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Seronegative Rheumatoid Arthritis in State Phase Manifesting as Rheumatoid Lung Associated with Co-Infection SARS-Cov-2 and *Klebsiella Pneumoniae*, In a Context of Probable Variable Expression Hypogammaglobulinemia. At the Intersection of Immunology and Infectious Diseases: Case Report and Literature Review

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Abstract **Case Report**

***Introduction*:** Pulmonary involvement during rheumatoid arthritis is frequent, severe, very polymorphic and is very often the site of a viral or bacterial superinfection. ***Observation*:** This article describes the case of a 54-year-old diabetic and asthmatic patient suffering from polyarthralgia and long-term fever, who was diagnosed with seronegative rheumatoid arthritis complicated by rheumatoid lung and associated with co-infection SARS-CoV-2 and *Klebsiella pneumoniae* was diagnosed. The article presents the therapeutic difficulties specific to this case in our context and also reviews the existing literature on the diagnosis and treatment. ***Conclusion*:** Rheumatoid lung is a serious and fatal complication of rheumatoid arthritis; a viral superinfection very often worsens the diagnostic prognosis.

Keywords: Rheumatoid Arthritis - SARS-Cov-2 - Internal Medicine.

INTRODUCTION

Rheumatoid arthritis (RA) is the most common and serious chronic inflammatory rheumatism in adults [1]. Extra-articular manifestations of rheumatoid arthritis are very common and can sometimes be serious [1], respiratory manifestations are second in frequency and certainly among the most serious, particularly rheumatoid lung [1]. Lung involvement can occur in 10-80% of rheumatoid arthritis patients, mostly within the first 5 years of RA diagnosis [2]. It includes interstitial lung disease (ILD), airways disease, pleural disease and nodules. Pulmonary hypertension and direct toxicity from RA therapy have also been described [2]. In 7.8% of RA patients, lung disease was the first disease manifestation, with recent data suggesting that the lung may be a potential mucosal site of generation of RA-related autoimmunity [3]. RA-ILD was the most prevalent type of lung involvement (70.1% of the patients with lung disease), which is in line with published data [3]. Its prevalence is estimated between

0.8 and 1% in the general population in the West [4]. In Africa, the prevalence of RA is poorly defined and varies by region. Recent studies estimate its prevalence between 0.1 and 0.9%, similar to that of the West [4]. In Mali, the prevalence of rheumatoid arthritis is not precise apart from a few hospital frequencies; the first case report of pulmonary involvement of RA was described and published for the first time in 2006 in Bamako [21], but since the advent of the Covid-19 pandemic, no case of SARS-CoV-2 infection in a rheumatoid lung has been published.

Hypotheses that patients with rheumatoid arthritis may be more susceptible to SARS-CoV-2 infection and suffer more severe complications from COVID-19 than the general population are described in the literature [5]. Jin *et al*., found in their meta-analysis that fourteen studies reported COVID-19-related hospitalizations in patients with rheumatoid arthritis. Significant heterogeneity ($I^2 = 99.61\%$, $p = 0.00$) led to the use of a random-effects model, which estimated an overall prevalence of 29% (95% CI 20–39%) [5]. But very few cases of pulmonary involvement associated with SARS-CoV-2 superinfection have been published in Mali, hence the interest in describing this case of a young 52-year-old patient suffering from a seronegative rheumatoid arthritis in the form of severe rheumatoid lung and associated with co-infection SARS-CoV-2 and *Klebsiella pneumoniae*; the particularity of his painting, its complex immunological context and the difficulties of specific management in this case.

OBSERVATION

We report the case of a 54-year-old patient of Malian nationality; housewife. She was received on May 6, 2024 in the Internal Medicine department of the University Hospital Center Point G in Bamako for polyarthralgia and long-term fever.

The onset of symptoms would go back about 3 months, marked by the progressive appearance of joint pain in both ankles, knees, elbows, wrists, shoulders and hand joints, symmetrical, of high intensity estimated at 8/10 according to the visual analog scale; without triggering factors, nor sedative, insomnia, intermittent, without deformations; associated with swelling of the above-mentioned joints, diffuse muscle pain concomitant with joint pain. This symptomatology was associated a week ago with dyspnea stage III of the NYHA and SADOUL, with chest pain rated at 7/10 according to the VAS radiating to the shoulders, a dry cough day and night, intermittent, without triggering factor or sedative. All this occurs in a context of fever not quantified for more than 3 months, of progressive installation, permanent without schedule, with hyperhidrosis day and night; non-selective anorexia, physical asthenia rated at 9/10 according to the global numerical scale and significant weight loss not quantified for 7 months. No therapeutic approach had been undertaken, she decides to consult us for management. In addition to anamnesis, she reports spontaneous intermittent daytime fronto-occipital headaches calmed by low-intensity meals. As background; she has been diabetic for about 20 years on metformin - Glimepiride and insulin, hypertensive for 2 months on amlodipine, bronchial asthma under salbutamol; undocumented ulcer syndrome. Of a diabetic and hypertensive father, she is 6th childbirth, 6th parent, 6 living children and 2 abortions; married in a monogamous diet. She would have taken cotrimoxazole and unspecified antihypertensives. She drinks coffee and her diet is mainly based on cereals.

The general condition examination showed a conscious, emaciated patient; athletic and afebrile to touch; her Karnofsky index was 80%. The blood pressure in the sitting position in the left arm was 120/78 mmHg; a heart rate of 96 bpm; a respiratory rate of 28 cycles per minute; a left axillary temperature of 39°C; a capillary blood glucose level at admission of 0.87g/L. Her measurements at admission were a weight of 63kg, height of 167cm for a body mass index (BMI) of 22.5 kg/m²; SpO2 at 89 %.

Physical examination reveals a "wind-like" ulnar deformity of the fingers, accentuated in the right hand; a swan-neck deformity of the 3rd finger of the right hand and the 3rd and 4th fingers of the left hand; a mallet deformity of the phalanget of the little finger of the right hand and a slight buttonhole deformity of the ring finger of the right hand. Permanently abducted thumbs, discomfort with pronosupination and a claw-shaped deformity of the toes with an outward deviation of the 2nd, 3rd and 4th toes **(Image 1)**. Symmetrical painful sensitivity of the metacarpophalangeal and proximal interphalangeal joints of both hands. The remainder of the physical examination revealed chills, increased vocal vibrations in both hemithorax, bilateral submatousness, decreased vesicular murmurs at both lung bases, and bilateral crepitan rales at both lung bases.

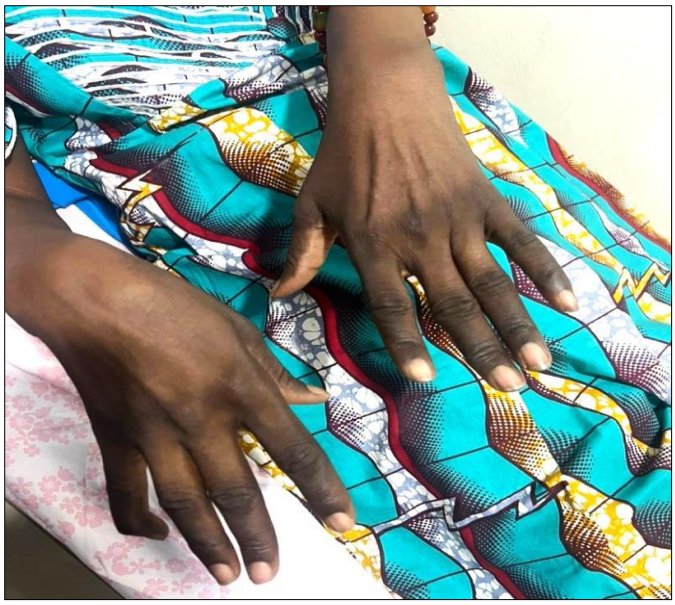

Image 1: Pictures of the patient's hands showing deformations secondary to rheumatoid arthritis (Dr Ibrahima A Dembélé - Dr Dongue T Léa Danielle)

The paraclinical assessment showed:

- Normochromic normocytic anemia with a hemoglobin level of 10.1 g/dL, the mean corpuscular volume of 86,2 fL, a CCMH at 35.6 g/dL. An inflammatory syndrome with a CRP of 48 mg/L, VS at 70mm/h (1st hour) - 105mm/h (2nd hour) and mild thrombocytosis at 488,000/mm^3. The reticulocyte rate at 51000 giga/L. White blood cells at 8450/mm3 with polynuclear neutrophils at 5790/mm3 and lymphocytes at 1538/mm3.
- Serum creatinine at 80µmol/L with clearance at 84.64 mL/min. Azotaemia at 3.1 mmol/L, uricemia at 155 µmol/L and HbA1c at 9%. Total protein at 66.5g/L, hypoalbuminemia at 35.01 g/L. 24-hour proteinuria at 131 mg/24h (Day 3) and 120mg/24h (Day 7) ; CPK at 125ui/L. Prothrombin rate at 89% (normal 70-100%) and factor V (pro-accelerin) at 72% (normal 70-120%). ALAT at 9ui/L and ASAT at 38ui/L; normal plasma ionogram.
- Serum protein electrophoresis revealed hypoalbuminemia (32.00g/L), hyper-alpha1globulinemia (3.8 g/L) and hypogammaglobulinemia (5.5 g/L); with decreased IgG (at 4g/L, normal 7-16g/L) and IgA (0.5g/L, normal 0.7-4g/L) subclasses on immunofixation; with predominance of IgG2 and IgG4; albumin/globulin ratio >2. Cryoglobulin assay was requested but not performed.
- Immunological assessment: anti-nuclear antibodies (ANA-Screen) at 0.10 (negative); anti-SSA antibodies not done; anti-SSB not done, anti-Sm 6.50ui/mL (negative), anti-CCP at 15.20 ui/mL (negative), anti-native DNA at 10.00 ui/mL (negative). Complement dosage showed normal C_3 (1.14 g/L) and hypo-C_4 (0.10 g/L). Rheumatoid factor at 62.3ui/mL (positivity threshold approximately 20 ui/mL). Total anti-HBc antibodies positive, HIV1-2 and HCV serologies negative; HbsAg negative.
- The cytobacteriological examination of the sputum isolated *klebsiella pneumoniae* sensitive to cefotaxime, ceftazidime, amikacin and chloramphénicol; and the SARS-CoV 2 PCR test came back positive.
- X-rays of both hands **(Image 2)** showed diffuse intracarpal, carpo-metacarpal and proximal interphalangeal pinching. Marginal erosions of the heads of the 2nd and 3rd metacarpals of both hands. Metacarpophalangeal epiphyseal demineralization in bands (metacarpal heads and proximal phalangeal bases) of both hands; no soft tissue damage.
- The chest X-ray in frontal incidence showed bilateral hilio-basal reticular opacities in favor of a bilateral interstitial syndrome.

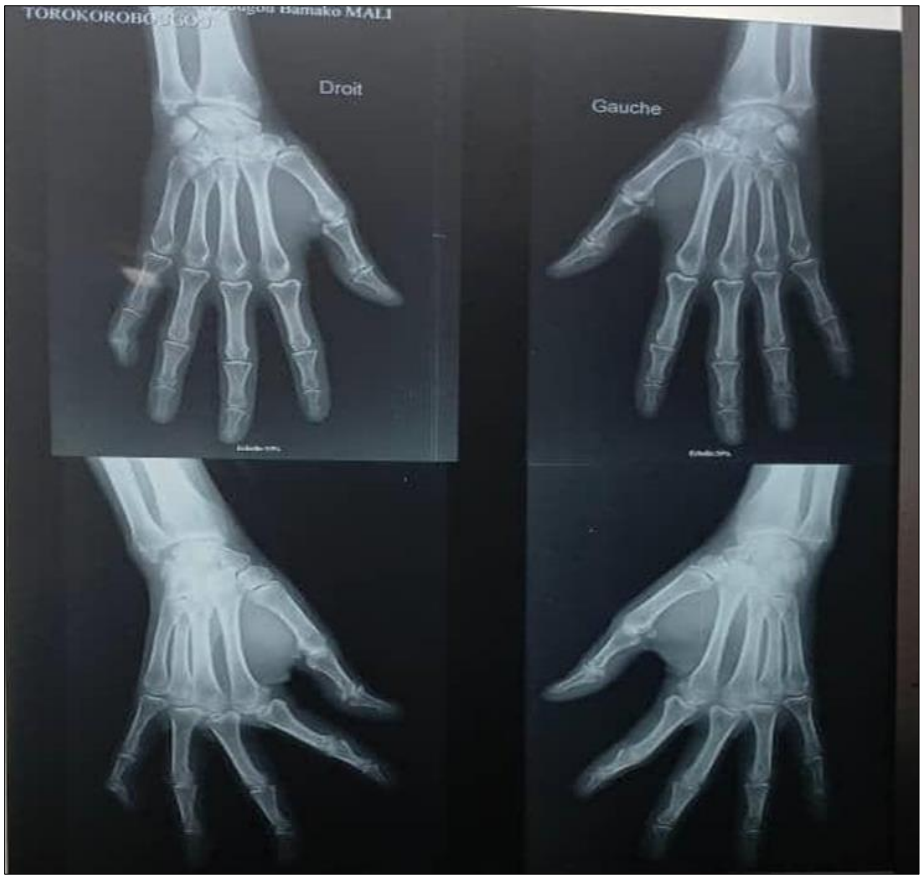

Image 2: Patient's hand X-ray (Dr Stéphane L Djeugoué – Dr Tientcheu T Dorette)

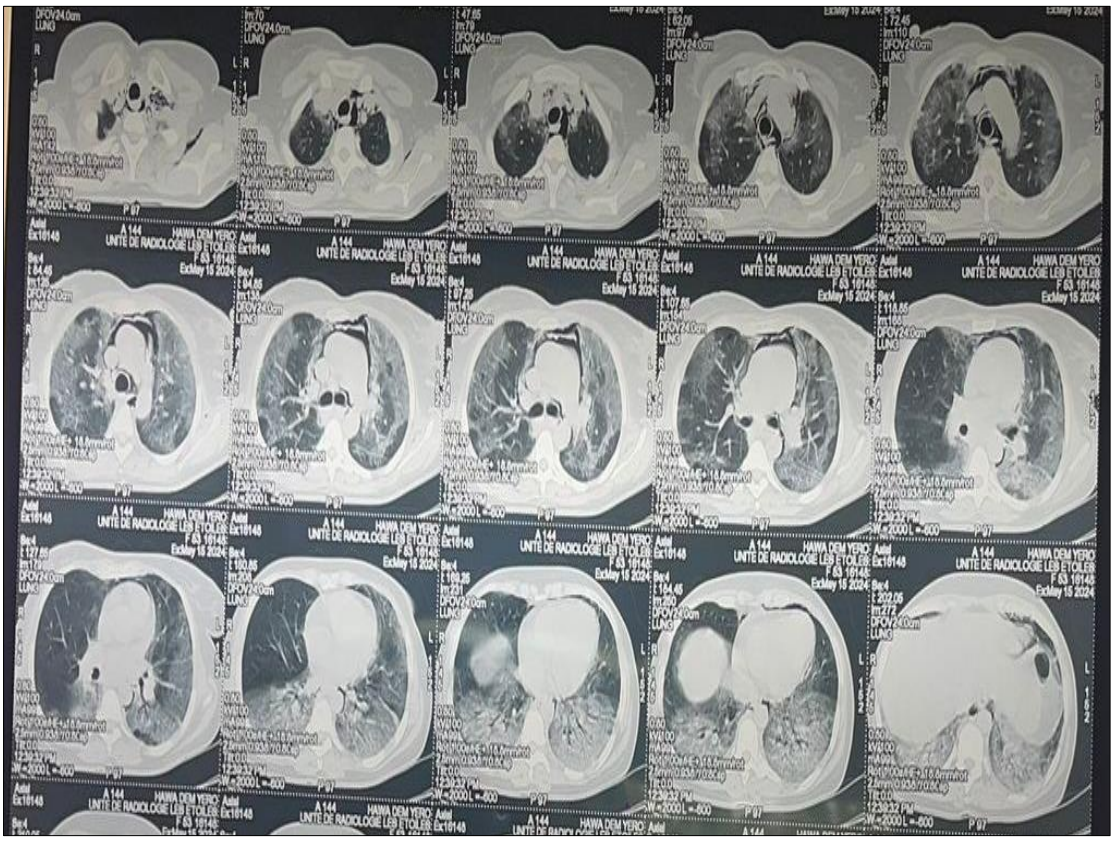

Image 3: Patient's chest CT-Scan (Dr Stéphane L Djeugoué – Dr Tientcheu T Dorette)

In front of the ACR/EULAR 2020 **(Figure 1)** criteria of classification at 10 (While excluding psoriatic arthritis - viral polyarthritis - gout - calcium pyrophosphate dehydrate rheumatism - systemic lupus), the patient was classified as having seronegative rheumatoid arthritis in the state phase manifesting as rheumatoid lung associated with co-infection SARS-CoV-2 and *Klebsiella pneumoniae*. The DAS 28-ESR score at 6.6, i.e. high severity rheumatoid arthritis. The assessment of functional impact by the HAQ index showed severe functional impact with an HAQ index of 2.428.

The patient was hospitalized, put on oxygen with a scope at a flow rate of 3L/min, rapid insulin 10iu every 8 hours, injectable omeprazole 40mg every 24 hours for the prevention of stress ulcers, Enoxaparin 4000iu subcutaneously per day, 0.9% saline 500mL every 8 hours; cefotaxime 1g every 8 hours. Paracetamol 1g every 8 hours, initial boluses of methyl-prednisolone 80mg in 250ml of 0,9% saline per day to be given over 1h30 for 3 successive days then Prednisone 1mg/kg (60mg/day), Calcium tablet 1000mg per day, Potassium tablet 600mg per day, Albendazole tablet 400mg for 3 days. She continued with her salbutamol spray in 4 puffs per day. Daily supportive psychotherapy and therapeutic education of the patient and those around her, and Azithromycin: 1g on day one then 500mg per day for 3 days. The evolution was marked first by a decrease in arthralgia, an improvement in dyspnea with a saturation between 91-94% and the DAS 28-ESR score 4.8 indicates moderate activity of rheumatoid arthritis. After a week, she presented an accentuation of dyspnea and chest pain, a cough in front of which the modified Geneva score returned to an average of 5, a flaring of the nasal wings, and a supraclavicular and intercostal indrawing; an intermittent evening-noctumal fever, a thick control drop came back positive and the patient was put on injectable Artesunate 60mg 3 vials (H_0 - H_{12} - H_{24}) ; then relayed per os with artemether-lumefantrine 80/480mg, 1 tablet per day for 3 days. An increase in rapid insulin to 14iu every 8 hours. The thoracic CT angiogram performed ruled out a pulmonary embolism **(image 3)** and objectified a focus of diffuse ground glass condensation at the level of the pulmonary fields more marked at the periphery and at the level of the 2 pulmonary bases; associated with a pneumomediastinum and some bubbles of centrilobular emphysema. Given the results of the thoracic CT angiogram and the onset of respiratory distress, she was put on high-concentration oxygen mask at a flow rate of 6L/min with nebulization based on salbutamol 5 mg (2,5 ml) 4 sessions in one hour then one session every 6 hours, paracetamol infusion 500mg + 50mg of tramadol every 8 hours and continue with corticosteroid therapy. After two days of intensive care based on oxygen therapy, nebulization and the rest of her treatment, the evolution was marked by persistent respiratory distress and the evolution was fatal.

DISCUSSION

RA is a potential source of significant disability, particularly in severe forms, which can also be life-threatening [2]. These autoimmune diseases represent a broad spectrum of consequences with multiple effects. In the case of rheumatoid arthritis, there may be up to 41% of pulmonary involvement (parenchyma, pleura, or vasculature). Notwithstanding its frequent presentation, the approach continues to be late, affecting the patient's quality of life and leading to reduced therapeutic options [5]. The incidence of ILD associated with RA (RA-ILD) is estimated at between 4 cases and 4.5 cases/1,000 patient-years [11]. Population-based studies in the USA suggest that the cumulative incidence is 3.5–5% at 10 years, 6.3% at 15 years, and 6.8–7.7% at 30 years of follow-up [11]. The prevalence of ILD varies considerably, ranging from 10% to 30% of cases of early RA (≤ 2 years) and between 3.6% and 42% in established RA [11] A.C. Duarte and his team had in their study: 9415 patients with RA registered in Reuma.pt, 7473 (79.4%) were women, with a mean age of 62.3 +/- 13.6 years and a median disease duration of 12.4 [IQR 6.5 20.6] years at the last visit [3]. Pulmonary disease was documented in 298 (3.2%) patients. The median interval between joint and pulmonary symptoms was 5 [IQR 1-15] years. Twenty-one (7.8%; 28 missing data) patients had pulmonary disease as their first manifestation [3]. Our patient was 54 years old; the main manifestations of RA were articular and respiratory.

➢ Seronegative Rheumatoid Arthritis

Patients with RA-associated lung disease had a higher frequency of smoking, positive RF and ACPA, and erosive disease, consistent with the literature [3]. However, in their study A.C. Duarte *et al* found that patients with lung disease were negative for rheumatoid factor and ACPA, and only 2 had smoking habits [3]. This means that other factors may contribute to the development of lung disease. Angalla Affleck RL *et al.*, in their study identified in 10 cases of Rheumatoid Arthritis, on the immunological level, the rheumatoid factors were positive in 7 patients (70%) and the anti-CCP were positive in 6 patients, i.e. 60% of the cases, therefore 30-40 of seronegative RA [4]. Godanga in his thesis found 128 files of seronegative PR patients were retained, or 0.55% of the consultants, of which 3 patients or 4.92% presented pulmonary involvement and it constituted 28.19% of all RA [6]. S. Touré reported 86 files of seronegative RA patients were identified, i.e. 15.11% of RA cases and 0.36% of consultants, including 16.3% with pulmonary involvement [7]; While Mejri reported a study of 10 cases of Rheumatoid Lungs including 20% of seronegative RA cases but no superinfection [8].

Anti-CCPs are not very sensitive but have a 90% accuracy for the diagnosis of RA [6, 7]. However, a quarter of patients initially anti-CCP negative turn out to be authentic cases of RA, for rheumatoid factors, they are very sensitive but not very specific [6, 7]. Our patient

also presented seronegativity for anti-CCP antibodies due to her hypogammaglobulinemia with IgG predominance. The critical assessment of the clinical use of serological tests in RA has made it possible to emphasize the importance of looking for diagnoses other than RA in seronegative patients [6-26]. A careful follow-up of such patients shows that some become positive for rheumatoid factor, some develop psoriatic arthritis, Reiter's disease and other non-rheumatological disorders [6-26]. However, others remain seronegative and do not produce clearly defined syndromes [6, 7]. Seronegative RA patients seem to have fewer erosive lesions and fewer extra-articular lesions [6]. Angalla Affleck RL *et al.,* found radiographic abnormalities in 8 cases (80%) were: demineralization in a band of the epiphyses and marginal erosion each in (8 cases), bone geodes (7 cases), radiocarpal pinching (5 cases), pinching of the IPP and MCP each in (5 cases), fusing rheumatoid carpititis (2 cases) [4]. These results are superimposable to those found in our patient.

The diagnosis of RA should be as early as possible because the effectiveness of treatment depends on the early diagnosis [2]. In the state phase as in our patient, the involvement of the hands is often inaugural and it will present characteristic deformations. The extra-articular manifestations of the state phase define the rheumatoid disease, in our patient it is the pulmonary involvement which predominated associated with an alteration of the general state. Diagnosis of RA is sometimes difficult at the early stage and is based on the comparison of clinical manifestations and biological tests. Classification criteria have recently been revised by the American College of Rheumatology [ACR] and the European League against Rheumatism [EULAR] [4-26].

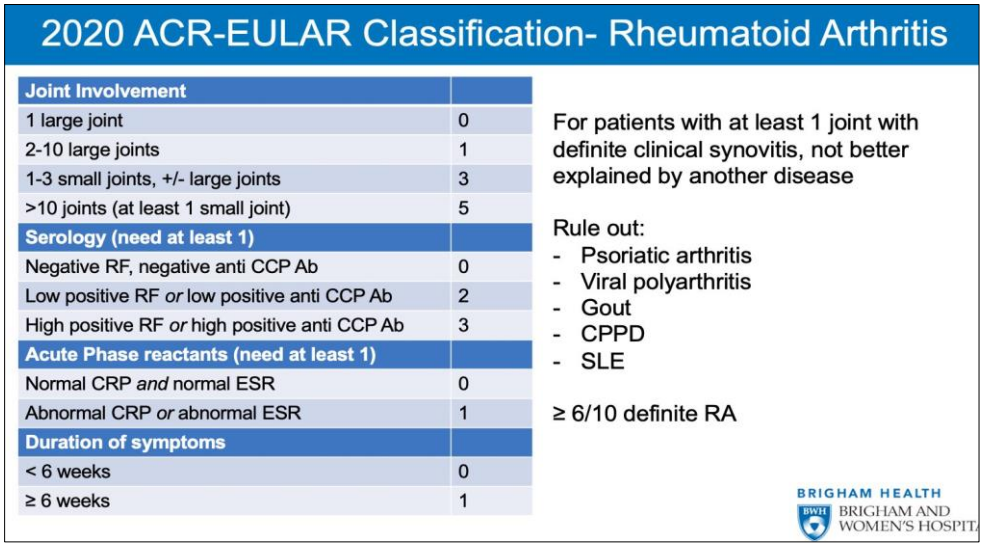

Figure 1: Rheumatoid Arthritis - 2020 ACR-EULAR Classification [20]

Seronegative RA is a disease whose management does not differ from that of seropositive RA. This management is multidisciplinary and may involve, among others: the rheumatologist, the orthopedic surgeon, the psychologist, the occupational therapist, the physiotherapist and the rehabilitation and functional rehabilitation physician [1-26]. Seronegative RA is a disease for which the therapeutic objective was well defined: to relieve pain, achieve remission or, failing that, the lowest possible inflammatory activity [6-26]. The new EULAR recommendations for the management of RA are intended for doctors and health authorities as well as patient associations [26]. They range from diagnosis to overall management, while developing the therapeutic strategy. Seronegative RA appears to have a benign prognosis compared to seropositive RA [1-6], and symptoms differ depending on the variants [1-6], however, in our observation, the patient's vital prognosis was engaged and this is explained by the dysimmune background she presented.

- **Interstitial Lung Disease in Rheumatoid Arthritis**

RA can affect any part of the lung; it can involve the parenchyma manifesting as ILD, or it can affect the pleura, causing inflammation and pleural effusions, small or large airways manifesting as cricoarytenoiditis, constrictive or follicular bronchiolitis, and bronchiectasis [2]. Finally, it can affect the pulmonary vessels causing vasculitis or pulmonary hypertension leading to significant morbidity and mortality [10]. Although it may be the initial presentation in 10–20% of patients, most RA-ILD occurs within the first 5 years after diagnosis [10]. RA-ILD can present clinically with a wide range of symptoms, the most common of which are dyspnea and cough [10], which was the case in our patient.

Usual interstitial pneumonia (UIP) is the most frequent one, followed by nonspecific interstitial pneumonia (NSIP); other patterns are seen less frequently **(Figure 2)** [10]. The consensus classification

for idiopathic interstitial pneumonias (IIPs) has been used to define RA-ILD, as there is no specific categorization for the condition [10]. Acute interstitial pneumonia, diffuse alveolar damage, organizing pneumonia (OP), desquamative interstitial pneumonia, lymphocytic interstitial pneumonia, and others have also been identified in patients with RA [10].

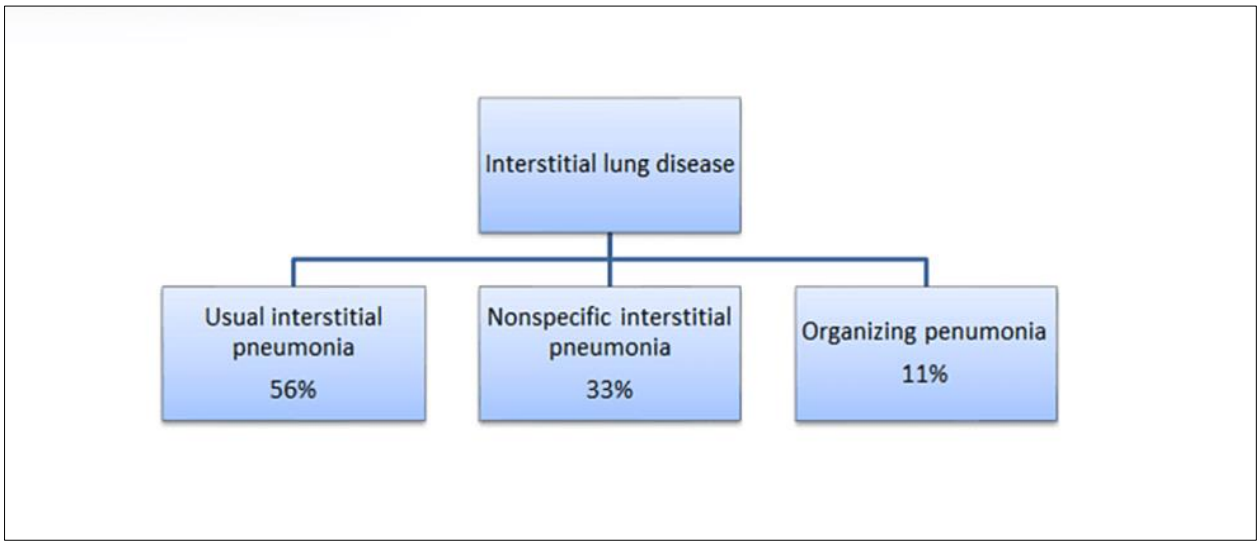

Figure 2: Common classification of interstitial lung disease in rheumatoid arthritis [10]

Several risk factors have been associated with ILD, including smoking [13], male sex, advanced age, late onset of RA, severe and erosive joint disease, and disease duration, with most cases of lung involvement occurring within 5 to 10 years of onset and positive anti-citrullinated peptide antibody (ACPA) titers [10, 11].

The pathophysiology of RA-ILD still needs to be better understood. Genetic and environmental factors are critical in how lung involvement develops in RA patients [10]. Some important variations in human leukocyte antigen (HLA) that may contribute to the emergence of PRD in RA patients include HLA-DRB1, HLA-DR4, and HLA-B40 [10]. Smoking has been shown to interact with HLA-DR shared epitope (SE) genes and play an important role in initiating the immune response to citrulline-modified proteins [10]. Injury to the lung parenchyma and airways due to exposure to environmental factors can increase protein citrullination in lung cells [10]. In a genetically predisposed individual, the pathological process begins with an inflammatory process that activates cytokines, chemokines and growth factors such as tumor necrosis factor (TNF), interleukins (IL) and vascular endothelial growth factor (VEGF) [21]. Matrix metalloproteinases (MMPs) become hyperactive and the extracellular matrix (ECM) is more easily deposited due to the proliferation and differentiation of fibroblasts, leading to the development of pulmonary fibrosis and interstitial lung disease **(Figure 3)** [10].

There are significant variations between Idiopathic Pulmonary Fibrosis and RA-ILD even though both conditions share immunological pathways [10]. Patients with RA-ILD have more inducible bronchus-associated lymphoid tissue in their lung tissue than those with IPF, indicating that immunological dysregulation may affect RA-ILD more than IPF [10]. The effect of immunosuppressants on typical interstitial pneumonia (TIP) in RA or connective tissue disease (CTD) is unclear. However, some retrospective research has found that immunosuppressants are more effective in ILD types other than TIP. Thus, immunosuppressive drugs may be more effective in RA-ILD with NSIP or OP regimens than in TIP regimen [13-15].

Early detection of ILD in patients with RA is very important because the disease is associated with significant morbidity and mortality. Subclinical ILD is highly prevalent in affected patients and can be characterized by clinico-radiological progression in approximately half of the reported cases [13, 14].

Given their efficacy in CTD-ILD rather than RA-ILD, glucocorticoids are frequently included in the first treatment regimen for clinically significant RA-ILD [10]. NSIP and OP ILD regimens are more likely to respond to glucocorticoids than TIP [10]. Corticosteroids increase the risk of life-threatening infections in patients with RA-ILD. Despite the use of DMARDs, it has been found that a higher frequency of infections was associated with a mean daily dose of prednisone greater than 10 mg [10]. As these, their best use lies in the early management of acute exacerbations or in their treatment until newer drugs with better long-term safety profiles are introduced.

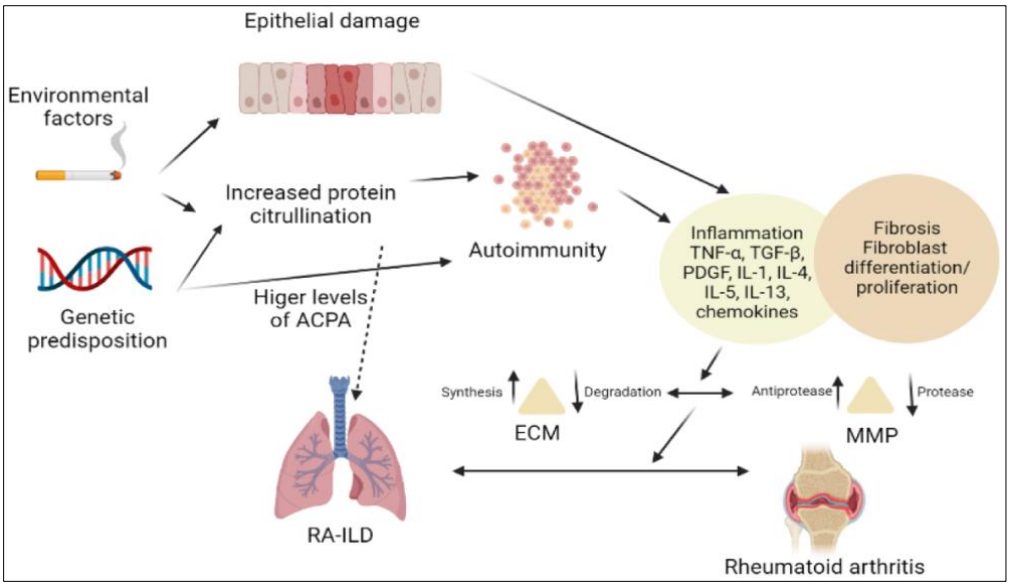

Figure 3: Pathogenesis of Rheumatoid Arthritis-Interstitial Lung Disease [15]

There is currently no consensus on the most appropriate treatment for patients with RA-ILD. Treatment should be integrated and individualized, and multidisciplinary teams should have access to the support of nurses, physiotherapists and pharmacists. Treatment with immunosuppressive drugs may further increase the risk of acquiring SARS-CoV-2 infection [13, 14]. Furthermore, the clinical features of RA flares and SARS-CoV-2 infection frequently overlap [14]. Patients with RA and COVID-19 present with common symptoms such as arthralgia, myalgia, and other inflammatory disorders. RA-mediated interstitial lung disease often mimics the symptoms of COVID-19. In addition, patients with RA frequently present with increasing evidence of comorbidities [14, 15]. Thus, the clinical management of RA itself is a challenging task in the current context of COVID-19. Among the possible therapeutic options, the American College of Rheumatology (ACR) and the European League Against Rheumatism (EULAR) have recommended several guidelines regarding the use of RA medications in the COVID-19 pandemic [14-26].

Glucocorticoids have been recommended at the lowest possible dose even in positive COVID-19 cases, and abrupt discontinuation has been discouraged. It has been suggested to continue nonsteroidal anti-inflammatory drugs (NSAIDs) unless severe multi-organ effects of COVID-19 occur [14]. The choice of therapeutic strategy in RA-ILD is complex as many factors need to be taken into account, for example, the severity of RA and ILD, the presence of prognostic factors associated with both progression and mortality, comorbidities and patient preferences [11]. The potential risk of pneumonitis induced by some of the disease-modifying antirheumatic drugs (DMARDs) used to treat RA has been reported.

- ***Conventional Disease-Modifying Antirheumatic Drugs (cDMARDs)***
  - Methotrexate (MTX) is a key drug in the treatment of RA, and recent data show that it is not a risk factor for RA-ILD, progression, or mortality [1-11]. However, MTX can induce pneumonitis, particularly during the first year of treatment, although recent data suggest that the risk is lower than previously thought. MTX is generally avoided in clinically significant or progressive RA-ILD [1-11]. The clinical symptoms of RA-ILD and M-pneu can be difficult to differentiate. RA-ILD, which can be asymptomatic for years, tends to develop insidiously over time in contrast to M-pneu which would more typically present acutely or subacutely with dyspnoea, cough, and fever [22]. When ILD is present early in RA, MTX should be evaluated on a case-by-case basis due to the risk of inducing pneumonitis, as other csDMARDs are preferred as a risk-minimization strategy [10, 11].
  - In patients with RA-ILD who are not of Asian origin, leflunomide (LEF) is considered a safe option [17=22], given that the risk of LEF-induced pneumonia has been mainly described in Asian populations [14, 15].
  - The role of other csDMARDs such as mycophenolate mofetil, cyclophosphamide, azathioprine (AZA), in the management of RA-ILD is even less clear. Moreover, these drugs are disadvantaged due to their lower toxicity profile and modest efficacy in RA joint involvement [14, 15].

- ***Biological Disease-Modifying Antirheumatic Drugs (bDMARDs)***
  - Anti-tumor necrosis factor (anti-TNF) agents have demonstrated excellent effectiveness in

slowing the advancement of articular disease and symptoms. However, warnings about possible pulmonary toxicity have come up as a result of its growing use [14, 15]. All anti-TNF drugs approved for RA have been correlated with new-onset or worsening of existing ILD: infliximab [14, 15], etanercept [14, 15], and adalimumab; also, some of the newer agents, including certolizumab [14, 15].

- Rituximab (RTX) is a monoclonal antibody targeting the B-cell marker CD20 and has been approved for treating RA in anti-TNF nonresponders. Follicular B-cell hyperplasia and interstitial plasma cell infiltrates were found in RA-ILD patients. This raised the possibility that B cells were involved in the disease's etiology and aroused interest in using RTX for the treatment of RA-ILD [10].
- IL-6 inhibitors such as tocilizumab demonstrated that the profibrotic effects of the proinflammatory cytokine IL-6 are countered by IL-6R inhibition [10], indicating a possible advantage of this therapeutic strategy in pulmonary fibrosis caused by RA [10].

ILD remains the second leading cause of premature death in RA after cardiovascular complications, accounting for 10–20% of deaths due to the disease [10, 11]. The clinical course and prognosis of ILD-RA are highly heterogeneous. This heterogeneous course makes it essential to identify prognostic factors for severe disease and mortality, which are essential for the follow-up and treatment of affected patients [10, 11]. The main predictors of ILD progression are the radiological pattern of ILD [13], high ACPA titers [13], the degree of impaired DLCO at baseline [14], a decrease of ≥ 10% (estimated theoretical value in percent) in FVC during follow-up [2=11], extensive lung involvement on chest CT [2-11], and elevated serum levels of IL-6 and KL-6 glycoprotein [2=11].

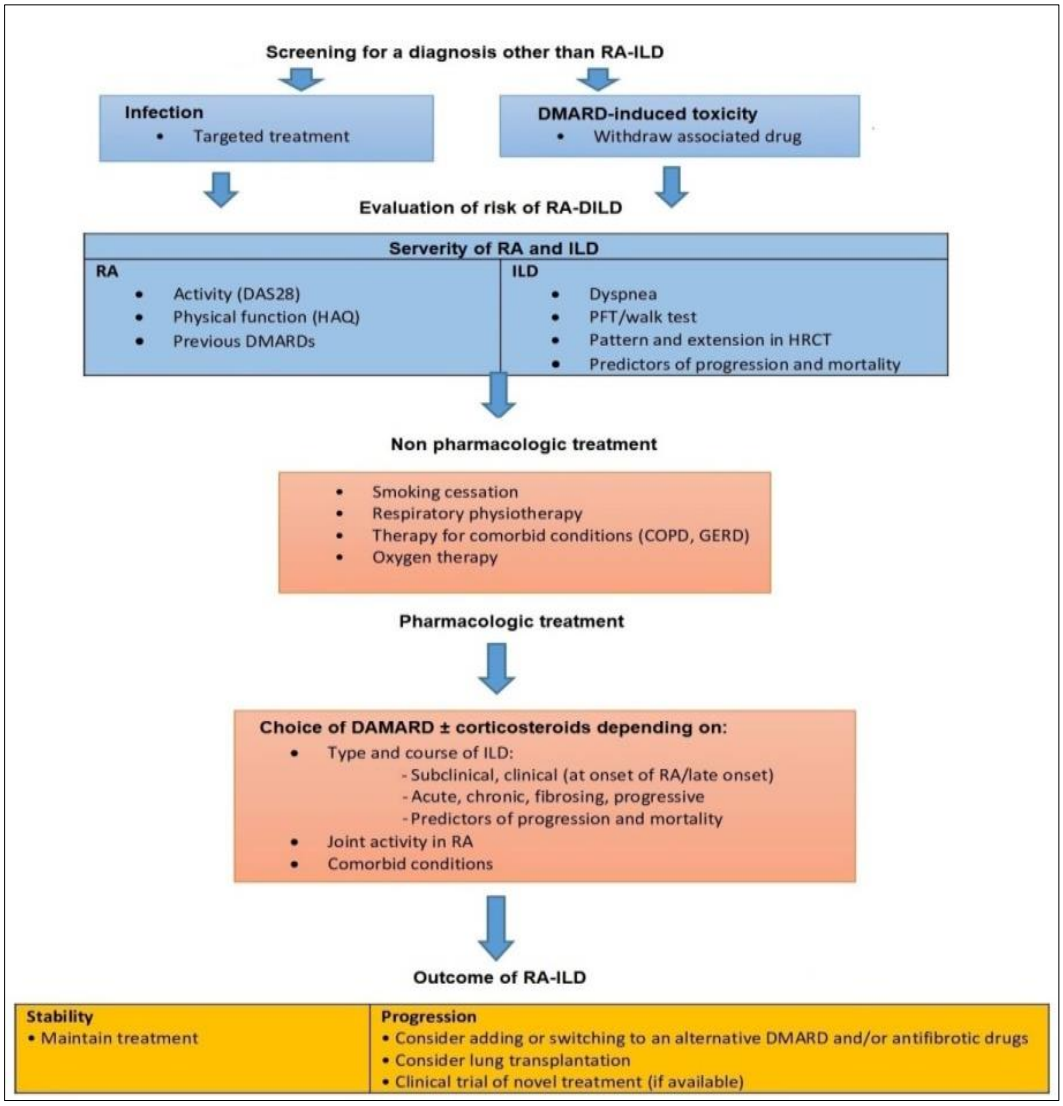

Figure 4: Algorithm for the management of RA-ILD [11]. COPD: chronic obstructive pulmonary disease; GERD: gastro-oesophageal reflux disease; HAQ: health assessment questionnaire

➢ **SARS-CoV-2 and Rheumatoid Arthritis**

Up to the end of April 2020, more than 2.5 million people in the world had been infected with SARS-CoV-2 under the pandemic situation of COVID-19 [8]. As a large population with underlying dysregulated immune system, rheumatic patients infected with SARS-CoV-2 are not rare. No significant association was found between rheumatoid arthritis and severe COVID-19 [5]. Many cytokines involved in the pathogenesis of rheumatic diseases (particularly rheumatoid arthritis, RA), such as IL-6, were elevated in COVID-19 [9]. Persistent and dramatic elevation of serum IL-6 level was associated with higher mortality in COVID-19 patients; its elevation can be a sign of cytokine release syndrome (CRS), which is always observed in severe COVID-19 patients [9].

At the level of pathogenic mechanisms, cytokines play important role in the progress of both COVID-19 and rheumatic diseases: Huang *et al*., revealed elevated serum level of many cytokines (including IL-1β, IL-7, IL-8, IL-10, GM-CSF, IFN-γ, TNF-α, etc.) in COVID-19 patients compared with healthy people, and these cytokines are also the pathogenic factors in many rheumatic diseases, including RA, systemic lupus erythematosus (SLE), and primary Sjögren's syndrome [1-9]. Thus, targeting these potential pathogenic proinflammatory cytokines is logical and can be a good strategy to realize the win-win mode to treat both COVID-19 and the underlying rheumatic conditions. Among all these candidate target cytokines, IL-6 seems to be one of the best choices, particularly for COVID-19 patients with RA: from the aspects of either availability of the products or the current evidences supporting the benefits in treating both of the diseases [9=14].

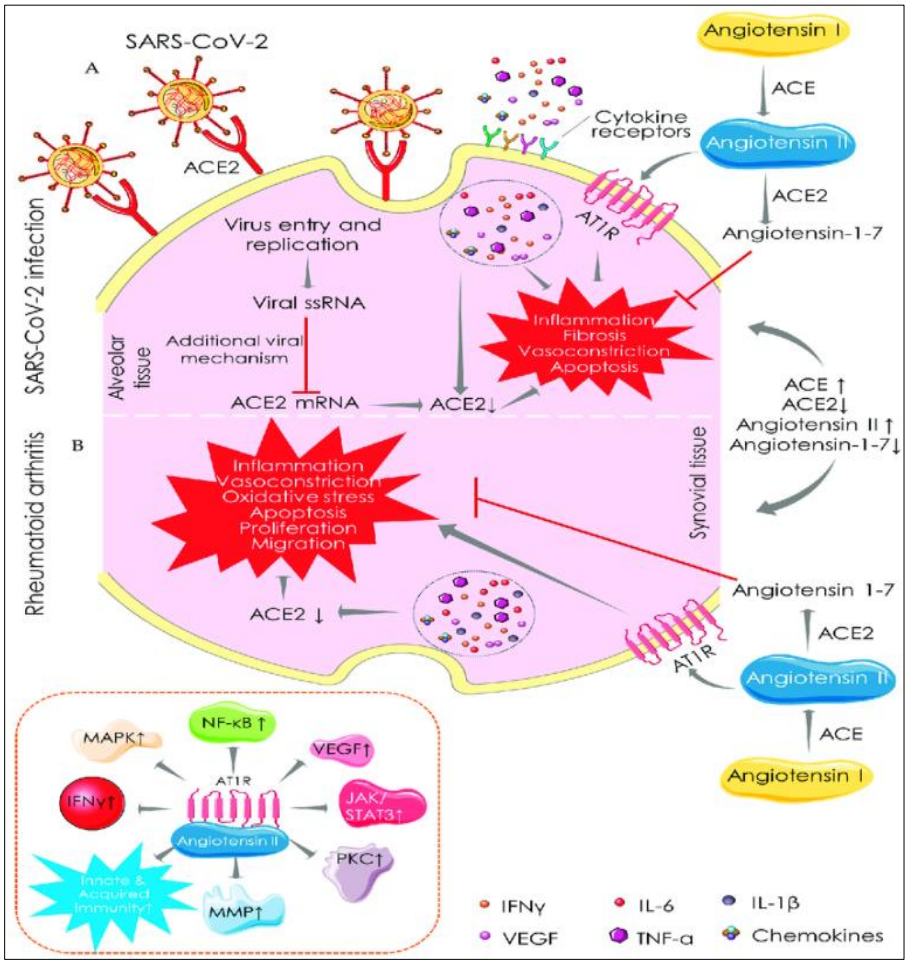

Figure 5 : Angiotensin-converting enzyme (ACE)-dependent pathway showing the mechanistic similarity between SARS CoV-2 infection (A) and RA (B) [18]

▪ ***Mechanistic Similarity between SARS-COV-2 Infection and RA***

COVID-19 and RA share similar immune-inflammatory features of disease pathogenesis executed by analogous mechanistic pathways.

- **Angiotensin-Converting Enzyme (ACE)-Dependent Pathway (Figure 5):**

ACE catalyses the conversion of angiotensin I to angiotensin II, which is involved in the pathogenesis of both COVID-19 and RA by promoting inflammation, fibrosis, vasoconstriction, and apoptotic activities. In

contrast, ACE2 catalyses the conversion of angiotensin II to angiotensin-1-7 and shares identical protective functions in both COVID-19 and RA [13, 14].

- **Macrophage-Mediated Pathway (Figure 6):**

The alveolar macrophages in healthy individuals share homologies in transcriptomic profiles and regulatory pathways with the macrophages in synovial tissue of healthy individuals. Similarly, macrophages in the alveolar tissue of COVID-19 patients are homologous to that of the synovial macrophages in RA patients. Thus, both SARS-CoV-2 infection and RA share a common mechanistic pathway of immunopathogenesis driven by the activities of analogous macrophage clusters [13, 14].

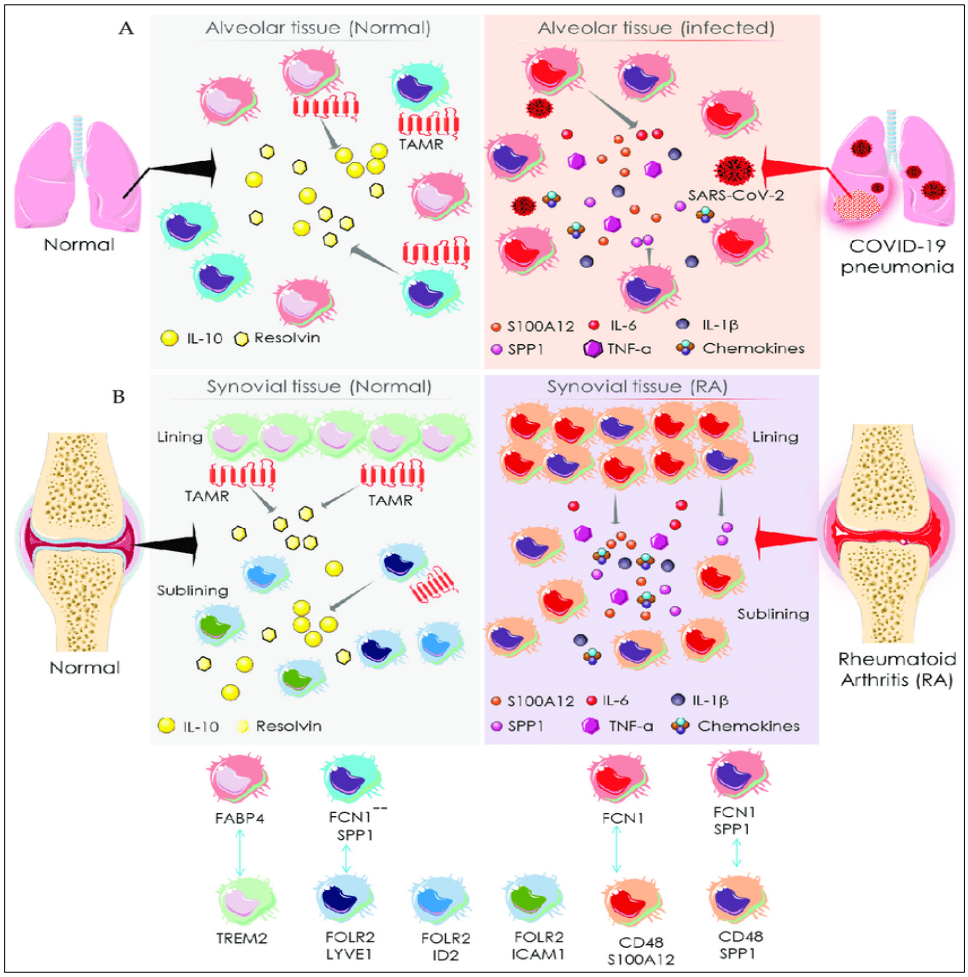

Figure 6: Macrophage-mediated pathway showing the mechanistic similarity between SARS-CoV-2 infection and rheumatoid arthritis [18]

- **Hypogammaglobulinemia with Variable Expression and Auto-Immunity [23-25]**

Hypogammaglobulinemia with variable expression or common immunodeficiency (CVID) is the most common primary immunodeficiency, characterized by a disorder of B lymphocyte differentiation and immunoglobulin deficiency. It can manifest in childhood or be late in manifestation. It is clinically manifested by recurrent infections, non-infectious pulmonary and digestive disorders, autoimmune diseases and susceptibility to certain types of cancers. Nearly 25% of patients with CVID have autoimmune manifestations. These arise from dysregulation in B cell development and the generation of multiple antibodies directed against variable antigenic targets. Hematological disorders are the most common, in particular autoimmune hemolytic anemia and immune thrombocytopenic purpura (ITP). Other frequently associated conditions are rheumatoid arthritis, vitiligo, autoimmune thyroiditis, and pernicious anemia. Multisystem granulomatous involvement is well known in CVID and affects 8–20% of patients. It is responsible for significant morbidity and mortality. The lungs are the most commonly affected site, but all organs can be affected.

When a diagnosis of CVID is suspected, an assessment of humoral immunity is carried out. The first step is the quantitative measurement of serum immunoglobulins (IgG and IgG subclasses, IgM, and IgA). In CVID, total IgG is typically low, most often below 4 g/l (normal between 7 and 14.5 g/l). IgM and IgA may be normal or low.

The pathogenetic mechanism of autoimmunity in CVID is paradoxical. It has been suggested that the underlying cause of autoimmunity lies in the inability of these patients to eliminate microbial antigens, leading to alternative immune pathways and an excessive and chronic inflammatory response, damaging not only infected cells but also surrounding tissues. The high antigenic load caused by recurrent or resistant infections is also thought to cause autoimmunity by affecting tolerance through superantigens or molecular mimicry. The mechanisms probably involve central and peripheral tolerance disorders and defects in autoreactive T and B cells. In CVID, defects in B cell maturation, CD21low B cells and cSMB cell development can be observed. As a result, the total proportion of B cells and cSMB cells is reduced.

Rheumatoid arthritis, Sjögren's syndrome, lupus erythematosus, and, more rarely, other rheumatic diseases may be seen in patients with IVCD. Other rheumatic diseases include Raynaud's phenomenon, Behçet's disease, familial Mediterranean fever, RA, ankylosing spondylitis, and eosinophilic granulomatosis with polyangeitis.

CONCLUSION

Rheumatoid arthritis is frequently complicated by interstitial lung disease (RA-ILD), an underestimated contributor to excess morbidity and mortality. The frequency and intensity of pulmonary symptoms may vary depending on severity, duration, coexisting conditions (including frequently associated infections), the terrain in which it occurs, and the form of lung involvement. High-resolution CT is considered the primary diagnostic modality. The spectrum of immune diseases is broad and requires skilled specialists who can adopt a multidisciplinary approach for diagnosis and timely treatment, in order to reduce the number of lesions and morbidity to ensure the best possible quality of life.

Consent: Written informed consent was obtained from the patient's family to publish this report in accordance with patient consent policies.

Conflicts of Interest: The authors declare no conflict of interest.

Author Contributions: All authors participated in the evaluation and follow-up of the patient, in the writing and correction of the case report. All the authors of the manuscript have read and agreed to its content.

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