Review Article

Relapsing polychondritis: tracheobronchial involvement and differential diagnoses

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Abstract: This review is describing the diagnostic and therapeutic approach to tracheobronchial involvement in relapsing polychondritis (RP), with a focus on differential diagnoses of inflammatory origin. RP is a systemic auto-immune disease that mainly affects cartilage structures, progressing through inflammatory flare-ups between phases of remission and ultimately leading to deformation of the involved cartilages. Besides the damage of auricular or nasal cartilage, tracheobronchial and cardiac involvement are the most severe, and can seriously alter the prognosis. Tracheobronchial lesions are assessed through a multimodal approach. Mapping of tracheal lesions is achieved using dynamic thoracic imaging and flexible bronchoscopy. Measurement of pulmonary function (with new emphasis on pulse oscillometry) is useful to diagnose obstructive ventilatory impairment, and can be used to follow RP patients, after therapeutics implementation. Diagnosis can be difficult in the absence of specific diagnostic tools, especially because there is a large number of differential diagnoses, in particular inflammatory diseases. Nuclear imaging can help with detection of metabolic activity on involved cartilages, leading to sharpen the final diagnosis. The prognosis has improved, thanks to the upgraded interventional bronchoscopy techniques, and the development of immunosuppressant including targeted therapies, such as tumor necrosis factor-α (TNF-α) inhibitors, offering patients several treatment options, in addition to supportive care.

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Introduction

Relapsing polychondritis (RP) is a rare auto-immune disease, characterized by inflammatory flare-ups of cartilaginous tissues, associated with systemic manifestations. It has been first described in 1923 (1), but has really been highlighted in 1960 by Pearson *et al.* (2). The aim of our review is to update the knowledge of RP on clinical and therapeutical aspects, and to emphasize the differential diagnoses of a tracheobronchial involvement, in the context of recent description of a new entity, the Vacuoles, E1-enzyme, X-linked, Autoinflammatory, Somatic (VEXAS) syndrome (3).

Epidemiology

RP mainly affects adults, with a mean age at diagnosis of 40 to 50 years old, but extreme ages of diagnosis have been described, ranging from 2 to 84 years (4,5). With a sex-ratio of two males for three females, there is a slight female predominance. However, it could be biased by the fact that VEXAS syndrome almost exclusively affects males, so the sex-ratio for RP could be closer to one male for three females (3,6-8). A study in the United Kingdom showed a prevalence of nine cases per million population between 2010 and 2012, with an overall incidence between 1990 and 2012 of 0.71 cases per million population (9).

Pathophysiology and histology

The cause of RP is still unknown. Genetic predispositions probably exist, with controversial findings regarding overrepresentation of some HLA genes, either *HLA-DR4* alleles, either *HLA-B*67:01*, *HLA-DRB1*16:02* or *HLA-DQB1*15:02* (10-12). Recently, a whole-exome sequencing study has revealed variants in the *DCBLD2* genes in two families of patients, with five carriers (13). Moreover, in the same study, RP patients had a higher plasma level of DCBLD2 protein compared to control patients, suggesting a possible role of this protein in the overall pathophysiology.

Histological analysis of chondritis during inflammatory phases shows a perichondral pleiomorphic infiltrate composed of lymphocytes T $CD4^+$ and antigen-presenting cells. Immunoglobulins and C3 fraction deposition can be observed in active lesions. As the disease progresses, the inflammatory milieu and proteolytic enzymes lead to chondrocytes apoptosis. Total destruction of cartilaginous tissue leads to fibrous development even gelatinous involution or calcifications (11).

Antigenic targets are not well known. However, autoantibodies against cartilage components may be detected in RP patients (14). Mouse and rat models of immunization have shown the development of cartilage inflammation following exposure to cartilage components. All of this suggests that autoimmunity is involved in the natural history of the disease in several ways (15).

Clinical manifestations

During inflammatory phases, systemic symptoms such as altered general condition, sometimes associated with fever (15-18) are often reported. However, beyond being a sign of infectious complications, fever may also be a sign of another autoinflammatory disease, such as VEXAS syndrome (6-8).

Respiratory manifestations

Tracheobronchial chondritis

Found in 60% of RP patients, with a time to onset of 2.5 years if absent at diagnosis (18), tracheobronchial chondritis is characterized by cough and progressive dyspnea, inspiratory or expiratory, depending on the severity of obstruction. Less than 50% obstruction may not be noticed by patients, leading to late diagnosis. Chest auscultation during inflammatory flare-ups may detect stridor or wheezing, indicating severe airway diseases, depending on the site of inflammation (15-18). Inflammation and destruction of cartilaginous tissue results in loss of rigidity of the tracheobronchial tree, leading to either malacia, stenosis, and/or bronchiectasis, creating the conditions for infectious complications, particularly with immunosuppressive therapies (19-21). As described by Dion *et al.* (18) in their cluster 2, tracheobronchial involvement leads to 25% of intensive care admission, making this

Table 1 Relapsing polychondritis' diagnosis criterias, according to Michet *et al.* (26)

Major criterias	Minor criterias
Auricular chondritis	Ocular inflammation
Nasal chondritis	Hearing loss
Laryngo-tracheal chondritis	Peripherical vestibular dysfunction
	Seronegative polyarthritis

Two major criterias or one major criteria with two minor criterias are needed to diagnose relapsing polychondritis.

manifestation one of the most severe in RP patients, in relation to its frequency.

Laryngeal chondritis

Laryngeal chondritis is observed in 40% of cases (15-18,21), with various manifestations such as dry cough, hoarseness, dysphonia/aphonia, or thyroid cartilage pain. The inflammatory aspect of the larynx can be visualized by flexible nasendoscopy or bronchoscopy, with edema of the supraglottic region or the appearance of false vocal cords (19,20). The evolution can be severe with laryngomalacia or laryngeal stenosis, responsible for inspiratory dyspnea, leading to respiratory failure, requiring tracheostomy (15,16,20-22).

Costochondritis

Costochondritis is responsible for chest wall pain, parasternal or lateral pain, or back pain for floating ribs, increasing on palpation. It can also affect ventilatory mechanisms, especially during inspiratory phases (16,17,20).

Other clinical manifestations

Among the whole range of manifestations of RP, we can list the following ones:

- Auricular chondritis is almost pathognomonic of RP, occurring in approximately 90% of cases during the natural history of the disease, and its presence can be reported within 2 years of diagnosis in 25% of cases (9). It is characterized in the acute phase, by pain on palpation or pressure, associated with redness and swelling, localized to the cartilaginous tissues, sparing the earlobe. The sequelae include damage and distortion of the auricular relief, with an aspect called "cauliflower ear" (15-18,21).
- Nasal chondritis is less symptomatic and more common, with a prevalence of 60% cases, and is characterized by inflammation of the nasal cartilage, with symptoms of pain, nasal discharge, or obstruction. A deformity of the nasal bridge may be observed over time, known as "saddle nose" (15-18,21). This deformity can be seen in granulomatosis with polyangiitis (GPA), which is usually preceded by more pronounced symptoms.
- Joint manifestations can be isolated at the onset of RP. They are characterized by oligo- or polyarthritis, intermittent, migratory and asymmetric, without destruction. Large joints may be affected as well as small ones, such as metacarpophalangeal and interphalangeal joints, knees, ankles, or wrists (15-18,21).
- Ocular involvement is observed in 60% of cases and often precedes other manifestations (9). Various manifestations have been described, but the most common are episcleritis, scleritis, and conjunctivitis (15-18,21).
- Cochleo-vestibular manifestations are described in 20% to 45% of cases (15-18,21), dominated by sudden or progressive hearing loss, sometimes associated with vestibular dysfunction.
- Skin involvement is polymorphic with either recurrent buccal aphtosis, erythema nodosum-like nodules, purpura, or livedo (15-17,21).
- Cardiovascular involvement with aortic valve regurgitation, often combined with ascending aortic root dilatation, and/or mitral regurgitation (which may be present alone). Thoracic and/or abdominal aortitis can also be observed during RP history, with an evolution up to aneurysm. Other clinical manifestations include myocarditis, pericarditis, and atrio-ventricular block. There is also an increased risk of venous thrombosis (15-18,21,23).
- Neurologic manifestations, mainly of the central nervous system, with encephalitis or aseptic meningitis (15-18,21).

Diagnosis

The first diagnostic classification was made by McAdam in 1976 focusing essentially on clinical aspects, followed by one made by Damiani including histologic evidence or therapeutic response to corticosteroids and/or dapsone (24,25). It was thus abandoned in favor of Michet's criteria, proposed in 1986 (26) (*Table 1*), which is the last known

classification. Cartilage biopsy should not be performed as histology is not necessary to confirm the diagnosis.

Biological investigations

Specific markers of RP for diagnosis or activity do not exist at this time. An increase in C-reactive protein (CRP) can be observed during flares (17,18,21), but its normality cannot be used to exclude the diagnosis. It should also raise the question of an infectious complication or a differential diagnosis such as VEXAS syndrome (6-8). Auto-immunity testing may detect antinuclear antibodies without specificity, rheumatoid factor, or anti-neutrophil cytoplasmic antibodies (ANCAs) with atypical fluorescence (17,18,21). However, ANCA positivity with anti-proteinase 3 (PR3) specificity must orient the diagnosis to GPA.

Autoantibodies to cartilage components such as type II collagen, matrillin-1 (for tracheobronchial involvement), or cartilage oligomeric matrix protein (COMP) can be detected but should not be used in routine practice due to their low specificity and sensibility. Other biomarkers have been studied, such as serum soluble triggering receptor expressed on myeloid cells 1 (sTREM-1), but none have been shown to be useful in diagnosis (14,27).

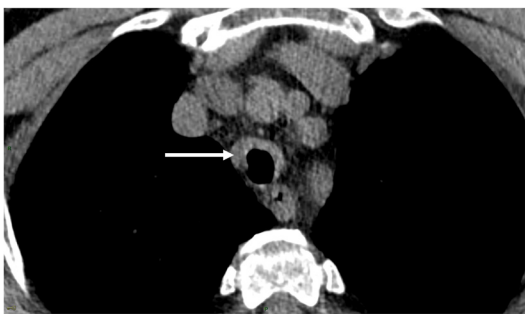

Figure 1 Thoracic CT scan, transverse section, non-injected, mediastinal window. Anterior tracheal wall thickening (arrow). CT, computed tomography.

Evaluation of tracheobronchial involvement

Thoracic computed tomography (CT)

The first test to assess airway compromise is a cervico-thoracic CT scan. It should include the cervical portion of the trachea in addition to the thorax, with thin slices during the inspiratory and expiratory phases, and dynamic slices, to assess stenosis, tracheobronchomalacia (TBM), and small airway involvement. CT scan is also useful in the follow-up of the disease. The following abnormalities may be observed, at different stages of the disease (20,28-32):

- Tracheal anterior wall thickening, isolated or associated with bronchial wall thickening, with a threshold of 2 mm. Isolated bronchial thickening has never been described. Absence of posterior tracheal wall involvement is often described but may not be sufficient to diagnose RP. In fact, circumferential thickening may also be observed during flare-ups or after complete destruction of the tracheal structure. Furthermore, the evaluation of the anterior wall is difficult, with low inter-observer reproducibility. The density of the thickening is variable, corresponding either to fatty remodeling or to subsequent calcifications. Tracheal wall thickening can result in focal stenosis or a homogenous and extensive reduction of the tracheobronchial lumen, defined by a 25% caliber reduction (*Figures 1*,*2*).
- TBM on the expiratory and dynamic sections, corresponding to the complete destruction of the

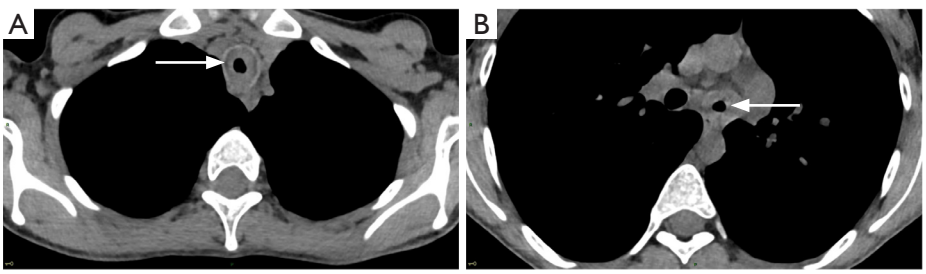

Figure 2 Thoracic CT scan, transverse section, non-injected, mediastinal window. (A) Circumferential thickening of tracheal wall, responsible for tracheal stenosis (arrow). (B) Circumferential thickening of main left bronchus wall, responsible for bronchial stenosis (arrow). CT, computed tomography.

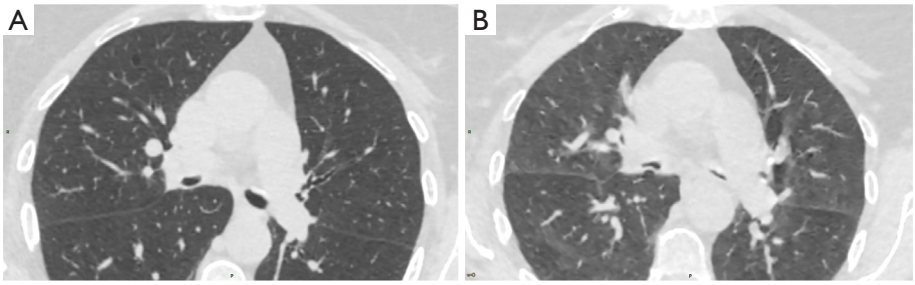

Figure 3 Thoracic CT scan, transverse section, non-injected, parenchymal window. Dynamic sections in inspiration (A) and expiration (B), showing a bronchial collapse during expiratory time, signaling a bronchomalacia. CT, computed tomography.

cartilaginous support (*Figure 3*).

- ❖ Small airway involvement by mosaic attenuation of lung parenchyma with air trapping, on expiratory slices, with a significance level of 25% of lung parenchyma affected.
- ❖ Bronchiectasis, but less frequent than other respiratory tract abnormalities.
- ❖ The role of magnetic resonance imaging has not been defined yet. Correlation between respiratory symptoms and airway damage at acquisition has been found, but its routine use should not be retained (20,30).

Positron emission tomography (PET)

18-Fluorodesoxyglucose (FDG)-PET scan is still a debatable place. Hypermetabolism can be found in ear, upper airway, tracheobronchial, costal, and articular cartilage, and can guide diagnosis in cases of asymptomatic involvement (33,34). When PET is helpful, at least two cartilaginous regions are involved in 80% of cases, with a median maximum standardized uptake value (SUVmax) between 4.94 and 6.47 (33,34). The correlation between clinical data and radiologic data seems to be excellent for the respiratory tract. Lei *et al.* described that 89.5% of patients with respiratory symptoms had hypermetabolism, and conversely, 89% of patients with hypermetabolism had respiratory symptoms (33). Hypermetabolism may also be a target for measuring treatment response (33,34) (*Figure 4*).

Fiberoptic bronchoscopy

Fiberoptic bronchoscopy allows mapping of airway damage and should be performed with caution, in patients with respiratory symptoms. The endoscopic aspect is unspecific, associating mucous edema and inflammation (19,20,35). RP-associated stenoses are localized to the trachea, with a vocal cords distance of approximately 4 cm and a mean length of 4 cm (31) (*Figure 5*). Changes in endotracheal and endobronchial caliber during breathing and coughing allow a good evaluation of TBM with a good correlation with CT scan data (19,20,35). The risk of respiratory failure seems to correlate with inflammatory flare but has never been fully evaluated (20,36,37). However, spirometry parameters seem to correlate with an excess risk of respiratory failure, especially a low percent predicted forced vital capacity (38). Thus, flexible bronchoscopy should be discussed on a case-by-case basis, with the goal of mapping airway damage prior to treatment initiation, investigating infectious complications, or following up after a rigid bronchoscopy procedure. A temporary preventive increase in corticosteroids before bronchoscopy could be a solution to prevent inflammatory flare-ups.

Pulmonary function tests (PFTs)

PFTs are essential in the initial assessment and during follow-up. Spirometry is the minimum test required, combined with inspiratory maneuvers. Obstructive ventilatory impairment may be observed, with a lack of response to bronchodilators, due to a reduction in bronchial size or a diffuse bronchiolar involvement. Proximal obstruction can also be observed on spirometry, with different phenotypes, depending on localization and compliance: isolated inspiratory limitation [laryngeal or compliant extra-thoracic tracheal stenosis, with a decrease in forced inspiratory vital capacity (FIVC) and forced inspiratory flow at 50% of the vital capacity (FIF_{50}), and a FIF_{50}/forced expiratory flow at 50% of the vital capacity

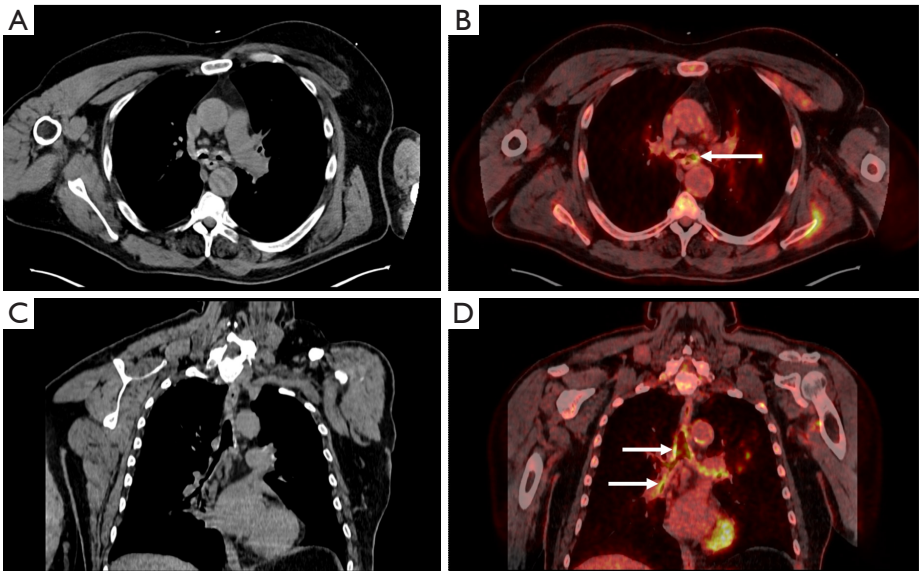

Figure 4 Tracheobronchial hypermetabolism during RP. Thoracic CT scan (A) related to 18-FDG PET scan (B) transverse section showing bronchial wall hypermetabolism (arrow). Thoracic CT scan (C) related to 18-FDG PET-CT (D) coronal section showing tracheobronchial wall hypermetabolism (arrows). RP, relapsing polychondritis; CT, computed tomography; 18-FDG, 18-fluorodesoxyglucose; PET, positron emission tomography.

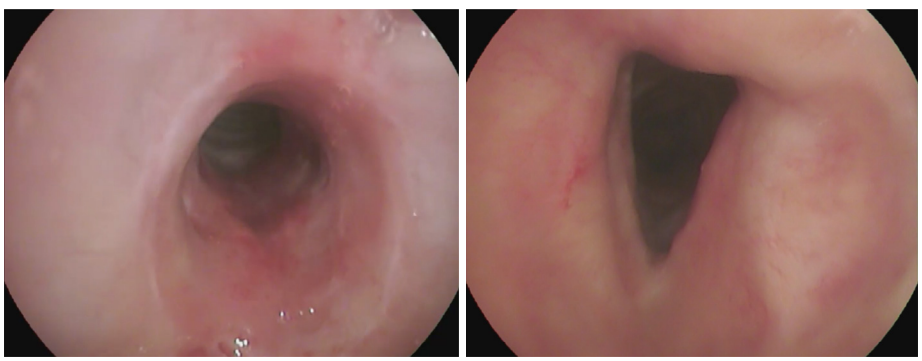

Figure 5 Bronchoscopic views of tracheal stenosis.

(FEF_{50}) ratio <1], isolated expiratory limitation [compliant intra-thoracic tracheal stenosis, with a decreasing in forced expiratory volume in the first second (FEV_1) and FEF_{50}] or both inspiratory and expiratory limitation (fixed tracheal stenosis) (20,39-42). The correlation between measurements and stenosis size is not perfect, but the temporal evolution is an essential element in the follow-up of RP.

Impulse oscillometry can be also used. Oscillometry can measure mechanical properties of the respiratory system in a passive manner, without the need to hold breath. Pressure oscillation is generating by a loudspeaker (or piston-type device or pneumatic valves) at specific frequencies (between 5 and 40 Hz). Flow modifications monitored by the sensor reflect the whole impedance of the respiratory system which can be linked to the resistance and the reactance of the respiratory system (43,44). It has already been used mainly in pediatrics. Recently, a Japanese study (45) found a correlation between radiological data of tracheal obstruction and lung function tests by spirometry and impulse oscillometry. It showed that FEV_1 and peak flow could be correlated to tracheal volume, tracheal volume/tracheal length, and minimal tracheal cross-section area. In addition, impulse oscillometry, particularly 5 Hz resistance, 20 Hz resistance, and 5 Hz reactance, could be correlated

with tracheal volume.

Finally, the severity of obstruction could lead to hypercapnia and ultimately to hypoxemia, due to alveolar hypoventilation. It should be noted that pulmonary diffusion capacity is not affected by the disease.

Differential diagnoses

VEXAS syndrome

First described in 2020 by Beck *et al.* (3) in male patients with autoinflammatory symptoms and hematological abnormalities, VEXAS syndrome is associated with a mutation on *UBA1* gene, located on the X chromosome. Its mutation leads to inactivation of the enzyme-1 protein, which is responsible for protein degradation through the ubiquitin-proteosome system (3,46).

Tracheobronchial chondritis in VEXAS syndrome is not always found in case series (6,7,46-49).

Besides overlap organ involvement between RP and VEXAS syndrome, particularly chondritis, arthritis, cochleovestibular, and central nervous system manifestations, some clinical manifestations appear to be more specific for VEXAS syndrome, and should help clinicians in their diagnosis:

- Male patients (X-linked mutation of UBA1) and age >60 years old (6-8,46-48).
- Fever at diagnosis (6-8,46-48), lymphadenopathy, or hepatosplenomegaly (47,48).
- Hematological abnormalities, ranging from macrocytosis, isolated thrombocytopenia, neutropenia, or monocytopenia, to myelodysplastic syndrome or other myeloid pathology. Lymphopenia, monoclonal gammopathy, or multiple myeloma have already been reported. Vacuolization within both erythroid and granulocytic immature forms can be seen in bone marrow aspiration smears can be found (6-8,46-48).
- Skin involvement, with neutrophilic dermatosis such as Sweet's syndrome, often rich in immature myeloid cells and leukocytoclasis, with flares. Cutaneous vasculitis is not always described (6-8,46-48,50).
- Polymorphic pulmonary manifestations (6-8,46-48), with ground-glass opacities, septal thickening, mediastinal lymphadenopathies and unilateral exudative pleural effusion (49). Broncho-alveolar lavage shows neutrophilic alveolitis (49).
- Orbital or periorbital edema, sometimes associated with scleritis, episcleritis, uveitis, or retinal vasculitis (6-8,46-48).
- Peripheral neurological system manifestations with sensitive neuropathy or multiple mononeuropathy (47,48).
- Gastro-intestinal manifestations with abdominal pain, diarrhea up to intestinal perforation (8,47,48).
- Cardiovascular manifestations with myocarditis or pericarditis. Unprovoked venous thrombosis is common, and arterial thrombosis has also been described (6-8,46-48).
- Rare renal involvement has also been described, but semeiology is still confused between interstitial nephritis or glomerulopathy (7,8,46-48).

Laboratory tests can guide the diagnosis, with hematological abnormalities as previously described, or an increase in CRP levels being more important in VEXAS syndrome than in RP patients (6-8,46-48). Confirmation of the diagnosis is based on *UBA1* mutation identification in peripheral blood (3,46).

VEXAS syndrome has a worse prognosis compared to RP, with a mortality rate of up to 40% at 5 years of diagnosis, mainly depending on *UBA1* variants, compared to 2–3% at 5 years of diagnosis in RP patients (6,7,18,46,48).

GPA

Tracheal involvement is one of the systemic manifestations of GPA. It represents 1–5% of localized forms (51,52), and may be the initiating event in 20% of cases (53,54). Bronchial involvement may be associated or rarely isolated (53). The age of diagnosis is younger than in RP patients, with a median age of 35 to 40 years (31,53). In cases of localized tracheal disease, the associated manifestations are dominated by ear, nose, throat (ENT) symptoms such as rhinitis and nasal crusts, with a prevalence of around 80%. Pulmonary involvement and arthritis can also be observed in 40% to 60% of cases, and finally skin manifestations and renal involvement in 25% of cases (53). ANCA are positive in 50–60% of cases, with a specificity of 90% for anti-PR3. Rare anti-myeloperoxidase (MPO) specificities have been described, in 10–25% of cases (31,53,54). Chest CT scan shows sub-glottic circumferential stenosis, with cartilaginous erosions and rare calcifications. In addition, lung parenchymal abnormalities such as nodules, ground glass opacities (corresponding to intra-alveolar hemorrhage or non-specific interstitial pneumonia), or the usual interstitial pneumonia pattern may be observed, suggesting another diagnosis than RP, which does not

have parenchymal abnormalities (29,31,32,54). Flexible bronchoscopy confirms the presence of a short subglottic stenosis (median distance to the vocal cords about 1 cm, with a length of about 1.5 cm) (29,31,35), sometimes with inflammatory ulcers. The previously described clinical manifestations and ANCA positivity are key in differentiating between GPA and RP.

Sarcoidosis

Sarcoidosis can cause bronchial stenosis, with a prevalence of 1%, mainly proximal, involving multiple bronchus on upper and middle lobes (55). CT scan shows irregular thickening of the bronchial wall with narrowing of the lumen (55). Stenoses are confirmed by flexible bronchoscopy, showing mucosal edema and fine whitish granulations or "cobblestone" nodules close to the narrowing (35,55). Histological examination reveals non-necrotizing epithelioid cell-rich granulomas (56). Stenosis is associated with obstructive ventilatory impairment, without reversibility to bronchodilator challenge (55). Such findings lead to corticosteroids therapy (56). Tracheobronchial obstruction may also be caused by lymph node compression or fibrosing mediastinitis (55-57).

Inflammatory bowel diseases (IBDs)

The prevalence of thoracic manifestations of IBDs, notably Crohn's disease or ulcerative colitis (UC) is difficult to assess. Case series have reported up to 50% of symptomatic patients, with variable radiological findings. Airway involvement is seen in 39% of cases, with a median age around 50 years, a female predominance and a previous diagnosis of UC (58,59). Patients usually present with other extra-thoracic and digestive manifestations, such as thrombotic microangiopathy, pyoderma gangrenosum, primary sclerosing cholangitis, episcleritis, or arthritis (58). In terms of airway involvement, bronchiectasis, and bronchiolar disease are the most common manifestations. Rare cases of tracheal disease have been reported. Circumferential thickening of the tracheal wall is seen on CT scan, while endoscopic evaluation may reveal mucosal ulceration, with fibrin deposition on an inflammatory mucosa (29,59).

Mucous membrane pemphigoid

The mucocutaneous pemphigoid group, which includes cicatricial pemphigoid, mucocutaneous epidermolysis bullosa acquisita, linear immunoglobulin A (IgA) dermatosis, and lichen planus pemphigoid is an autoimmune bullous dermatosis with mucosal manifestations. It is a rare disease, with two cases per million population, a mean age at diagnosis of 65 years, and a slight female predominance. The mucosal manifestations are localized in order of frequency, to the mouth, eyes, ENT, genitals, anus, esophagus, and then larynx, while the skin is involved in 35% of cases. The pathophysiology is explained by the production of autoantibodies against the basal membrane, leading to dermo-epidermal sloughing and blistering. Tracheobronchial involvement has recently been described. It appears to affect younger patients, with more severe and multifocal disease. Respiratory symptoms (dyspnea, cough, dysphonia, hemoptysis) are rare but should alert clinicians to the appearance of such involvement. Flexible bronchoscopy findings are variable, with inflammatory mucosa, erosions, and ulcerations, sometimes associated with subsequent stenosis. The diagnosis is confirmed by dedicated mucosal or cutaneous histological examination with basal membrane C3 and immunoglobulin G (IgG) deposits on direct immunofluorescence (60-64).

Tracheobronchial amyloidosis

Tracheobronchial amyloidosis is a rare disease, accounting for 1.1% of all amyloidosis involvements (65), but reaching a prevalence of 10% in multi-organ amyloidosis (66). Focusing on localized thoracic amyloidosis (including lung parenchyma), tracheobronchial amyloidosis represents 50% of cases, sometimes combined with parenchyma nodular disease or diffuse interstitial disease (65,67). The majority of tracheobronchial amyloidosis is AL type, but the association with multiple myeloma is rare. Diagnosis occurs at around 50–60 years of age, with a balanced sex-ratio. Respiratory symptoms are non-specific except hemoptysis (65,68). CT scans show irregular circumferential thickening of the tracheal wall, associated with calcifications, and sometimes lung parenchymal lesions including isolated nodules, cysts, or association between micronodules, septal thickening, and reticulations. Lung involvement or mediastino-hilar lymph node findings must lead to investigation for systemic amyloidosis (66,68). Flexible bronchoscopy is a key investigation, with diffuse grey or whitish "cobblestone" submucosal deposits, spontaneous contact bleeding leading to tracheal lumen narrowing (65,68). Biopsy should be performed to increase the diagnostic yield, but with caution,

due to easily bleeding lesions (68), consequences of specific vascular involvement or coagulation factor IX and X deficiency mainly seen in systemic amyloidosis.

IgG4-related disease

IgG4-related disease is a systemic chronic fibro-inflammatory disease characterized by a non-clonal lymphoplasmacytic infiltrate, secreting IgG4 associated with storiform fibrosis and obliterating phlebitis. The age at diagnosis is 60 years old, with a balanced sex ratio. Thoracic involvement is pleomorphic, involving all compartments from the airways to the pleura, including the mediastinum, and occurs in 35% of cases overall, but is isolated in 20% of cases (65,69). Chest imaging may reveal lung parenchymal nodules, ground glass opacities, peribronchovascular thickening, associated with interstitial lung disease, mediastino-hilar lymph nodes or pleural thickening. Mediastinal involvement (3–6% of cases) may be fibrosing, leading to compression of vascular structure, lower part of the trachea and main bronchi (57,69). One of the characteristic aspects on CT scan is thoracic paravertebral band-like soft tissue thickening, right-localized, with two-vertebral height (69,70). An elevated plasma or serum IgG4 level >135 mg/dL is present in more than 50% of cases (65,69,70). Other organ involvement such as lachrymal and salivary glands, pancreas, biliary tree or kidney and biological findings like CRP elevation, hypergammaglobulinemia or hypereosinophilia can guide the diagnosis (70). 18-FDG PET scan can be useful to assess organ involvement, with particular sensitivity for arteries, lymph nodes or salivary glands. It also can be used to target an active disease site before biopsy, to monitor therapeutic response or to detect disease relapse (69). Salivary gland biopsy may be useful as a first-line test before moving to more invasive procedures such as endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) or CT-guided transthoracic needle biopsy (69,70).

Anthracofibrosis

Anthracofibrosis is an association between endobronchial anthracosis deposits and peribronchial fibrosis resulting in stenosis. Anthracosis deposits are a consequence of inhalation of particles such as tobacco smoke, biomass smoke (from home heating or cooking), or occupational exposures associated with coal mining or other carbon particles (e.g., silica) from rock drilling (71,72). No element can predict the development of fibrosis although coal exposure appears to be one of the key elements (72). The topography of the lesions is mainly in the upper and middle lobes, with multiple involvement in 50% of cases. CT scan may show bronchial wall thickening, stenosis and segmental atelectasis secondary to bronchial obstruction. Flexible bronchoscopy is necessary to visualize and map the lesions to confirm the diagnosis (29,72).

Tracheobronchopathia osteochondroplastica

Tracheobronchopathia osteochondroplastica is a rare disease, of unknown origin with a prevalence between 0.01% and 0.8% based on overall flexible bronchoscopy findings, according to a Chinese cohort study (73). It occurs around 50 years of age, mostly in male patients, with active or former smoking status or occupational exposure to particles. It is characterized by submucosal osteo-cartilaginous nodules in continuity with the tracheobronchial cartilage, which explains a strict localization on the antero-lateral tracheal wall and complete sparing of the posterior wall. CT scan and bronchoscopy findings show a pearly appearance of the tracheal wall, with antero-lateral calcified nodules, including the main bronchus, leading to stenosis (29,73,74).

Idiopathic subglottic stenosis

Idiopathic subglottic stenosis is a predominantly female disease, diagnosed between 30 and 60 years of age, with a prevalence of one case per 400,000 population (75). The pathophysiology remains unclear but the female predominance suggests that an underlying hormonal mechanism may be at the origin of the disease. A recent histologic study on surgical resection specimens (76) showed an overexpression of progesterone and estrogen receptors on fibroblasts of idiopathic subglottic stenosis compared to post-traumatic stenosis. Symptoms are not specific and are indicative of the disease when the stenosis exceeds 50% of tracheal caliber. CT scan and flexible bronchoscopy allow a complete evaluation of stenosis and malacia, before deciding on treatment (75).

The remaining differential diagnoses of tracheobronchial stenosis are detailed in *Table 2*.

Evolution and prognosis

RP evolves through inflammatory flares and remission phases, with the risk of developing severe manifestations

Table 2 Alternative diagnoses for relapsing polychondritis

Inflammatory diseases	Infectious diseases	Sequelae	Others
VEXAS syndrome	Tracheobronchial tuberculosis (29,77)	Traumatic lesions	Subglottic idiopathic stenosis
Granulomatosis with polyangiitis	Fungal infections (29,57)	Burning	Tracheal tumors (squamous cell carcinoma, adenoid cystic carcinoma, metastases) (78)
Sarcoidosis	Rhinoscleroma (29,79)	Post-intubation tracheal stenosis (80)	Mucopolysaccharidosis (81)
Inflammatory bowel diseases	Recurrent respiratory papillomatis (82)		
Mucous membrane pemphigoid			
Tracheo-bronchial amyloidosis			
IgG4-related diseases			
Anthraco-fibrosis			
Tracheobronchopathia osteochondroplastica			

VEXAS, Vacuoles, E1-enzyme, X-linked, Autoinflammatory, Somatic; IgG4, immunoglobulin G4.

such as respiratory manifestations. Myelodysplastic syndrome was considered a poor prognosis marker prior to the discovery of VEXAS syndrome, explaining the specific phenotype described in previous studies (9,18,26). Besides myelodysplastic syndrome, respiratory and cardiac involvement remain the most severe disease manifestations that affect the prognosis. The study conducted by Dion *et al.* (18) found an overall survival probability of 94% and 83% at 5 years and 10 years, respectively, from the first symptoms but the respiratory manifestation cluster shows a decrease in survival later, after 20–30 years of follow-up. Recently, Shimizu *et al.* (83) compared cohorts of RP patients in 2009 and 2019. Mortality decreased significantly over the decade, from 9% in 2009 to 2% in 2019, which could be related to a decrease in the prevalence of airway involvement (49% in 2009, 37% in 2019). The improvement in survival can be explained by the expansion of therapeutic options, with immunosuppressive therapies and biotherapies, that allow rapid and prolonged control of the disease, as soon as the diagnosis is made with less side effects due to steroid treatments. Activity [Relapsing Polychondritis Disease Activity Index (84)] and damages [Relapsing Polychondritis Damage Index (85)] scores have been developed to facilitate the follow-up of RP patients and the assessment of treatment response. However, many items in these scores overlap with the manifestations of VEXAS syndrome, questioning their actual use in routine practice.

Treatment

Medical management

Respiratory involvement in RP is considered as one of the most severe manifestations, which can lead to life-threatening outcomes and functional sequelae if treated late. Most recent guidelines are not based on strong evidence due to the low prevalence of the disease but also to the majority of retrospective studies available.

High-dose corticosteroid therapy should be initiated as first-line treatment with 1 mg/kg prednisone, preceded by methylprednisolone pulses (250–1,000 mg/day for 1 to 3 days) in case of acute respiratory failure (17). Concomitant adjunction of immunosuppressive therapy is usually given with cyclophosphamide (0.5–0.7 g/m^2), following the same pattern as in necrotizing vasculitis. Rituximab is not recommended because of the low response rate (86-88). Maintenance treatment after induction phase is also based on immunosuppressive therapy, with methotrexate, azathioprine and, more recently, mycophenolate mofetil (MMF) often used (17,88). The emergence of biotherapies has opened new perspectives in treatment, especially for cortico-resistant/dependent form or refractory to classical immunosuppressive therapies. Their use could be alone or in combination with

another immunosuppressive agent such as MMF. A recent review published in 2018 (88) seems to indicate that for respiratory involvement, the use of tumor necrosis factor-α (TNF-α) inhibitors (infliximab, adalimumab, etanercept), tocilizumab or abatacept could allow a significant reduction in activity for 6 months, with an impact on overall survival. These data have been confirmed by Petitdemange *et al.* (89) with a response rate around 64% for TNF-α inhibitors (and perhaps better for tocilizumab and abatacept, but with less solid results because of their rare use).

Surgical management

Management of the sequelae of tracheobronchial stenosis is the main goal of local treatment. Advances in rigid bronchoscopy have multiplied the therapeutic options. A complete laryngeal and tracheobronchial evaluation must be performed before any treatment decision.

The choice of treatment depends on the focal or diffuse nature of the residual stenosis. In case of focal stenosis, balloon dilatation may be preferred. In case of recurrence of focal stenosis, or the presence of diffuse stenosis, or an association with malacia, tracheal prosthesis, straight or "Y" shaped, could be proposed, depending on the topography (90,91). Nevertheless, specific complications of tracheal prostheses cannot be ignored, such as prosthesis migration, obstruction with granulomatous tissue, or infectious complications due to endotracheal secretion stagnation (20,90-93). In extreme cases, perforation or complete rupture of tracheal wall (due to loss of stiffness) have been reported (93). Veno-venous extracorporeal membrane oxygenation may be required during rigid bronchoscopy in the most severe cases (93,94). Long-term benefit seems encouraging with a prolonged improvement, in subjective and objective assessment of dyspnea, FEV_1 or 6-min walk test (92).

Tracheotomy or Montgomery tube should be considered in case of initial acute respiratory failure with recourse to orotracheal intubation or subglottic stenosis (95). In the study by Catano *et al.* (31), balloon dilatation was used in 52% of RP patients, prosthesis in 38% and tracheotomy in 14% of patients. In the case of severe isolated TBM, external airway splinting could be proposed, consisting of posterior tracheal wall fixation on non-resorbable synthetic splints (e.g., Gore-Tex®) (90,95). Although tracheobronchial reconstruction with stented aortic matrices (96,97), has made steady progress in recent years, it has not been evaluated in RP patients.

Supportive care

Finally, non-invasive positive pressure ventilation may be used in addition to systemic and surgical treatment to manage respiratory involvement. No clinical evaluation has been done, but positive pressure ventilation could benefit patients with malacia, even more if chronic hypercapnia has been demonstrated (20,98).

It is important not to neglect general infection prevention measures, such as up-to-date vaccinations [pneumococcal, influenza and severe acute respiratory syndrome coronavirus (SARS-CoV)] and infections related to immunosuppressive therapies (such as *Pseudomonas aeruginosa* colonization). Respiratory kinesitherapy and maintaining daily physical activity is also strongly encouraged in the context of these chronic diseases characterized by reactive psychological disorders.

A multidisciplinary approach, with appropriate support, can help to Improve the overall quality of life of RP patients.

Conclusions

RP is a rare auto-immune disease. Pathophysiology understanding has progressed but there are still gray areas, which limits improvement in therapeutical management. Differentiating RP from its differential diagnoses can be challenging, because of the absence of specific markers leading to RP diagnosis. Although therapeutic strategies are improving, the evidence base is poor and includes retrospective studies. A multidisciplinary approach including at least pulmonologists, rheumatologists, and surgeons is essential to ascertain an accurate diagnosis before deciding the best management between medical treatment, surgical treatment, and supportive care.

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