Relapsing Polychondritis with Tracheobronchial Involvement: A Detailed Description of Two Pediatric Cases and Review of the Literature

Relapsing Poychondritis mit Beteiligung der Atemwege: Eine detaillierte Beschreibung von zwei pädiatrischen Fällen und Literaturübersicht

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ABSTRACT

Relapsing polychondritis (RP) is a rare immune-mediated disease that primarily affects the cartilaginous structures of the ears, nose and airways. The clinical spectrum ranges from mild to severe disease characterized by progressive destruction of cartilage in the tracheobronchial tree leading to airway obstruction and acute respiratory failure. Early diagnosis is crucial to prevent irreversible airway damage and life-threatening complications. Due to its rarity and variability of symptoms, the diagnosis of RP is often delayed particularly in childhood. To address this and increase awareness of this rare disease, we present a detailed case report of two adolescent females

affected by RP. We aim to describe the clinical findings, consequences of a delayed diagnosis and provide a review of the current literature.

ZUSAMMENFASSUNG

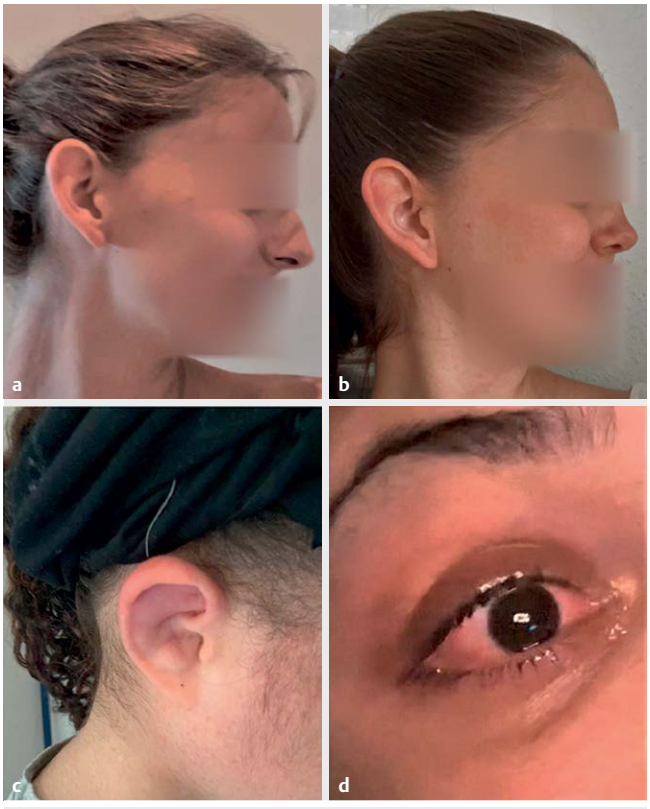
Die rezidivierende Polychondritis (RP) ist eine seltene immunvermittelte Erkrankung, die in erster Linie den Knorpel der Ohren, der Nase und der unteren Atemwege betrifft. Das klinische Spektrum reicht von leichten Symptomen mit rezidivierenden Entzündungen an Ohren und/oder Nase bis hin zu schweren Verlaufsformen mit fortschreitender laryngotracheobronchialer Knorpeldestruktion. Letzteres kann unbehandelt zu einer lebensbedrohlichen und irreversiblen Atemwegsobstruktion führen. Eine frühzeitige Diagnose ist unerlässlich, um die Betroffenen vor schweren Komplikationen zu bewahren. Aufgrund der Seltenheit und der Variabilität der Symptome wird die Diagnose RP häufig verzögert- oder gar nicht gestellt, insbesondere im Kindesalter. Um das Bewusstsein für diese potentiell lebensbedrohliche Erkrankung zu schärfen, die typischen klinischen Befunde zu veranschaulichen und die fatalen Folgen einer verzögerten Diagnose aufzuzeigen, beschreiben wir den Krankheitsverlauf von zwei betroffenen weiblichen Jugendlichen und geben eine Übersicht über das Krankheitsbild anhand der aktuellen Literatur.

Introduction

Relapsing polychondritis (RP) is a rare disease that primarily affects cartilaginous tissues of the ears, nose and airways [1, 2]. Respiratory tract involvement, specifically severe airway stenosis, can lead to acute respiratory failure, which is associated with a poor prognosis if not timely treated [3]. Due to the rarity of RP, the diagnosis is often delayed resulting in increased morbidity and mortality. We present a case report of two adolescent females affected by RP and describe the clinical features, complications and management of RP based on the current literature. We also include a personal account to shed light on the impact of this condition on the daily life of a previously healthy teenager.

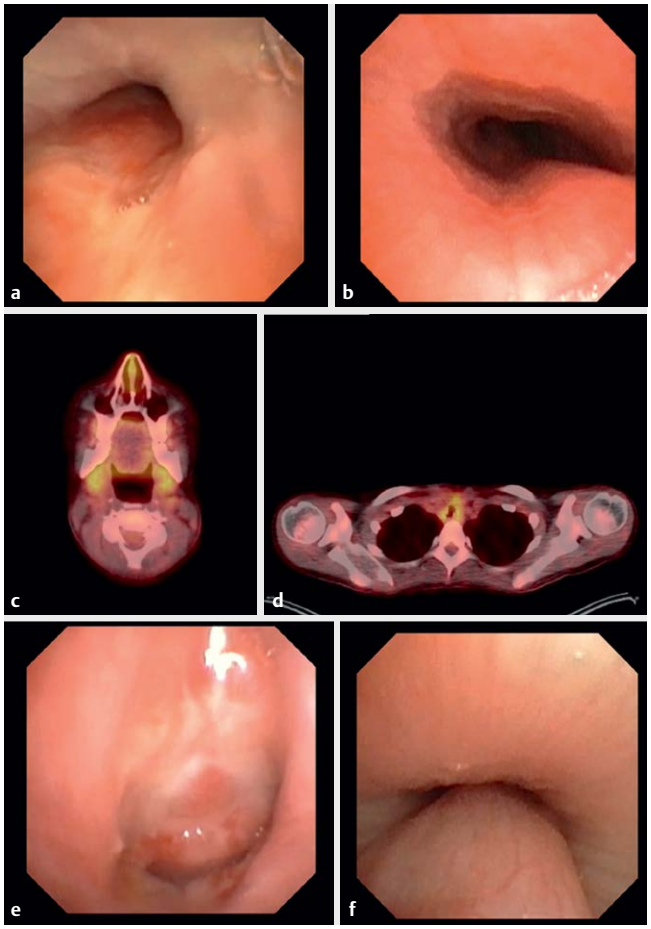
Case 1

A previously healthy 15-year-old girl initially presented in spring with symptoms of nasal congestion and throat ache. She was diagnosed with a viral upper respiratory tract infection and improved with ibuprofen. Her symptoms relapsed one month later with additional complaints of right sided earache together with intermittent swelling and discoloration of the right external ear, pain on the bridge of the nose, throat tightness and hoarseness. These symptoms progressed and she was once again treated with ibuprofen. Additionally, an antibiotic for a suspected bacterial respiratory tract infection and a proton pump inhibitor for suspected gastro-esophageal reflux were given with minimal improvement of symptoms. Three months after initial presentation she developed difficulty breathing and was treated for laryngitis and sinusitis with antibiotics and ibuprofen. Her symptoms worsened and four weeks later, infectious laryngitis was suspected again and she was treated with clindamycin which was changed to azithromycin after 5 days because of the development of a generalized maculopapular exanthema. The exanthema regressed over several days and the girl's symptoms improved. Five months after initial presentation she had another relapse with exacerbation of symptoms including dyspnea, chest pain, stridor, cough, and hoarseness. She was admitted and treated for croup with inhaled suprarenine, salbutamol, systemic steroids, and antibiotics with minimal improvement of symptoms. One months later the dyspnea and stridor worsened and a subglottic stenosis was suspected. She was transferred to a pediatric hospital for further evaluation and treatment. On examination she had severe dyspnea, hoarseness, and inspiratory stridor. Apart from a saddle nose deformity, no other abnormalities were found (▶ **Fig. 1a, b**). During her hospitalization, various diagnostic tests were performed including a laryngoscopy which demonstrated decreased vocal cord mobility and subglottic stenosis secondary to an inflamed and swollen mucosa. A bacterial infection was suspected and antibiotic therapy with ampicillin/sulbactam and erythromycin was initiated. She deteriorated and required intubation six months after initial presentation due to respiratory failure. A computed tomography (CT) scan of the neck and chest did not reveal



▶ **Fig. 1** Clinical features of RP for patient 1 and 2. **a**, **b**: Progression of saddle-nose deformity; **c**: chondritis of the ear; **d**: scleritis/episcleritis.

any significant findings except for the subglottic stenosis noted on laryngoscopy. Laboratory examination showed a leukocytosis (13,500/µl) and an increased C-reactive protein (CRP 67 mg/l). Microbiological work up was negative. She was transferred to our institution 2 days later for further work up. Her laboratory work up showed a leukocytosis (16,700/µl), and CRP (19.7mg/L) was on a downward trend. All other laboratory parameters, including immunoglobulins, coagulation, renal and hepatic parameters were within normal range. An autoimmune work up revealed elevated thyroglobulin antibodies (208 IU/ml; normal range < 115) and antinuclear antibodies (ANA Hep2; 1:2560, normal range < 1:160) but no anti cytoplasmic antibodies (pANCA, cANCA). Bronchoscopy revealed a subglottic stenosis as described before as well as severe tracheomalacia with partial loss of the tracheal cartilage rings noted in the upper and middle third of the trachea (▶ **Fig. 2a, b**). The distal third of the trachea and bronchi was not affected. Cytology and microbiological examination of bronchoalveolar lavage fluid (BALF) were also normal. PET-CT scan showed increased metabolic activity in the nose and the upper two thirds of the trachea (▶ **Fig. 2c,d**).



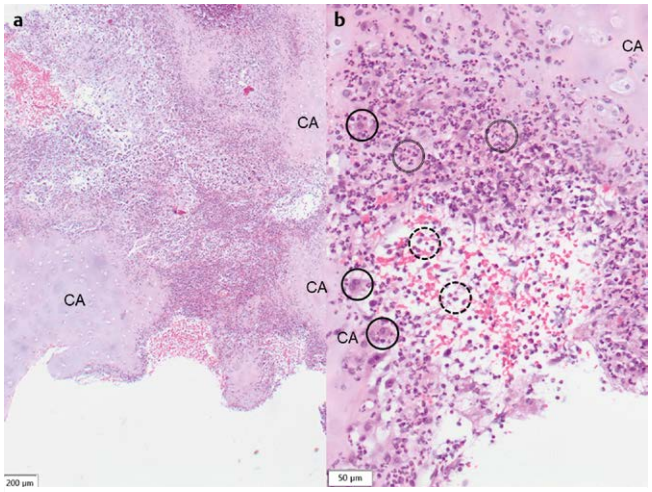
▶ **Fig. 2** Images of patient 1 (**a-d**) and 2 (**e, f**). **a, b**: Bronchoscopy images of the upper and middle third of the trachea showing severe tracheomalacia with partial loss of the cartilage. **c, d**: PET-CT scan showing increased metabolic activity in the nose and the upper two thirds of the trachea colored in yellow. **e, f**: Bronchoscopy demonstrating inflammation of the subglottic mucosa resulting in severe subglottic stenosis with subtotal collapse during expiration.

Echocardiography, electrocardiography as well as ultrasound of the thyroid gland, kidneys and abdomen were normal. In view of the clinical, laboratory and imaging findings a diagnosis of RP was made, and treatment was commenced (▶ **Table 1**). The patient required reintubation after an unsuccessful attempted extubation. A plastic tracheostomy was performed by in-house ENT surgeons. During the dissection of the anterior wall of the trachea, only a few cartilage fragments could be identified macroscopically. The majority of the cricoid cartilage and the proximal trachea consisted of scar tissue. A T-tube was inserted and a biopsy of the right auricle was taken in addition. Histology showed hyaline cartilage with multifocal necrosis and a marked neutrophilic inflammation (▶ **Fig.3**). Surveillance bronchoscopies prior to discharge showed an overall decrease in airway inflammation. She was discharged after a month, but readmitted 8 weeks later after prednisolone was tapered. She presented with pain in the nose, throat, joints, costochondral junction, dyspnea, and cough. After a multidisciplinary discussion, her therapy was modified (▶ **Table 1**). She has remained stable but does have relevant limited physical mobility.

▶ **Table 1** Treatment course for patients 1 and 2.

Patient 1	
Initial treatment	▪ Methylprednisolone; 20mg/kg/d on 3 consecutive days ▪ Plasmapheresis five times within one week ▪ Immunoglobulines; 1g/kg once ▪ Prednisolone; 2mg/kg/d following Methylprednisolone
Treatment at first discharge	▪ Prednisolone; 1 mg/kg/d ▪ Methotrexate; 20mg 1x/week ▪ Adalimumab; 40 mg s.c. every two weeks ▪ Naproxen; 375mg twice daily
Treatment changes and reasons	▪ **Relapse under Prednisolone taper 8 weeks after first discharge** ▪ Switch from Adalimumab to Tocilizumab ▪ Methylprednisolone; 10mg/kg/d iv on 3 consecutive days
Current treatment	▪ Prednisolone; 3.5 mg once daily ▪ Methotrexate; 20mg 1x/week ▪ Tocilizumab; 400mg iv every 4 weeks ▪ Naproxen; 375mg twice daily
Patient 2	
Initial treatment	▪ Methylprednisolone; 20mg/kg/d iv on 3 consecutive days ▪ Prednisolone; 2mg/kg/d following Methylprednisolone
Treatment at first discharge	▪ Prednisolone; 1mg/kg/d ▪ Methotrexate; 15mg 1x/week ▪ Tocilizumab; 400mg iv every 4 weeks
Treatment changes and reasons	▪ **Relapse under Prednisolone taper 2 weeks after first discharge** ▪ Prednisolone; 2mg/kg/d following Methylprednisolone
Current treatment	▪ Prednisolone; 15 mg once daily ▪ Methotrexate; 15mg 1x/week ▪ Tocilizumab; 400mg iv every 4 weeks

Abbreviations: d = days, s.c. = subcutaneous; iv = intravenous.



▶ **Fig. 3** Histology of chronic polychondritis (ear, HE): The low magnification (A, 50x) shows residual islands of cartilage (CA) with adjacent dense inflammatory infiltration. In higher magnification (B, 200x), the cartilage (CA) in the border zone shows activated chondrocytes (solid line circle) and a predominantly granulocytic infiltrate (double line circle) with multifocal infiltration of the residual cartilage. Areas further away from the cartilage/inflammation border zone show a predominantly lympho-histiocytic infiltrate (broken line circle). HE: hematoxylin and eosin stain

Patient's Perspective at age 16

"Living with a rare disease is anything but easy. There is a lot more work and suffering behind it than you think. My disease has taken away many things in my life, for example my passion for sports since I was little. But even small, perhaps self-evident things in everyday life suddenly become big challenges. For example, gardening, my daily way to school, climbing stairs and much more. Living with a rare disease also means constantly worrying and thinking. Thoughts about whether you have taken all your medications or whether you have all the emergency items with you. My biggest fear is that the disease flares up again any moment despite therapy, it harms me even more than it did before or I even die from it. Because of my tracheal involvement and my tracheotomy, I must inhale with NaCl several times a day. I depend on this, which also makes it difficult for me in everyday life. Dealing with such a sudden change in life is hard because it has an extreme impact on the psyche. I am still learning how to deal with it and how to accept my fate. I try to stand by it every day and always try to think and act positively, in which I want to talk openly about my story and put attention on to my rare disease. I hope that one day there will be more knowledge, studies, and research about relapsing polychondritis, but also other rare diseases."

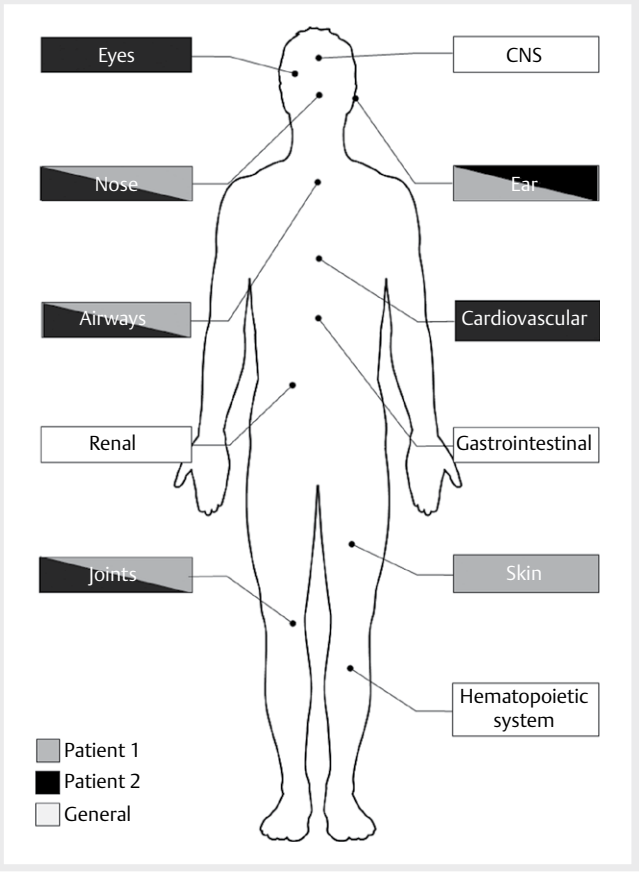
Case 2

A 16-year-old female with preexisting allergic rhinitis and asthma presented with fever, intermittent cough, chest pain, dyspnea, swelling, and discoloration of external ears pain on the bridge of the nose, throat tightness and hoarseness in the winter period. She visited her pediatrician twice and was suspected as having a bacterial respiratory tract infection and uncontrolled asthma. Antibiotics were prescribed together with salbutamol and budesonide twice daily. While her fever decreased, the other symptoms worsened and she was subsequently diagnosed with bacterial ear chondritis by the otolaryngologist and treated with both an oral and topical antibiotic. She also had significant weight loss (lost 5kg over 8 weeks) with ongoing fevers during this period. Two months later she presented to the emergency department of a children's hospital with dyspnea, stridor, dry cough and chest pain. She was treated for an asthma exacerbation and intercostal neuralgia, and discharged with cetirizine, inhaled corticosteroids and ibuprofen. She was admitted a week later for ongoing dyspnea, hoarseness and of note both auricles were swollen and tender to touch. Laboratory tests revealed an elevated CRP (100 mg/L), leukocytosis (25,000/µl) and IgM antibodies against Mycoplasma pneumonia. She was treated with antibiotics and a short course of oral prednisolone for suspected pneumonia, bilateral auricular perichondritis and an acute asthma exacerbation (▶ **Fig. 1c**). She was once again admitted a week later due to intense thoracic and epigastric pain, dyspnea, right-sided conjunctivitis and intermittent fever (▶ **Fig. 1d**). Laboratory tests revealed an elevated CRP (124.6mg/L) and leukocytosis (15,300/µl). An autoimmune work up revealed a positive ANA titer (not quantified). Echocardiography showed a pericardial effusion. Both the chest CT and abdominal ultrasound were normal. Despite treatment her symptoms continued to worsen. In view of the positive ANA, prednisolone (2mg/kg/d) was initiated for a suspected autoimmune condition. She had a marked clinical improvement, however relapsed after the prednisolone was tapered and required admission. Her symptoms included dyspnea, stridor, chest pain, conjunctivitis and tender swelling of the right knee and upper ankle. Her right auricle was tender and swollen with a livid discoloration and a saddle nose was recognized for the first time. In view of the symptoms and clinical course, RP was suspected and the prednisolone dose was increased to 2 mg/kg/d. She improved within a few days and was transferred to our institution for further work up four months after initial presentation. Lung function demonstrated an impaired peak expiratory flow consistent with fixed upper airway stenosis. Laboratory tests revealed a leukocytosis (15,400/µl) with a normal CRP. Bronchoscopy showed inflammation of the subglottic mucosa resulting in severe subglottic stenosis with subtotal collapse during expiration (▶ **Fig. 2e, f**). The distal trachea and bronchi were normal. BALF showed no inflammatory cells and a normal microbiology. A repeat CT scan and MRI of the chest and airways did not yield any additional information, however a PET-CT scan showed increased metabolic activity in the left auricle, subglottic region and the cartilaginous structures of the nose. Ophthalmologic examination showed bilateral episcleritis and scleritis. Echocardiography, electrocardiography and ultrasound of the thyroid gland, kidneys and abdomen were normal. These features were in keeping with RP and treatment was commenced (▶ **Table. 1**). She had an improvement in symptoms except for a mild inspiratory stridor which persisted. Two weeks later, following the tapering of prednisolone, she had another exacerbation and required intubation for severe subglottic stenosis (▶ **Fig. 2e**). A tracheostomy with insertion of a T-tube was performed a week later. She had multiple postoperative complications which included wound breakdown at the tracheotomy site, mediastinal emphysema and pneumothoraces requiring repeated surgical interventions. She was discharged a month later and has since had no re-

lapses. Her physical capacity is limited resulting in emotional distress.

Discussion

RP is a systemic inflammatory disease with progressive destruction of cartilaginous structures. The pathophysiology of RP is unknown; however, studies have shown a dysregulation of both the cellular and humoral immune system. Abnormal cellular interactions between cartilage, proteoglycans, type II collagen-specific T cell clones and circulating antibodies against native and denatured type II, IX and XI collagens as well as to Matrilin 1 have been identified in patients with RP [4–10]. Additionally, an association between HLA-DR4 and RP has also been reported [11]. Organ involvement in RP is variable. The external ear, nose, larynx, and tracheobronchial tree are commonly affected. Additionally, other organs may also be involved (▶ **Fig. 4**) [12–18]. The disease course is often unpredictable and varies from mild intermittent auricular and/or nose chondritis to life-threatening tracheobronchial and cardiovascular involvement. Clinical symptoms are variable and include painful ear swelling, throat ache, hoarseness, cough or stridor, and is often misdiagnosed as an acute infection or asthma. The two cases described provide the typical clinical presentation and progression of RP with airway involvement as well as the consequences of a delayed diagnosis. Both of our patients responded well to immunosuppressive treatment. However, the delayed diagnosis resulted in severe damage to the lower airways and the rapid reduction of prednisolone dose resulted in relapse in both patients despite being on additional immunosuppressive therapy.



▶ **Fig. 4** Organ involvement of patient 1 (grey), 2 (black) and in general.

Epidemiology

RP is a rare disease that predominantly affects females between 40–50 years of age [12], however pediatric cases particularly within the adolescent age groups have been described [2, 13]. The incidence and prevalence of RP ranges between 0.7–3.5 and 4.5–9 per million adults per year respectively [16, 17, 19]. To date, less than 100 pediatric cases have been published in case reports or small case series [13].

Organ involvement and clinical features

Ears

Auricular chondritis is the most common clinical manifestation and has been reported in approximately 60–90 % of patients [20]. It is characterized by painful, warm, red pressure-sensitive swelling of the helix, antihelix, tragus and antitragus with sparing of the non-cartilaginous lobule. As the cartilage thins out, the underlying vasculature is more visible resulting in a bluish discoloration of the skin and is therefore called the "blue ear sign" [20–22]. The middle and inner ear are less frequently affected and present with tinnitus or sensorineural hearing loss, highlighting the importance of regular audiometric examinations. [20–22].

Nose

Nasal chondritis is characterized by inflammation of the nasal cartilage. Patients typically experience pain and/or a sensation of pressure in the bridge of the nose and persistent nasal obstruction. Recurrent epistaxis, rhinorrhea and crusting may also occur. A saddle nose deformity develops due to damage of the nasal cartilage and occurs in about 20 % of all patients [22, 23].

Airways

In patients with RP, up to 50 % may experience airway involvement, and if unrecognized and left untreated it can lead to life threatening airway obstruction, as noted in both of our patients. Laryngeal chondritis presents with a range of symptoms which include throat ache, hoarseness, cough, dyspnea and stridor. Tracheobronchial involvement can result in severe tracheobronchomalacia, where the airway collapses during expiration due to the loss of the tracheal and bronchial cartilages. [13–15, 18, 24, 25]. Tracheobronchial involvement is thought to be more frequent in children than in adults and accounts for approximately one third of all fatalities in RP [26].

Eyes

Ocular involvement may present as uni- or bilateral scleritis, episcleritis, or conjunctivitis with ocular erythema and/or lid edema. Rarely, keratitis or uveitis have been described. Serious but rare

complications include occlusion of retinal arteries or veins, optic neuritis, retinopathy, or retinal detachment [27, 28].

Joints

Costochondritis presents with chest pain and sternal tenderness. As in both patients described here, the sternal pain is often misinterpreted as a sign of gastroesophageal reflux. However, costochondritis can be distinguished from reflux by the presence of a clearly localized tenderness at the costochondral junction. The presence of costochondritis after remission of symptoms is a good indicator of relapse and in some cases, pain can be so severe that it impairs breathing. Intermittent, non-erosive, seronegative asymmetric oligo- or polyarthritis affecting the small and/or large joints are also common. In RP, arthritis typically spares the axial skeleton. [12, 13, 29, 30].

Cardiovascular system

Cardiovascular involvement is the second common cause of death after respiratory complications and has been reported in 25 % of adult RP patients. The most common vascular complication is aneurysmal disease, predominantly involving the ascending aorta with aortic insufficiency. Aneurysms can also occur in other vessels such as the cerebral or iliac arteries. Pericarditis, myocarditis, sinus tachycardia, atrioventricular block and peripheral vasculitis have also been described [31–33].

Skin

Skin manifestations include nonspecific changes such as purpura, papulonodular exanthema, maculopapular rash, annular eruptive urticaria, or ulcerative lesions of the skin or oral and genital mucosa [22, 23, 34]. We were unable to determine whether the exanthema described in patient 1 was a skin manifestation of RP or caused by a delayed allergic reaction to the antibiotic.

CNS

Neurologic manifestation, although rare, is associated with high morbidity and mortality. Cranial nerve palsies of the fifth and seventh cranial nerves are most common, however sterile meningitis, encephalitis, stroke and aneurysms have also been described [12, 29, 35].

Renal

Renal involvement can occur as segmental necrotizing glomerulonephritis, tubulointerstitial nephritis, or IgA nephropathy. Other immune mediated diseases such as granulomatosis with polyangiitis (GPA), microscopic polyangiitis or renal involvement in systemic lupus erythematosus (SLE) should be considered as differential diagnosis.

Gastrointestinal tract

Gastrointestinal involvement in RP remains unclear. However, inflammatory bowel diseases and motility disorders have been described in patients with RP [23].

Myelodysplasia

Myelodysplasia occurs in up to 10–15 % of patients with RP and affects males, over the age of 50 years. [2, 12, 36].

Associated diseases

RP is associated with other autoimmune diseases in up to 25–35 % of patients. These include various forms of vasculitis (12 %), Sjögren`s sydrome (10 %), Hashimoto thyroiditis (6 %), SLE (4 %), rheumatoid arthritis (3 %), and less commonly antiphospholipid syndrome, Behcet disease. [23, 37].

Diagnosis

RP is a clinical diagnosis based on a detailed history and physical examination. Due to the rarity of this condition, the diagnosis of RP is often delayed. In a case series published by Belot et. al., the diagnostic delay in children was five years compared to two years or less in adults [38]. Both patients met the diagnostic criteria at an early stage, and despite confirming the diagnosis within 3–7 months, irreversible cartilage destruction still occurred. The diagnostic criteria for RP was initially proposed by McAdam and has subsequently been modified (▶ **Table 2**) [1, 2, 37, 39]. RP is characterized by spontaneous flares and remissions. Spontaneous remissions in both our patients may have given a false impression of a response to repeated antibiotic treatments and of note both patients also had treatment with corticosteroids which likely induced a temporary remission. Immediate referral to a specialized center for patients with suspected RP is recommended [37]. Elevated CRP lev-

▶ **Table 2** Proposed diagnostic criteria for Relapsing Polychondritis [1, 2, 39].

McAdam's criteria	Damiani's criteria	Michet's criteria
Clinical features		
1. Auricular chondritis 2. Nasal chondritis 3. Laryngotracheal chondritis 4. Ocular inflammation 5. Seronegative Polyarthritis	1. Auricular chondritis 2. Nasal chondritis 3. Laryngotracheal chondritis 4. Ocular inflammation 5. Seronegative Polyarthritis 6. Histologic proofed chondritis	**Major criteria** 1. Auricular chondritis 2. Nasal chondritis 3. Laryngotracheal chondritis **Minor criteria** Ocular inflammation Hypoacusis Vestibular dysfunction Seronegative polyarthritis
Diagnosis		
≥ 3 clinical features	≥ 3 clinical features OR 1. clinical feature and histology OR 2. clinical features and response to corticosteroids or dapsone	2 major criteria OR 1 major plus 2 minor criteria

els are found in 60–70 % of RP patients. It has been shown to be a risk factor for relapse, and can also be used as a tool to monitor relapse [37, 40]. Antinuclear antibodies (ANA) and rheumatoid factor are found in 20 % and in 15 % of patients respectively [37, 41]. Patients typically do not have antibodies to double-stranded DNA or antineutrophilic cytoplasmatic antibodies (ANCA). If anti-PR-3 or MPO antibodies are detected together with proteinuria and/or renal dysfunction, GPA or microscopic polyangiitis should be considered.

Although collagen type II antibodies have been shown to correlate well with disease severity, [42, 43], they are neither sensitive nor specific for RP and can also be detected in rheumatoid arthritis and SLE [44]. Initial evaluation should also include pulmonary function testing, to detect and quantify airway obstruction, echocardiography and ECG to exclude cardiac involvement, ophthalmologic examination, and audiometry. CT of the neck and chest is recommended in the presence of clinical signs of airway involvement, however cartilage is difficult to visualize, especially in children as demonstrated in both our patients. [36, 37]. Magnetic resonance imaging (MRI) with contrast enhancement may be useful in evaluating the airways of patients with RP. Even in the presence of subclinical disease, it distinguishes fibrosis from inflammation (unlike a CT scan) and inflammation from edema [45]. PET-CT may help to detect chondritis indirectly, as in our cases [46, 47]. However, a PET-CT is not recommended as a standard diagnostic procedure [37]. In the presence of airway involvement, a diagnostic laryngotracheobronchoscopy should be performed during spontaneous breathing to assess the presence and extent of inflammation, trachobronchomalacia and/or airway stenosis. It should only be carried out in an experienced centre due to the high risk of perforations and life-threatening airway complications caused by mucosal swelling or hemorrhage. Before undergoing invasive diagnostic procedures, the potential risks and benefits should be carefully evaluated. Routine cartilage biopsy is not recommended for confirming the diagnosis of RP as there are no pathognomonic histological findings. However, in the appropriate clinical setting demonstration of cartilage necrosis with variable inflammatory infiltrates can help to confirm the diagnosis and exclude differential diagnoses as bacterial infection or vasculitis [48].

Differential diagnosis

Several conditions can mimic RP and should be considered as the differential diagnoses.[26, 37] These include bacterial auricular chondritis, of which both of our patients were incorrectly treated for. In contrast to an erysipelas of the auricle, the lobes of the ear are typically excluded in RP. Ear deformities may be caused by leprosy, leishmaniasis, frostbite, or trauma. Other causes of a saddle nose include trauma, congenital syphilis, sarcoidosis or GPA. Ocular inflammation is most often caused by infection but may also be seen in allergic conjunctivitis as well as various connective tissue diseases such as GPA, Behçet's disease, SLE, polyarteritis nodosa or sarcoidosis. Tracheal stenosis may also develop in the setting of GPA, sarcoidosis, or amyloidosis.

Management of RP

The management of RP is challenging. Treatment guidelines are based on case studies and expert opinion [13, 37, 41]. Management of RP requires treatment of both the underlying disease and any flare ups that may occur. The aim of treatment is to effectively control symptoms, prevent cartilage destruction and minimize cardiovascular and respiratory complications, all while maintaining a good quality of life and preserving vision and hearing [37]. Patients should be managed in a specialized center by a multidisciplinary team involving medical doctors and supporting staff that includes a physiotherapist, dietician, psychologist and social worker [37]. Corticosteroids are almost always effective and are used for both long-term treatment and exacerbations [37, 41]. Steroid-sparing drugs are added to limit side effects. These include nonsteroidal anti-inflammatory drugs (NSAIDs) like naproxen as well as colchicine and dapsone for minor nasal or auricular involvement [41]. However, dapsone is associated with multiple side effects and its use is not routinely recommended [37]. Biological disease modifying anti-rheumatic drugs (DMARDs) have been used with variable success. These include methotrexate, anti-TNF (infliximab, adalimumab), anti-IL-6 (tocilizumab), anti IL-1 (anakinra), abatacept, and antiCD20 monoclonal antibodies (rituximab) [37, 41]. Case studies have shown that infliximab is effective in treating saddle nose deformities, severe episcleritis, pyoderma gangrenosum and tracheal chondritis [13]. Rituximab appeared to be effective in treating a 10-year-old male with RP after failing other immunosuppressive regimens, however a case series showed no improvement in 9 adult patients with RP [13]. Anakinra showed improvement in a 14-year-old who had previously failed steroid therapy, methotrexate, cyclophosphamide and infliximab [13]. Cyclophosphamide may be effective in life threatening forms of RP [37, 41]. Abatacept has shown effectiveness in treating nasal or auricular chondritis and articular involvement, however it can worsen respiratory or neurological disease [41]. Tocilizumab, abatacept, and certolizumab have been shown to be effective in some refractory adult cases [41]. Treatment should be based on the disease phenotype (e. g. using methotrexate for joint involvement) as well as the tolerance and cost-effectiveness of the agent. Combination treatment can also be used to improve treatment efficacy and/or avoid the development of antidrug antibodies [41]. Stem cell transplants, performed in a few refractory cases, showed variable success [49, 50]. Interventional airway management is the mainstay of non-pharmacologic treatment. These include endoscopic stenting, balloon dilatation of the airway, tracheostomy, endobronchial laser therapy, and laryngotracheal reconstruction [51]. Cartilage deformities can be corrected by plastic surgery improving overall quality of life [52, 53].

Prognosis

RP is associated with a high morbidity and mortality. Overall RP survival has improved considerably during the last decade. The 10-year survival rate has increased from 55 % in the 1980s to 83 % in 2016 as a result of immunosuppressive drugs and advances in interventional airway procedures [39, 54].

Conclusion

RP is a rare condition and clinicians should maintain a high level of suspicion in patients presenting with recurring chondritis involving the ear, nose, larynx, tracheobronchial tree and arthritis. Diag-

nosis of RP is clinical, with laboratory and imaging providing supporting evidence. Given the complexity of this disease, it is recommended that children be managed in a specialized center involving a multidisciplinary team. Treatment for RP should be tailored to each individual based on symptoms and severity, as current guidelines are primarily based on case reports and expert opinion.

Contributor's Statement

N. Schwerk, K. Schütz and G.Winter did the literature research and designed the study. N.Schwerk, K.Schütz, G.Winter, T.Löffelmann, H. Kaiser and F. Länger constructed the figures and wrote the first draft of the manuscript. All authors critically reviewed the manuscript and contributed according to their expert field. All authors approved the final manuscript for submission.

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Conflict of Interest

The authors declare that they have no conflict of interest.

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