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POST-COVID-19 IMMUNOLOGICAL DISORDER: A POSSIBLE PATHOLOGICAL ENTITY IN A 43 YEAR OLD MAN

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Abstract

Background. *Post-COVID-19 systemic inflammatory syndrome is considered to be an aquired immunological disorder, which may develop in some individuals after the remission of infection with SARS-CoV-2 and defined by inflammatory clinical manifestations (fever, arthralgias, cutaneous and mucosal pallor, physical weakness) and modified biological parametres (normochromic normocytic anaemia, increased serum levels of C reactive protein and rheumatoid factor), with no proof of an infectious process, to which corticotherapy may be a suitable therapeutic strategy.*

Case report. *A 43 year old male was admited in the Department of Internal Medicine for high fever (39,4^{o}C), moderate polyarthralgias and physical weakness, with a negative test result of SARS-CoV-2 RT-PCR. The patient had been previously diagnosed with a moderate-to-severe form of COVID-19, a month prior to the current admission. The patient also experienced transitory dry cough for a month, with no other relevant clinical abnormalities. Upon physical examination, cutaneous and scleral pallor was observed and lung auscultation revealed hardened vesicular murmur bilaterally. Blood analysis revealed normochromic normocytic anaemia and increased serum levels of rheumatoid factor and of C reactive protein, which suggested a nonspecific inflammatory syndrome.*

Although blood cultures and other microbiological tests were negative for an infectious process, a chest X-ray was performed, which detected the presence of a nodular formation in the superior left lung lobe. Several differential diagnoses were taken into consideration, including pulmonary sarcoidosis and granulomatosis with polyangiitis, both of which were excluded, clinically and biologically.

A thoracic computed tomography (CT) was later performed, which revealed the presence of a tumoral nodule in the left lung, associated with multiple mediastinal and supraclavicular lymphadenopathies, indicative of lung cancer. However, lung cancer was also excluded upon the histopathological examination of paratracheal lymphnodes, which detected multiple areas of parenchymal necrosis surrounded by dense inflammatory infiltrates, formed predominantly by histiocytes. All of these findings resulted in the diagnosis of a post-COVID-19 rheumatoid syndrome, the only therapeutic strategy being the administration of high doses of intravenous and oral methylprednisolone, which improved the patient's health.



Conclusion. *Post-COVID-19 immunological disturbances should be taken into consideration in patients who experience repetitive clinical and biological inflammatory manifestations after the remission of the infection with SARS-CoV-2, which may be improved through high dose corticosteroid therapy.*

Keywords: *post-COVID-19, immunological disturbance, inflammation, corticotherapy.*

Rezumat

Introducere. *Sindromul inflamator sistemic post-COVID-19 este considerat o perturbare imunologică dobândită, ce se poate dezvolta, la anumiți indivizi, după remisiunea infecției cu SARS-CoV-2, și definită de manifestări clinice inflamatorii (febră, artralgii, paloare cutaneo-mucoasă, astenie fizică) și parametri biologici modificați (anemie normocromă normocitară, niveluri serice crescute ale proteinei C reactive și ale factorului reumatoid), fără dovada unei infecții, la care corticoterapia ar putea fi o strategie terapeutică potrivită.*

Prezentare de caz. *Bărbat în vârstă de 43 de ani se internează în secția de medicină internă pentru febră înaltă (39,4^{o}C), poliartralgii moderate și astenie fizică, având test RT-PCR negativ pentru SARS-CoV-2. Pacientul fusese diagnosticat anterior cu formă moderat-severă de COVID-19, cu o lună înaintea prezentei internări. Pacientul prezintă, de asemenea, tuse seacă tranzitorie de o lună, fără alte modificări clinice.*

La examenul fizic se observă paloare cutaneo-mucoasă, iar auscultația pulmonară decelează murmur vezicular înăsprit bilateral.

Analizele de sânge decelează anemie normocromă normocitară și creșterea nivelului seric al factorului reumatoid și al proteinei C reactive, sugerând astfel un sindrom inflamator nespecific. Deși rezultatele hemoculturilor și ale altor teste microbiologice au fost negative pentru un proces infecțios, s-a efectuat o radiografie toracică, ce a relevat prezența unei formațiuni nodulare la nivelul lobului pulmonar superior stâng. S-au luat în considerare mai multe diagnostice diferențiale, incluzând sarcoidoza pulmonară și granulomatoza cu poliangiită, ambele fiind excluse, atât clinic, cât și biologic. Ulterior a fost efectuată o tomografie computerizată toracică, care a relevat prezența unei formațiuni tumorale la nivelul pulmonului stâng, asociată cu multiple adenopatii mediastinale și supraclaviculare, sugestive unui cancer bronhopulmonar.

Cu toate acestea, cancerul bronhopulmonar a fost, la rândul său, exclus, ca urmare a examinării histopatologice a ganglionilor limfatici paratraheali, care a evidențiat multiple arii de necroză parenchimatoasă încojurate de un bogat infiltrat inflamator, predominant format

din histiocite. Toate aceste aspecte revelatoare au condus la diagnosticul de sindrom reumatoid post-COVID-19, unica strategie terapeutică fiind administrarea intravenoasă și orală de doze mari de metil-prednisolon, care a ameliorat starea clinică a pacientului.
***Concluzie**. Perturbările imunologice post-COVID-19 ar trebuie luate în considerare la pacienții care exprimă manifestări clinice și biologice inflamatorii repetitive în urma remisiei infecției cu SARS-CoV-2, ce ar putea fi ameliorate prin terapia cu doze mari de corticosteroizi.*
***Cuvinte-cheie**: post-COVID-19, perturbare imunologică, inflamație, corticoterapie.*

Introduction

Over the last two years through the on-going pandemic, COVID-19 (coronavirus disease 2019), determined by the infection with SARS-CoV-2 (severe acute respiratory syndrome coronavirus type 2), has been proved to be not only an infectious respiratory disease, but also a systemic pathological entity, given the multicelullar distribution of the ACE-2 (angiotensin-converting enzyme type 2) receptor for SARS-CoV-2 and the host's violent immune response to the infection, associated, in the severe forms of the disease, with an hyperinflammatory state due to the massive secretion of proinflammatory cytokines (such as IL-1β, IL-6, TNF-α), with hyperferritinemia, lymphopenia and increased levels of inflammatory markers, such as C reactive protein.

Although the complications of COVID-19 are well-defined, such as acute respiratory distress syndrome (ARDS) and multiorgan dysfunction syndrome (MODS), less is known about the post-COVID-19 syndrome, which may developed in some patients previously infected with SARS-CoV-2 and which is characterized by persistent clinical manifestations, with no proof of other infectious processes, as the World Health Organisation (WHO) stated in October 2021: "Post-COVID-19 condition occurs in individuals with **a history of probable or confirmed SARS CoV-2 infection**, usually **3 months from the onset of COVID-19 with symptoms and that last for at least 2 months and cannot be explained by an alternative diagnosis"[1]. Although the molecular and cellular pathophysiology that governs the onset and development of post-COVID-19 syndrome is currently unknown, recent studies have suggested several potential pathogenic mechanisms: virus-specific pathophysiological changes, immunologial aberrations and inflammatory damage induced by the acute infection and post-critical disease sequelae[2].**

Case report

The following case report describes a 1 year clinical and biological evolution of a patient admitted in the Department of Internal Medicine for prolonged inflammatory clinical manifestations, with no proof of an infectious process.

A 43 year old male was admitted in the Department of Internal Medicine, in January 2021, for high fever (39,4^{o}C), moderate polyarthralgias and physical weakness, the onset of these manifestations being described 10 days before the current admission. The patient was previously diagnosed with moderate-to-severe form of



COVID-19, in december 2020. Upon admission, the SARS-CoV-2 RT-PCR test was negative. During the patient's history, it was noted that the febrile state was continuous or sustained during the day and unresponsive to antipiretics and associated with moderate generalized myalgias.

Furthermore, the patient had loss of appetite and a weight loss of aproximately 5 kilograms in the last month.

It should be emphasized that 12 days before the current admission, the patient was discharged from the Department of Pulmonology, to which he had been admitted for dry cough and dyspnea. Having had a negative SARS-CoV-2 RT-PCR test, during the admission he underwent a thoracic computed tomography, which revealed a nodular formation in his left superior lobe. Suspecting a malignant pulmonary tumor, the pulmonologists performed a bronchoalveolar lavage, which did not reveal any cancerous cells, hence removing the suspicion of lung cancer . Eventhough the patient was clinically stable at the time of the discharge from the Department of Pulmonology, within a week he developed the signs and symptoms which determined his re-admission in January 2021.

Upon physical examination, the patient had an altered clinical state, with fever (39,4^{o}C), associated with shivers, physical weakness and cutaneous and mucosal pallor. The superficial lymph nodes were not palpable or sensitive; the lung auscultation revealed hardened vesicular murmur at the base of the lungs bilaterally, a heart rate of 97/min and an arterial pressure of 135/90 mmHg, with no other clinically significant findings.

An electrocardiogram was performed, which showed sinus rhythm and mildly accelerated heart rate (98/min), with no other electrical abnormality. An abdominal ultrasound was also performed and revealed grade II hepatic steatosis, with no enlarged spleen or dimensional anomalies of the portal venous system and no fluid accumulation in the peritoneal cavity.

The patient underwent a chest X-ray, which revealed a round-shaped opacity, with high intensity and with a diameter of approximately 1,5-2 cm (Figure 1).

Blood analyses were also performed and they included blood biochemistry, complete blood count and immunology. Blood biochemistry showed mixed dyslipidaemia and cholestasis, as shown in table 1. Mixed dyslipidaemia was revealed by increased serum levels of total cholesterol and of triglycerides, whereas cholestasis was diagnosed based on the increased levels of alkalin phosphatase and GGT (Table 2). The analysis of the complete blood count showed a mild form of normochromic normocytic anaemia, with a haemoglobin value of 12,00 g/dl (Table 2).

It must be noted that the C reactive protein serum levels were increased, up to 85,27

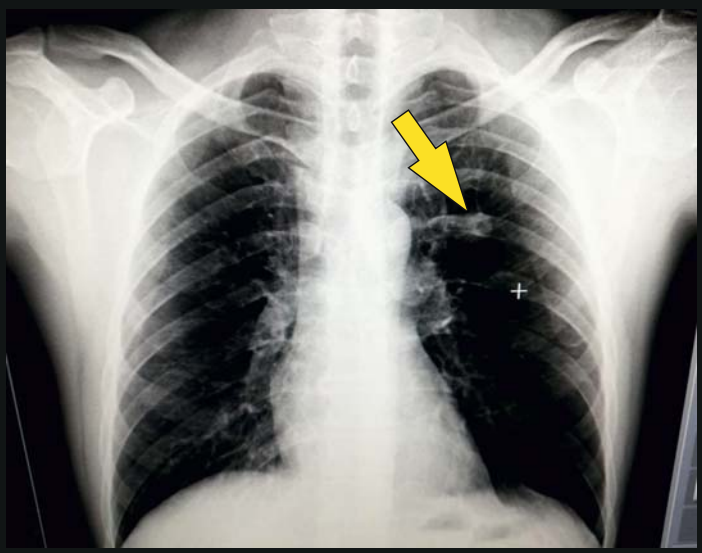


Figure 1. *Patient's X-ray (January 2021), showing a nodular formation in the left upper lobe (yellow arrow)*

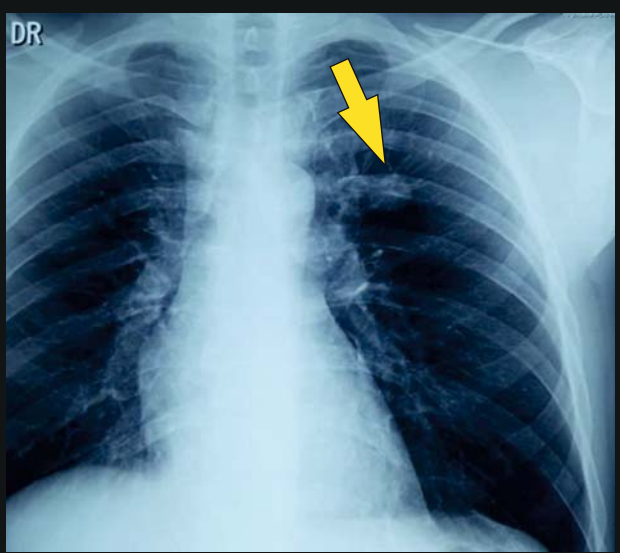


Figure 2. *Persistent nodular formation in the patient's left upper lober (yellow arrow)*

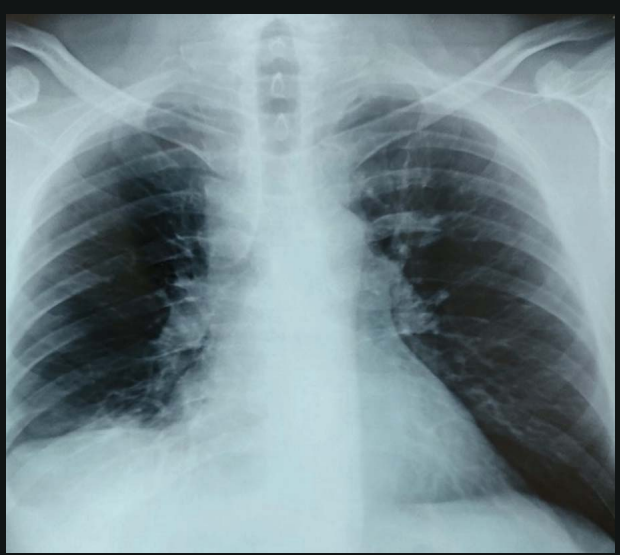


Figure 4. *Patient's chest X-ray – the absence of the nodular opacity (March 2022)*



mg/dl (normal values: 0-5 mg/dl). Thus, a diagnosis of a nonspecific inflammatory syndrome associated with normochromic normocytic anaemia was formulated. Along with the patient's clinical manifestations, defined by dry cough, high fever and physical weakness, a pulmonary infection was suspected, which laid the foundation of a sputum culture.

However, the sputum culture was negative for the following bacteria: Mycobacterium tuberculosis, Staphylococcus aureus, Streptococcus, other Gram-negative bacteria, which excluded the possibility of a pulmonary infection.

Other biological findings showed the following modifications: increased serum levels of rheumatoid factor (14,63 U/mL, with a normal range of 0-14 U/mL), increased serum levels of C3 complement fraction (192 mg/dL, with a normal rage of 90-180 mg/dL) and increased levels of D-dimers (1,94 µg/mL, with a normal range of 0-0,5 µg/dL).

Taking all of these clinical and biological modifications into consideration, several differential diagnoses were confronted: autoimmune diseases, infectious diseases and other pathological entities, such as lung cancer, pulmonary plasmocytoma and pulmonary sarcoidosis.

1. Autoimmune diseases were suspected since the patient expressed polyarthralgias, high fever, high serum levels of rheumatoid factor and of C reactive protein.

The prototype of autoimmune diseases, represented by systemic lupus erythematosous (SLE), was excluded from the beginning, since the patient did no express small joint inflammation, skin lessions or rash and there were no incresed levels of anti-nuclear antibodies (ANA) or lupus cells (Hargraves cells) in the serum. It must be noted that the diagnosis of SLE is very rare in males and more commonly aknowledged in young fertile women, since one of the pressumed risk factors for the development of this autoimmune disease is the hormonal status of the female biology.

However, two autoimmune diseases were confronted: rheumatoid arthritis and granulomatosis with polyangiitis.

a. Rheumatoid arthritis was taken into consideration since the patient experienced moderate arthralgias, high fever, developed a pulmonary nodule – which was suspected to be rheumatoid in nature – and expressed high levels of serum rheumatoid factor and of C reactive protein.

   However, this disease was excluded, both clinically and biologically, because the patient did not manifest signs of joint inflammation – the absence of some of the Celcian signs: redness, swelling, heat – or rheumatoid nodules. Furthermore,

PARAMETRE	RESULT	NORMAL VALUES
Serum uric acid	5,49	3,40 – 7,00
Serum amilase	37,13	28,00 – 100,00
Total serum bilirubin	0,20	00,00 – 0,30
Total serum cholesterol	241,03	**120,00 – 200,00**
Serum creatinin	0,74	0,70 – 1,20
Alkalin phosphatase	**188,53**	**40,00 – 129,00**
GGT	**145,98**	**8,00 – 61,00**
Glucose	87,34	65,00 – 115,00
Glycated haemoglobin	5,20	4,80 – 5,60
Serum K^+	3,72	3,50 – 5,10
Serum proteins	6,78	6,60 – 8,70
Serum iron	158,03	59 – 158,00
Serum Na^+	139,10	135,00 – 148,00
GOT	21,57	<32 U/L
GPT	**96,41**	**<33 U/L**
Serum triglycerides	**307,45**	**40,00 – 150,00**
Serum urea	37,91	10,00 – 50,00

Table 1: *Patient's blood biochemistry (January 2021). Modified parametres are highlighted in yellow*

PARAMETRE	RESULT	NORMAL VALUES
Basophil count	0,09	00,00 – 0,20
Eosinophil count	0,38	0,00 – 0,70
Hematocrit (%)	**35,50**	**37,00 – 52,00**
Haemoglobin (g/dl)	**12,00**	**12,30 – 17,00**
Lymphocyte count	3,18	1,50 – 4,50
Medium cell haemoglobin (MCH)	31,10	27,00 – 32,00
Medium cell volume (MCV)	92,00	80,00 – 100,00
Monocyte count	0,45	0,20 – 1,00
Neutrophil count	5,67	2,00 – 8,00
Platelet count	343,00	150,00 – 450,00
Red blood cells	**3,86**	**4,50 – 6,20**
Leukocyte count	9,77	4,00 – 11,00

Table 2: *Patient's complete blood count (January 2021)*

PARAMETRE	RESULT	NORMAL VALUES
Basophil count	0,02	00,00 – 0,20
Eosinophil count	0,00	00,00 – 2,00
Hematocrit (%)	**23,50**	**37,00 – 52,00**
Haemoglobin (g/dl)	**7,10**	**12,30 – 17,00**
Lymphocyte count	3,05	1,50 – 4,50
Medium cell haemoglobin (MCH)	29,80	27,00 – 32,00
Medium cell volume (MCV)	98,50	80,00 – 100,00
Monocyte count	0,25	0,20 – 1,00
Neutrophil count	4,51	2,00 – 8,00
Platelet count	235,00	150,00 – 450
Red blood cells	**2,15**	**4,00 – 11,00**

Table 3. *Patient's complete blood count (March 2021)*

PARAMETRE	RESULT	NORMAL VALUES
Basophil count	0,02	00,00 – 0,20
Eosinophil count	0,01	00,00 – 0,70
Hematocrit (%)	**33,30**	**37,00 – 52,00**
Haemoglobin (g /dl)	**11,10**	**12,30 – 17,00**
Lymphocyte count	3,23	1,50 – 4,50
MCH	24,50	27,00 – 32,00
MCV	99,80	80,00 – 100,00
Monocyte count	0,41	0,20 – 1,00
Neutrophil count	**8,31**	**2,00 – 8,00**
Platelet count	213,00	150,00 – 450.00
Red blood cells	**3,26**	**4,50 – 6,20**
Leukocyte count	**11,98**	**4,00 – 11,00**

Table 4. *Patient's complete blood count (April 2021)*

although increased serum levels of rheumatoid factor would suggest a possible rheumatoid arthritis, this element, once increased in the plasma, should not be aknowledged as a specific marker of this particular autoimmune entitity, but a nonspecific element, which increases in numerous diseases, which may be autoimmune, as well as infectious in nature.

b. Granulamatosis with polyangitiis, the most severe of ANCA-positive systemic vasculitides, was also suspected based especially on the patient's pulmonary manifestations – dry cough and the radiological expression of a pulmonary lession in particular, and based on the presence of increased inflammatory markers. However, none of this systemic vasculitis' suggestive clinical manifestations were completely expressed – absence of upper respiratory symptomes, absence of cutaneous petechiae or purpura, blood in the urine, nor the biological findings were compatible with this autoimmune disease: cANCA were negative. Also, the patient's chest X-ray showed a solitary pulmonary nodule, whereas the lung involvement in granulomatosis with polyangiitis is usually expressed by multiple pulmonary nodules.

2. Infectious disease were also excluded. These included pulmonary tuberculosis and luetic pneumonia.

Pulmonary tuberculosis was the main infectious disease suspected, because the patient expressed several suggestive manifestations: loss of appetite, weight loss, fever associated with shivers, dry cough and the pulmonary nodule found on the chest X-ray. However, the fever expressed by the patient was continuous, which was not associated with hyperhydrosis and presence during the night and the cough was not accompanied by chest pain or hemoptysis. The main biological finding which removed pulmonary tuberculosis from the diagnosis was the negative test result for Mycobacterium tuberculosis in the sputum culture.

Other respiratory infectious diseases were excluded based on the patient's history, physical examination and absence of epidemiological relevant aspects.

3. Pulmonary sarcoidosis, including its acute form of manifestation, represented by Löfgren's syndrome - defined by the triad erythema nodosum - bilateral hilar lymphadenopathy - arthritis, was excluded, based on the patient's physical examination and biological findings: absence of skin nodules or lessions and arthritis, absence of lymphadenopathy and diffuse pulmonary infiltrates on the chest X-ray and, most importantly, the presence of a normal serum level of angiotensin-convertase. The serum calcium levels were also in normal range, whereas in the majority of cases of sarcoidosis there is hypercalcaemia.

4. Pulmonary plasmocytoma may develop, in some rare cases, in the context of multiple myeloma. This entity was suspected based not only on the patient's symptoms - fever, physical weakness, weight loss and loss of appetite, but also on the presence of the nodular formation revealed by the chest X-ray: a solitary nodular formation.

However, the patient did not have bone pains and the laboratory findings did not reveal hyperproteinaemia, indicative of increased serum levels of abnormal immunoglobulins (paraproteinaemia), hypercalcaemia, which would suggest osteolysis and the CRAB

tetrad, defined by the association of calcium elevation – renal failure – anaemia – bone lessions. The only element which was revealed by this clinico-biological tetrad was anaemia, all other biological parametres being in normal range: normal range of serum calcium levels, normal serum levels of creatinin, no bone lessions discovered.

5. Lung cancer was excluded by the Department of Pulmonology in which the patient was previously admitted, through the bronchoalveolar lavage, which revealed the absence of cancerous cells. In the Department of Internal Medicine, the patient had no clinically relevant findings during the clinical examination of the respiratory system and also no associated risk factors: non-smoker and no exposure to respiratory irritants.

The only elements which determined the suspicion of lung cancer was the tumoral nodule found on the chest X-ray, polyarthralgias and increased levels of serum rheumatoid factor and of C reactive protein, which could have been indicative of a rheumatoid paraneoplastic syndrome associated with lung cancer.

Having excluded all of these diseases, the only therapeutic alternative to relieve the patient's altered clinical

state (fever, polyarthralgias, physical weakness, which suggested a noninfectious systemic inflammatory process) was the administration of 500 mg of intravenous methyprednisolone. Wihin 12 hours of administration, the patient's general clinical state was improved; the improvement included regain of appetite, decrease of body temperature down to normal values and relief of arthralgias.

The main diagnosis that was formulated was post-COVID-19 rheumatoid syndrome, which, at the time, was considered to be a systemic inflammatory reaction to the previous infection with SARS-CoV-2, with no other diagnostic alternative.

The patient was later discharged in good clinical condition, but it was decided that he would begin corticotherapy at home, with 16 mg of methyprednisolon per day.

March 2021 admission

The patient was readmitted in the Department of Internal Medicine during March 2021, for the same clinical manifestations - high prolonged fever (38,5 - 39^{o}C) associated with shivers, polyarthralgias and physical weakness. The patient also experienced moderate and diffuse muscle cramps, but he denied any episodes of dry cough during the last two months.

The physical examination of the patient yet again revealed cutaneous and mucosal pallor, decreased temperature of the

extremities, but also decreased blood pressure, with a value of 100/60 mmHg, and a heart rate of 98/min.

Laboratory tests revealed a dramatic decrease in haemoglobin, with a value of 7,10 g/dL, with no other modifications regarding the complete blood count, which suggested a severe normochromic normocytic anaemia (Table 2). Also, along with this severe modified biological parametre, a dramatic increase in serum C reactive protein was also revealed, with a value of 135,33 mg/dL, associated with a slight increase in serum rheumatoid factor (14,74 UI/mL), which suggested a systemic inflammatory process, as in during the first admission.

Regarding the patient's chest X-ray, there were no significant changes, the round-shaped opacity in the upper left lobe being still present at the time of the patient's second admission.

The first step in improving the patient's general clinical state was to provide red blood cell transfusion, which helped increase the patient's haemoglobin concentration. During the admission, the patient also received 500 mg of methyprednisolone intravenously.

The patient later underwent a thoracic computed tomography, to elucidate the exact anatomical expansion of the lung mass revealed by the chest X-ray.

The computed tomography not only did reveal a lung mass in the upper left lobe, but also multiple mediastinal and supraclavicular lymphadenopaties, which clearly suggested a possible metastasized lung cancer. Hence, the patient was reffered to the Department of Thoracic Surgery, in order to have a clear vision on the nature of the lung mass.

However, thoracotomy was not possible to be performed, given the post-COVID-19 status of the patient, the only alternative being the biopsy and histological examination of the paratracheal enlarged lymphnodes. The result of the examined tissue revealed multiple areas of parenchymal inflammation surrounded by dense inflammatory infiltrates, predominantly formed by histiocytes, with no cellular abnormalities indicative of a cancerous growth. Thus, lung cancer was eventually excluded from the entire diagnostic algorithm. It should also be noted that, prior to the lymphnode biopsy, the patient underwent several laboratory tests.

The most important biological features which were revealed at the time were as follows: very increased levels of C reactive protein (388,88 mg/dL), increased levels of procalcitonin (12 µg/mL, with a normal range of < 0,5 µg/mL) and dramatic increase in ferritin levels (2437,75 µg/L, with a normal range of 20-259 µg/L), which suggested the presence of a hyperferritinemic syndrome. This pathophysiological and clinical entity develops during severe forms of COVID-19 and in other pathological conditions as well (such as autoimmune or autoinflammatory, but also in some forms of malignancies), being associated with macrophage activation syndrome or cytokine storm and defining a hyperinflammatory state.

Given the fact that the patient had a negative SARS-CoV-2 RT PCR test and was haemodinamically stable at the time of these investigations occured, COVID-19 was excluded, but other possible diseases, in which hyperferritinemia develops, were taken into consideration for another differential diagnosis. Two of these possible diseases were adult-onset Still disease – an autoinflammatory syndrome – and catastrophic antiphospholipid syndrome, yet none of these diseases coresponded to the patient's clinical manifestations and laboratory findings.

Eventually, the main diagnosis, as in the first admission, was post-COVID-19 inflammatory



syndrome, which it came to be defined as a chronic inflammatory reaction induced by the infection with SARS-CoV-2, which was most probably responsive to high doses of corticosteroids. Regarding the round-shaped lung mass revealed by the chest X-ray and thoracic computed tomography, it was proposed that it was inflammatory in nature and not cancerous, given the previous biopsy result.

Although the patient was discharged with good clinical condition, he received a higher dosage of methylprednisolone compared with the previous recommendation; it was decided that the dose should be increased from 16 mg to 24 mg per day.

April 2021 admission

The patient returned for admission for the third time, in April 2021, for fever and polyarthralgias, associated with multiple episodes of vomiting and loss of appetite. The physical examination of the patient revealed not only persistent cutaneous and mucosal pallor, but also one of the adverse effects of long-term corticotherapy: the cushingoid facies. The complete blood count, however, showed moderate normochromic normocytic anaemia, associated with discrete leukocytosis with neutrophilia.

Even though the patient's inflammatory markers were still increased (C reactive protein, rheumatoid factor), the chest X-ray did not reveal a dimensional expansion of the nodular formation. As in during the last admissions, the patient's condition clinically improved after high doses of methylprednisolone.

Given the known adverse effects of long-term use of corticosteroids, it was decided that the patient should receive calcium, vitamin D_3, potassium and Metoprolol. Also, because the patient developed generalized anxiety, a psychiatric consult proposed the oral administration of anxiolytics.

Further admissions: September 2021, November 2021, March 2022

In September 2021, the patient was reinfected with SARS-CoV-2, according to a RT-PCR test and experiencing mild symptoms: dry cough, moderate fever, headache. A week after the remission of the infection, the patient was admitted in the Department of Internal Medicine for diarrhea, physical weakness and headaches.

During admission, the patient received symptomatic treatment, but also 500 mg of methylprednisolone intravenously, which determined the patient's health improvement. At home, it was decided the patient should dose from 24 mg to 32 mg methylprednisolone per day.

In November 2021, however, the patient was readmitted for severe dorsalgia, with no

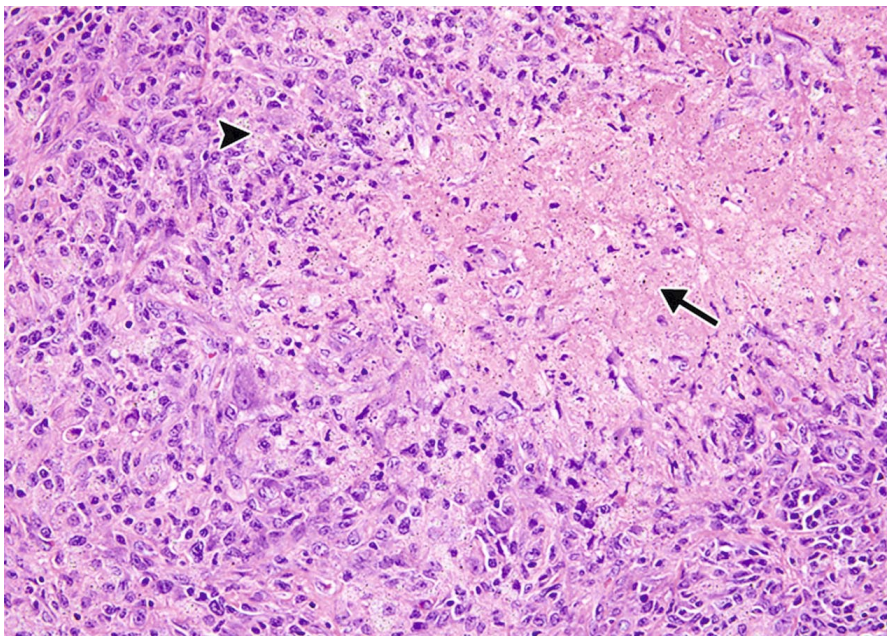


Figure 3. *Parenchymal necrosis (long black arrow) associated with dense inflammatory infiltrates (short black arrow)*

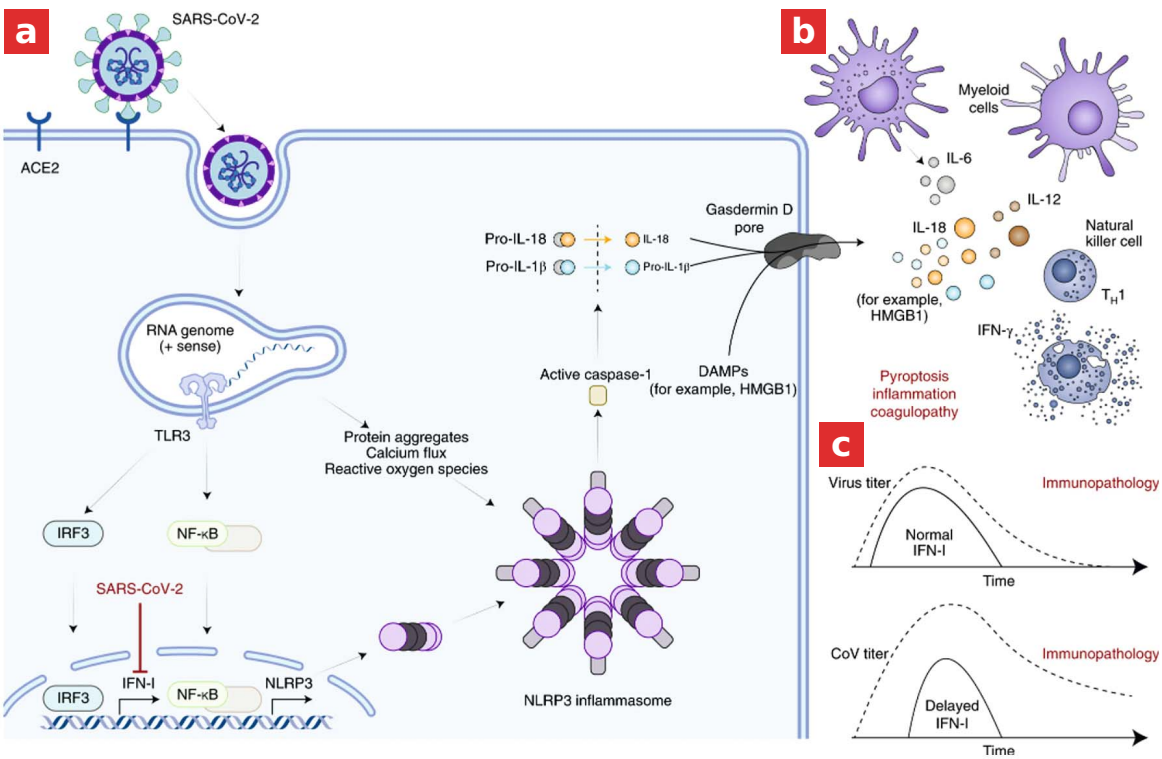


Figure 5. *Immune pathology of SARS COV-2 virus* ***a.*** *SARS-CoV-2 viruses bind to the ACE2 receptor for cell entry. Viral RNA is recognized by TLR3, which triggers transcriptional responses and cytoplasmic changes that activate the NLRP3 inflammasome. This leads to cleavage of precursor IL-1β (pro-IL-1β), pro-IL-18 and gasdermin D, allowing secretion of IL-1β and IL-18. These changes collectively induce pyroptosis, inflammation and coagulopathy.* ***b.*** *Secreted IL-18 together with IL-12 from myeloid cells stimulate TH1 immunity and natural killer cells to secrete IFN-γ.* ***c.*** *A key feature of coronaviruses (MERS-CoV, SARS-CoV) is a capability to inhibit and delay the type I IFN response, leading to increased viral replication and severe immunopathology. Adapted from: Petter Brodin, immune determinants of COVID-19 diseas presentation and severity, Nature Medicine volume 27, pages28-33 (2021)*

other clinically significant manifestations. The patient underwent a lumbar region magnetic resonance imaging, which revealed multiple lumbar vertebra compression fractures, affecting the lumbar nerves, which explained the pain. The vertebral fractures were induced by one of the most severe effects of long-term corticotherapy: osteoporosis.

Given the fact that the decision to lower the doses of corticosteroids would have "reignited" the previous inflammatory manifestations, neurosurgical intervention was no possible. Hence, the patient received moderate doses of analgesics for the pain management, but also calcium gluconate, vitamin D_3 and 1 capsule of ibandronic acid per month.

The last admission of the patient took place in March 2022. A month prior to the admission, however, the patient was infected with SARS-CoV-2 for the third time in the last year, experiencing a mild form of COVID-19.

After the remission of the infection, the patient was readmitted for multiple episodes of vomiting, severe headaches and physical weakness. Mild polyarthralgias and muscle were also present, along with mild cutaneous and mucosal pallor, low temperature of the extremities, blood pressure of 95/90 mmHg and very increased heart rate (130/min). Although normochromic normocytic anaemia was still present, D-dimers were also increased in the serum. However, the last chest X-ray of the patient revealed the absence of the lung mass, which was interpreted as a clear effect of the long-term corticotherapy.

The patient's general condition improved after several days of 500 mg of intravenous methylprednisolone, intravenous fluids and antiemetic therapy. At home, the patient increased the dose from 24 mg to 32 mg methylprednisolone per day.

Discussions

Since the start of the COVID-19 pandemic, an increasing number of studies have focused on rapid diagnosis, development, and redirection of new therapies. However, it was discovered that COVID-19 is more than just a respiratory syndrome[3,4,5]. High levels of endogenous chemical substances produced in response to the inflammation caused by this virus are capable of generating alterations and disturbances in target tissues.

They even go beyond the barriers of protection of the innate tissue immunity, reaching the systemic level through hematogenous transmission[6]. Furthermore, during the development of the sepsis process, a high level of proinflammatory cytokines (IL-6, IL-1 and TNF-α) with pleiotropic abilities have been found to

interact with their high-density receptors, immune cells, and vasculature[7]. These cytokines can stimulate a large number of processes involved with the activation of immune cells in response to changes in the vascular environment, promoting greater adhesion and blood procoagulation[8]. As a consequence, this signaling stimulates immunity cells involved in chronic inflammatory processes that can lead to pulmonary degeneration, pulmonary fibrosis, loss of function (with impaired oxygenation, culminating in a state of delayed hypoxia), hypoxemia, and anoxia (in more severe conditions), ultimately causing death[9].

A review has proposed that T-cells dysfunction may promote long COVID pathophysiology similarly in autoimmune diseases[10].

B-cells may also be involved in long COVID autoimmunity. In a study analysing serum samples from hospitalized COVID-19 patients, antiphospholipid autoantibodies were detected in 52% of samples, which were further associated with neutrophil hyperactivity and more severe clinical outcomes[11]. Other studies have also identified autoantibodies against interferons, neutrophils, connective tissues, cyclic citrullinated peptides, and cell nucleus in 10–50% of patients with COVID- 19[12,13,14,15]. While it is unconfirmed if such autoantibodies are long-lasting in COVID-19, research review has strongly linked these autoantibodies to chronic autoimmune diseases, such as antiphospholipid and Sjogren syndromes, lupus erythematosus, and rheumatoid arthritis[16].

Furthermore, numerous cases of multisystem inflammatory syndrome (MIS) occurring 2–6 weeks after SARSCoV- 2 infection in children and adults have been documented. These patients do not necessarily have a positive SARS-CoV-2 status or severe respiratory disease. Yet they showed elevated levels of systemic pro-inflammatory markers (e.g. CRP, interleukin-6; IL-6, ferritin, and Ddimer) and severe shock, cardiac, gastrointestinal, or neurological symptoms[17,18,19,20,21]. Therefore, it may be possible that residual inflammation and symptoms from post-SARS-CoV-2 MIS could lead to long COVID in children and adults. Indeed, increased levels of pro-inflammatory markers (e.g. CRP, IL-6, and D-dimer) and lymphopenia have been associated with long COVID (section 'Patient and Clinical Characteristics')

Elevated blood urea nitrogen (BUN) and D-dimer levels were found to be risk factors for pulmonary dysfunction among survivors of COVID-19 at three-month post-hospital discharge[22]. Other studies have shown that COVID-19 pulmonary lesions at two-month post-admission were associated with elevated systemic inflammatory biomarkers, such as D-dimer, interleukin-6 (IL-6), and CRP[23,24].

Systemic inflammatory biomarkers (e.g. CRP, procalcitonin, and neutrophil count) also correlated with radiological abnormalities of the heart, liver, and kidney in a 2- to 3-month follow-up study of discharged COVID-19 patients[25]. In another study, increased D-dimer and CRP levels and decreased lymphocytes were more common in COVID-19 survivors who developed persistent symptoms than their fully recovered counterparts [26].

Another report also found that lymphopenia correlated with chest tightness and heart palpitations, whereas elevated troponin-1 correlated with fatigue, among sufferers of long COVID [27]. Therefore, changes in levels of D-dimer, CRP, and lymphocyte appeared consistent in a few studies, and may serve as potential biomarkers of long COVID.

Before confirming long COVID (as it remains a diagnosis of exclusion), SARD (Systemic Autoimmune Rheumatic Diseases) should be considered in a differential diagnosis as manifestations of several rheumatic diseases may mimic long COVID. A study made in 2020 that included a total of 29 patients, 69% of patients were found to have one of the following autoantibodies suggesting post-COVID-19 autoimmune reaction: antinuclear antibody (ANA), antineutrophil cytoplasmic antibodies (ANCA), anti-cardiolipin (aCL), anti-beta-2-glycoprotein-1 (anti-β2GP1) and anti-cyclic citrullinated peptide (anti-CCP)[28]. But the top three most commonly observed autoantibodies in COVID-19 patients were ANA, aCL and anti-β2GP1. The only probleme is that pre-COVID immunology status was not available in this study.

However, it is unclear how often ACPA occur after COVID-19 and whether they differ from ACPA normally found in patients with RA, but ANCA and RA after SARS-Cov-2 infection have also been described[29,30].

Another study showed that Elevated IL-6 is associated with persistent pulmonary lesions in COVID-19 patients following their acute recovery[31]. Study done by Marvisi et el. patients with evidence of pulmonary fibrosis after recovering from acute COVID-19 had a higher level of systemic inflammation at admission (ESR, CRP and D-dimer) and bone marrow suppression as evidenced by thrombo-cytopenia, leukopenia and low haemoglobin[32]. The main difficulty is that the result of those studies where not consistently replicated in others, and we can observ that in Moreno-Perez et al., in their study they found that baseline clinical features such as CRP, D-dimer were not associated to predict long COVID[33].

Conclusion

The patient's medical history is governed by prolonged clinical and biological inflammatory manifestations, with no proof of a classic autoimmune or infectious disease. Given the fact that the clinical and biological inflammatory manifestations of the patient became apparent secondary to the infection with SARS-CoV-2 and that the only therapeutic strategy which proved to be clinically suitable is represented by high doses of corticosteroids, a possible aquired autoimmune disease or autoinflammatory syndrome should be taken into consideration. In this case, it should be considered whether or not SARS-CoV-2 would operate on a genetically predisposed background which would induce, at some point in time, important immunological disturbances, similarly to those encountered in autoimmune or autoinflammatory diseases.

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