A Case of Relapsing Polychondritis with Tracheobronchial Involvement

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Abstract
Relapsing Polychondritis (RPC) is a rare systemic inflammatory disorder of unknown etiology and characterized by recurrent and progressive inflammation of the cartilaginous structures, particularly involving the auricles, nose and tracheobronchial tree, sometimes leading to their destruction. RPC can also inflame other proteoglycan-rich structures, such as the eye, heart, skin, central nervous and hematological systems. Its diagnosis can be difficult when the typical clinical features such as auricular chondritis are absent. Here, we report on a case of 43-year-old woman who presented with recurrent sore throat, dysphagia, exertional dyspnea, cough and noisy breathing initially misdiagnosed as acute laryngitis who was eventually diagnosed as Relapsing polychondritis with tracheobronchial involvement. Chest computed tomography showed the diffuse involvement of tracheobronchial cartilage. Based on the, Damiani’s criteria, she was diagnosed as relapsing polychondritis even though there was no unique involvement of auricular cartilage, and high dose steroid and immunosuppressive therapy were then started. This case indicated that patients who have tracheobronchial cartilage involvement without definite auricular chondritis should be considered for relapsing polychondritis as a differential diagnosis. This case is reported to raise awareness of airway involvement in RPC and discuss its current management.

Introduction
Relapsing Polychondritis (RPC) is an uncommon, chronic, and potentially life-threatening multisystem disorder characterized by recurrent inflammatory episodes affecting the cartilaginous tissues of the external ears, nose, peripheral joints, larynx and tracheobronchial tree, sometimes leading to their destruction. RPC can also inflame other proteoglycan-rich structures, such as the eye, heart, blood vessels and inner ears. Systemic symptoms are common, as well as vasculitis affecting skin or internal organs may occur. Its onset is often insidious, with acute painful inflammatory crisis followed by spontaneous remission of variable duration. This may render diagnosis very difficult at an early stage, with therapeutic delay and consequent increased risk of permanent or life-threatening sequelae [1]. The clinical features and course of RPC vary considerably from one patient to another patient. Since, the early manifestations of RPC often remain unrecognized for prolonged period the diagnosis is frequently obtained only after the emergence of classic features. Patients with RPC typically present with unilateral or bilateral inflammation of the external aspects of the ears. Additional clinical features include audiovestibular dysfunction, ocular inflammation, vasculitis, myocarditis, and nonerosive arthritis [3]. The incidence is estimated to be between 3.5 and 4.5 per million people per year. Airway involvement in RPC occurs in approximately 50% of cases. Cardiovascular and respiratory complications of RPC are associated with high morbidity and mortality. The first case of RPC was described in 1923 by Jaksch-Wartenhorst [4]. The term “relapsing polychondritis” was first used by Pearson et al. in 1960 in their review of 12 cases [5]. Men and women are affected equally but much about the epidemiology of RPC remains unknown because of the relatively

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small number of affected patients. RPC is most prevalent in White individuals. The annual incidence has been estimated at 0.71, 2.0, and 3.5 per million persons from population studies in the United Kingdom, Hungary, and Minnesota, respectively [6-8]. Patients eventually diagnosed with RP may initially present with general, nonspecific symptoms, such as fever and malaise, which may delay the diagnosis. Retrospective study done showed the CT findings in patients with RPC consisted mainly of airway wall thickening, airway stenosis, airway malacia, airway wall calcification, and air trapping [9]. Because of the rarity, the diagnosis of RPC is mainly based on empirical criteria proposed by McAdams [10], Damiani [11], Michet [12] and their colleagues. According to McAdams et al., the diagnosis of RPC can be made if three or more of the six clinical features (auricular chondritis, nonerosive inflammatory polyarthritids, nasal chondritis, ocular inflammation, respiratory tract chondritis, audiovestibular damage) are present, requiring no histologic confirmation [10]. These criteria were later modified by Damiani who expanded the spectrum of diagnostic criteria, adding the presence of at least one McAdam criterion and positive histologic confirmation, or two McAdam criteria and positive response to administration of corticosteroids or dapsone [11]. In this report, we describe an unusual case of RPC that had tracheal chondritis as the initial and main manifestation.

Case Report

A 42 year old lady, non smoker presented to our emergency department with a 16 days history of throat pain and difficulty in swallowing associated with exertional dyspnea, hoarseness of voice, feverish feeling (temperature not recorded), productive cough (scanty) and noisy breathing since 2 days prior to presentation. There were no chest pain, no haemoptysis, no joint pain or skin eruption, and no visual, nasal, or auditory complaints. She had no significant past medical illness and her personal and family history was unremarkable. Examinations at local hospitals had not identified the cause of her illness and she had not responded to any treatments. Hence, she presented to our institution for further evaluation and management. On arrival to our institution her vitals signs were: T:99.6, Spo2-93% in RA, BP-130/70mmhg and HR-118 bpm. On auscultation of her chest polyphonic wheeze was ausculted in both lung fields. Physical examinations including Ophthalmologic, auricular, and nasopharyngeal examinations were unremarkable. Laboratory findings showed a low hemoglobin level of 9.5 gms%, high total leucocyte count of 16360 cells/cumm, platelet count of 499000, elevations of erythrocyte sedimentation rate of 108 mm/hr and C-reactive protein of 494 mg/L. Other pertinent blood workups including renal and hepatic parameters, reported normal values. X-ray neck done showed no significant changes. Patient was evaluated and was admitted under ENT department with a provisional diagnosis of Acute Laryngitis. Nasopharyngolarygoscopy done showed no significant changes. At this stage, she was treated with ceftriaxone, levocetirizine and some pain killers. Neck USG done reported few centimeters sized lymph nodes in pre tracheal and level VI, probably reactive lymph nodes and thyroid gland appears normal in size. On the second day of admission pulmonary medicine consultation was done for cough, exertional dyspnea and noisy breathing as per ENT department to rule out any respiratory illness. Patient still had bilateral polyphonic wheeze on auscultation with saturation level of 93% in Room Air. Initial, chest-X-ray showed evident narrowing of trachea (fig. 1-A). Patient was advised to do HRCT chest, sputum-grain stain, culture, KOH, AFB-III, gene expert and serology for Antinuclear Antibody (ANA), Anti-cyclic citrullinated peptide (Anti-ccp) and Extractable Nuclear Antigens (ENA). As per pulmonary medicine bronchodilator nebulisation with ipratropium bromide and fluticasone propionate was started. HRCT chest done showed diffuse thickening of wall of trachea with mild luminal narrowing and mild thickening of wall of bronchi, sub-segmental collapse of right middle lobe, patent bronchus within collapsed segment of middle lobe (fig. 3-A). Serology tests for ANA, ENA and Anti-CCP were all negative. On the third day of admission patient was handed over to Pulmonary medicine department. Under fiberoptic bronchoscopy, significant narrowing of the mid to lower portion of the trachea was readily observed with thickening of the bronchial mucosa and there was no evidence of nodular formation or erosion of the mucous membrane (fig. 1-B). During the test, the oxygen saturation was decreased by 70%, so the test was stopped so the biopsy were not performed. Based on the findings of HRCT chest and bronchoscopy patient was treated in the line of RPC and initiated on high dose methylprednisolone 500 mg once a day intravenously, which led to an improvement in her symptoms. Sputum culture reported normal oral flora with negative gene xpert. Repeat laboratory investigations including ESR, CRP and TLC were in decreasing trend. Since patient's vitals were stable, clinically better and hemodynamically stable she was discharged on the 4th day of admission under a tapering dose of steroids orally. She was discharged with the impression of Relapsing Polychondritis under evaluation. Prednisolone was tapered as 40 mg once a day for 3 days followed by 30mg once a day for next 4 days followed by 20mg once a day for 4 weeks followed by 10mg once a day to be continued. The patient remained well during her first and second follow up after 1 week and 1 month of discharge consecutively. During her third follow up after 2 months of discharge she complained of throat pain as steroid was tapered to 10mg once a day. Therefore, Steroid was again increased to 15 mg once a day for 15 days followed by 10 mg once a day to be continued and asked to do follow up in a month. She presented to OPD with a complain of recurrent symptoms during her 4th follow up after 3 months of discharge as her steroid was reduced to low dose. Her vitals were stable whereas investigations reported elevations of ESR of 80 mm/hr, TLC of 16110 and CRP of 83.8. Hence, patient was treated in the background of relapsing tracheobronchial chondritis. This time patient was started on immunosuppressant Azathioprine 25 mg once a day along with increased dose of steroid 30 mg once a day to be continued. Patient visited our OPD after 7 months of discharge as 5th follow up during which she was under regular steroid therapy of prednisolone 10 mg once a day as maintenance dose and Azathioprine 25 mg once a day. Laboratory investigations showed deranged liver function test with rise in the value of ALT-395 and AST-137 for which ursodeoxycholic acid was added and the value came to normal after 1 week. Patient did her 6th follow up after 14 months of discharge during which she complained of recurrent cough and multiple joint pain and stiffness on bilateral hands mainly metacarpophalangeal joints, proximal interphalangeal joints and knee with stable vitals signs. Repeat ANA, ENA, Anti-CCP and RA factor tests done were all negative. Hydroxychloroquine 200 mg once a day was added with azathioprine and low dose steroid thinking seronegative polyarthritids. During her 7th follow up which is after 22 months of discharge patient complained of shortness of breath on exertion (MMRC grade II). However, patient's joint pain and stiffness got better than before after starting hydroxychloroquine. At this stage, patient was under regular treatment with Azathioprine, Hydroxychloroquine and prednisolone. Her vitals were stable with oxygen saturation of 95% in Room Air. Laboratory investigations were unremarkable with normal liver function test, renal function test and total leucocytes count. HRCT chest was again repeated which showed no any diffuse thickening of tracheal wall and luminal narrowing of walls of bronchi as compared to previous HRCT(fig. 3-B). Pulmonary Function Test done showed severe obstructive airway disease with post bronchodilator reversibility being significant (fig. 2). Bronchodilator via metered dose inhaler was started along with Hydroxychloroquine, Azathioprine and low dose steroid of 2.5 mg for 1 month and then stop. Likewise, patient recently visited our OPD as her 8th follow up which is 28 months after discharge her symptoms got better with occasional breathlessness on exertion only.
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Currently, patient is under Hydroxychloroquine, Azathioprine and MDI bronchodilator as her regular medications. She is under regular OPD follow up in our department without any recurrent symptoms so far. Two years had passed since the first onset of her symptoms, and the patient still receives active surveillance and has not developed new symptoms, with prolonged follow-up, a majority of patients develop four or more of the above mentioned criteria by Damiani [11] which shows that diagnosis of RPC takes a prolong opd follow up. Because of the pleomorphic nature of the disease, with non-specific symptoms at the onset, the diagnosis of relapsing polychondritis is often delayed. Likewise, in our case as well it took almost 2 years to make a final diagnosis of RPC with tracheobronchial involvement as our patient met Damiani’s three criteria of chondritis of 2 anatomic locations which were tracheobronchial chondritis and polyarthritis and response to steroids.

Figure 1. (A) The initial chest radiograph showed evident narrowing of the trachea. (B) Bronchoscopy showed narrowing of the mid to lower portion of the trachea with loss of integrity of the cartilaginous rings.

Figure 2. The Pulmonary function Test revealed severe obstructive lung disease.

Discussion
Recent studies show that patients of Relapsing Polychondritis with tracheobronchial involvement are distinct from others in terms of clinical characteristics, therapeutic management, and disease evolution. The etiology of RPC is still unknown, but the pathogenetic role of the autoimmunity is suggested by frequent overlaps with various autoimmune diseases, and by the presence of autoantibody against cartilage in the serum of patients with RPC [13]. Although several reports have demonstrated the clinicopathologic manifestations and radiologic findings of RPC, there are no specific features of RPC. The diagnosis of RPC is a real challenge for clinicians, because of the pleomorphic nature and insidious onset of the disease. Significant delays in diagnosis have been described in various studies so far due to its rarity, the episodic nature and its diverse clinical presentation [13,14,15]. Airway involvement occurs early during the course of the disease, at a mean of 2.5 years after diagnosis [16]. When inflammation is limited to the larynx, initial symptoms include pain and tenderness over the thyroid cartilage and trachea, leading to laryngomalacia or permanent stenosis with hoarseness of voice, non-productive cough, dyspnea, stridor, and wheezing. Tracheobronchial involvement leads to inflammation or even destruction of the cartilage, which can result in tracheo and bronchomalacia [17]. We can relate these presenting complaints in our case as well since she presented with a history of pain over trachea and gradually hoarseness of voice, stridor and wheezing which reflected the stenosis of trachea as per CT chest findings. Several sets of diagnostic criteria, which are mainly based on the presence of symptoms suggesting chondritis or arthritis at multiple sites, have been proposed previously [18–21]. These sets of criteria, however, have limitations in terms of sensitivity and accuracy, as was demonstrated by recent retrospective case analyses [18,20]. Tracheobronchial involvement affects 20 to 50% of patients and may reveal the disease however, only 10% of patients have symptoms or signs suggesting airway involvement at presentation [22]. A recent large case series reported that only 4% and 3.5% of patients had cough and dyspnoea, respectively, as their initial symptoms [23]. In the present case, there was no sign of cartilaginous inflammation except for airway symptoms during her presentation. Considering the non-specific and airway only manifestation of our patient, it was not helpful to diagnose her RPC by applying those aforementioned sets of criteria. Laboratory findings are suggestive of inflammation and sometimes organ damage, but specific tests are yet to be established. The levels of C-reactive protein and erythrocyte sedimentation rate are usually raised along with leukocytosis, thrombocytosis and anemia during the inflammatory crisis, but findings of normal values during the remission phase do not allow exclusion of the diagnosis. Other laboratory investigations, such as rheumatoid factor, antinuclear antibody (ANA), anti-phospholipid antibodies, and complement levels, can be useful to evidence the presence of concomitant diseases but the prevalence of ANA observed in RPC is low, and the finding of a significant titre of ANA
in a patient with RPC strongly suggests the presence of an associated disorder [19,20]. In our case ANA, ENA and Anti-CCP were all negative but association with other autoimmune disorders is found in 30% of all adult RPC patients, rheumatoid arthritis (RA) being the most common. The main imaging method used to diagnose RPC was computed tomography (CT) and bronchoscopy should be routinely performed at diagnosis, even in the absence of respiratory symptoms. The CT findings in patients with RPC consisted mainly of airway wall thickening, airway stenosis, airway malacia, airway wall calcification, and air trapping [20]. Bronchoscopy can evaluate mucositis, define the severity (narrowing or stenosis), and allow the dynamic assessment of possible collapse (expiratory maneuver or coughing). Pulmonary function testing must be performed at diagnosis and repeated annually to detect airway impairment and estimate its progression. Spirometry, volume-flow curves, and the measurement of upper airway resistance may show early involvement in asymptomatic patients. Obstructive disease (FEVI/FVC <70%) and reduced exercise capacity (walk test desaturation and decreased distance walked) should be sought [24]. PFT (Pulmonary Function Test) done in our patient also showed severe obstructive lung disease. RPC is considered as an immune origin, involving humoral and cellular immunity as: there is an associated autoimmune disease in up to 30% of cases, chondritis lesions contain a CD4+ T-cell lymphocyte infiltrate and plasmocytes, as well as immune deposits, autoantibodies directed against type II collagen are detected in approximately 30% of cases, or against other types of minor collagen (IX and XI) or cartilage proteins, such as oligomeric proteins of the cartilaginous matrix (COMP) and matrilin-1, 4) a specific T-cell response against collagen II peptides, which represents 95% of cartilage collagen, or specific to matrilin-1 is sometimes observed and high-dose glucocorticoids (GCs) are generally effective. Thus, according to current data, RPC is a probable autoimmune disease, with specific immunization against cartilage structures and matrilin-1 shown to be responsible for the tracheobronchial phenotype. Nevertheless, with a multidisciplinary approach integrating his past histories, symptoms, and serologic-biochemical, bronchoscopic, radiographic, and spirometric findings, other diseases with similar clinico-radiological presentations such as tuberculous tracheitis, anti-neutrophilic cytoplasmic autoantibodies (ANCA)-associated vasculitis, sarcoidosis, amyloid deposition, tracheomalacia, excessive dynamic airflow collapse, tracheal involvement in inflammatory bowel disease, rhinoscleroma, or tracheobronchopathia osteochondroplastica were ruled out. Our patient received the correct diagnosis within 2 years after the onset of her symptoms, which might be considered a relatively short delay. The mechanism of respiratory involvement, including tracheal or bronchial obstruction, depends on the stage of the disease: inflammatory edema occurs during the active phase, followed by malacia, resulting from cartilage destruction, and then stenosis due to fibrous replacement of the impaired cartilage [17]. Histological specimens of the anterior tracheal cartilage are sometimes obtained during fibroscopy but there is no histological specificity. If performed, there is perichondral lymphoplasmocytic cellular infiltration of the cartilage, with the loss of basophilic staining of the cartilaginous matrix, corresponding to the loss of proteoglycans. The cartilage is gradually replaced by fibrous tissue.

The goal of therapy is the control of the inflammatory crisis and the long-term suppression of the immune-mediated pathogenic mechanisms. The treatment of RPC is largely based on experiences from previous case reports and small series, and there are still no evidence-based guidelines [28]. Oral prednisone is usually started with a dose ranging from 0.25 to 1 mg/kg daily, reducing the dose, if possible, during the course of the disease. If a rapid effect is necessary, intravenous pulse methylprednisolone (500–1000 mg/bed) can be helpful. Glucocorticoids (GCs) are used to control acute airway flare-ups and reduce their severity, duration, and frequency [29]. Continued steroid therapy is often recommended in long-term follow-up to prevent relapses, but it does not modify the progression of the disease. For this reason, several other drugs such as cyclophosphamide, azathioprine, cyclosporine and methotrexate have been used, alone or in association with systemic corticosteroids, as second line options in case of organ or life threatening disease when there is corticosteroid-intolerant or corticosteroid-dependent patients or in cases of lack of response to corticosteroids or necessity of corticosteroid-sparing therapy. In our case we started with high dose intravenous methylprednisolone and tapered as patient's symptoms were under control with oral route. During her regular follow up we had to start patient on immunosuppressant as steroid couldn't be tapered to low dose as well as patient became steroid dependent to some extent. Several trials were done to reduce the steroid's dose and that led to the recurrence of symptoms. With the addition of immunosuppressant and bronchodilators finally we were able to stop steroids without recurrence of symptoms. The use of local therapeutic interventions must be considered when medical treatments fail or for patients awaiting the effect of the medical treatment who have major bronchial involvement associated with a high risk of morbidity and mortality. They consist of interventional endoscopic treatment most often using rigid bronchoscopy and include thermocoagulation, laser, balloon dilation or bronchoscopes of increasing size, and tracheobronchial prosthesis. In a study by Dion et al., 15% of patients with tracheobronchial involvement required local endoscopic treatment. Overall RP survival has improved considerably. It was 55% at 10 years in 1986 and 94% at 8 years in 1998 and 83% at 10 years in the most recent study.

Conclusion

Early diagnosis of RPC is essential to allow prompt treatment and to decrease the risk of life-threatening airway collapse. As demonstrated in this case, relapsing polychondritis involving airways could have an airway-only manifestation leading to great diagnostic difficulties. To date, therapy of RPC is still empiric, due to the lack of standardized guidelines on treatment, and is defined on the basis of disease activity and severity of organ involvement as the number patients treated are still limited, and the majority of studies is heterogeneous and with different outcomes. Early diagnosis is necessary to prevent irreversible airway stenosis and progression to tracheobronchomalacia.

References