RELAPSING POLYCHONDRITIS AND SARS-CoV2, A POSSIBLE TRIGGER OF AUTOIMMUNITY

VIRGIL PĂTRAȘCU*, LILIANA GABRIELA GEOLOAICA*, RALUCA NICULINA CIUREA**

Summary

Relapsing polychondritis is a rare, autoimmune inflammatory condition that involves cartilaginous structures, predominantly those of the ears, nose, and tracheobronchial tree. Other affected structures may include the cardiovascular system, peripheral joints, skin, middle and inner ear, eyes, and central nervous system. Systemic corticosteroid therapy is the treatment of choice. In recent decades, viral infections have been proposed as environmental factors that trigger autoimmunity in genetically predisposed individuals. Respiratory viruses, especially parainfluenzae and coronaviruses, have been associated with the onset of rheumatoid arthritis, while growing evidence describes the occurrence of autoimmune disorders in COVID-19.

***Clinical case.** A 31-year-old patient presented in October 2020 for infiltrated erythematous-edematous plaques, highly painful, located in the auricles, bilaterally. The disease started a month ago. The patient applied the antibiotic and dermatocorticoid cream locally, without a favorable evolution. From the medical history we notice that the patient presented 4 months ago pain in the radio-carpal joints, later in the joints of the knees and ankles for which she presented to the Rheumatology department. Two weeks ago, she presented with pain in the nasal pyramid and at the eye level. She was diagnosed with chronic hypertrophic rhinitis and conjunctivitis, respectively. The pharyngeal exudate showed Klebsiella pneumoniae present. The other laboratory tests were within normal limits. The patient had a history of asymptomatic infection with SARS-VOC-2 virus, diagnosed by highlighting specific antibodies during investigations to establish the etiology of polychondritis. We performed a biopsy of a fragment of the skin, along with the underlying cartilage, in the pavilion of the left ear. Based on the clinical examination and the histopathological examination, we specified the diagnosis of relapsing poly-chondritis. We started treatment with Methylprednisolone 32 mg / day, Famotidine 40 mg / day, Rupatadine 10 mg / day, Levofloxacin 500 mg / day, with a slightly favorable evolution. Methotrexate 10 mg / week treatment was also initiated in December 2020.*

***Discussions.** Relapsing polychondritis is a pro-gressive autoimmune condition that affects several organs and tissues. Early recognition of the signs of this rare disease and prompt initiation of anti-inflammatory and immunosuppressive therapy can relieve symptoms and prevent complications, especially those affecting the respiratory tract and heart.*

***Conclusions.** The number of case reports describing autoimmune phenomena in COVID-19 is increasing, and these conditions may involve different organs and systems. Although the chronology of pathologies in our case suggests the possible involvement of SARS-CoV-2 infection in the occurrence of Polychondritis, we mention that so far no cases of relapsing Polychondritis associated with this viral infection have been reported.*

***Keywords**. Relapsing polychondritis, SARS-CoV-2, treatment.*

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Introduction

Relapsing polychondritis is a rare, autoimmune inflammatory condition that involves cartilaginous structures, predominantly those of the ears, nose, and tracheobronchial tree. Other affected structures may include the cardiovascular system, peripheral joints, skin, middle and inner ear, eyes, and central nervous system.

Jaksch-Wartenhorst described the first case in the literature in 1923 when he used the term "polychondropathy".[1] The term "relapsing polychondritis" was first used by Pearson et al. in 1960 to highlight the episodic nature of the disease observed in 12 patients.[2]

The average age of onset is, in most cases, between the fourth and fifth decade of life. The disease occurs with a similar frequency in both sexes, although a slight predominance of females has been described. It affects all ethnicities, with variability in clinical presentation between the Caucasian and Asian populations. The estimated incidence is 3.5/10,000/year. Relapsing polychondritis is considered a complex disorder involving cartilaginous structures, involving both the humoral and cellular immune systems. As for the role of the genetic factor, HLA class II molecules also appear to be associated with recurrent polychondritis. There is no evidence of family transmission. Mono- or, more commonly, bilateral atrial chondritis is the most common feature of the disease.[3]

The variability of symptoms and the episodic nature of polychondritis can delay diagnosis. In addition, there are no specific laboratory explorations for recurrent polychondritis. Systemic corticosteroid therapy is the treatment of choice. [4, 5]

Various clinical manifestations of COVID-19 disease appear as a sign of SARS-CoV-2 virus infection. While the initial target of the virus is the respiratory tract, it is becoming increasingly clear that there is a complex interaction between the virus and the immune system, from mild to moderate responses to dysfunctional autoimmune responses directed to multiple tissues. The immune system plays a dual role in COVID-19, being involved in both the antiviral response and the acute progression of the disease, with an irregular response, represented by marked cytokine release, macrophage activation and systemic hyperinflammatory response. It has been speculated that these immunological changes may induce loss of tolerance and/or trigger chronic inflammation, a phenomenon present in relapsing polychondritis. [6]

Clinical case

A 31-year-old patient presented to the Dermatology Clinic of Craiova in October 2020 for infiltrated erythematous-edematous plaques, highly painful, located in the auricles, bilaterally (Fig. 1, Fig. 2). The disease started a month ago. The patient applied the antibiotic and dermatocorticoid cream locally, without a favorable evolution.

From the medical history we notice that the patient presented 4 months ago pain in the radiocarpal joints, later in the joints of the knees and ankles for which she presented to the Rheumatology department, where she was recommended treatment with Diclofenac ointment and Arthrostop 1 tb/day. Two weeks ago, she presented with pain in the nasal pyramid and at the eye level. She was diagnosed with chronic hypertrophic rhinitis and conjunctivitis, respectively.

One week ago she had an episode of precordial pain with irradiation in his right arm, but cardiological examination and echocardiography were normal.

The patient presented asymptomatic infection with SARS-COV-2 virus, diagnosed by particle-based chemiluminescence method of the immune profile on infection with this virus, in order to establish the etiology of polychondritis. The result was positive for both anti-nucleoocapsid Ig G antibodies and anti-spike Ig G antibodies.

The written consent of the patient was obtained, who agreed to the publication of these data.

Laboratory tests: ESR, blood count, fibrinogen, uric acid, blood glucose, FT3, FT4, TSH, complement C3, C4, ATPO, Atc anti dc DNA, ASLO, RF, CRP, AMA M2, DFS70, 25-OH-vit D were within normal limits.

Figure 1. Infiltrated erythematous-edematous plaques, highly painful, located in the auricles, bilaterally

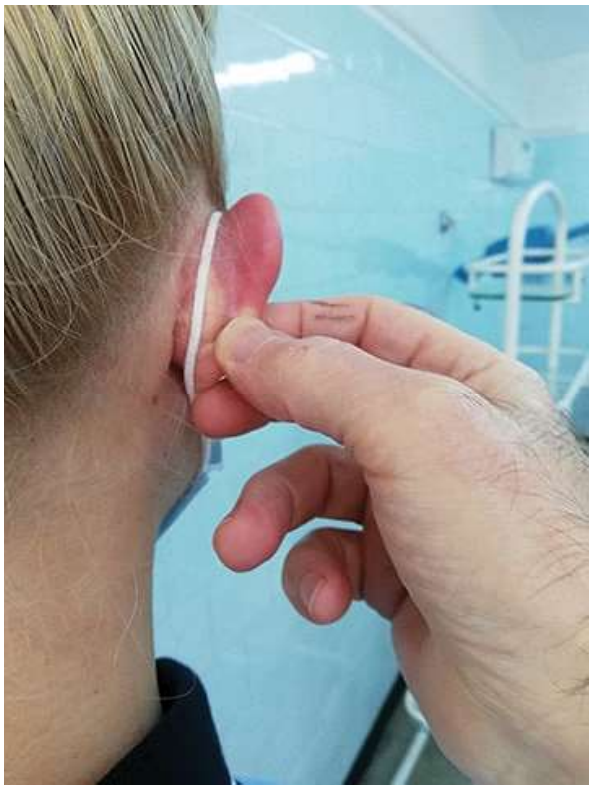

Figure .2. Infiltrated erythematous-edematous plaques, highly painful, located in the auricles, bilaterally

Pharyngeal exudate showed Klebsiella pneumoniae.

Coproparasitological examination: normal.

Under local anesthesia with Xiline 1%, we performed the biopsy of skin, respectively cartilage lesions from the pavilion of the left ear. The specimens were submitted to the Pathology Laboratory, where they were processed according to classical histopathological technique. The histopathological examination revealed:

- fragment covered by the epidermis with orthokeratosis (Fig. 3), underlying, including in the hypodermis, nodular foci composed of perivascular, perianexial (Fig. 4) and perineural lymphocytes, surrounded by fibro-collagen tissue and blood infiltrate (Fig. 5).
- microscopic structure of fibrocollagen and adipose tissue with lymphocytic infiltrate that dissects the structures, adjacent striated muscle tissue, fibrosis and cartilaginous tissue with pericartilaginous inflammatory infiltrate (Fig. 6).

Based on the clinical and on the histopathological examination, we specified the diagnosis of ***Relapsing polychondritis***.

We initiated treatment with Methylprednisolone 32 mg/day with gradual dose reduction up to 4 mg/day, Famotidine 40 mg/day, Rupatadine 10 mg/day, Levofloxacin 500 mg/day, with a slightly favorable evolution. Treat-ment with Methotrexate 10 mg/week was also initiated in December 2020. In January 2021, the patient presented with an erythematous, annular rash on the chest, remitted after increasing the dose of Methylprednisolone. Currently, the patient is receiving maintenance treatment with Medrol 4 mg every 48 hours, Methotrexate 10 mg/week, Folic acid 5 mg/week, Aspacardin 1 cp/day, vit D3 1 cp/day.

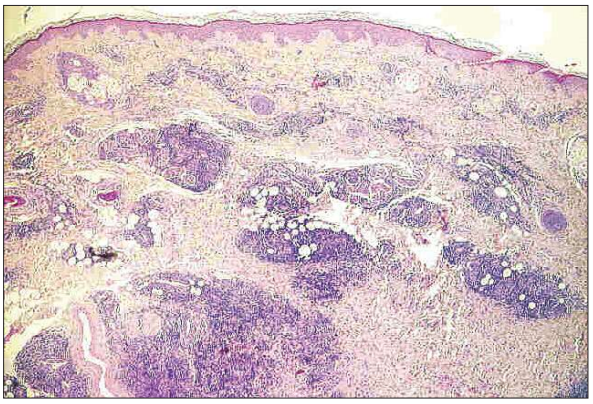

Figure 3. Skin covered by the epidermis with orthokeratosis; nodular foci of inflammatory lymphocytic infiltrates into the dermis, Col HE, X20

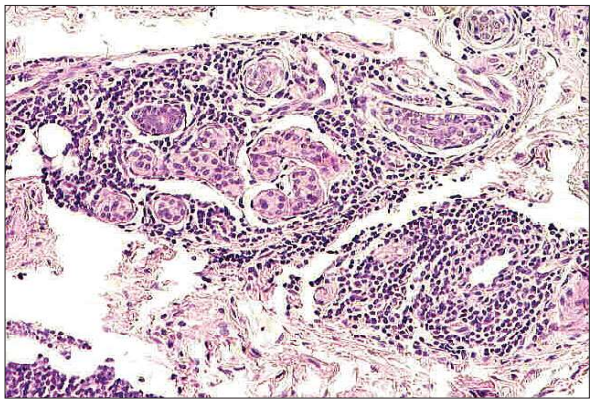

Figure 4. Nodular foci of perivascular and perianexial lymphocytes, Col. HE X100

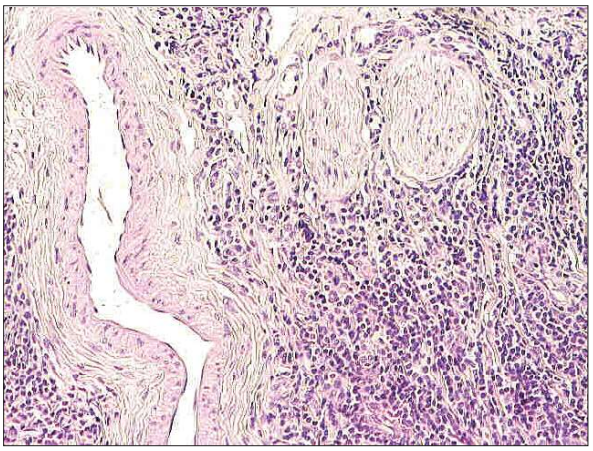

Figure 5. Nodular foci composed of perineural lymphocytes, Col. HE X100

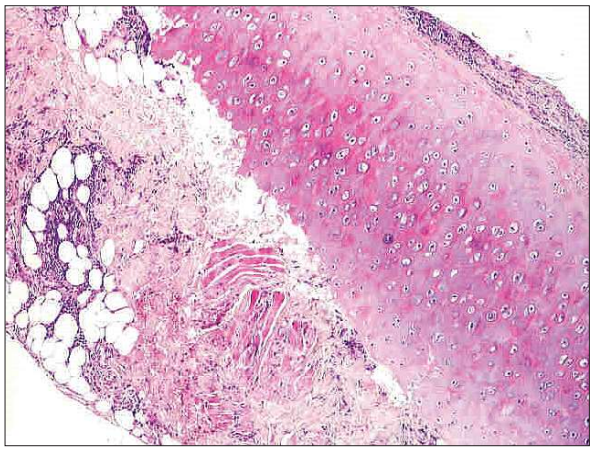

Figure 6. Fibrocollagen and adipose tissue with lymphocytic infiltrate; adjacent striated muscle tissue and cartilaginous tissue including inflammatory infiltrate COL HE X40

Discussions

Etiopathogeny

Both the humoral and the cellular immune system are involved in the etiopathogenesis of relapsing polychondritis (RP). Cellular immune reactivity to cartilage structures has been demonstrated using techniques to transform lymphocytes or inhibit macrophage migration. Buckner et al. described in a RP patient T cell clones specific for peptides corresponding to residues 261-273 of the type II collagen molecule. [7] Abnormal cellular response to cartilage proteoglycans and T lymphocyte subset imbalance have also been described in patients with RP. [8]

Both circulating antibodies and immune complexes present in the affected tissues have been described in patients with RP. They are generated by native and denatured type II collagen and collagen types IX and XI that form the major extracellular skeleton in cartilage. [9] Studies have shown that 33% of patients with RP had circulating antibodies against type II collagen in the active phase of the disease and that their titers corresponded to the activity of the disease. [10,11]

HLA class II molecules also appear to be associated with RP. Genetic studies have identified HLA-DR4 as a major risk allele for RP, while there is a negative association between the severity of organ involvement and HLA-DR6. [12] There is no evidence of family transmission.

Other known target autoantigens are matrilin-1 and cartilage oligomeric matrix proteins(COMP). Matrilin-1 is an intercellular matrix protein, widely expressed in the tracheal, nasal, atrial and chondro-sternal cartilages, but not in the normal articular cartilages of adults. COMP is found predominantly in the extra-cellular matrix of cartilage, ligaments and tendons. In a case report, Saxne and Heinegard found that serum levels of the two cartilage matrix proteins varied inversely during monitoring of a patient with RP. [13]

Unknown factors (perhaps infectious agents and/or mechanical and chemical aggression) could cause protein degradation with the consistent release of cryptic cartilage antigens. In genetically predisposed subjects, immunization may occur against these autoantigens, partially recognized in CII, matrilin-1 and COMP. This can be perpetuated by releasing pro-inflammatory cytokines and recruiting infiltrating cells in RP lesions, ultimately resulting in MMP-mediated cartilage destruction released by apoptotic chondrocytes. [14]

The clinical presentation of COVID-19 varies from asymptomatic or mild individuals with influenza-like symptoms to severe conditions with interstitial pneumonia and acute respiratory distress syndrome. In the early stages of the disease, the viral infection triggers a strong immune response, which is fundamental to viral clearance, with a cascade of events involving both innate and adaptive immunity, which can become harmful when they become irregular. Immunological changes associated with COVID-19 include an increased number of macrophages, hyperactivity of T lymphocytes, an increased plasma level of proinflammatory cytokines (IL-1B, IL6, TNF-alpha), leading to a "cytokine storm" that seems to be correlated with the severity of the disease. [15]

Several studies illustrate immunological and clinical similarities between COVID-19 disease and hyperinflammatory diseases, leading to the hypothesis that SARS-CoV-2 infection could trigger an autoimmune response in genetically predisposed subjects. [16]

Moreover, HLA (both class I and class II) and non-HLA polymorphisms are associated with autoimmune diseases, and the control of viral infections is largely mediated by the recognition of viral peptides in association with HLA-class I molecules by CD8 + effectors T cells. Notably, a recent study identified an association of HLA-DRB1 * 15:01, HLADQB1 * 06:02 (MHC-class II) and HLAB * 27:07 (MHC-class I) in 99 Italian patients with severe COVID-19 disease. Each of these alleles is associated with autoimmunity. Thus, patients with COVID-19 expressing one of these alleles may be at increased risk of developing autoimmune manifestations. [17]

In recent decades, viral infections have been proposed as environmental factors that trigger autoimmunity in genetically predisposed individuals. Respiratory viruses, especially parainfluenzae and coronaviruses, have been associated with the development of rheumatoid arthritis.[6]

Clinical aspects

RP is characterized by acute inflammatory episodes of cartilaginous structures that may show spontaneous remission, but which recur frequently and culminate in the destruction of the cartilaginous structure. It may involve systemic damage with fever, weight loss, and damage to organs such as the central nervous system, kidneys, airways, and blood vessels. [3]

Auricular chondritis, mono- or, more frequently, bilateral is the most common feature of RP, which is seen in up to 90% of patients during the disease and is the inaugural symptom in 20% of cases. The onset is sudden, with painful red-purple erythema and edema limited to the cartilaginous part of the ear, sparing the lobe, which has no cartilage. Acute inflammatory episodes tend to resolve spontaneously in a few days or weeks, with recurrence at variable intervals. As a long-term consequence of repeated eruptions, the cartilage matrix is severely damaged and replaced by fibrous connective tissue. The ears gradually lose their normal morphology, sometimes acquiring the appearance of cauliflower ears.

Nasal chondritis is present at the time of diagnosis in 24% of patients and develops later in 53% of cases. The inflammatory process involves the nasal bridge, with acute redness, tenderness and pain, usually less marked than in the ears. It may occasionally be accompanied by epistaxis. It leads to the destruction of the cartilaginous part of the nasal septum, giving the nose a "saddle" appearance. [18]

Joint damage is the second most common symptom in RP and occurs in about 50-85% of patients during the disease, but only in 33% of them is an initial feature, as in our case. The main pattern of joint damage is acute asymmetric intermittent polyarthritis or oligoarthritis that affects the metacarpophalangeal joints, proximal interphalangeal joints, knees and, less frequently, metatarsophalangeal joints and elbows. Erosions or deformities are usually not observed, although several cases of joint destruction have been reported. [19]

Ocular changes are nonspecific and include conjunctivitis, uveitis, retinopathy, optic neuritis, eyelid edema and proptosis. Episcleritis is the most common, occurring in 39% of cases. [18]

Laryngeal-tracheo-bronchial involvement is observed at first presentation in only 10% of cases, but eventually develops in half of all patients, more commonly in women. Respiratory manifestations include hoarseness, dyspnea, suffocation, wheezing, and pain in the larynx-tracheal joints. Tracheobronchial involvement has a poor prognosis, being the major cause of morbidity and mortality. [20]

Hearing loss may occur due to obstruction of the external auditory canal, otitis media or damage to the auditory branch of the cranial nerve VIII due to vasculitis. [3]

Renal complications of RP are rare. Approximately 22% of patients with RP develop some type of kidney injury, with microhematuria and/or proteinuria, but biopsy-proven nephropathy has been reported in less than 10% of patients. Renal involvement is associated with a poor prognosis, with a 10-year survival rate of 10%. In a study of 129 patients with RA, 29 had renal impairment. Mesangial expansion, cell proliferation, and necrotizing glomerulonephritis have been observed. [21,22]

Neurological manifestations are found in 3% of patients with RP, most commonly affecting the cranial nerves V and VII. Symptoms are often associated with concomitant vasculitis of the central or peripheral nervous system. Clinical manifestations include headache, meningitis, limbic encephalitis, stroke, hemiplegia, ataxia, convulsions, confusion, psychosis, and dementia. [23, 24]

Skin manifestations are found in approximately 20-30% of people with recurrent polychondritis, including: foot-and-mouth ulcers, genital ulcers and a number of nonspecific rashes, such as erythema nodosum, livedo reticularis, urticaria (present during the course of our case) and erythema multiform.

Cardiovascular system: RP can cause inflammation of the aorta, damage to the heart valves (aortic insufficiency in 4-10%, mitral regurgitation in 2%). Other charges: chest pain, abnormal heart rhythm, syncope. [25]

Associated conditions. About 25% of cases of RP are associated with other diseases. It includes autoimmune disorders (systemic lupus erythematosus, systemic sclerosis, mixed connective tissue disease, Sjögren's syndrome, dermatomyositis), rheumatic diseases (spondyloarthropathy and, more frequently, rheumatoid arthritis) and vasculitis. [26] An increasing number of cases of RP have been reported in association with malignancies, especially myelodysplastic syndrome (MDS) and, less frequently, solid tumors (bladder, breast, lung, colon, pancreas) or other haematological malignancies (lymphoma). The association of PR with MDS has been reported in the literature. Up to 27% of patients with RP have concomitant MDS. [27]

Positive diagnosis

There are no specific laboratory results for RP. Anemia, if present, is usually normochromic and normocytic and is associated with a poor prognosis. Non-specific indicators of inflammation (ESR, elevated PCR) are often present. Mild leukocytosis can be detected.

Because RP is associated with systemic disorders, an assessment based on the symptoms described to indicate the presence of associated conditions is indicated. Antinuclear antibodies, rheumatoid factor, and antiphospholipid anti-

bodies are tests that can help assess and diagnose autoimmune connective tissue diseases. [12]

Cartilage biopsy in patients with RP reveals chondrolysis, chondritis and perichondritis. Cartilage loses its basophilia, probably by the release of sulfated proteoglycans from the matrix, and chondrocytes are reduced in number and may appear pycnotic. Early RP is characterized by a mixed inflammatory infiltrate of lymphocytes, neutrophils and plasmacytes into the perichondrium. As cartilage degenerates, mononuclear cells and macrophages infiltrate the matrix. The cartilage matrix is eventually destroyed and replaced by fibrous connective tissue. Despite the presence of clinical erythema, the overlying skin is normal. [28]

The diagnosis of RP is still based on clinical manifestations, as there are no specific laboratory tests. According to McAdam et al., the diagnosis of RP can be made if three or more of the six clinical features are present: recurrent auricular chondritis; non-erosive inflammatory polyarthritis; nasal chondritis; eye inflammation; respiratory tract chondritis; audio-vestibular impairment, no histological confirmation being required. [29]

These criteria were later modified by Damiani and Levine, who expanded the spectrum of diagnostic criteria by adding the presence of at least one McAdam criterion and positive histological confirmation, or two McAdam criteria and a positive response to corticosteroids or dapson. [30] Another variant of the McAdam criteria was proposed by Michet et al. in 1986. According to the latter, the diagnosis of RP requires a confirmed inflammation in two of the three auricular, nasal or laryngotracheal cartilages or, a proven inflammation in one of the above cartilages and two other minor criteria (hearing loss, eye inflammation, vestibular dysfunction, seronegative arthritis). [31]

Our patient met the diagnostic criteria proposed by Damiani and Levine (at least one McAdam criterion and positive histological confirmation).

Differential diagnosis

RP ear chondritis should be differentiated from infectious perichondritis, chronic external otitis, trauma, insect bites, ear erysipelas, frostbite, nodular chondrodermatitis of the ear, congenital syphilis, lupus pernio. [26]

Prognosis

The 5-year survival rate was 66-74% (45% if RP is associated with systemic vasculitis). The most common causes of death associated with RP include infections secondary to corticosteroid treatment or respiratory disorders, systemic vasculitis, malignancy. Renal involvement and anemia are a poor prognostic factor at all ages. [32, 33]

Treatment

RP treatment involves the use of non-steroidal anti-inflammatory drugs and low-dose corticosteroids in cases of mild auricular/nasal chondritis or arthritis. For cases with severe manifestations, such as laryngotracheal or ocular symptoms, inflammation of the inner ear, severe auricular or nasal chondritis, systemic vasculitis, aortitis or glomerulonephritis, prednisone at 1 mg/kg/day is indicated. The use of immunosuppressants such as methotrexate, azathioprine and cyclophosphoamide is reserved for cases refractory to steroid therapy. The use of dapsone, colchicine, anti-CD4 monoclonal antibodies, D-penicillamine and antimalarials has also been described. Cyclosporine A at a dose of 5 mg/kg /day had beneficial effects for corticosteroid-resistant cases. [34 Immunosuppressive refractory cases include the use of immunomodulatory agents such as infliximab, etanercept, adalimumab and abatacept. Tocilizumab has been shown to be useful in patients who do not respond to TNF antagonists. Allogeneic and autologous hematopoietic stem cell transplantation may be an option. [35]

Relapsing polychondritis is a progressive autoimmune condition that affects several organs and tissues. Early recognition of the signs of this rare disease and prompt initiation of anti-inflammatory and immunosuppressive therapy can relieve symptoms and prevent complications, especially those affecting the respiratory tract and heart.

Conclusions

The number of case reports describing autoimmune phenomena in COVID-19 is increasing,

and these conditions may involve different organs and systems. Although the chronology of pathologies in our case suggests the possible involvement of SARS-CoV-2 infection in the occurrence of Polychondritis, we mention that so far no cases of relapsing Polychondritis associated with this viral infection have been reported.

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Conflict of interest
NONE DECLARED

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