Seronegative Erosive Arthritis Following SARS-CoV-2 Infection

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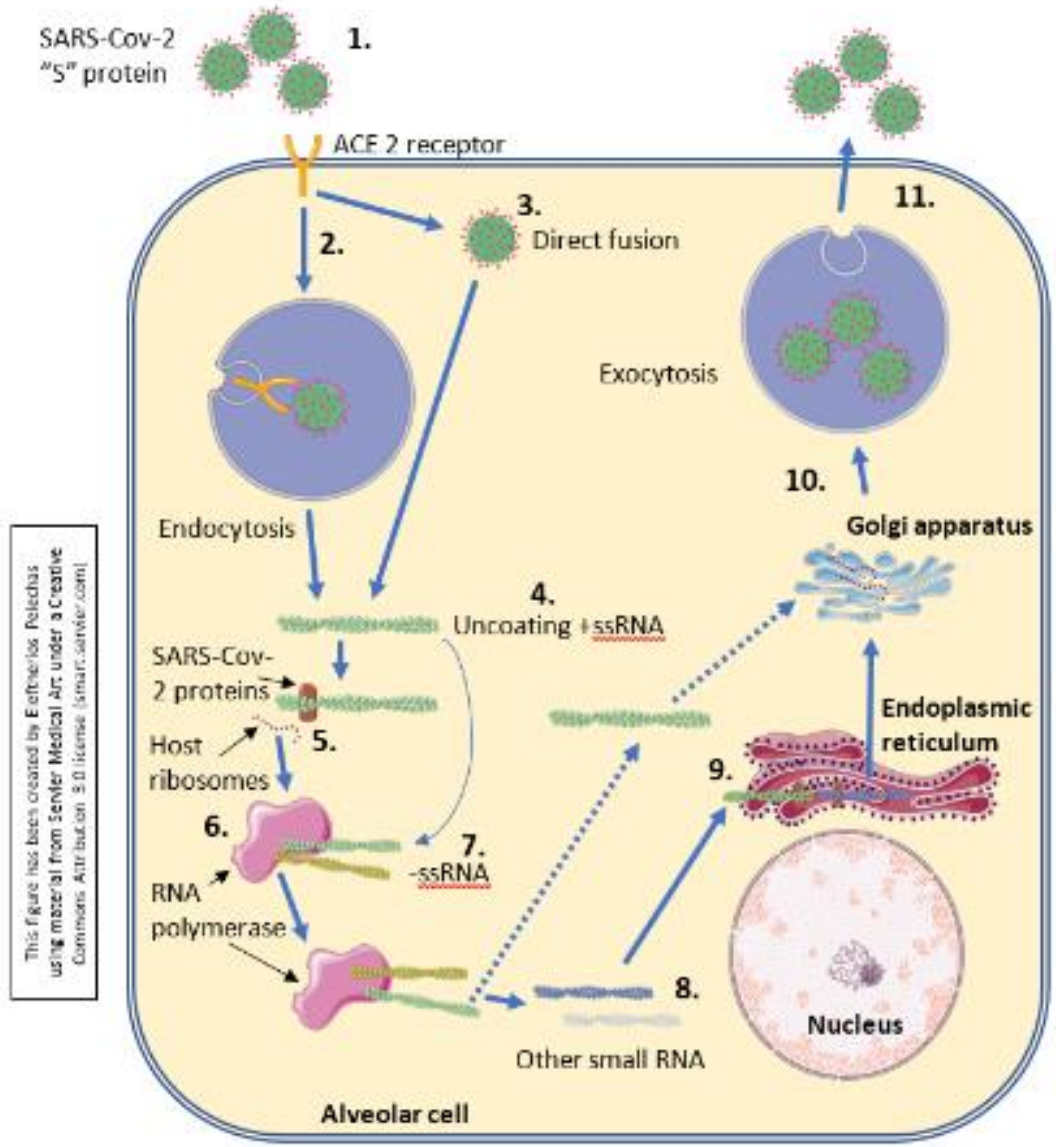
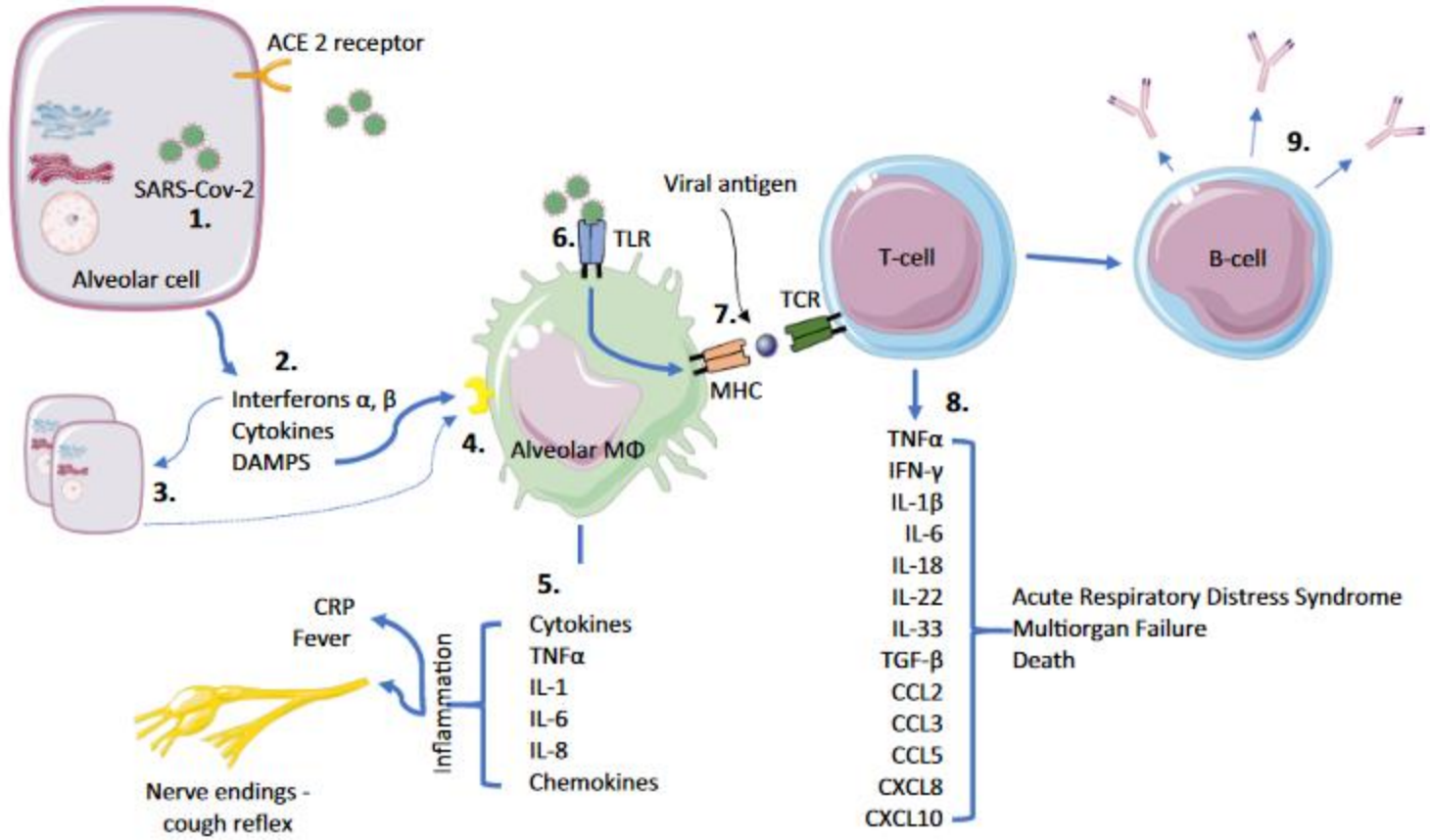


Mediterr J Rheumatol 2020;31(Suppl 2):259-67

https://doi.org/10.31138/mjr.31.3.259



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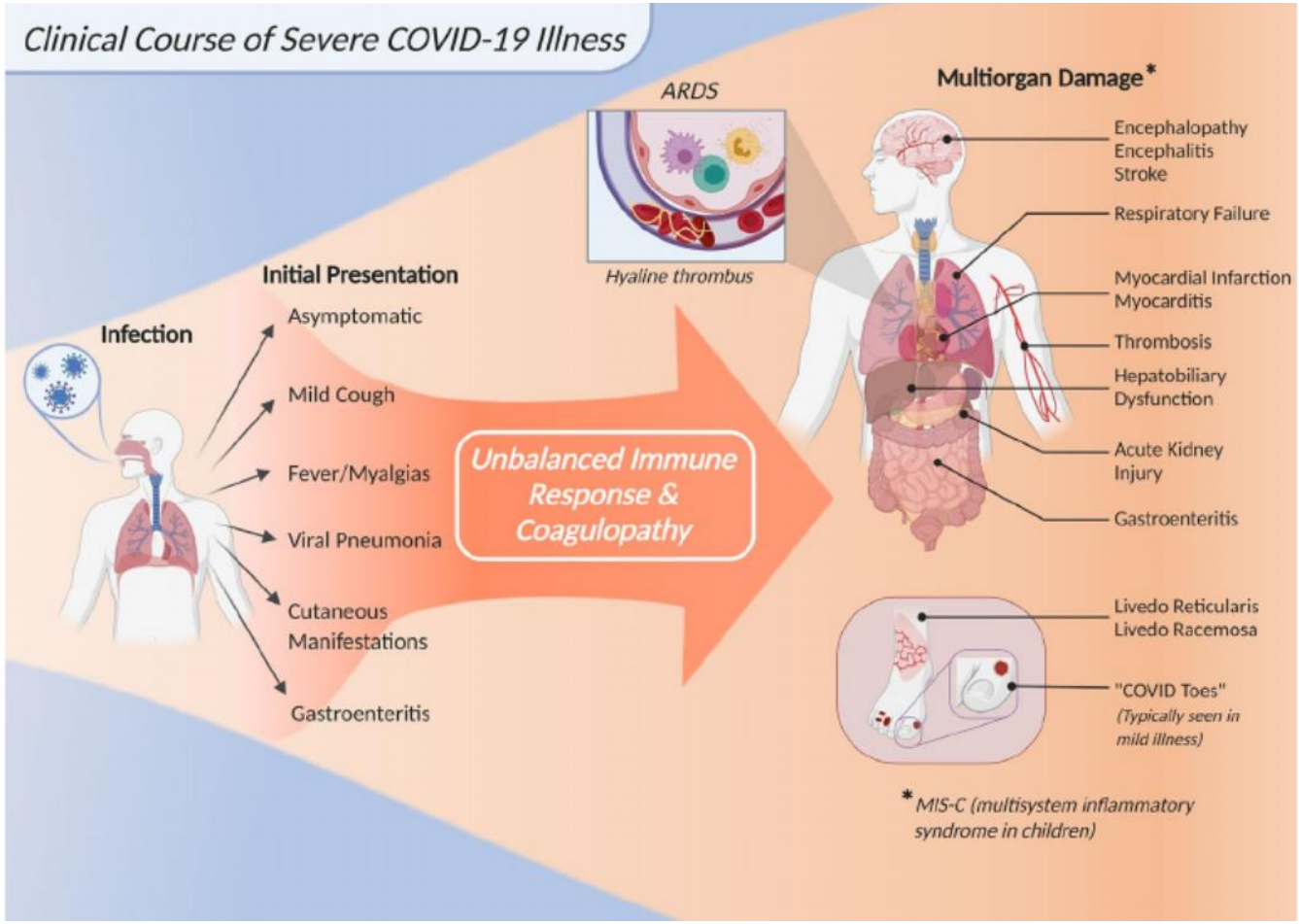

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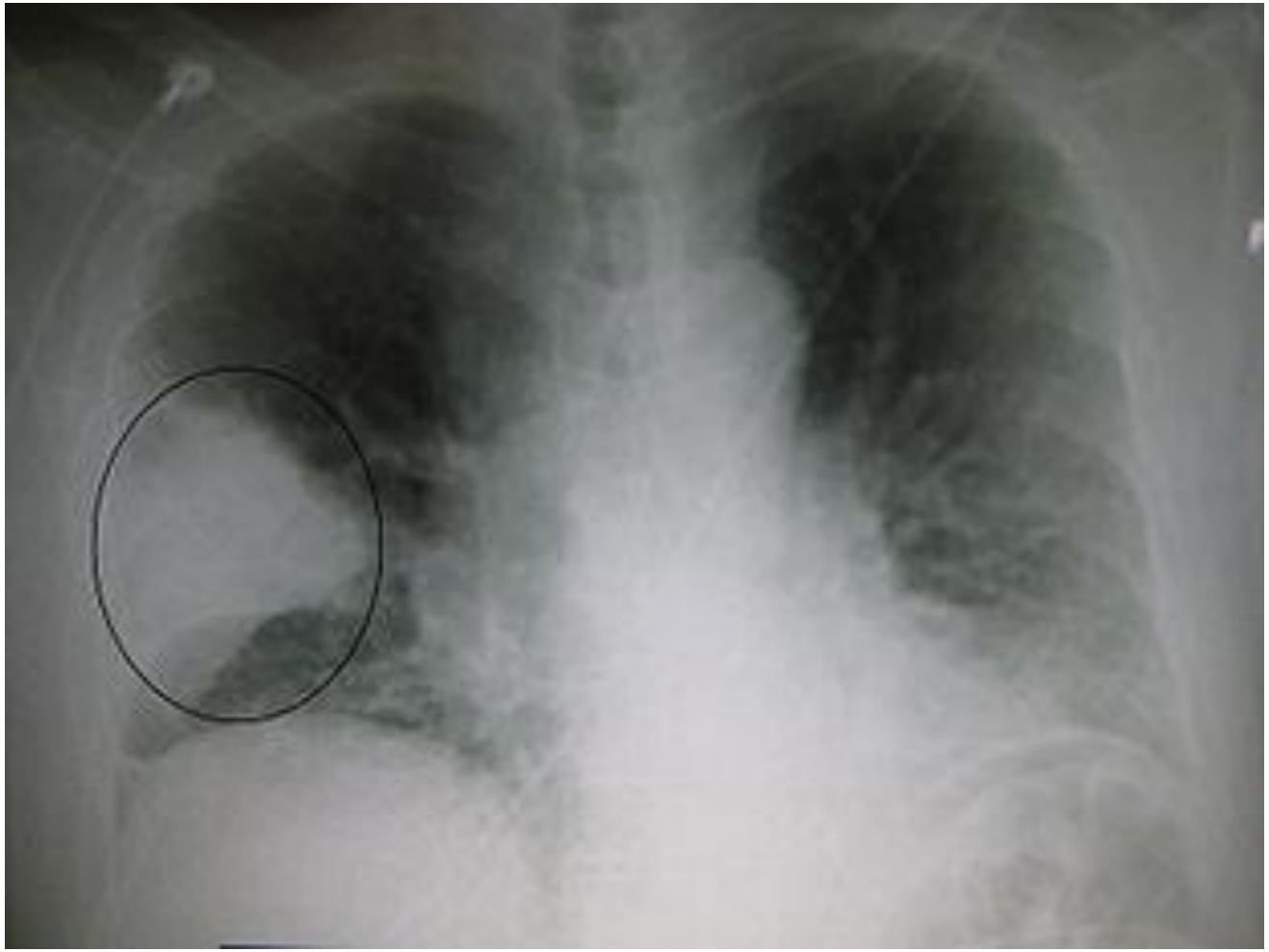
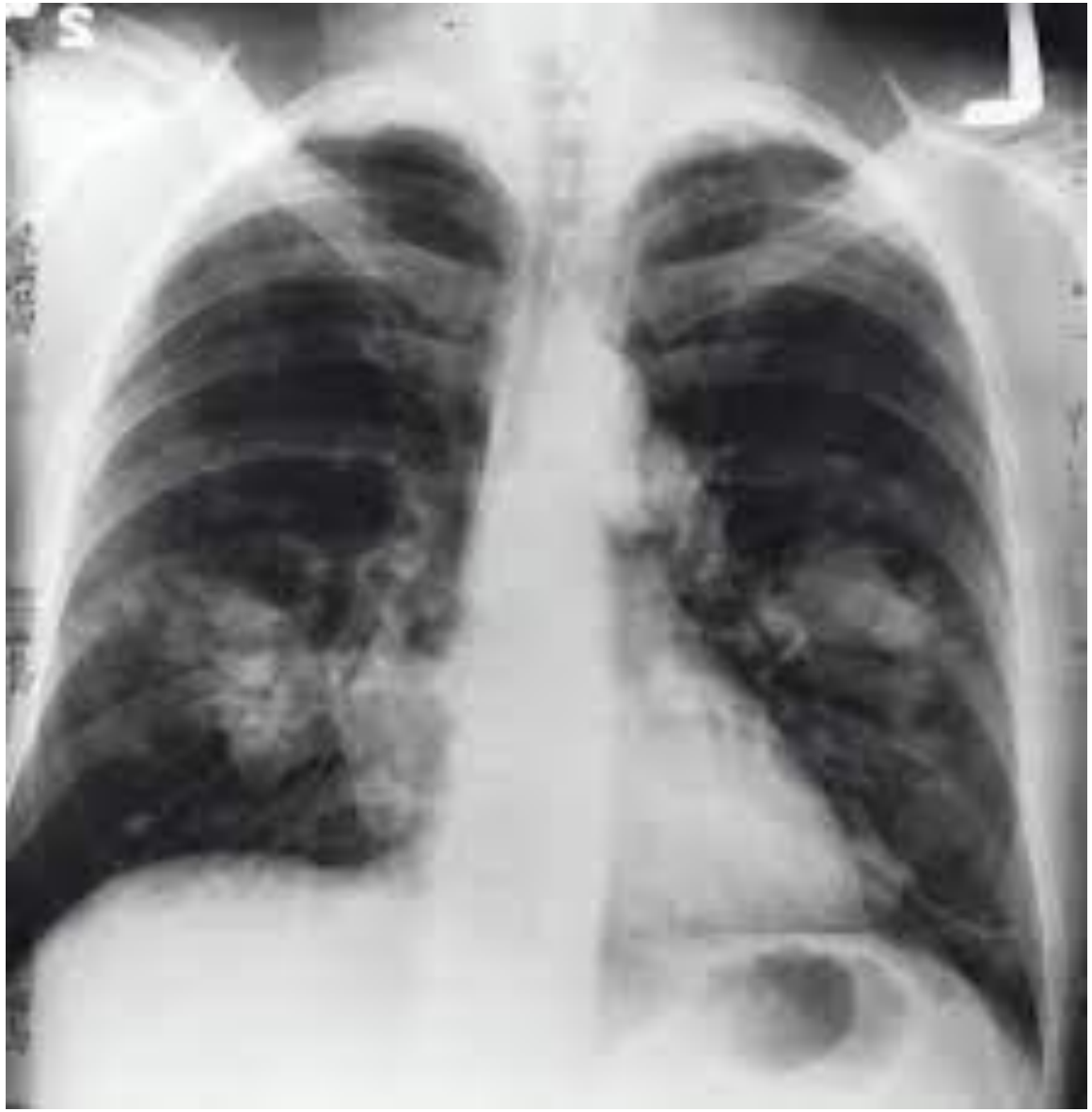
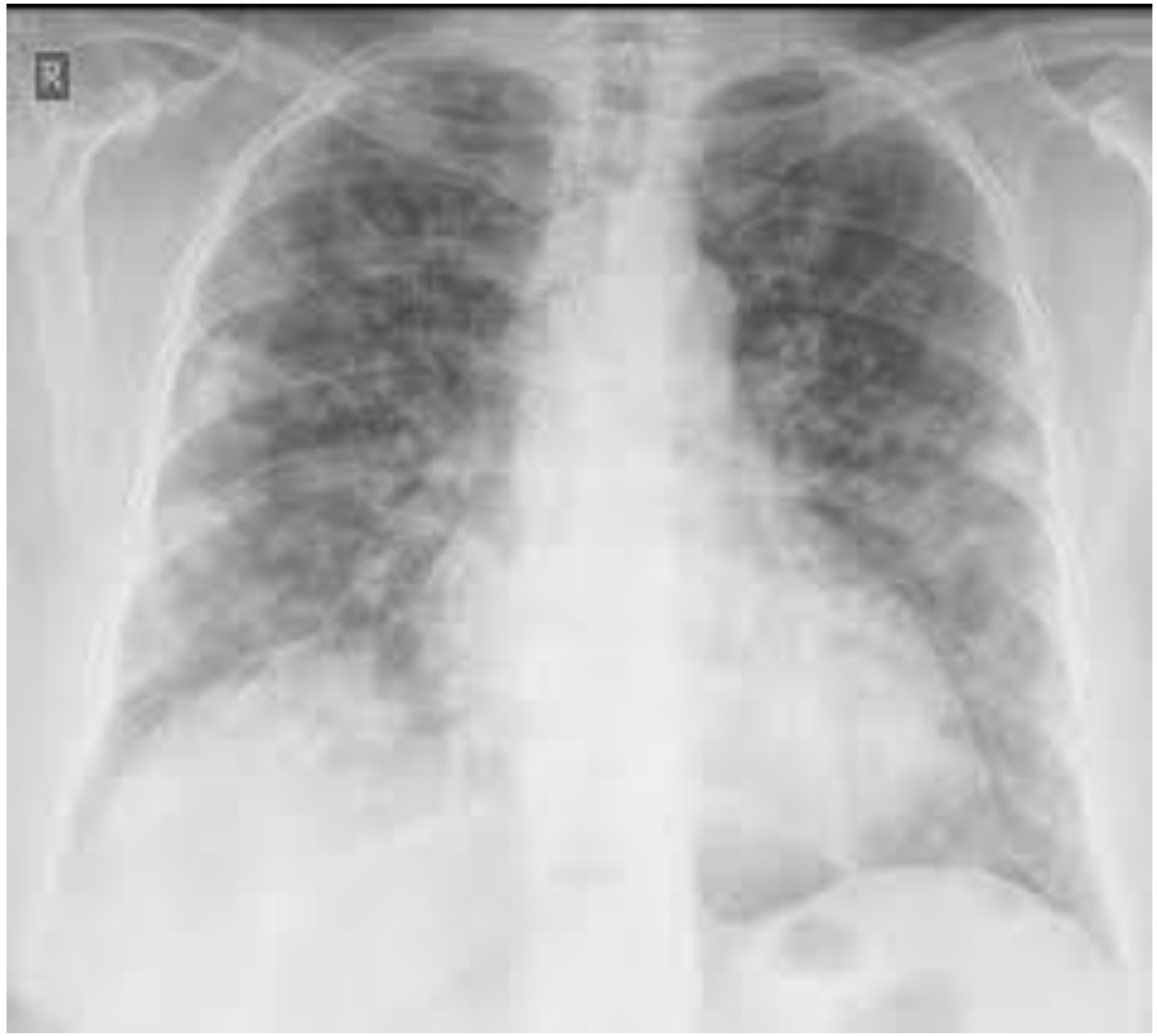






Systemic and organ-specific immune-related manifestations of COVID-19

Manuel Ramos-Casals[1,2]✉, *Pilar Brito-Zerón*[3] *and Xavier Mariette*[4]

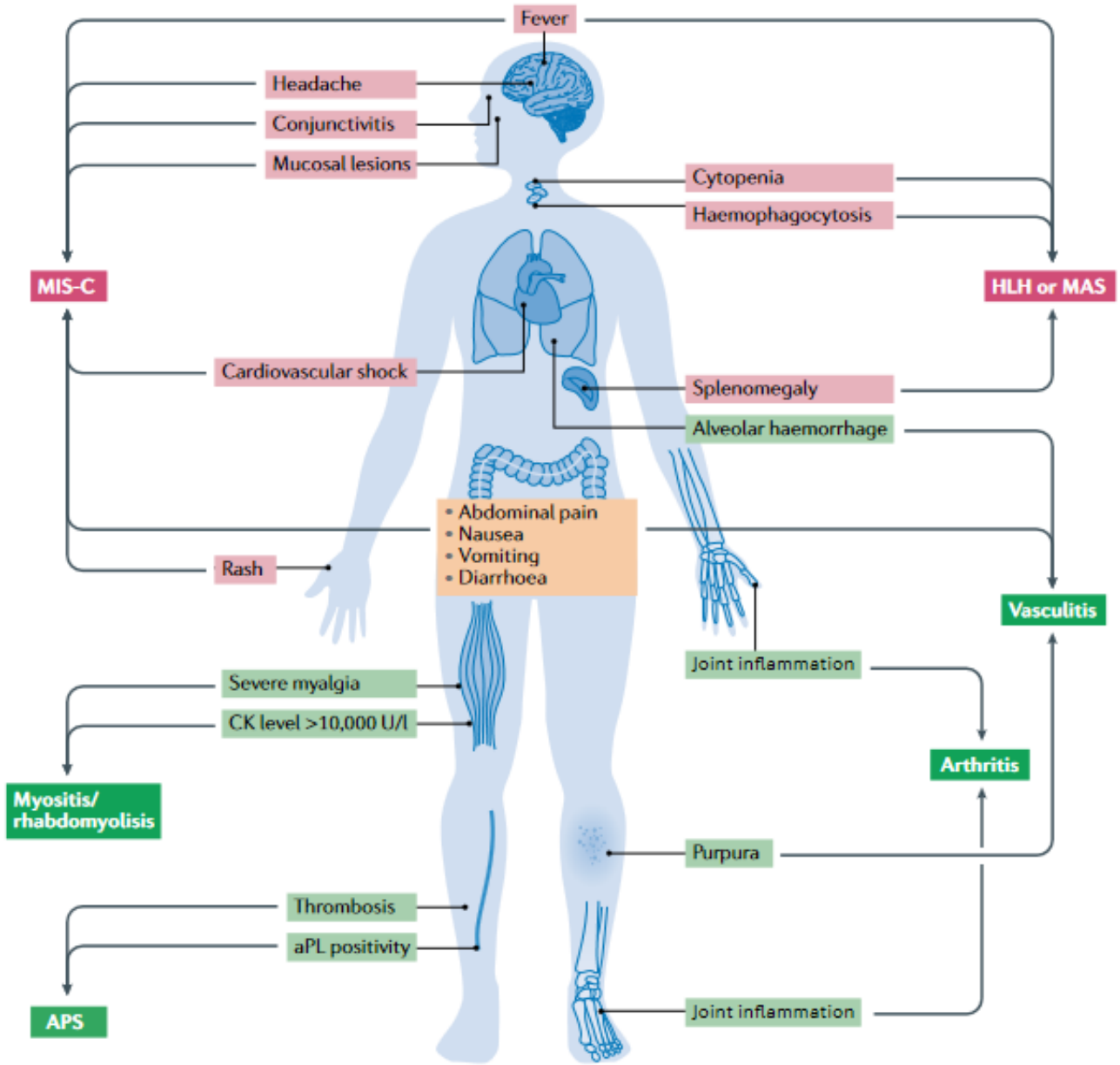
Box 1 | **Immune-related disorders reported in patients with COVID-19**

Systemic immune-related manifestations

- Multisystem inflammatory syndrome in children
- Haemophagocytic syndromes or macrophage activation syndrome
- Vasculitis
  - Kawasaki disease in children and adults
  - Retinal vasculitis
  - Cutaneous leukocytoclastic vasculitis
  - IgA vasculitis
  - Small and medium-sized vessel gastrointestinal vasculitis
  - Diffuse alveolar haemorrhage
  - Central nervous system vasculitis
- Antiphospholipid antibodies
- Myositis
  - Acute myalgia
  - Rhabdomyolysis
  - Autoimmune inflammatory myopathy
  - Necrotizing autoimmune myopathy
- Arthritis
  - Acute arthralgias
  - Symmetric polyarthritis
  - Asymmetric oligoarthritis
  - Monoarthritis
  - Psoriatic arthritis
- Other systemic autoimmune diseases
  - Systemic lupus erythematosus-related symptoms
  - Sicca symptoms and/or parotid enlargement
  - Sarcoidosis

Organ-specific immune-related manifestations

- Cutaneous
  - Chilblain lesions
  - Erythema multiforme
  - Livedo reticularis
  - Retiform purpura
  - Oral ulcers
  - Erythema nodosum
  - Periorbital erythema
  - Generalized pustular figurate erythema
  - Sweet syndrome
  - Livedo racemose
- Haematological
  - Immune thrombocytopenic purpura
  - Thrombotic thrombocytopenic purpura
  - Autoimmune haemolytic anaemia
  - Evans syndrome
- Neurological
  - Guillain–Barré syndrome
  - Miller Fisher syndrome
  - Meningoencephalitis
  - Autoimmune encephalitis
  - Acute disseminated encephalomyelitis
  - Acute necrotizing encephalopathy
  - Mild encephalitis or encephalopathy with reversible splenial lesion
  - Longitudinal extensive transverse myelitis
  - Neuromyelitis optica-like syndrome
  - Transversal myelitis
  - Polyneuritis cranialis
  - Optic neuritis
  - Plexopathy
  - Myasthenia gravis
- Pulmonary
  - Interstitial lung disease
  - Post-viral organizing pneumonia
  - Mediastinal lymphadenopathies
  - Pleural effusion
- Cardiac
  - Acute myocarditis
  - Pericardial effusion
  - Cardiac tamponade
- Renal
  - Proximal tubular dysfunction
  - Collapsing glomerulonephritis
  - Focal segmental glomerulonephritis
  - Minimal change disease
  - Crescentic glomerulonephritis
  - ANCA-associated renal vasculitis
  - Membranous glomerulonephritis
  - IgA glomerulonephritis
- Endocrine
  - Clinical hyperthyroidism or thyrotoxicosis
  - Subclinical hypothyroidism
  - Adrenal haemorrhage
  - Adrenal infarction
  - Adrenal insufficiency
- Pancreatic
  - Acute pancreatitis
- Ocular
  - Uveitis
  - Conjunctivitis


Fever
Headache
Conjunctivitis
Mucosal lesions
Cytopenia
Haemophagocytosis
MIS-C
HLH or MAS
Cardiovascular shock
Splenomegaly
Alveolar haemorrhage
• Abdominal pain
• Nausea
• Vomiting
• Diarrhoea
Rash
Vasculitis
Joint inflammation
Severe myalgia
CK level >10,000 U/l
Arthritis
Myositis/
rhabdomyolisis
Purpura
Thrombosis
aPL positivity
APS
Joint inflammation

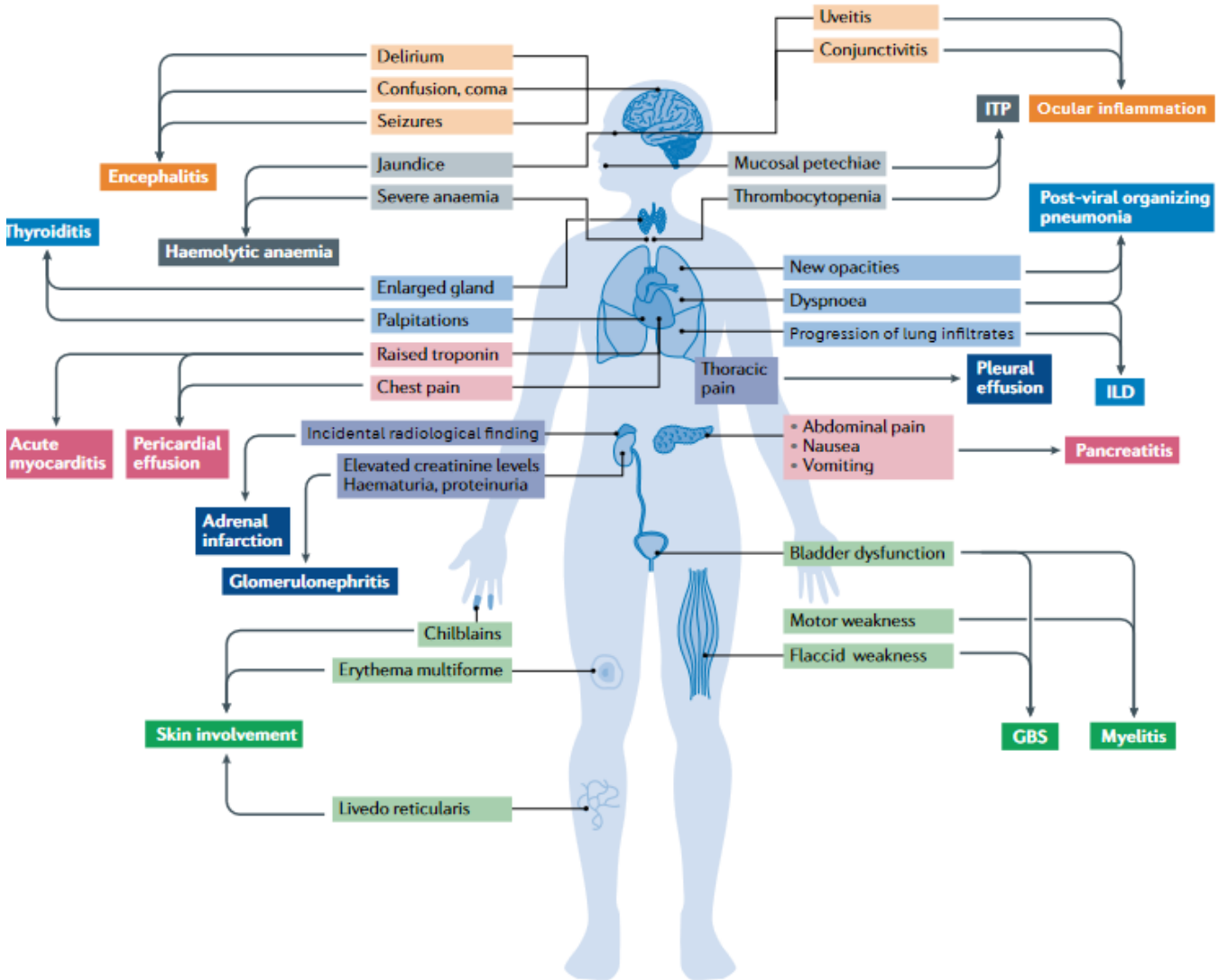


Fig. 2 | **Guiding signs and symptoms of suspected organ-specific immune-related diseases in patients with COVID-19.**

Key points

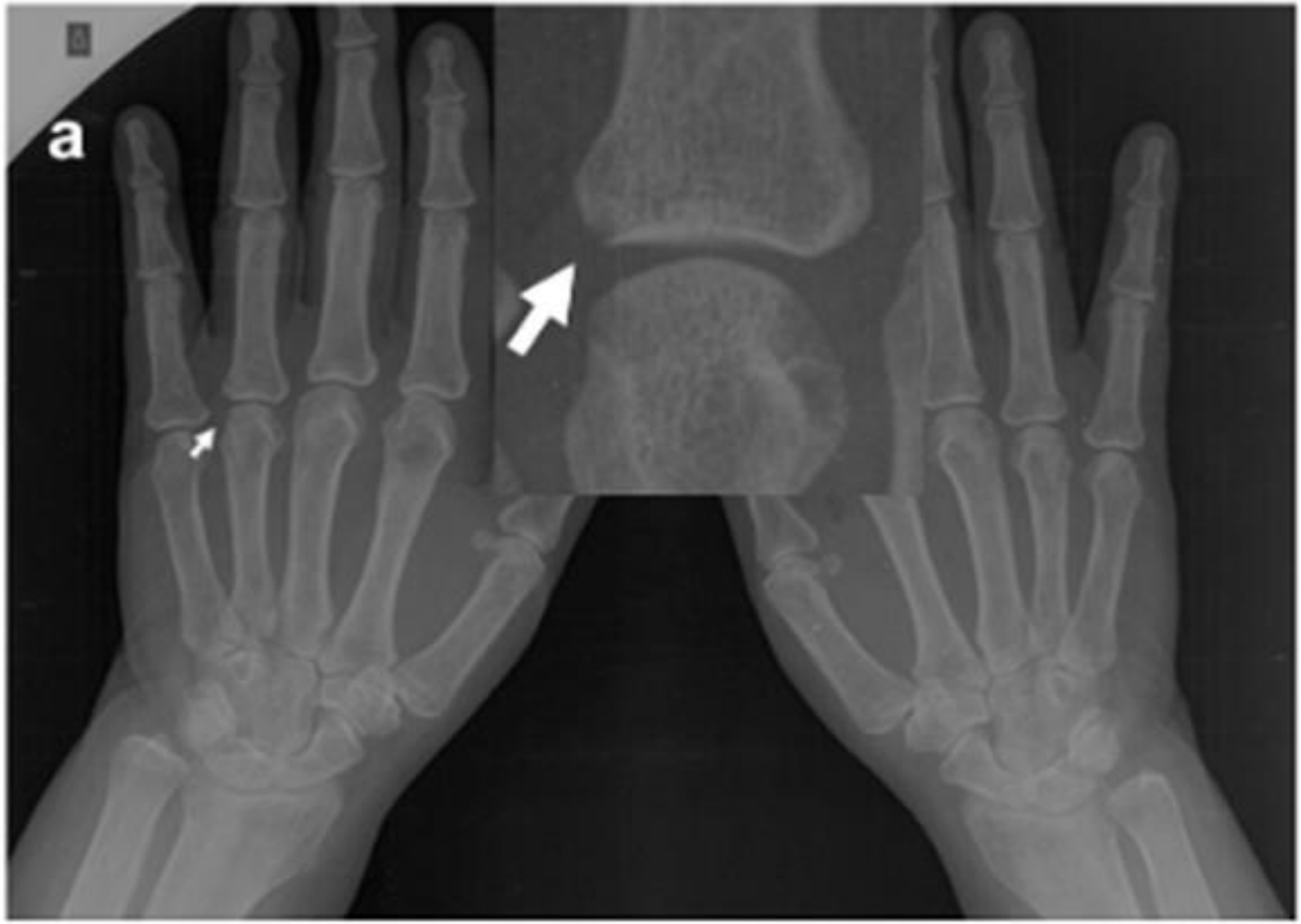
- COVID-19 can produce a systemic inflammatory reaction involving extra-pulmonary organs.
- Immune-related manifestations are increasingly recognized conditions in patients with COVID-19.
- ~3,000 cases involving >70 different systemic and organ-specific immune-related disorders have been reported.
- The clinical phenotype varies and seems to be influenced by age, sex and/or ethnicity.
- The severity of immune-related manifestations of COVID-19 ranges from completely benign, self-limiting manifestations to systemic, life-threatening syndromes.
- Some features tend to appear within the first 2 weeks of SARS-CoV-2 infection, and others emerge in a late post-infectious stage or even in asymptomatic patients.

Case presentation (I)

- A 46year old female presented on May 4, 2021 with pain and swelling affecting the small joints of the hands bilaterally, lasting for 6 weeks.
- She received paracetamol and diclophenac without improvement.
- She was single, no smoker with negative past medical and family history.
- On February 1, 2021 she was diagnosed with SARS-CoV-2 infection: **low grade fever**, **sore throat**, **myalgias**, **arthralgias** and **positive PCR test** for Covid-19.
- She remained isolated at home, receiving occasionally paracetamol and 3 weeks later she was free of her symptoms with negative PCR test.
- However, one month later she complained about arthralgias, morning stiffness and swelling of the small joints of the hands. She repeated a new test for Covid-19, which was negative.

Case presentation (II)

- Clinical examination revealed **swelling and tenderness affecting the MCP's and PIP's bilaterally**.
- She denied photosensitivity, skin rashes, psoriasis, oral ulcers, Raynaud's phenomenon, uveitis, urethritis and diarrhea.
- Laboratory tests showed **ESR:82mm/h**, **CRP 60mg/dl**, **high igG**, **SARS-CoV2 antibodies**, while PCR test was negative.
- The rest of laboratory tests including CMV, EBV, hepatitis B, C, as well as ANA, RF and ACPA were negative.
- Chest x-rays were normal while **hand x-rays showed soft tissue swelling, joint space narrowing and erosive changes affecting mostly the 3rd and 4th MCP of the right hand**.
- MSUS identified better the above changes.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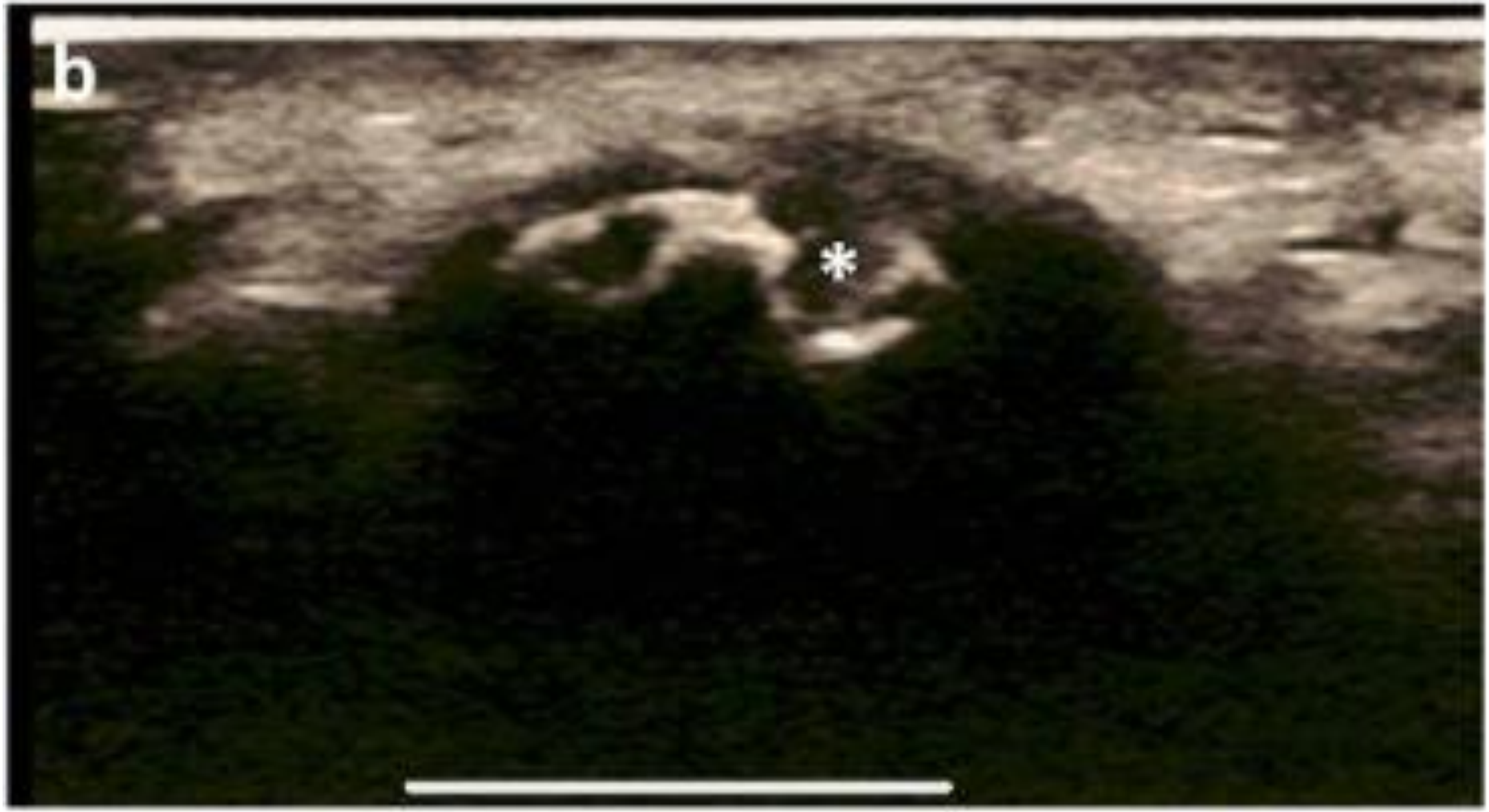
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Diagnosis of RA: ACR criteria

At least four of the following criteria

- ❑ Morning stiffness >1 hour
- ❑ Arthritis of ≥3 joint areas
- ❑ Arthritis of hand joints
- ❑ Symmetric arthritis
- ❑ Rheumatoid nodules
- ❑ Serum rheumatoid factor
- ❑ **Radiographic changes**

Must be present for at least 6 weeks

Arnett FC et al. Arthritis Rheum 1988;31:315–24

2010 ACR/EULAR Classification Criteria for RA

JOINTS (0-5)	
1 large joint	0
2-10 large joints	1
1-3 small joints (large joints not counted)	2
4-10 small joints (large joints not counted)	3
>10 joints (at least one small joint)	5
SEROLOGY (0-3)	
Negative RF AND negative ACPA	0
Low positive RF OR low positive ACPA	2
High positive RF OR high positive ACPA	3
SYMPTOM DURATION (0-1)	
<6 weeks	0
>=6 weeks	1
ACUTE PHASE REACTANTS (0-1)	
Normal CRP AND normal ESR	0
Abnormal CRP OR abnormal ESR	1

Definite RA: score of ≥ 6/10

Case presentation (III)

- According to the 1987 classification criteria and the ACR/EULAR 2010 classification criteria for RA, this patient was classified as having seronegative erosive RA.
- She was treated with **MTX 15mg/w, plus prednisone 10mg/day.**
- Two months later she had a significant clinical and laboratory improvement. Prednisone was tapered.
- After 4 months she had a complete remission, thus the dose of prednisone was tapered to 2,5mg/day and she continued receiving MTX.

Differential diagnosis

Other types of seronegative arthritis:

- Reactive arthritis
- Coincidence of RA and Covid-19 disease
- Presence of RA and flare up during SARS-CoV-2 infection
- Long Covid disease

Etiologic factor in RA

Several viruses have been postulated as possible etiologic factors in RA:

- EBV
- Parvovirus-19
- Others

COVID-19 and autoimmune diseases

Yu Liu[a], *Amr H. Sawalha*[b], *and Qianjin Lu*[a,c]

Table 1. Similarities in immunopathogenesis of COVID-19 and autoimmune diseases

Items	COVID-19 immunological features similar to autoimmune diseases	Refs.
Innate immune cells	Overactivation of monocytes, macrophages, mast cells and neutrophils. Increased proportion of mature natural killer (NK) cells.	[12,27,29,32,33▪]
Adaptive immune cells	Decreased T-cell numbers, altered B-cell subsets, dysregulation of T cells and B cells.	[17,30,31]
Cytokines and chemokines	Increased levels of IL-1, IL-2, IL-6, IL-8, IL-10, IL-17, IL-18, CXCL10, CCL2.	[22–24]
Autoantibodies	ANA, APL, lupus anticoagulant, cold agglutinins, anti-Ro/SSA antibodies, anti-Caspr2 antibody, anti GD1b antibody, anti-MOG antibody	[14,51▪,52▪,53,54▪,55–58]
Clinical conditions	Immune-mediated haemolysis, decreased white blood cell counts, cytokine storm syndrome, macrophage activation syndrome, procoagulant condition	[25,28,57,74]
Other immunopathogenesis	Increased levels of DAMPs, molecular mimicry	[26,46]

Table 1 The main clinical, laboratory and immunological findings are presented

Patient No	Sex/age	Medical history	Anti-SARS-CoV-2 IgG	COVID-19-related symptoms	SOFA score	Pulmonary imaging	Outcome	Elevated muscle enzymes	Prolonged aPPT	Autoantibodies
1	M/78	None	POS	Dyspnoea	10	Diffuse infiltrates and ground glass	Death	Yes	Yes	a-CL (IgG)
2	M/59	Sleep apnoea	POS	Fever, cough, dyspnoea	3	Diffuse infiltrates and ground glass	Alive	No	No	a-CL (IgG+IgM)
3	M/70	Hypertension	POS	Fever, dry cough, dyspnoea	10	Diffuse infiltrates and ground glass	Alive	No	No	NEG
4	M/46	Dyslipidaemia	POS	Fever	8	Diffuse infiltrates and ground glass	Alive	No	No	NEG
5	M/62	None	POS	Fever, cough, dyspnoea	8	Diffuse infiltrates and ground glass	Alive	No	No	NEG
6	M/54	Smoking	POS	Fever	4	Diffuse infiltrates	Alive	Yes	Yes	ANA 1/320 fine speckled cytoplasmic
7	M/79	None	POS	Fever, cough, dyspnoea	9	Diffuse infiltrates and ground glass	Alive	No	No	NEG
8	M/70	None	POS	Fever, productive cough	11	Diffuse infiltrates and ground glass	Alive	No	Yes	NEG
9	M/71	None	POS	Fever, cough, dyspnoea	9	Diffuse infiltrates and ground glass	Alive	Yes	Yes	p-ANCA 1/20
10	M/61	Coronary artery disease	POS	Fever, cough, dyspnoea	3	Diffuse infiltrates and ground glass	Alive	No	No	ANA 1/320 speckled cytoplasmic, p-ANCA 1/20 a-CL (IgG+IgM)
11	M/64	Hyperthyroid, dyslipidaemia	POS	Fever, cough, dyspnoea	11	Diffuse infiltrates	Alive	Yes	Yes	c-ANCA 1/640
12	M/61	Hypertension, diabetes mellitus	NEG	Fever, cough	10	Diffuse infiltrates	Alive	No	No	NEG
13	M/62	Smoking, arrhythmia	POS	Fever, cough, dyspnoea, diarrhoea	7	Diffuse infiltrates and ground glass	Alive	Yes	Yes	a-CL (IgG+IgM), a-CCP 70 IU
14	F/65	None	POS	Fever, cough, dyspnoea	8	Diffuse infiltrates	Alive	No	No	ANA 1/160 fine speckled nucleolar
15	F/58	Asthma, dyslipidaemia, hypertension, psoriasis, hepatitis	POS	Fever, productive cough, dyspnoea	11	Diffuse infiltrates	Death	Yes	No	a-CL (IgG)

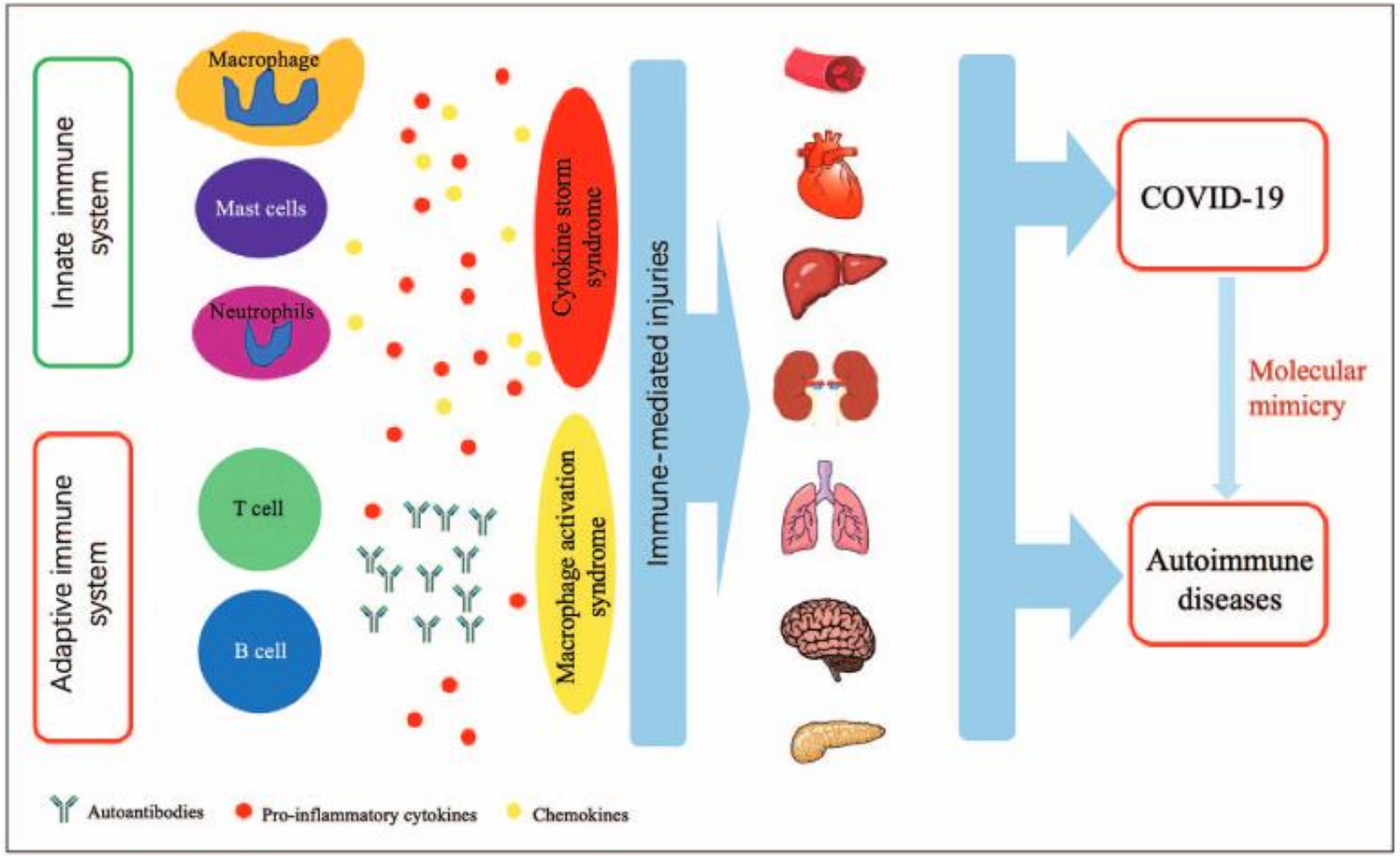
Panayiotis G Vlachoyiannopoulos et al. Ann Rheum Dis 2020;79:1661–1663.

16	F/85	Dyslipidaemia, hypertension	POS	Fever, cough	8	Diffuse infiltrates	In ICU	No	No	ANA 1/160 fine speckled nucleolar, a-β2GPI (IgG+IgM)
17	M/75	Hypertension, G6PD (–), hypothyroidism, renal CA	POS	Fever, cough, dyspnoea	9	Diffuse infiltrates and ground glass	In ICU	Yes	No	ANA 1/320 fine speckled nucleolar, Ro60, a-β2GPI (IgG)
18	F/60	Dyslipidaemia	POS	Fever	9	Diffuse infiltrates and ground glass	Alive	Yes	Yes	NEG
19	F/53	Obesity	POS	Fever, myalgia	10	Diffuse infiltrates	Alive	Yes	Yes	NEG
20	M/61	Hypertension, dyslipidaemia	POS	Fever, cough, dyspnoea	6	Diffuse infiltrates and ground glass	In ICU	Yes	No	ANA 1/320 fine speckled nucleolar, a-β2GPI (IgG)
21	F/56	Hypertension, obesity	POS	Fever, cough, dyspnoea	9	Diffuse infiltrates and ground glass	In ICU	Yes	Yes	a-CL (IgG)
22	M/67	Diabetes, hypertension, dyslipidaemia	POS	Headache, cough, fever, fatigue	5	Diffuse infiltrates and ground glass	Alive	No	Yes	c-ANCA 1/20, a-β2GPI (IgM)
23	F/66	Obesity	POS	Fever, cough	9	Diffuse infiltrates and ground glass	Alive	Yes	No	ANA 1/160 fine speckled nucleolar, a-β2GPI (IgM)
Patient No	**Sex/age**	**Medical history**	**Anti-SARS-CoV-2 IgG**	**COVID-19-related symptoms**	**SOFA score**	**Pulmonary imaging**	**Outcome**	**Elevated muscle enzymes**	**Prolonged aPPT**	**Autoantibodies**
24	M/43	None	POS	Fever, cough	8	Diffuse infiltrates and ground glass	Alive	No	No	ANA 1/320 fine speckled nucleolar, 1/160 AMA, a-β2GPI (IgM)
25	M/75	Hypertension	POS	Fever, cough, dyspnoea	9	Diffuse infiltrates and ground glass	Death	No	Yes	ANA 1/320 speckled cytoplasmic, a-CL (IgG), a-β2GPI (IgM)
26	F/82	Hypertension	POS	Fever, cough, dyspnoea	8	Diffuse infiltrates and ground glass	Death	No	No	ANA 1/160 fine speckled nucleolar, 1/160 AMA, a-β2GPI (IgG+IgM)
27	M/55	Hypertension	POS	Fever, cough, fatigue	8	Diffuse infiltrates and ground glass	Alive	No	No	a-β2GPI (IgM)
28	M/64	Hypertension, dyslipidaemia	POS	Fever, dyspnoea	7	Diffuse infiltrates and ground glass	Alive	No	Yes	NEG
29	M/59	None	POS	Fever, diarrhoea	2	Diffuse infiltrates	Alive	No	Yes	a-β2GPI (IgG+IgM)

Panayiotis G Vlachoyiannopoulos et al. Ann Rheum Dis 2020;79:1661–1663.

Table 2. Autoantibodies detected in patients with COVID-19

Autoantibodies	Clinical significance	Refs.
ANA	Poor prognosis and a significant higher respiratory rate	[14]
APL	Poor prognosis and a significant higher respiratory rate Possible association with a hyperinflammatory state and thrombosis and thromboembolism	[14,52▪]
Lupus anticoagulant	A higher rate of thrombosis	[51▪]
Cold agglutinins	Haemolytic anaemia. Complicating laboratory assessment and renal replacement therapy	[55,58]
Anti-Ro/SSA antibodies	Possible association with severe pneumonia	[56]
Anti-Caspr2 antibody	Unclear	[54▪]
Anti-GD1b antibody	Unclear	[54▪]
Anti-MOG antibody	Unclear	[53]
Red cell bound antibodies	Associated with the severity of anaemia	[57]



COVID-19 and autoimmune diseases Liu *et al.*

Pathogenesis

Little is known about the pathogenesis of the autoimmune manifestations, since autoantibodies are absent in many cases, as in our patient.

- Autoantibodies against IFN type I, or inborn errors in type I IFN immunity.
- SARS-CoV-2 infection can disturb immunological tolerance by exposure of antigens epitopes that elicit cross-reactive antibodies.
- Antigenic mimicry between viral and human proteins.

Bastard P, Rosen LB, Zhang Q, et al. Autoantibodies against type I IFNs in patients with life-threatening COVID-19. Science. 2020;370(6515): eabd4585. https://doi.org/10.1126/science.abd4585.

Zhang Q, Bastard P, Liu Z, et al. Inborn errors of type I IFN immunity in patients with life-threatening COVID-19. Science. 2020;370(6515): eabd4570. https://doi.org/10.1126/science.abd4570.

Molecular mimicry in Covid-19

Molecular mimicry as a possible mechanism underlying the development of autoimmune phenomena in SARS-CoV-2 infection.

Gammazza AM, Légaré S, Bosco GL, et al. Human molecular chaperones share with SARS-CoV-2 antigenic epitopes potentially capable of eliciting autoimmunity against endothelial cells: possible role of molecular mimicry in COVID-19. Cell Stress Chaperones. 2020;25(5):737–41. https://doi.org/10.1007/s12192-020-01148-3.

Lucchese G, Flöel A. SARS-CoV-2 and Guillain–Barré syndrome: molecular mimicry with human heat shock proteins as potential pathogenic mechanism. Cell Stress Chaperones. 2020;25(5): 731–5. https://doi.org/10.1007/s12192-020-01145-6.

Lucchese G, Flöel A. Molecular mimicry between SARS-CoV-2 and respiratory pacemaker neurons. Autoimmun Rev. 2020;19: 102556. https://doi.org/10.1016/j.autrev.2020.102556.

Venkatakrishnan AJ, Kayal N, Anand P, Badley AD, Church GM, Soundararajan V. Benchmarking evolutionary tinkering underlying human-viral molecular mimicry shows multiple host pulmonary-arterial peptides mimicked by SARS-CoV-2. Cell Death Discov. 2020;6:96. https://doi.org/10.1038/s41420-020-00321-y.

KEY POINTS

- COVID-19 infection can be complicated by involvement of multiple organ systems.
- Immune-mediated injury contributes to the manifestations and complications of COVID-19.
- Organ damage in COVID-19 is at least in part caused by perpetuated inflammatory responses, similar to autoimmune diseases.
- SARS-CoV-2 might trigger autoimmune responses through molecular mimicry.
- COVID-19 might be complicated by the development of autoantibodies and possibly de-novo autoimmune diseases.

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LETTER TO THE EDITOR

Long COVID from rheumatology perspective: a simple mimicker or promoter of autoimmunity?

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CASE REPORT

Seronegative Erosive Arthritis Following SARS-CoV-2 Infection

Alexandros A. Drosos · Eleftherios Pelechas · Paraskevi V. Voulgari

Conclusions

This is the first case report making an association between SARS-CoV-2 infection and erosive polyarthritis.

Physicians dealing with patients infected from SARS-CoV-2 should be aware for the possible development of musculoskeletal disorders, among them symmetrical polyarthritis.

Thus, a close follow-up and monitoring are mandatory.