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# Respiratory subtype of Relapsing Polychondritis (RP) frequently presents as difficult asthma: a descriptive study of respiratory involvement in RP with 13 patients from a single UK centre

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# Respiratory subtype of Relapsing Polychondritis (RP) frequently presents as difficult asthma: a descriptive study of respiratory involvement in RP with 13 patients from a single UK centre

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Introduction

Relapsing polychondritis (RP) was described by Pearson *et al.* in 1960 [1] as a rare multisystem disease characterised by recurrent episodes of inflammation and subsequent degeneration of cartilage and connective tissue throughout the body. RP most commonly affects the respiratory tract, nose, ears and joints [1-4]. McAdam et al described 6 classical features of relapsing polychondritis, namely bilateral auricular chondritis, nasal chondritis, respiratory tract chondritis, seronegative inflammatory arthritis, ocular inflammation and audiovestibular damage [3]. McAdam's diagnostic criteria needed 3 out of 6 of the aforementioned clinical features for confirmation of diagnosis. Additional diagnostic criteria were developed by Damiani and Michet [2,5]. Both these groups have developed A and B criteria with Damiani criteria keeping all 6 primary clinical features as A criteria and additionally including histological confirmation as a B criterion and response to corticosteroids or Dapsone as a C criterion. 3 A criteria or 1 A and B, or 2 A with C are needed for diagnosis. Michet criteria include nasal, auricular and laryngotracheal cartilage inflammation as A criteria with the rest as B criteria, and 2 A or 1 A and 2 B criteria are needed for diagnosis.

Respiratory tract chondritis is thought to affect up to 50% of patients during the course of their disease [2,3,6] and remains the primary cause of mortality in RP [3].

Patients often experience airway symptoms such as dyspnoea, cough, chest discomfort, hoarseness, stridor [7] and even complete aphonia in some cases [4] due to inflammatory oedema of the larynx, trachea and bronchi. The underlying chronic cartilage inflammation in the tracheobronchial tree leads to tracheomalacia [8]; or tracheobronchomalacia (TBM) when this extends to one or both primary bronchi. Both phenomena can result in exaggerated airway narrowing during expiration and widening during inspiration [9-11], demonstrable in pulmonary function tests and computerised tomography (CT) scans of the chest. Unless early diagnosis and appropriate medical or surgical interventions are in place, the progressive cartilage destruction in the airways due to recurrent cartilaginous inflammation may ultimately result in life-threatening airway obstruction and dynamic airway collapse [12]. RP can involve the eyes, neurological system, heart and blood vessels and there is an association with HLA DR4 allele [13]. Respiratory problems can be particularly difficult to treat, and very little data exist to guide us with regards to optimal screening and assessment modalities for tracheomalacia or tracheobronchomalacia (TBM). Management of these patients continues to remain a challenge and the diagnostic delay can often result in significant damage, which necessitates long term mechanical support through stents or pneumatic support through continuous positive airway pressure (CPAP) [14, 15]. Despite best treatment, patients are often left with substantial life changing disability.

We describe a series of patients with RP all of whom had respiratory involvement. Most had presented to respiratory clinics or had been admitted to hospital with severe shortness of breath. All patients attended University Hospital Coventry and Warwickshire NHS Trust which is based in Coventry in West Midlands in UK, and is a secondary care provider for a population of around 500,000. This case series

describes the respiratory manifestations and aims to increase the awareness of RP in patients presenting with respiratory symptoms, particularly in individuals who appear to have oral corticosteroid dependent asthma.

## Materials and Methods

We reviewed the medical records of thirteen patients with relapsing polychondritis; all of whom had respiratory involvement. Patients were identified through the respiratory and rheumatology clinics at a single centre between 2013 and 2018 and patients were often seen together in a combined clinic. The diagnosis of RP was made clinically using the clinical diagnostic criteria [2,3,5]. Disease activity was assessed using Relapsing Polychondritis Disease Activity Index (RPDAI) which includes scoring on each organ that can be affected by RP as well as C-Reactive Protein (CRP) [16]. There are 28 different items with scores ranging from 1 to 24. Respiratory chondritis scores 14 without and 24 with respiratory failure and is the highest scoring item in RPDAI. Patients' demographic characteristics, clinical features, diagnostic test results and therapeutic interventions were noted. The database was set up in 2016 and details of patients were updated regularly. Ethical approval was obtained from Research and Development office within our Trust; approval number – GF 0267. Statistics are predominantly descriptive, and MS Excel programme was used to assimilate the data.

## Results

We identified 13 patients with relapsing polychondritis, all of these patients had respiratory involvement. We did not need to exclude any patients due to lack of respiratory involvement. Most of these patients (10 out of 13) were identified in 'difficult asthma' clinics with 2 being diagnosed following an inpatient admission

with acute shortness of breath and 1 diagnosed from a rheumatology clinic. The demographics are described in table 1. Male to female ratio was 1:3 with 3 males and 9 females. The median age of the patients was 65 (range 28 to 76) years. Most patients had other co-morbidities with diabetes being the commonest in 5 patients and hypertension seen in 4 patients. Other auto-immune disorders were diagnosed in 7 of these patients. Psoriasis and hypothyroidism were noted in 2 patients each. One patient had overlap with Behcet's disease (mouth and genital ulcers with inflamed cartilage - MAGIC syndrome), another had ankylosing spondylitis. [Table 1, figures 1-5]

We found that 8 patients (62%) had bilateral auricular chondritis and nasal chondritis, whilst 10 patients (77%) had seronegative polyarthropathy with 2 patients (15%) having ocular inflammation and 5 patients (38%) had audiovestibular damage [Figure 6]. All patients had good response to oral Prednisolone and fulfilled criteria for diagnosis of RP (Damiani). Most patients (10 out of 13) were picked up from the difficult asthma clinics. All patients had wheeze and persistent cough and hence a diagnostic label of asthma, but it was the presence of monophonic wheeze, presence of inspiratory stridor in 2 patients, barking nature of cough in 2 patients and lack of classical reversibility and response to steroids that led to the suspicion of underlying more complex airway issues and possible expiratory airway collapsibility. Patients with good response to oral prednisolone demonstrated return of their signs and worsening of other symptoms with dosage reduction below 20mg daily leading to further suspicion about the underlying diagnosis. Dynamic CT (inspiratory and expiratory) images were obtained along with flexible bronchoscopy. Bronchoscopy was performed in 4 patients. Mild sedation using intravenous midazolam and local analgesia with 2% lignocaine was instilled. Patients were able to co-operate and

forcibly exhale. Views were taken from the proximal and distal trachea, right and left main bronchi and segmental bronchi during inspiration and forced expiration. 50% or more reduction in the cross sectional area of the airway during the dynamic bronchoscopy and CT were used as the diagnostic cut off for the diagnosis of TBM. Two of our patients demonstrated smooth thickening of the airway wall and luminal narrowing of the distal trachea and main bronchi and one demonstrated symmetrical stenosis of the large airways, whereas the remaining had >50% reduction of the airway luminal area with crescentic appearance of the airway due to flattening of airway walls during expiration.

Although other features such as bilateral auricular chondritis or nasal chondritis had been present in 8 patients, they had rarely complained about these symptoms to their clinicians as other symptoms, particularly severe breathlessness were their primary concern. Eliciting these symptoms required direct questioning. One patient had classical nasal bridge collapse which they previously told several clinicians (via interpreters) was the result of childhood trauma, although on detailed questioning there was in fact no history of trauma. Seronegative inflammatory arthritis was a presenting feature in 2 patients (predominantly large joints), and had been noted in 10 patients.

Laboratory testing showed anaemia in seven patients and raised inflammatory markers including CRP or erythrocyte sedimentation rate in 6 patients. As a number of patients were on long term corticosteroids for ‘difficult asthma’, it was difficult to get accurate trends of inflammatory markers prior to treatment. None of the patients had evidence of eosinophilia at any point. Rheumatoid factor, anti-cyclic citrullinated antibodies, antinuclear antibodies, anti-double stranded DNA antibodies and

neutrophil cytoplasmic antibodies were all negative, although one patient had antiphospholipid antibodies. Chest radiographs were normal in 11 patients, 2 had shown features of pleural effusions and these were confirmed on CT scans later. None of the patients had any other features to suggest ANCA associated vasculitis.

In 12 out of 13 patients, flow-volume loops demonstrated flattening of either inspiratory or expiratory curves, or both. Flattening of the expiratory limbs in flow-volume loops was prevalent in most, suggesting large airway collapsibility during expiration. [Figures 7,8]. There was no evidence of reversibility with beta 2 agonists in 11 patients, whilst 1 patient with small airway disease showed reversibility with likely co-existent asthma.

Treatment: Corticosteroids were used in all patients, and disease modifying anti rheumatic drugs (DMARDs) such as Methotrexate 15 to 25 mg weekly (6 patients), Azathioprine 1-2.5 mg/kg/d (2 patients) and Mycophenolate mofetil 1-2 grams daily (2 patients) were successful in reducing disease activity (Table 2). One patient developed hypogammaglobulinemia which was thought to be secondary to immunosuppression and was treated with replacement IV Immunoglobulin (IVIG) as she was having recurrent infections (predominantly chest infections). Prednisolone was usually started at 1 mg/kg/day orally in patients with respiratory failure and 0.5 mg/kg/day in patients without respiratory failure with gradual tapering every 2-4 weeks initially. Dose reduction was achieved in all cases but 4 patients struggled to wean Prednisolone dose down below 10 mg. In 2 patients, we only used <20 mg Prednisolone, higher doses were not needed. IV Cyclophosphamide was used in 4 cases, but was thought to be unsuccessful in 3 of these on the basis of lack of symptomatic benefit. Cyclophosphamide was only used after failure of conventional

DMARDs and was used primarily for TBM. Patients with severe airway collapse >90% of airway area with disabling symptoms were considered for large airway stenting alongside medical therapies. Successful stenting was performed in 3 patients; in one other patient the stent had to be removed as it was exacerbating infections and another due to continuous coughing. Six patients with moderately severe airway compromise (75%-90%) and significant breathlessness on exertion were receiving intermittent ambulatory CPAP, 2 discontinued due to lack of tolerance. NIV was used with maximum inspiratory pressure (IPAP) of 24 and expiratory pressures (EPAP) of 10cm H2O whilst CPAP pressures were between 10 and 13 cm H2O. Overnight sleep studies excluded significant sleep disordered breathing in these patients. Within this cohort, 7 patients have had recurrent admissions for 'flare of asthma' prior to the diagnosis with 3 of these not requiring further inpatient admissions once immunosuppression was instituted. [Table 2 here]

Biological DMARDs were tried in 4 patients with anti-TNF therapies being successful in 1 and unsuccessful in 3 patients (two due to inefficacy, another due to allergic reactions to both Etanercept and Adalimumab). Of the 3 patients who failed anti-TNF therapy, 2 were tried on other agents, with one patient responding well to Abatacept whilst another patient was started on Secukinumab for ankylosing spondylitis and had good response for spinal disease, but no change in RPDAI. Eight patients are still under regular follow-up (FU) and have been under FU for more than 5 years since diagnosis, one has been lost to follow up and 4 patients have died. In two of these cases, primary cause of death was chest infection, in the other two, it was unrelated causes, one from complications of myelodysplasia.

Discussion

A number of studies have described small numbers of patients with respiratory features and some have shown airway involvement to be the leading cause of death in RP [1,3,6,15,17]. TBM has been reported in literature in up to 50% of patients with RP. Our series saw TBM as the commonest presentation of RP, although it is quite likely that a number of patients with less serious problems might not have been appropriately diagnosed given the rarity of this condition. A French series reported 142 patients with RP who formed three distinct patterns – haematological, respiratory and 'mild' phenotypes [18]. Within the respiratory phenotype which formed 22.5% of their series, auricular involvement was less common, something we have seen as well. Similar to our series, they found that these patients received more intensive treatment, were prone to infections, and were frequently admitted to the ICU. Our series provides more detail about the respiratory sub-type of RP with specific focus on presentation and management. We did not need to exclude any patients with RP due to lack of respiratory involvement. Given its rarity, it is likely that there are other patients with less serious manifestations that have not reached rheumatology or respiratory clinics and have not been given the diagnosis yet. The majority of these patients were originally thought to have oral corticosteroid dependant asthma, and once TBM was suspected or diagnosed, physicians started searching for and finding other features of RP. Patients had not complained about the other manifestations such as chronic auricular chondritis or nasal chondritis as the symptom of breathlessness predominated.

Physical treatments of TBM with stenting and CPAP are well recognised [6-9,17,19], however, there is very little information in literature about pharmacological treatment of TBM through immunosuppression. This is important as TBM can be the only manifestation of RP [20]. In our series, most patients had responded well to

pharmacological therapy, although some needed stent insertion to support the bronchial tree. Stenting also had mixed results and it is unclear as to whether there are specific features that would indicate use of stents in preference to drug therapy. Stenting is most likely to be useful after optimal control of active disease (to stabilise damaged section of the tracheobronchial tree once medical treatment has controlled active inflammation). Complications following stenting are relatively common with one study showing 49/58 patients having a complication commonest of which are stent migration, infection and partial obstruction [21]. Aggressive early management can be difficult to achieve when the patient has been symptomatic for so many years and airway damage has accumulated before the diagnosis is made. Intermittent ambulatory continuous positive airway pressure has been described previously with variable results [22-24]; our group has previously described successful use of CPAP in TBM. Such long term use of portable NIV combined with overnight CPAP has not been reported to our knowledge. We have seen good symptomatic improvement and long term stability with CPAP used in this fashion together with medical treatments.

Clinical and symptomatic evaluation, dynamic (inspiratory and expiratory) CT scans and flexible bronchoscopy were critical in establishing the diagnosis of TBM which is consistent with reports from literature [8-10]. Other features of RP were identified clinically although recent reports suggest Positron Emission Tomography (PET CT) might be an additional resource for defining the severity and extent of disease [25]. PET CT has other potential advantages as it can a) differentiate damage from active inflammation, and b) provide information about large vessel vasculitis and other organs that are not easy to assess clinically. We have not used this modality in our patients, and this can be evaluated in future studies.

The prevalence of relapsing polychondritis in Coventry appears to be at least 26 per million on the basis that we have 13 patients locally within our catchment area of around 500,000. If these prevalence data were true for the rest of UK as well, one would expect roughly 1500 additional patients! It is difficult to estimate the true prevalence for a rare condition, and the literature has offered very wide estimates (between 3.5 per million to 23 per million). Hungarian data suggest similar numbers (23 per million) to the numbers estimated here based on 233 cases from a population of 10 million [26]. Incidence in that study was around 3.5 per million patient years. Incidence of RP in a UK study was 0.71 per million patient years and prevalence was estimated at 9 per million [27]. In Rochester (Minnesota), the incidence of RP was estimated at 3.5 per million [4]. Given the rarity of the condition and difficulty in diagnosis, it is not a surprise that there is such wide variation. This study provides new impetus to looking for specific features of RP which may have a major influence on incidence and prevalence estimates.

There are no controlled clinical trials in this area (as is the case for a number of rare diseases), and it may be possible to set up trials in this area if the prevalence is significantly higher than was previously thought. There is a need to increase awareness of this disease amongst all the specialties that are likely to come across these patients. Optimal management of these patients continues to remain a challenge. The exact pathogenesis is not clearly understood. Various immune processes that have been described include reduction of immunoregulatory cells, antibodies attacking cartilage tissue elements like type-II, type-IX, and type-XI collagen and matrilin1, changes in cytokine profiles, deposition of immune complexes, and insufficient tissue regeneration [28-34]. This makes it quite challenging when choosing drugs for refractory patients. Within our cohort, we observed some

responses to DMARDs with Methotrexate, Azathioprine and Mycophenolate being successful. In fact, in one patient we were able to completely stop corticosteroids and have not needed to go back to corticosteroids for more than 2 years. Responses to biological agents and intravenous (IV) Cyclophosphamide have been modest in this cohort – this may be due to delay in diagnosis which can sometimes be a number of years. Also, we have not routinely used IV Cyclophosphamide for induction, but tended to use it when other agents have failed. Disease activity and damage scores have been developed [16, 35] and are of use in documenting response to treatment; and also serve as a reminder of the various manifestations of this rare illness. Multiple biological agents have been tried, but due to the rarity of the condition, there are no randomised controlled trials in this field. A French national study looking at biologics in RP did not demonstrate any clear trends that would help guide use of biological agents [36].

## Limitations

This is a retrospective review and studies of this sort are subject to systemic biases which are applicable to this study. Prevalence data are affected by referral pathways and other biases which would be applicable to this study. Also patients presenting with respiratory symptoms were selected so this is a referral bias. There is also likely to be left censorship bias as some patients who may have died or were lost to follow-up would not have been included.

## Conclusions

Relapsing Polychondritis, although rare, with prevalent respiratory involvement may be the cause of significant morbidity and mortality. Patients may be misdiagnosed with other respiratory diseases in particular being labelled as '**difficult asthma'**.

There is an important need to recognise and diagnose relapsing polychondritis, as there are specific treatment options including DMARDs that these patients are likely to benefit from. Awareness of this condition is crucial to enable early diagnosis and clinical interventions to reduce the risk of life threatening airway collapse.

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**Table 1: Clinical features of patients with Relapsing polychondritis.**

| Patient | Sex | Age | Co-morbidities | BAC | NC | RTC | SP | OI | AD | Response to corticosteroids | TBM proven |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | M | 65 | T2DM, hypothyroid, psoriasis | Y | Y | Y | N | Y | N | Y | Y |
| 2 | F | 70 | Memory loss | N | Y | Y | Y | N | N | Y | Y |
| 3 | F | 50 | T2DM | Y | Y | Y | Y | N | Y | Y | Y |
| 4 | F | 53 | Hypothyroid, fibromyalgia, HTN, Behcet's, obesity | Y | Y | Y | Y | N | N | Y | Y |
| 5 | F | 76 | Previous TB, immunodeficiency, HTN, T2DM, OA | N | N | Y | Y | N | Y | Y | Y |
| 6 | F | 74 | HTN, Angina, AF, T2DM, anti-phospholipid Abs | Y | Y | Y | Y | N | N | Y | Y |
| 7 | F | 76 | Emphysema | N | N | Y | N | N | N | Y | Y |
| 8 | F | 70 | HTN, obesity, acoustic neuroma, hyperlipidaemia | N | N | Y | Y | N | N | Y | Y |
| 9 | F | 78 | T2DM, obesity, MI, AF, CKD, dementia, asthma | Y | Y | Y | Y | N | Y | Y | Y |
| 10 | M | 31 | Hypoadrenalism, bronchiectasis | Y | Y | Y | Y | N | N | Y | Y |
| 11 | F | 52 | obesity, COPD, anklyosing spodylitis, psoriasis | Y | Y | N | Y | N | Y | Y | N |
| 12 | M | 79 | Myelodysplasia, Follicular lymphoma, Osteoporosis. | Y | N | Y | N | Y | N | Y | N |
| 13 | M | 78 | T2DM, IHD, CKD, myositis | N | N | Y | Y | N | Y | Y | Y |

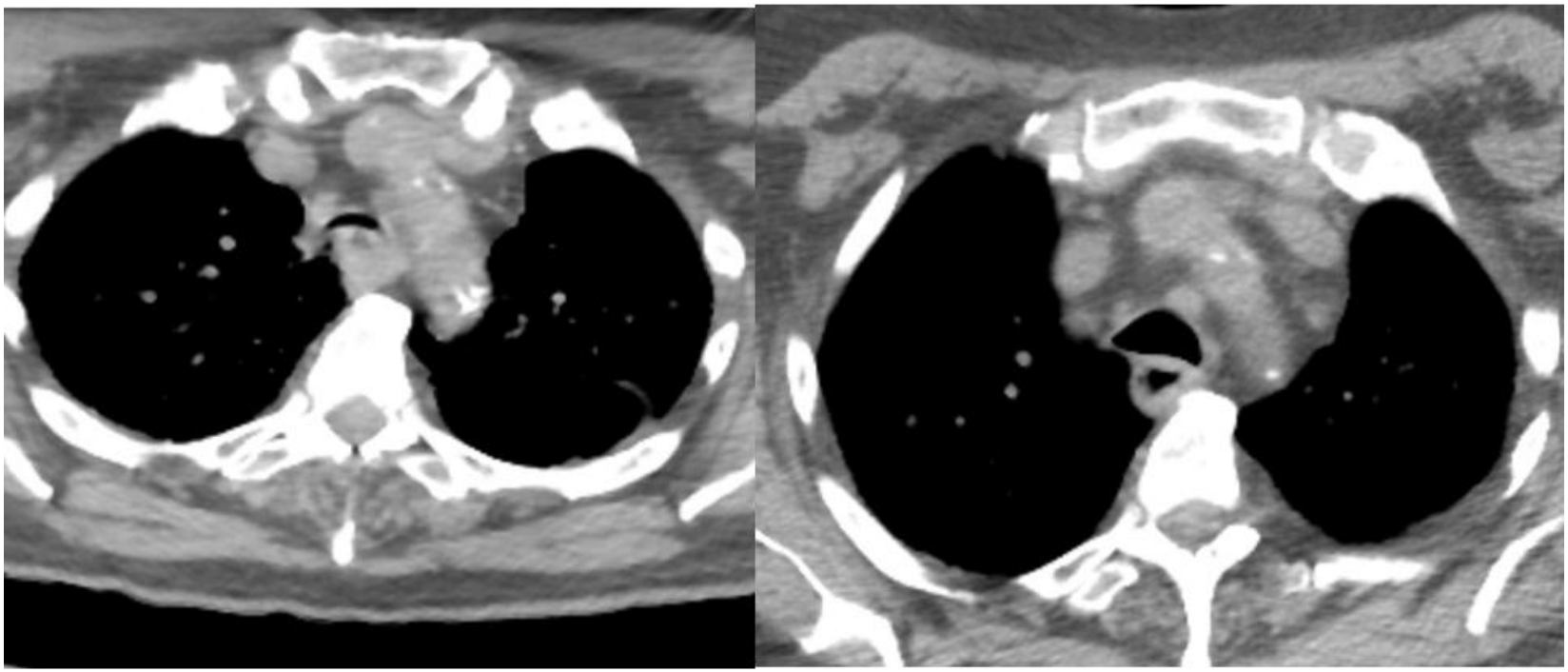
BAC: Bilateral auricular chondritis, NC: Nasal chondritis, RTC: Respiratory tract chondritis, SP: seronegative polyarthritis, OI: Ocular inflammation, AD: Audiovestibular damage. T2DM: Type 2 Diabetes mellitus, HTN: Hypertension, TB: Tuberculosis, OA: Osteoarthritis, AF: Atrial fibrillation, MI : Myocardial infarction, CKD : Chronic kidney disease, COPD: Chronic obstructive pulmonary disease.

**Table 2: Pharmacological and non pharmacological treatment for patients with RP**

| Patient | Sex | Age | CPAP | Stent | IS Drugs | Corticosteroid dose | Previous Drugs | Baseline RPDAI |
|---|---|---|---|---|---|---|---|---|
| 1 | M | 65 | N | N | MTX | - | Pred | 37 |
| 2 | F | 70 | N | N | MMF, Infliximab | Pred 5mg | SSZ | 27 |
| 3 | F | 50 | DNT | N | MTX | - | Pred | 45 |
| 4 | F | 53 | Y | Y | MMF, MTX | Pred 10 mg | AZA, Cyclophosphamide, ADA and ETN | 47 |
| 5 | F | 76 | Y | N | SSZ, HCQ, ABT, IVIG | Pred 7.5 mg | MTX, ETN, leflunomide, AZA | 44 |
| 6 | F | 74 | Y | Y | MTX, AZA | Pred 10 mg | Cyclophosphamide | 43 |
| 7 | F | 76 | Y | N | Cyclophosphamide | Pred 10 mg | MTX | 27 |
| 8 | F | 70 | N | N | AZA | Pred 5 mg | - | 15 |
| 9 | F | 78 | DNT | N | | Pred 5 mg | MTX, AZA, HCQ | 24 |
| 10 | M | 31 | N | N | | HCT 20/10/10 | - | 33 |
| 11 | F | 52 | N | N | Secukinumab | Pred 10 mg | MTX, ETN, HCQ, Cyclophosphamide, ADA | 38 |
| 12 | M | 79 | N | N | | Pred 5 mg | - | 35 |
| 13 | M | 78 | Y | Y | MTX | Pred 5 mg | AZA | 40 |

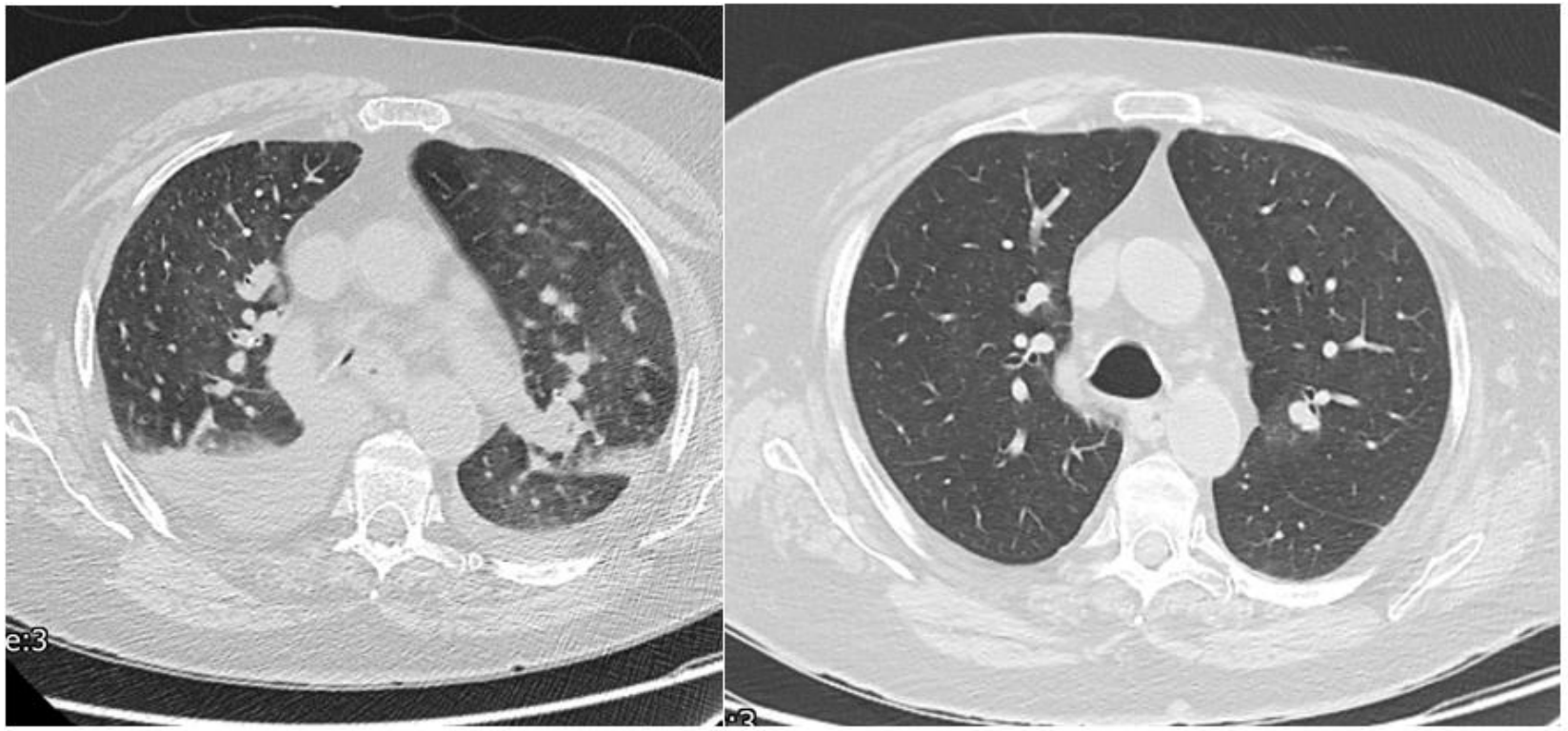
IS: Immunosuppressant drugs, MTX: Methotrexate, MMF: Mycophenolate mofetil, SSZ: Sulfasalazine, HCQ: Hydroxychloroquine, ADA: Adalimumab, AZA: Azathioprine, ABT: Abatacept; IVIG: Intravenous immunoglobulin, ETN: Etanercept, Pred: Prednisolone, HCT: Hydrocortisone, RPDAI: Relapsing Polychondritis Activity Index.

FIGURES



A B

Figure 1:
A: Admission CT scan showing near complete collapse of trachea in a patient that was subsequently diagnosed with RP.
B: Repeat CT after IV corticosteroids with inspiratory and expiratory films showing significant improvement of tracheal narrowing (expiratory phase CT).



A B

Figure 2:
A: Another patient with admission CT chest showing near complete collapse of trachea and pleural effusions
B: Repeat CT after treatment with high dose corticosteroids with improvement in trachea and resolution of pleural effusions.

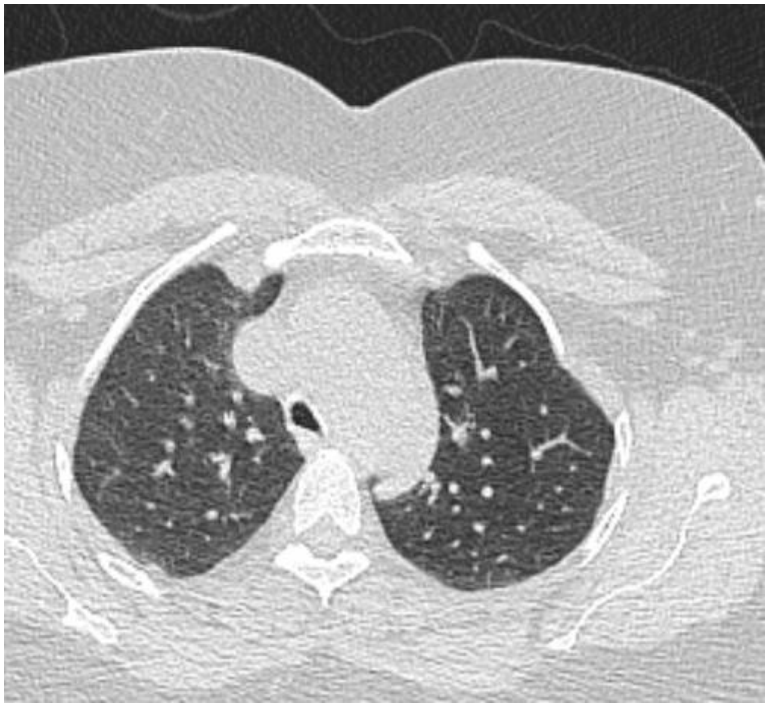
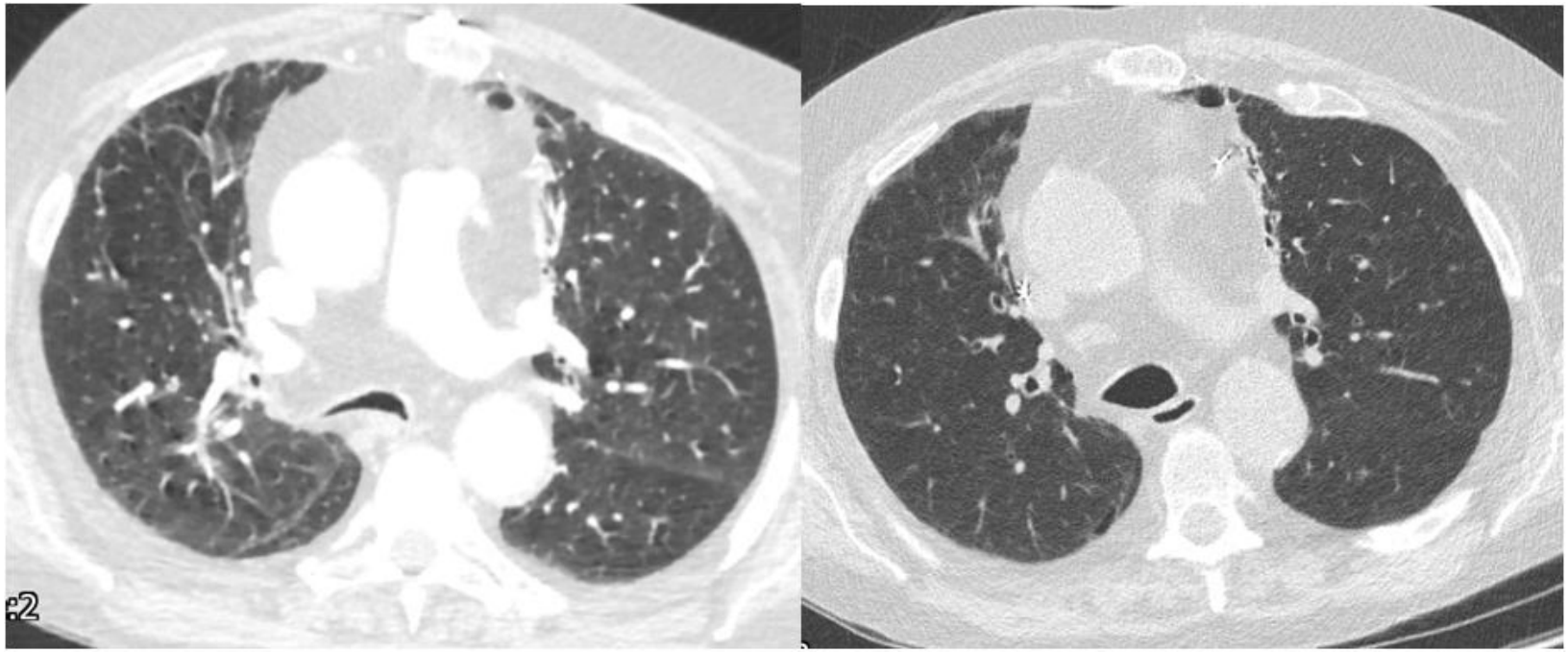


Figure 3: Another patient with collapse of trachea.



A B

Figure 4
A: Another patient with presentation CT showing significant narrowing of trachea
B: Post treatment imaging showing improvement in dimensions of trachea.

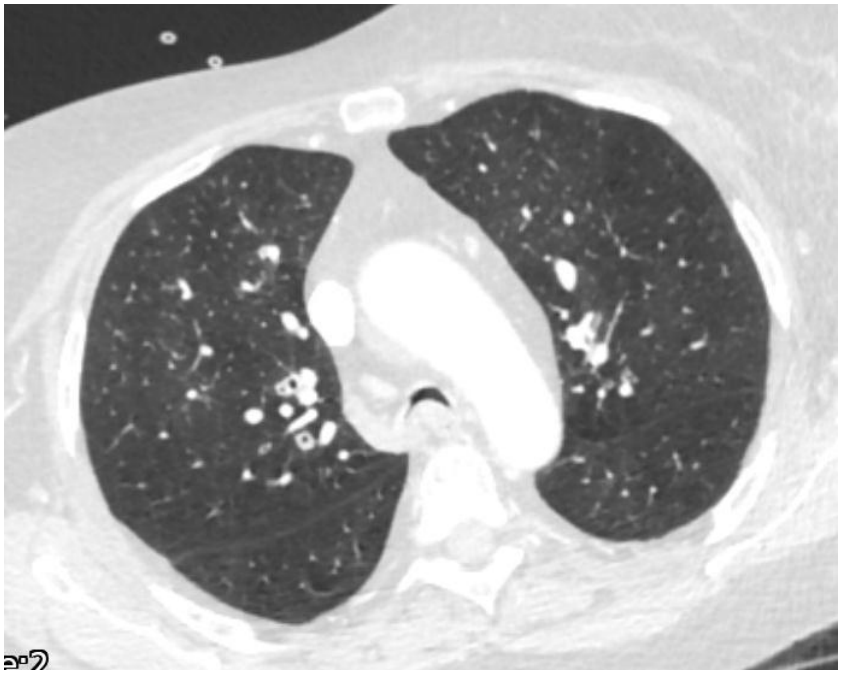


Figure 5: Pre-treatment tracheal collapse in another patient

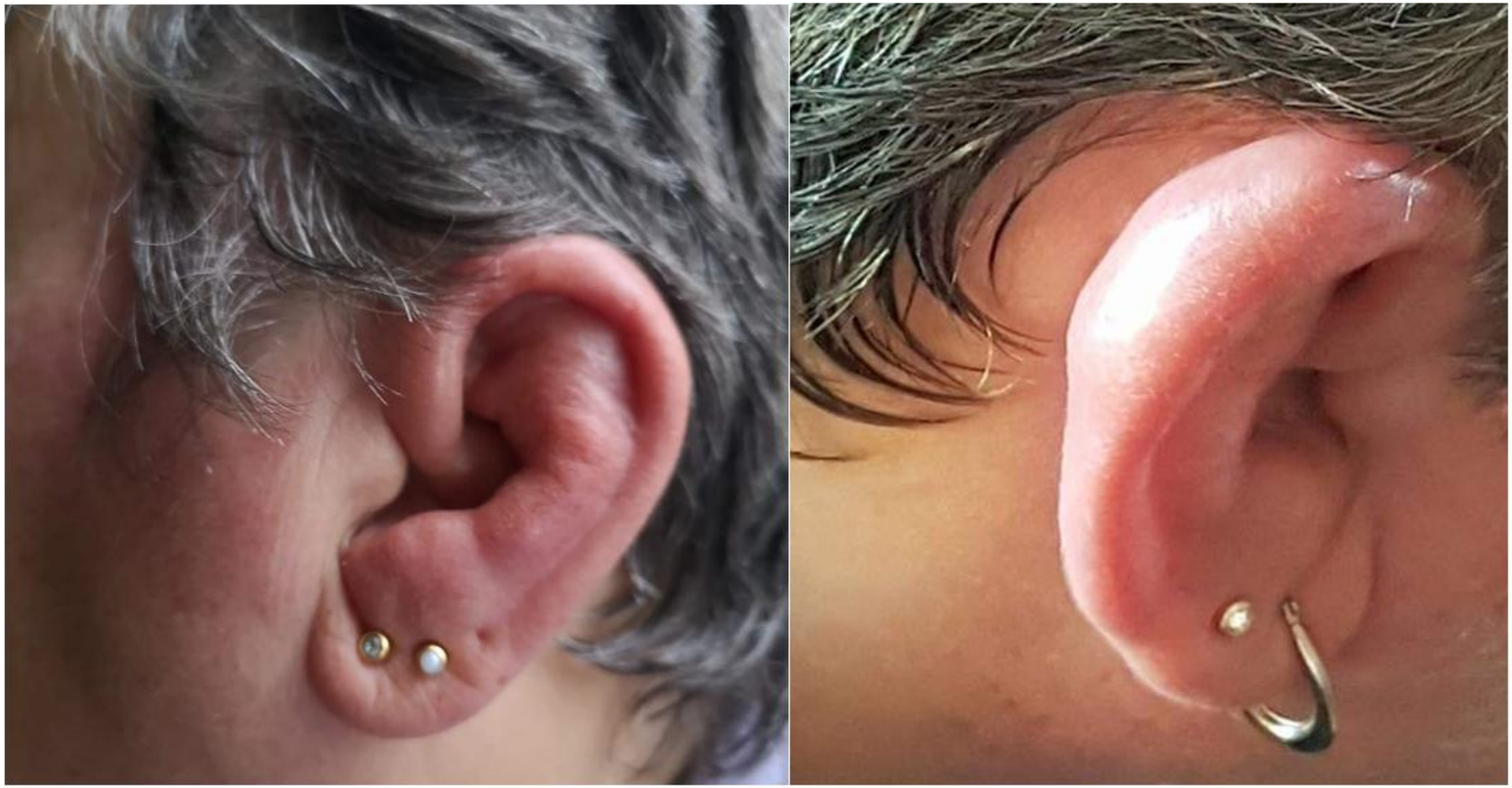


Figure 6: Patient images demonstrating auricular chondritis with inflammation of the external ear with sparing of non-cartilaginous part.

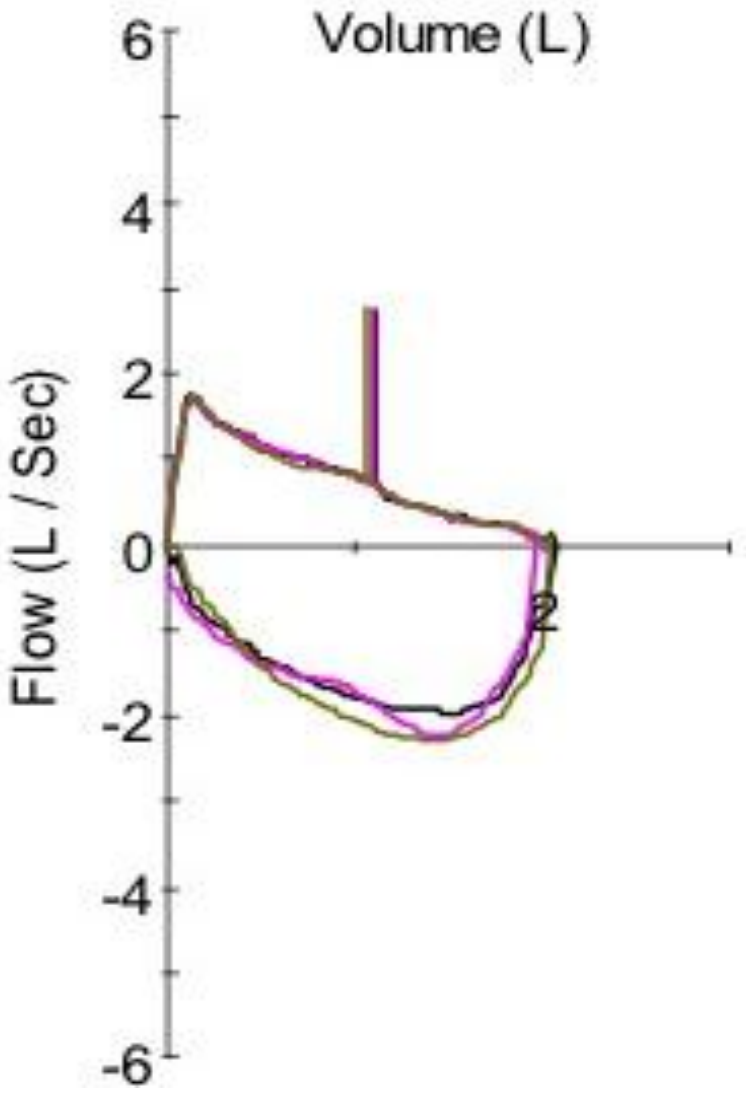



Figure 7: Flow volume loop of patient 4 showing flattening of the expiratory limb and inspiratory limb to a lesser extent

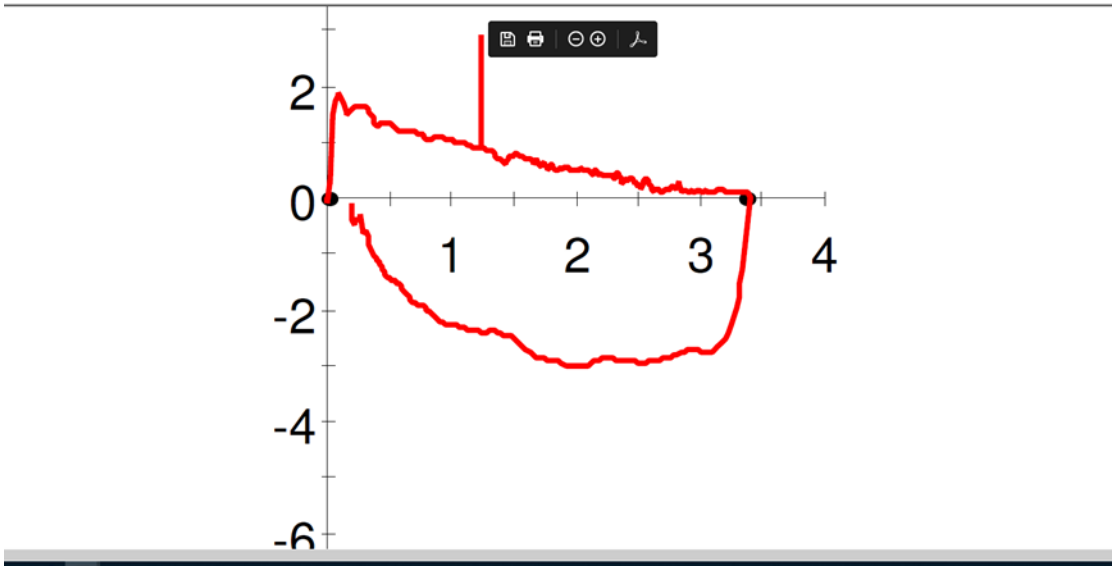



Figure 8: Flow-volume curve of patient 6 showing flattening of the expiratory limb and inspiratory limb to a lesser extent.