CASE REPORT

Silent tracheobronchial chondritis in a patient with a delayed diagnosis of relapsing polychondritis

Faraz Afridi,¹ Seema Frosh^{1,2}

¹Internal Medicine, University of Central Florida College of Medicine, Orlando, Florida, USA
²Rheumatology, Orlando VA Medical Center, Orlando, Florida, USA

Correspondence to
 Dr Faraz Afridi,
 faraz.afриди@ucf.edu

Accepted 22 June 2017

SUMMARY

Relapsing polychondritis is a very rare autoimmune disease characterised by a relapsing inflammation of hyaline, elastic and fibrous cartilaginous tissues. The incidence is estimated to be between 3.5 and 4.5 per million people per year. Clinical signs and symptoms can be very subtle, and if left undiagnosed for a prolonged period, airway involvement can cause fibrosis of the tracheobronchial wall, leading to a fixed tracheobronchial stenosis. Eventually, this can progress to life-threatening tracheobronchomalacia due to irreversible damage and loss of tissue integrity. We report an elderly man who presented with recurrent bilateral ear inflammation and intermittent polyarthritis who was diagnosed with relapsing polychondritis with asymptomatic involvement of his large airways.

time from symptom onset to the diagnosis is estimated to be 3 years.³ During the first occurrences of symptoms, patients are most likely to present to primary care providers, rheumatologists, ophthalmologists and otolaryngologists.

CASE PRESENTATION

A 72-year-old man with a medical history significant for recurrent episcleritis/scleritis, benign prostatic hyperplasia, obesity, obstructive sleep apnoea, hyperlipidaemia, tobacco use and a remote history of non-steroidal anti-inflammatory drug (NSAID)-induced gastrointestinal (GI) bleeding presented to the rheumatology clinic with a 4-month history of bilateral hand pain associated with swelling and stiffness of the hand joints. He reported recurrent episodes of arthralgia and arthritis of the wrists and ankles, which had been treated with oral corticosteroids on several occasions. NSAIDs were avoided by previous providers given the history of NSAID-induced GI bleeding. Further, he reported multiple intermittent episodes of bilateral ear pain with redness and swelling, previously diagnosed and treated as cellulitis by multiple providers without response. His most recent course of oral antibiotics was 2 weeks prior to presentation to our clinic, with no improvement. Review of systems was significant for a recent episode of episcleritis in the right eye, 1 week prior to presentation, with complete resolution. He denied fevers, chills, night sweats, fatigue, weight loss, hearing loss, tinnitus, vertigo, shortness of breath or haemoptysis. Social history was significant only for a 30 pack-year smoking history. Family history included rheumatoid arthritis in his father. Physical exam was remarkable for erythema,

BACKGROUND

The first case of relapsing polychondritis (RPC) was described in 1923 by Jaksch-Wartenhortst, but the term 'relapsing polychondritis' was first used by Person *et al* in 1960.¹ RPC is a very rare autoimmune disease with an incidence estimated to be between 3.5 and 4.5 cases per million people per year.² It is characterised by recurrent episodes of inflammation of the hyaline, elastic and fibrous cartilaginous tissues involving the cartilage of the ears, nose, upper and lower airways, larynx, cardiovascular system and joints. Recurrent inflammation can lead to cardiovascular and respiratory complications with significant morbidity and mortality. The highly variable presentation combined with its rarity makes this condition difficult to diagnose, which can lead to a delay in treatment. The average

Figure 1 Left: Bilateral erythema and swelling of the antihelices of the ears with sparing of the ear lobes (yellow arrows). Right: CT chest showing thickening of the tracheal wall extending down to the level of left mainstem bronchus with sparing of the posterior trachea suggestive of cartilaginous calcification (yellow arrow).

To cite: Afridi F, Frosh S. *BMJ Case Rep* Published Online First: [please include Day Month Year]. doi:10.1136/bcr-2017-220172

swelling and profound tenderness of the bilateral antihelices of the ears with sparing of the ear lobes (figure 1, left). There was no redness or excessive tearing of the eyes and hearing was grossly normal. The remainder of the physical exam, including the chest and musculoskeletal exam, was unremarkable.

INVESTIGATIONS

Laboratory evaluation including complete blood count and complete metabolic profile was unremarkable. Rheumatoid factor, anticyclic citrullinated peptide antibody, antineutrophil cytoplasmic antibody, human leukocyte antigen-B27 (HLA-B27), Lyme and viral hepatitis serologies were all negative. Uric acid was within normal limits. Radiographs of the bilateral hands, wrists and ankles were unremarkable.

Given the patient's constellation of steroid-responsive, non-erosive, seronegative inflammatory polyarthritis, episodic auricular chondritis and history of recurrent scleritis/episcleritis, the diagnosis of RPC was made based on meeting three out of six features of the McAdam's criteria for RPC (see Discussion). Due to the potential involvement of cardiac and pulmonary airway structures in this disease, echocardiogram, pulmonary function tests (PFTs) and CT scan of the chest were performed. Echocardiogram and PFTs were normal; however, CT of the chest revealed thickening of the tracheal wall extending down to the level of left mainstem bronchus with sparing of the posterior trachea, suggestive of cartilaginous calcification due to chronic chondritis of the tracheobronchial tree (figure 1, right).

TREATMENT

Prednisone 20 mg per oral daily was initiated at that time, with a subsequent taper. Given the likely chronic nature of the tracheobronchial tree involvement, recurrent inflammatory arthritis and episodic auricular swelling, he was transitioned to a steroid-sparing regimen of methotrexate 12.5 mg per oral weekly.

OUTCOME AND FOLLOW-UP

His symptoms of auricular chondritis and polyarthralgia improved after a few weeks. At 1-year follow-up, he has not had any recurrence of these symptoms and continues to deny shortness of breath, wheezing, cough or haemoptysis. He follows closely with rheumatology with regular monitoring of methotrexate therapy.

DISCUSSION

RPC is a very rare autoimmune disease characterised by a relapsing inflammation of the hyaline, elastic and fibrous cartilaginous tissues.⁴

Epidemiology

Epidemiological data for this rare entity are poorly documented and likely underestimated. The incidence is currently estimated to be between 3.5 and 4.5 cases per million people per year based on a study in Rochester, Minnesota, and from a recent study by the US Department of Defense of their beneficiary population.^{2 5 6} RPC on average bcr-2017-220172 begins at age 50 and affects men and woman equally.^{4 bcr-2017-220172}

Pathophysiology

The pathogenesis of RPC is largely unknown, but the main hypothesis is an autoimmune reaction that initially targets cartilage and subsequently affects non-cartilaginous tissues. Many features of the disease support this autoimmune aetiology. The inflammatory infiltrates seen in the affected tissues consists of a

collection of lymphocytes (mostly CD4+ T cells), macrophages, neutrophils and plasma cells. This infiltration of tissues by cellular components with the addition of inflammatory mediators leads to a cascade releasing degradative enzymes such as matrix metalloproteinase and reactive oxygen metabolites by inflammatory cells and chondrocytes, which eventually leads to the destruction of cartilage and proteoglycan-rich tissues.⁷ The provoking event that triggers the cascade has been hypothesised to be an initial damaging event to cartilage, which exposes immunogenic epitopes of the chondrocytes or extracellular cartilage matrix.⁷ This hypothesis of cartilage destruction being the inciting event has been supported by studies showing the development of RPC following piercing of cartilage of the pinna of the ear and ingestion of glucosamine chondroitin supplements.⁸ Autoantibodies can also be found in patients with RPC directed against cartilage, collagen, matrilin-1 and matrix proteins, but the diagnostic utility of these autoantibodies is poor in light of them only being found in approximately 30% of patients with RPC.⁹ Furthermore, they can also be detected in conditions such as rheumatoid arthritis, which reduces their specificity.

Clinical presentation

The clinical features of RPC change with severity and duration of the disease. The most common and characteristic feature of RPC is auricular inflammation, but other structures may be involved, including the eyes, nose, heart, lungs and joints.

Systemic involvement

During flares of the disease process, fatigue and fever can be seen.³

Auricular involvement

The most common feature of RPC is chondritis of the pinna of the ear, which is present in up to 90% of patients with the disease.² During acute episodes, the pinna of the ear, which contains a large amount of cartilage, becomes swollen, tender and red, and can often be mistaken as cellulitis as in our patient's case. Classically the ear lobe is spared as it contains a minimal amount of cartilage. There may be associated external auditory canal obstruction due to the swelling, which can lead to a conductive hearing loss and/or otitis externa. Chronic inflammation may cause a 'cauliflower' pinna deformity in which the auricular cartilage is severely damaged to the extent that it causes the pinna to have a persistent swollen appearance and have a structural deformity.⁴ In some cases, there may be cochlear or vestibular involvement, which can result in progressive sensorineural hearing loss or vertigo, respectively.¹⁰

Nasal involvement

Acutely, patients may report pain at the base of the nose, with swelling and a sensation of fullness at the nasal bridge. There may be associated nasal obstruction, rhinorrhoea, crusting or epistaxis.³ Chronic involvement may also lead to permanent destruction of the septal cartilage causing a septal perforation. This is the cause of the nasal collapse and the characteristic saddle nose deformity, which is seen in up to 29% of patients.⁴

Eye involvement

Ocular involvement can be seen in 20%–60% of patients and can present as episcleritis, scleritis or conjunctivitis.³ Scleritis is the most common ocular presentation.

Figure 2 Diagram showing the cross-section of normal tracheal airways (top) with normal tracheal cartilage (light blue), fixed airway stenosis (middle) and tracheal collapse due to tracheobronchomalacia secondary to relapsing polychondritis (bottom).

Pulmonary involvement

Pulmonary structures extending from the larynx to the bronchi may be involved, with initial symptoms of a dry cough, hoarseness, dysphonia, aphonia, stridor, choking or anterior neck pain. When there is larynx involvement causing laryngeal chondritis, it can manifest initially as pain above the thyroid gland, dysphonia or aphonia. Ongoing laryngeal inflammation may result in irreversible laryngeal stenosis with inspiratory dyspnoea, which may require an emergency tracheotomy.⁸ With tracheobronchial involvement, inflammation and destruction of the cartilaginous structures cause fibrosis of the tracheobronchial wall, which results in luminal narrowing of the tracheobronchial tree. This represents fixed tracheobronchial stenosis, which is the start of the life-threatening nature of airway involvement seen in RPC. Eventually, this cartilaginous destruction causes dynamic expiratory collapsibility of the tracheobronchial tree, referred to as tracheobronchomalacia (figure 2). This can eventually progress to respiratory failure due to the irreversible expiratory collapse of the tracheobronchial tree, and this represents a significant cause of mortality. These respiratory complications, mostly tracheal collapse, are the leading cause of mortality.¹¹ Furthermore, anti-inflammatory treatment is ineffective at this stage. Due to the severity of this process, any patient diagnosed with

RPC should have mandatory imaging to evaluate for laryngeal and tracheobronchial tree involvement so that early treatment can be initiated. Work-up includes PFTs and chest CT imaging.¹² If tracheobronchial involvement is present, PFTs may show either an obstructive, restrictive or mixed ventilatory defect with low maximum forced expiratory flow.¹³ CT chest may show smooth anterior and lateral airway wall thickening, with increased attenuation of the cartilage with sparing of the posterior membrane wall.¹⁴ Chronic involvement may be demonstrated by calcification of these structures.

Cardiovascular involvement

Cardiovascular involvement is the second most common cause of death in RPC, mainly from the associated vasculitis and valvular heart disease.^{11 15} Vasculitis can present in RPC, which affects any vessel size, and the clinical presentation can range from cutaneous leucocytoclastic vasculitis to large vessel vasculitis with aneurysmal involvement.¹¹ The prevailing presenting feature is aortic valve disease secondary to progressive dilatation of the aortic ring with an associated ascending thoracic aortic aneurysm. The mechanism involves aortitis with progressive destruction of the tunica media, which itself increases the risk of aortic rupture.¹⁵ Considering this serious complication, repeated monitoring with two-dimensional echocardiography is warranted in all patients diagnosed with RPC.¹⁶

Musculoskeletal involvement

Musculoskeletal involvement represents the second most common feature of RPC, in the form of non-erosive, non-deforming oligoarthritis or polyarthritis affecting both small and large joints. Characteristically, the arthritis is asymmetric and intermittent, with flare-ups often spontaneously resolving without treatment.⁴ Costochondral cartilage can also be affected, which presents as parasternal and rib pain that is reproducible on palpation. In severe cases, dislocation of the ribs and pectus deformity can be seen.⁴

Diagnosis

The diagnosis of RPC is based on an empiric diagnostic criterion that encompasses clinical features, radiographic evidence and occasionally biopsy of the affected cartilaginous structures. Laboratory blood testing is generally non-specific. Anticartilage and anticollagen (type II) antibodies have poor sensitivity and specificity and are only tested by a limited number of laboratories. Acute phase reactants, in particular serum C reactive protein, can be normal during acute flares in over 10% of patients and therefore are not routinely checked.⁴

The original diagnostic criteria was the McAdam's criteria, introduced in 1976 which is primarily based on clinical features at a particular given time and requires three out of six features to make a diagnosis of RPC (figure 3, left).¹¹ However, due to the variability of clinical manifestations occurring at a given point in time, Damiani's criteria has frequently been used. It includes histological features and therapeutic responses, which can confirm the diagnosis of RPC with any single feature, in addition to that met by McAdam's criteria (figure 3, middle). The latest criteria, which is the Michet's criteria, avoids the need for histological biopsy and is used presently. This criterion requires the presence of inflammation in at least two out of the following three cartilages: auricular, nasal or laryngotracheal cartilages. Additionally, criteria can be met if one of the above cartilages are affected, but with two other signs which include ocular inflammation,

McAdam's criteria	Damiani's criteria	At least three of McAdam's diagnostic criteria	Michet's criteria
Bilateral auricular chondritis			Inflammation in at least two out of three cartilages
Nonerosive, seronegative inflammatory polyarthritis			
Nasal chondritis		One clinical finding with positive histologic confirmation	
Ocular inflammation			One of the above cartilages affected with two other signs
Respiratory tract chondritis		Chondritis at two or more separate anatomic locations with response to steroids and/or dapsone	
Cochlear and/or vestibular dysfunction			

Figure 3 Left: McAdam's criteria for the diagnosis of relapsing polychondritis, which requires meeting any three out of six clinical features. Middle: Damiani's criteria for the diagnosis of relapsing polychondritis, which can diagnose relapsing polychondritis based on a single histological feature, therapeutic response or meeting McAdam's criteria. Right: Michet's criteria, which requires the presence of inflammation in at least two out of three specific cartilage sites or one cartilage site with two other specific signs.

vestibular dysfunction, hearing loss or seronegative inflammatory arthritis (figure 3, right).⁷

Treatment

Considering the rarity of RPC, there are few clinical trials that compare the treatment modalities of this condition. The pharmacological approach is based on a collection of case reports and case series. Despite the improvement of clinical features seen in RPC, no treatment modality has been proven to change the natural course of the disease.¹⁷

Treatment is tailored to disease severity and extent of involvement of the disease. The assessment of severity can be quantified by a disease activity scoring system, which has recently been developed for RPC: the Relapsing Polychondritis Disease Activity Index (RPDAI).¹⁸ The scoring system is comprised of 27 items with individual scores ranging from 1 to 24, with a maximum RPDAI score of 265. In general, patients with localised nasal, auricular or articular chondritis without visceral involvement can be treated with NSAIDs, colchicine or dapsone, although efficacy is variable.¹⁵ Glucocorticoids are often used during acute flares. In patients with visceral involvement including the airways, heart or eyes, oral glucocorticoids are

the initial treatment of choice. However, manifestations such as severe laryngeal or tracheobronchial chondritis often warrant intravenous methylprednisolone bolus therapy (15 mg/kg/day) combined with a steroid-sparing immunomodulating agent as initial therapy.¹⁷ Frequently used immunomodulatory treatments include cyclophosphamide, methotrexate, azathioprine and ciclosporin. More recently, biological agents (in particular infliximab) have been reviewed in the treatment of RPC; however, the results have been variable.¹⁹

Surgery is sometimes warranted in selected patients due to complications of visceral involvement including airway collapse and intractable heart failure due to valvular involvement or an aortic aneurysm formation.¹⁷

Prognosis

With increasing recognition and a better understanding of this rare disease, improvements in the outcomes of patients with RPC have been recognised. Survival rates have been estimated to have increased from 70% at 5 years to 91% at 10 years in the last decade according to a recent review in 2014.¹⁶ The main causes of mortality are airway collapse with respiratory failure and infectious complications of the treatment itself.

CONCLUSION

RPC is a rare autoimmune disorder and if left undiagnosed for a prolonged period, untreated airway involvement can cause fibrosis of the tracheobronchial wall, leading to a fixed tracheobronchial stenosis. Eventually this can progress to life-threatening tracheobronchomalacia due to irreversible damage and loss of tissue integrity. These respiratory complications, mostly tracheal collapse, are the leading cause of mortality seen in RPC. The diagnosis of RPC is established by the combination of clinical findings, supportive laboratory data, and imaging as per McAdam's, Damiani's and Michet's criteria. We would like to highlight the importance of early recognition of RPC by primary care providers so that early specialist referrals can be made. This can allow the functional and anatomic assessments of the upper and lower airways to be made and earlier treatment to be initiated in seemingly asymptomatic patients.

Contributors FA developed the design of the case report, collected data regarding the patient, analysed the data, drafted the article and approved the final version to be published. SF collected data regarding the patient, analysed the data, revised the manuscript critically for important intellectual content and approved the version of the manuscript to be published.

Competing interests None declared.

Learning points

- ▶ Relapsing polychondritis (RPC) is a rare destructive autoimmune disorder of the cartilaginous structures with an incidence estimated to be between 3.5 and 4.5 cases per million people per year.
- ▶ The diagnosis of RPC is established by the combination of clinical features, radiographic evidence and occasionally biopsy of the affected cartilaginous structures as per McAdam's, Damiani's and Michet's criteria.
- ▶ There is a crucial need for functional and anatomic assessment of the upper and lower airways in seemingly asymptomatic patients.
- ▶ If left undiagnosed for a prolonged period of time, airway involvement can cause a fixed tracheobronchial stenosis, which can ultimately lead to life-threatening tracheobronchomalacia due to irreversible damage and loss of tissue integrity.
- ▶ Rapid recognition and treatment of RPC by primary providers may ultimately prevent misdiagnosis and help prevent delays in treatment, which could otherwise lead to irreversible damage or death.

Patient consent Obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

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