent with the previously reported 20 cases of RP that had been diagnosed using FDG PET-CT, the two patients in the present study showed the involvement of multiple organs, including the nose, throat, trachea, bronchi, costicartilage and joint cartilages, and increased FDG uptake was found in these areas. The mean value of SUVmax was 5.14. PET-CT revealed that 86.4% of the patients with RP had airway involvement. TBNA technique was used for biopsy of the hypermetabolic lesions, and pathologic examinations confirmed the diagnosis of RP. The time to diagnosis in these two patients and the 20 cases reported previously was about 6.9 months, significantly shorter than the average diagnosis time (20 months).

Conclusions: FDG PET-CT has several advantages for diagnosing RP, especially atypical RP. TBNA is a minimally invasive and safe technique for obtaining airway cartilage. Combining PET-CT with TBNA may play an important role in shortening the time to diagnosis in patients with RP involvement of airway.

Keywords: Relapsing polychondritis (RP); positron emission tomography-computed tomography (PET-CT); transbronchial needle aspiration (TBNA); cartilage; fluorodeoxyglucose (FDG); standard uptake value (SUV)

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Introduction

Relapsing polychondritis (RP) is a disease of unknown etiology characterized by recurrent non-infectious inflammation of cartilaginous and connective tissues. Previous studies have shown that autoimmunity may play a role in the pathogenesis of this disease (1,2). Clinical presentations of RP vary considerably from patient to patient, and the involvement of multiple organs has been reported. However, there is currently no specific diagnostic method available; as a result, the rates of misdiagnosis and missed-diagnosis are very high, particularly

with regard to the early diagnosis of atypical RP.

To date, very few studies have reported the use of ^{18}F -fluorodeoxyglucose positron emission tomography-computed tomography (FDG PET-CT) combined with transbronchial needle aspiration (TBNA) for the diagnosis of RP. Here, we have analyzed the clinical features of two cases of atypical RP that had been diagnosed in our hospital using FDG PET-CT combined with TBNA, and performed a literature review to evaluate the value of this approach in diagnosing RP and in shorting the time to diagnosis in patients with RP.

Methods

Data from two patients with atypical RP, which had been diagnosed in our hospital using FDG PET-CT combined with TBNA, were retrospectively analyzed. Articles published up to June 2014 were searched for in several databases, including the Cochrane Library, PubMed and EMBASE, using “RP” and “PET-CT” as keywords. Duplicated articles were excluded. Information concerning the patient’s age, sex, clinical symptoms, PET-CT features [abnormal uptake sites and the maximum standard uptake value (SUV_{max})], and biopsy sites was extracted and analyzed.

Results

Case 1

A 42-year-old male patient was admitted to our hospital in 2012 with symptoms of cough and intermittent fever for more than 2 months. The patient had not been diagnosed with any previous disorders, and reported no alcohol consumption or tobacco smoking. The patient had been experiencing cough, expectoration and fever during the preceding 2 months, without obvious predisposing causes. The highest temperature of the patient had been recorded as 39.0 °C. No other symptoms, including chest congestion and shortness of breath, were reported. After a trial of anti-inflammatory medication had resulted in no improvement, the patient had been admitted to our hospital for further diagnosis and treatment. On admission, the temperature of the patient was 36.7 °C, the heart rate 82 beats/minute, respiration 16 times/minute, and blood pressure 115/85 mmHg. No enlargement of the superficial lymph nodes was detected, and breath sounds were clear in the bilateral lungs. CT scanning of the chest was performed, and no abnormalities were found. Routine blood tests revealed a white blood cell count of $5.44 \times 10^9/L$, a neutrophil count of $3.33 \times 10^9/L$, a hemoglobin level of 99 g/L, and a platelet count of $305 \times 10^9/L$. Examination of a panel of tumor biomarkers showed that the levels of neuron-specific enolase, tumor specific growth factor (TSGF) and ferritin were 21.8 ng/mL, 72.4 U/mL and 811.6 ng/mL, respectively. Examination of a panel of lupus, blood transfusion and antineutrophil cytoplasmic antibodies identified no abnormalities. Blood culture, mycobacterium tuberculosis-specific gamma interferon release assays (T-spot), and ultrasound examination of the heart were also performed, and no abnormalities were detected. Increases in erythrocyte sedimentation rate (ESR, 124 mm/h) and

C-reactive protein level (CRP, 14.89 mg/L) were found, while assessment of pulmonary function suggested an obstructive disturbance of ventilatory function. A bone marrow biopsy was performed, but the bone marrow smear and culture showed no abnormalities. As the underlying disease could not be diagnosed, FDG PET-CT scanning was performed. There were no abnormalities in the density and distribution of the radioactivity in the bilateral lungs, and no enlargement of the mediastinal and hilar lymph nodes. In addition, no lesions showing abnormal FDG uptake were found in the neck or the organs of the abdominal and pelvic cavities. In contrast, a symmetric increase in uptake was found in the costicartilage, trachea and bilateral bronchial walls, while no enhancement of uptake was identified in the skeletal system of other sites (*Figure 1A*), suggesting the possibility of chondritis. Therefore, tracheoscopic examination was performed; these revealed mucosal hypertrophy and slight bronchial stenosis, particularly stenosis of the bronchus in the right upper lobe (*Figure 1B*). The TBNA technique was used to obtain cartilage biopsies, and these showed infiltration of neutrophils, lymphocytes and plasma cells around hyaline cartilage (*Figure 1C*). These findings helped us to diagnose RP in this patient. Careful re-taking of the medical history revealed that the hearing of the patient had deteriorated during the past 6 months; a hearing test was then performed, and this showed moderate neural hearing loss in both ears. No symptoms or signs of chondritis were evident in the ears and nose, and pain was not elicited by pressure on the costicartilage. Intravenous injections of methylprednisolone (40 mg, qd) were given for 7 days; at the end of this treatment, the temperature of the patient had returned to a normal level, only an occasional cough remained. Intravenous methylprednisolone was then replaced by oral prednisone (10 mg, tid); no fever was identified, and the patient was discharged showing substantial improvement. Follow-up assessments were performed 6 weeks after discharge: no symptoms or discomfort were reported, and tracheoscopic examination showed substantial improvement of the mucosal congestion and edema, with no tracheal stenosis (*Figure 1D*). In addition, endobronchial ultrasound examination demonstrated normal cartilaginous rings and no thickening of the bronchial wall (*Figure 1E*).

Case 2

A 51-year-old male patient was admitted to our hospital in 2013, with symptoms of a relapsing cough, expectoration

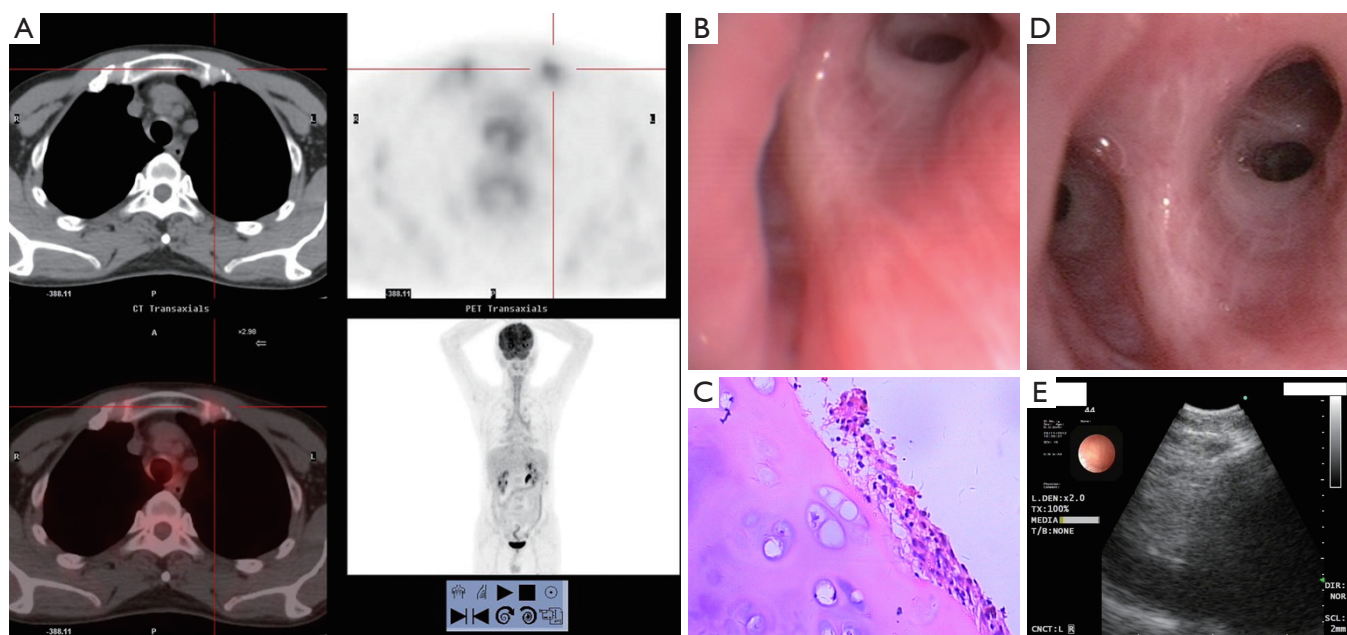


Figure 1 (A) FDG PET-CT images showing symmetric increases in FDG uptake in the bilateral costicartilage and the walls of the trachea and bronchi; (B) before treatment, there was congestion and edema of the walls of the bronchus in the right upper lobe, as well as slight stenosis of the bronchus; (C) TBNA biopsy showed an infiltration of neutrophils, lymphocytes and plasma cells around the hyaline cartilage (HE staining, $\times 200$); (D) after treatment, tracheoscopic examination showed no congestion or edema of the walls of the bronchus in the right upper lobe, and the diameter of the bronchus was normal; (E) after treatment endobronchial ultrasound examination showed no thickening of the walls of the trachea and no cartilage ring abnormalities. FDG PET-CT, fluorodeoxyglucose positron emission tomography-computed tomography; TBNA, transbronchial needle aspiration.

and fever for more than 1 month. Prior to admission, the patient had not been diagnosed with any previous disorders, and no predisposing causes for the symptoms had been identified. The patient had a 20-year history of smoking approximately 1 pack per day. The highest temperature of the patient had been recorded as 38.5 °C. No other symptoms, including chest tightness and shortness of breath, were present. The patient had been admitted to our hospital after the failure of anti-infectious treatments administered in a local hospital. On admission, the temperature of the patient was 37.0 °C, the heart rate 84 beats/minute, respiration 18 times/minute, and blood pressure 110/74 mmHg. There was no enlargement of the superficial lymph nodes, and the breath sounds were clear in the bilateral lungs. CT scanning of the chest demonstrated increased lung markings and enlarged mediastinal lymph nodes. The white blood cell count was $10.64 \times 10^9/L$, the neutrophil count $6.36 \times 10^9/L$, the hemoglobin level 129 g/L, and the platelet count $419 \times 10^9/L$. Abdominal ultrasound examination suggested the presence of a hepatic cyst and gallbladder polyps. Ultrasound examination of the heart

found no abnormalities. Other investigations were also performed to evaluate the levels of rheumatoid factor, serum procalcitonin, anti-tuberculosis antibody and 24-hour urinary calcium, but the results were negative. Examinations of panels of blood transfusion, thyroid function, lupus, and antineutrophil cytoplasmic antibodies showed no abnormalities. Blood culture and T-spot also showed no abnormalities. The ESR (57 mm/h) and CRP (15.06 mg/L) of the patient were increased. Examination of the levels of a panel of tumor biomarkers demonstrated that the ferritin level was 697.8 ng/mL. FDG PET-CT scanning was performed to further clarify the diagnosis. No lesions showing abnormal uptake were found in the neck, and the density and distribution of the radioactivity in the bilateral lungs was not abnormal. Although the mediastinal lymph nodes were enlarged, no abnormal uptake of radioactivity was found. In addition, no lesions showing abnormal uptake were found in the organs of the abdominal and pelvic cavities. Increased uptake was found in costicartilage near the xiphisternum, the trachea, and the walls of the bilateral main bronchi. No enhancement of uptake was evident in the

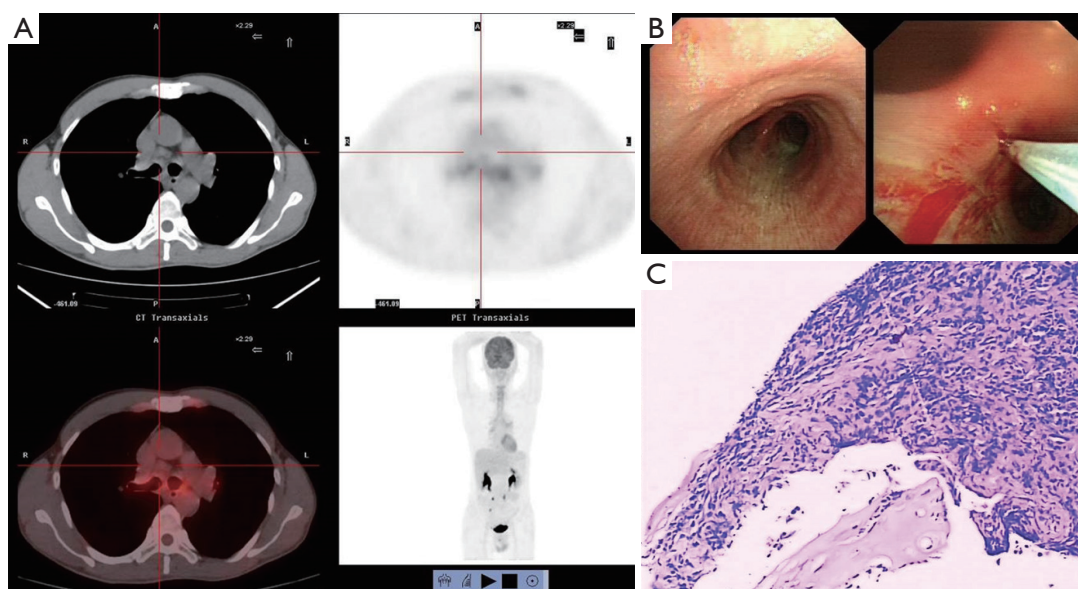


Figure 2 (A) FDG PET-CT images showing a symmetric increase in FDG uptake in the walls of the trachea and bilateral main bronchi, as well as in the costicartilage near the xiphisternum. An enlarged mediastinal lymph node was also shown; however, it did not exhibit an increase in FDG uptake; (B) tracheoscopic examination showed congestion and edema of the tracheal walls but no abnormality of the cartilage ring; airway collapse was not evident, while the carina was widened. TBNA was then used for biopsy of the S8 lymph nodes; (C) pathologic examination of the TBNA biopsy revealed a small amount of hyaline cartilage with infiltration of a large number of neutrophils, lymphocytes and plasma cells. No tumor cells were found (HE staining, $\times 200$). FDG PET-CT, fluorodeoxyglucose positron emission tomography-computed tomography; TBNA, transbronchial needle aspiration.

skeletal system of other sites. These findings suggested the possibility of chondritis (*Figure 2A*). As the symptoms of the patient were atypical, and enlargement of the mediastinal lymph nodes was found, bronchoscopic biopsy was performed to exclude malignancy: there were no obvious abnormalities in the cartilaginous rings, whereas congestion and edema of the tracheal mucosa was found, as well as slight bronchial stenosis. The TBNA technique was used to biopsy the S8 lymph nodes (3) (*Figure 2B*): inflammatory cell infiltration was evident around the cartilage, but tumor cells or granulomatous inflammation were not found (*Figure 2C*). On the basis of the findings, the patient was diagnosed with RP. The medical history of the patient was carefully re-visited, and additional physical examinations performed; however, no other positive signs were found. After a 10-day course of oral prednisone (10 mg, qd), the temperature of the patient had returned to a normal level, although an occasional cough remained. Follow-up assessments performed 6 months later found no positive signs.

The clinical manifestations of both patients were fever, cough and expectoration, while no other symptoms were reported. Hearing loss was identified in one patient after the

medical history was carefully re-taken. Increases in ESR, CRP and ferritin were found in both patients, while the other examinations demonstrated no abnormalities. In both patients, FDG PET-CT revealed increased FDG uptake in costicartilage and/or the trachea, as well as in the walls of the bilateral main bronchi. Although enlargement of the mediastinal lymph nodes was also found in the second case, FDG PET-CT scanning did not show evidence of enhanced FDG uptake in these lymph nodes. The findings of these two cases demonstrate that targeted biopsy of the lesion with TBNA, performed after FDG PET-CT scanning, could facilitate the diagnosis of RP. The time to final diagnosis in these two patients was about 1.5 months.

Twelve articles (4-15), involving 20 cases, were identified that reported the diagnosis of RP using PET-CT. Thus, a total of 22 cases (15 males and 7 females; mean age, 55.5 years) of RP, diagnosed using PET-CT, have been reported, including the two cases described in the present study. The main clinical symptoms of these patients included fever and cough. Common features of the PET-CT images included symmetric involvement of cartilage and joints, evident as ^{18}F -FDG hypermetabolic lesions. The SUV_{max}

Table 1 Clinical and PET-CT characteristics of RP patients

Patient No.	Age	Gender	Symptoms	Uptake focuses of PET-CT	SUV _{max}	Biopsy
P1 (4)	47	M	1, 2, 3, 4	16, 17, 18, 19	6.25	Tracheal mucous membrane
P2 (5)	67	M	1, 2, 3, 5	16, 17, 20, 21	NR	Costicartilage
P3 (6)	60	M	1, 2, 3, 6	16, 21	NR	Aurical cartilage
P4 (7)	59	F	1, 2, 4, 5, 7, 8	16, 17, 20, 21, 22	6.41	Undone
P5 (8)	77	M	3, 5, 8, 9, 10, 11, 12	22, 23, 24	NR	Undone
P6 (9)	57	M	1, 6	18, 20, 21, 25, 26	4.5	Undone
P7 (10,14)	37	M	1, 2, 7	16, 17, 20, 21, 27	NR	Costicartilage
P8 (11)	55	F	1	16, 21	4.5	Undone
P9 (12)	50	F	2, 3, 5, 7	16, 17	NR	Undone
P10 (13)	79	F	3, 4, 8, 10, 11, 12, 13	20, 24, 28	3.38	Undone
P11 (13)	61	M	1, 4, 6, 10, 11, 14	19, 22, 24, 29	6.44	Undone
P12 (13)	74	F	7, 8, 12	17, 18, 19, 21, 25, 30	13.03	Nasal cartilage
P13 (13)	66	M	1, 2, 3, 6	16, 17, 19, 21	4.75	Laryngeal cartilage
P14 (13)	44	F	2, 3, 5	17	1.93	Undone
P15 (14)	38	M	2, 15	16, 17, 20, 21, 27	4	Aurical cartilage
P16 (14)	55	M	1, 2	20, 21, 24, 27	4.8	Costicartilage
P17 (14)	66	F	2, 3	21	3.6	Aurical cartilage
P18 (14)	41	M	2, 3	16, 17, 20, 22, 24	5	Aurical cartilage
P19 (14)	55	M	2	16, 17, 24	4.2	Aurical cartilage
P20 (15)	39	M	2, 3, 5, 6	16, 17, 21, 22	NR	Lymph node, trachea and tonsils
P21 (16)	42	M	1, 2, 8	16, 17, 20	3.73	Tracheal rings
P22	51	M	1, 2	16, 17, 20	5.04	Tracheal rings and lymph nodes

P, patient; M, male; F, female; 1, fever; 2, cough; 3, chest tightness; 4, hoarseness; 5, sore throat; 6, weight loss; 7, arthralgia; 8, hearing loss; 9, headache; 10, conjunctivitis; 11, swelling and redness of the aurical; 12, swelling and redness of the nasal bridge; 13, dizziness; 14, shoulder pain; 15, chest pain; 16, trachea; 17, bronchus; 18, wrist joint; 19, shoulder joint; 20, costicartilage; 21, throat; 22, lymph nodes; 23, auditory canal; 24, auricle; 25, elbow joint; 26, sternum; 27, nose; 28, annular cartilage; 29, aorta; 30, sinus and paranasal sinus; NR, not record; SUV_{max}, maximum standard uptake value.

was recorded for 16 of the 22 cases; it ranged from 1.93 to 13.03, with a mean value of 5.14. *Table 1* showed the clinical characteristics and PET-CT features of the 22 patients.

Discussion

RP is a relapsing degenerative disease of cartilaginous tissues characterized by the involvement of multiple organs and vessels, including the nose, ears, throat, trachea, eyes, joints and cardiac valves; however, the etiology of RP is still not fully understood. Previous studies have suggested that autoimmunity may be associated with the pathogenesis of RP. No ethnicity, sex or age differences have been reported for RP, but most patients with RP are between 40 and 60 years of age (1,2). Currently, most medical practitioners

and researchers apply the criteria proposed by Damiani *et al.* (17) for the diagnosis of RP.

As RP is a rare disease with clinical manifestations that vary from patient to patient, it is very hard to diagnose, especially in patients with atypical symptoms. The early diagnosis of RP is even more challenging (1). The clinical symptoms of the two cases reported here were fever and cough, and no other abnormalities were found. After the diagnosis of RP, the clinical history of each patient was carefully re-taken. In the first case, hearing loss was identified as an additional symptom in the first patient, but there was no involvement of the cartilage of the ears, joints, nose and eyes. FDG PET-CT scanning showed inflammation of the costicartilage, trachea and bilateral main bronchi. In the second case, no involvement of the

cartilage of the ears, joints, nose and eyes was identified, and there were no lesions in the cochlea and ear vestibules. FDG PET-CT scanning suggested inflammation in the costicartilage near the xiphisternum, as well as in the trachea and the walls of the bilateral main bronchi. TBNA was used for biopsy of the sites showing increased FDG uptake in FDG PET-CT scans; the results obtained helped to determine the final diagnosis, and no obvious complications occurred. Glucocorticoids were used to treat both of the patients, and effectively alleviated the symptoms. The findings in these two patients suggested that FDG PET-CT could play an important diagnostic role in patients with atypical RP.

Laboratory investigations in these two cases revealed increased ESR and CRP, in accordance with previous studies (18); interestingly, we also found an increased ferritin level in both patients, consistent with the findings of Fujiki *et al.* (19). In addition, an elevated ferritin level had been found in 4 other cases of RP diagnosed recently in our hospital. These findings suggested that an increased ferritin level could also be valuable in the diagnosis of RP.

Previous studies have shown that FDG PET-CT is of great value in diagnosing diseases presenting as fever of unknown origin, with a sensitivity and specificity of 92% and 94%, respectively (20). FDG is a non-specific imaging agent that can be taken up by tumor tissues to result in an increased SUV; thus, FDG can play an important role in the diagnosis and staging of tumors, the planning of therapeutic strategies, the prediction of prognosis, and the evaluation of treatment efficacy in patients with cancer (21,22). FDG can also accumulate in tissues showing infective or non-infective inflammation, due to their high glucose metabolism and expression of cell surface glucose transporters; the resulting increase in SUV can play a critical role in diagnosing such inflammatory diseases (23–25). In our literature review, 12 articles were identified that described the diagnosis of RP with FDG PET-CT. The first case of RP diagnosed with FDG PET-CT was reported by Nishiyama *et al.* in 2007 (4); in 2013, we also reported the use of FDG PET-CT for the diagnosis of RP in a patient (16). In the cases reported previously, symmetric, multiple, hypermetabolic lesions were found in the cartilages of the trachea, bronchi, costicartilage, throat and lymph nodes. PET-CT revealed that 86.4% (19/22) of the patients with RP had airway involvement. The SUV_{max} was reported in 16 of these cases, and ranged from 1.93 to 13.03, with a mean of 5.14. These findings suggested the existence of chondritis, which had been acknowledged to be a reliable indicator of RP.

Therefore, FDG PET-CT played an important role in the diagnosis of RP in all 22 of these cases.

Both of the cases reported here were diagnosed within 1.5 months of disease onset. Complete medical records were available in 17 of the 22 cases (including the present 2 cases) diagnosed using FDG PET-CT; the time to diagnosis in these 17 patients was within 6.9 months of onset, significantly shorter than the average time to diagnosis of 20 months (26). Such earlier diagnosis could potentially decrease the risk of the development of late complications. These findings demonstrated that FDG PET-CT could potentially play an important role in the diagnosis of RP, especially atypical RP, and effectively shorten the time to diagnosis.

In 10 of the 22 reported cases, FDG PET-CT was used for re-examination of the patient after treatment had been administered; these assessments showed that FDG uptake had decreased substantially or disappeared after treatment, and that no other hypermetabolic lesions were evident (5–8,11,14). This indicated that FDG PET-CT could also play an important role in the evaluation of treatment efficacy.

For atypical RP patients, the main biopsy sites are costicartilage, auricular cartilage and nasal cartilage. And the primary complication is infection and collapse of auricles (27). However, TBNA, as a minimally invasive and safe technique, has never presented with obvious complication in both adults and children (28,29). The clinical symptoms of the two cases reported here were not typical, and only a limited number of organs (including the cartilage of the trachea and bronchi) were involved. TBNA was used for biopsy of cartilage from the sites with increased FDG uptake, and yielded satisfactory pathologic results with minimal trauma and no complications. This would suggest that combining FDG PET-CT with TBNA could be an effective means with which to diagnose RP. In particular, TBNA might show particular promise for the diagnosis of RP in patients with atypical symptoms, especially those with airway involvement. To our limited knowledge, the present study is the first to report the application of TBNA for pathologic examinations of patients with RP, and the first to report the use of endobronchial ultrasound to examine the tracheal walls after treatment (this showed normal cartilaginous rings and no thickening of the tracheal wall). However, endobronchial ultrasound examination (30) was not performed in these two cases before treatment. In the second case reported here, there was enlargement of the mediastinal lymph nodes, a very rare finding in previous studies (7,14,15); moreover, biopsy of the mediastinal

lymph nodes using TBNA technique played an important role in the differential diagnosis. In addition, the use of tracheoscopic examination to observe the airway and obtain biopsies of the tracheal mucosa may also prove valuable for the differential diagnosis of RP from bronchial asthma and other trachea-involving diseases (31,32). Besides bronchoscope and TBNA technique, the dynamic expiratory CT and three-dimensional image reconstructions are valuable for diagnosis and following up of RP involved bronchotracheal (33).

In summary, FDG PET-CT scanning was able effectively to display increased FDG uptake in the trachea, bronchi, costicartilage and joints; these findings could be used as reliable signs of joint cartilage involvement in RP. PET-CT revealed that 86.4% of the patients with RP had airway involvement, so we recommend that clinicians should improve their understanding of RP, and apply TBNA and targeted biopsy in the diagnosis of this disease in order to shorten the time to diagnosis.

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