Respiratory Medicine Case Reports 55 (2025) 102216

Contents lists available at ScienceDirect

Respiratory Medicine Case Reports

journal homepage: www.elsevier.com/locate/rmcr

Case series

From infection to autoimmunity: can COVID-19 spark new auto-immune conditions?

Mourad Elghali [a,*], Mariem Mhiri [b], Imen Chaabene [c], Ines Bayar [d], Bilel Ben Amor [d], Imen Jaziri [e], Maha Changuel [a], Rihab Ben Dhia [f], Narjes Gouta [g], Jamel Saad [h], Rym Hadhri [i], Ahmed Zrig [h], Soumaya Boudokhane [j], Hela Marmouche [d], Mahbouba Jguirim [k], Nabil Sakly [a,l]

[a] *Laboratory of Immunology, University Hospital FB Monastir, University of Monastir, Tunisia*
[b] *Neurology Department, University Hospital FB Monastir, University of Monastir, Tunisia*
[c] *Internal Medicine Department, University Hospital FB Monastir, University of Monastir, Tunisia*
[d] *Endocrinology Department, University Hospital FB Monastir, University of Monastir, Tunisia*
[e] *Faculty of Pharmacy, University of Monastir, Tunisia*
[f] *Laboratory of Technology and Radiological Imagery, Faculty of Medicine, University of Monastir, Tunisia*
[g] *Laboratory of Cardio-thrombosis (code Lr16sp12), Faculty of Medicine, University of Monastir, Tunisia*
[h] *Radiology Department, University Hospital FB Monastir, University of Monastir, Tunisia*
[i] *Laboratory of Anatomical Pathology, University Hospital FB Monastir, University of Monastir, Tunisia*
[j] *Physical Medicine Department, University Hospital FB Monastir, University of Monastir, Tunisia*
[k] *Rheumatology Department, University Hospital FB Monastir, University of Monastir, Tunisia*
[l] *Laboratory of Medical and Molecular Parasitology-Mycology (code LR12ES08), Department of Clinical Biology B, Faculty of Pharmacy, University of Monastir, Tunisia*

ARTICLE INFO

Handling Editor: DR AC Amit Chopra

Keywords:
Autoimmunity
COVID-19
SARS-CoV-2
Infection

ABSTRACT

Background: Some studies have described a probable relationship between SARS-CoV-2 infection and autoimmunity.
Aim: to present a case series of autoimmune manifestations (AIM) following COVID-19 infection.
Methods: A consecutive series of patients from January 2020 to December 2023 was collected from the various departments of Fattouma Bourguiba University Hospital, Monastir, where all clinical assessments were performed. Anti-nuclear antibody (ANA) screening was performed using indirect immunofluorescence on HEp-2 cells (Euroimmun, Germany) with a positivity titer of $\geq$1/180. Typing was performed using ELISA (Biosystems, Spain) or line blot (Euroimmun, Germany). The assessment of other autoantibodies was performed using various techniques (indirect immunofluorescence, ELISA, and line blot).
Results: Sixteen patients presented with AIM after the COVID-19 infection. Their ages ranged from 12 to 67 years (44.6 $\pm$ 15.5 years). The sex ratio was 1 (eight men to eight women). Clinical manifestations began between one week and three months after infection. The clinical presentation was polymorphic (general, cutaneous, neurological, ophthalmic, muscular, articular, and abdominal features). Biological, radiological, and histopathological investigations revealed principal abnormalities in endocrine, articular, muscular, or neurological functions in the presence of ANA and/or specific autoantibodies. Fiveteen patients were diagnosed with autoimmune

* Corresponding author.
E-mail address: mouradghali3@gmail.com (M. Elghali).

https://doi.org/10.1016/j.rmcr.2025.102216
Received 16 October 2024; Accepted 17 April 2025
Available online 26 April 2025

diseases (AID) and treated with specific treatments. The diagnosis retained for the other case was non-specific autoimmune stimulation with spontaneous recovery.
Conclusion: These cases suggest that AID or AIM can be triggered or unmasked by SARS-CoV-2 infection.

Abbreviation list

AHPT	autoimmune hypoparathyroidism
AID	autoimmune diseases
AIM	autoimmune manifestations
AM	acute myelitis
ANA	anti-nuclear antibodies
COVID-19	coronavirus disease 2019
D1	type 1 diabetes
GBS	Guillan-barré syndrome
GD	Graves' diseases
HT	Hashimoto's thyroididtis
IIF	indirect immunofluorescence
jAS	juvenile ankylosing spondylarthritis
NAM	necrotizing autoimmune myositis
RA	Rheumatoid arthritis
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SS	Sjögren syndrome

1. Introduction

Coronavirus disease 2019 (COVID-19) is a pulmonary disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) [1]. To date, seven million deaths and 776 million confirmed cases have been reported [2]. As of August 2024, more than 90 countries are battling COVID-19, with ongoing cases and deaths reported despite the spread of anti-COVID-19 vaccination [2,3].

Fueled by a growing number of studies reporting post-COVID-19 autoimmune diseases (AID), concerns are rising regarding the potential link between COVID-19 infection or vaccination [4,5] (We also have an accepted article about vaccination that is currently under publication) and the onset of these conditions. In fact, the interaction between SARS-CoV-2 and the immune system can break immune tolerance and lead to autoimmunity, which may affect multiple organs with the occurrence of various autoimmune manifestations (AIM) [6–8]. Remarkably, many authors have reported the occurrence of AID in patients with post-COVID19-syndrome supporting that SARS-CoV-2 could trigger or reveal autoimmunity [9].

Although many studies on the temporal association between COVID-19 infection and autoimmune conditions have been published, most of them are single or few case reports describing patients with newly developed AID [10–15], including Tunisian and African publications [16–21]. Therefore, we report, to the best of our knowledge, the largest African case series presenting with clinical and biological AIM occurring after COVID-19 infection, gathered over three years (2020–2023).

2. Patients and methods

2.1. Patients

In this case series, patients presenting with AIM after SARS-CoV-2 infection were collected from several departments (internal medicine, endocrinology, rheumatology, neurology, and physical medicine) of the Fattouma Bourguiba University Hospital of Monastir, Tunisia, from January 2020 to December 2023. We included patients who consulted for new clinical manifestations within 1 week–3 months after SARS-CoV-2 infection and in whom COVID-19 vaccines were administered after the onset of AID or before the infection (6 months or more). A comprehensive clinical evaluation ensured that these manifestations were not pre-existing. The study focused solely on patients with AIM.

2.2. Methods

Patient medical records were meticulously reviewed, encompassing past medical history, current medications (daily, and most recent use), and the events leading to their current presentation. Detailed physical examinations were conducted during the hospitalization to rule out critical conditions affecting vital signs (consciousness, respiration, and circulation) and identify complaint-

Table 1
Summary of the cases included in our study.

Case No	Gender	Age (year)	Delay between AIM and the last COVID-19 infection (Week)	Associated conditions	Medications	Clinical manifestations	Investigations	Diagnosis (Criteria used)	Treatment	Evolution
Case 1 (Fig. 1)	Female	29	4	- COVID-19 infection in 2021	-	- persistent frontal acne. - slightly increased-size thyroid on clinical examination	- TSH <0.01 µUI/mL (cut-off: 0.25–4 µUI/mL). - T4: 15 ng/L (cut-off: 7.5–19.4 ng/L) - positive ANA (AC-7: titer: 1/400) with anti-SSA (Ro60) antibodies on typing. - positive antithyroid antibodies[a]: antithyroperoxidase = 837.7IU/mL (cut-off= 100 IU/mL),antithyroglobulin = 531.2 IU/mL,(cut-off = 50 IU/mL)]. - positive anti-RTSH antibodies[a] (>40 UI/L, cut-off = 2 UI/mL). - ultrasound of the thyroid gland: thyroiditis.	Graves' disease	Seliniuim (200 µg/day) + vitamin D.	Good evolution
Case 2	Female	39	12	- COVID-19 infection in June then December 2021. - familial history of type 1diabetes (father) and systemic lupus erythematosus (mother)		- weight loss, palpitations, hand tremor, photophobia, hypersudation, lacrimation. - grade 1 exophthalmos with homogeneous goiter on clinical examination.	- TSH <0.005 µUI/mL (cut-off: 0.25–4 µUI/mL). - T4: 77.3 pmol/L (cut-off: 10.6–19.4 pmol/L). - glycemia: 10.8 mmol/L (cut-off: 4–6 mmol/L). - glycated hemoglobin: 6.8 % (cut-off: 4.2–6.5 %) - positive ANA (AC-8, titer: 1/200) with negative typing. - positive anti-thyroperoxidase = 125 IU/mL (cut-off = 50 IU/mL). - positive anti-RTSH antibodies (>40 UI/L, cut-off = 2 UI/mL). - positive anti-acid glutamic decarboxylase[a] (>2000 UI/mL, cut-off: <10 UI/mL). - ultrasound of the thyroid gland: hypoechoic gland and hypervascular on color Doppler.	Graves' disease + type 1 diabetes	Benzylthiouracilin (300 mg) Propranolol (120 mg) intensified insulin therapy radioactive iodine (20 mCi)	Good evolution
Case 3	Female	23	4	- COVID-19 infection in 2022 - familial history of Sjögren syndrome		- headache, photosensitivity, abdominal pain, bloating	- TSH: 3.5 µUI/mL (cut-off: 0.25–4 µUI/mL).	Hashimoto's thyroididtis	Symtomatic treatment	Good evolution

(*continued on next page*)

Table 1 (*continued*)

Case No	Gender	Age (year)	Delay between AIM and the last COVID-19 infection (Week)	Associated conditions	Medications	Clinical manifestations	Investigations	Diagnosis (Criteria used)	Treatment	Evolution
				and systemic lupus erythematosus (ants)			- positive ANA (AC-1, titer: 1/800) with anti-dsDNA antibodies found on tying. - positive antithyroid antibodies: antithyroperoxidase = 128 IU/mL (cut-off = 100 IU/mL), antithyroglobulin = 351 IU/mL,(cut-off = 50 IU/mL)]. - normal complement (C3, C4) levels[b], negative anti-phospholipid antibodies[a]. - radiological testing (ultrasound of the thyroid gland, cerebral magnetic resonnace imaging): normal.			
Case 4	Male	44	2	- COVID-19 infection in 2023 - peptic ulcer	Ipproton	- fever, diffuse myalgia, muscle cramps, distal and perioral paresthesia, dysphagia, polyarthralgia, blurred vision; - moderate muscle weakness on clinical examination	- TSH: 1.56 3.5 µUI/mL (cut-off: 0.25–4 µUI/mL). - calcemia: 1.8 mmol/L (cut-off: 2.2–2.6 mmol/L). - phosphoremia: 2.57 mmol/L (cut-off: 0.8–1.45 mmol/L). - parathyroid hormone: 12 pg/mL (cut-off: 14–65 pg/mL). - creatinine kinase: 2160 UI/L (cut-off: 10–200 UI/L), lactate dehydrogenase: 300 UI/L (cut-off: 140–245 UI/L). - positive ANA (AC-15, titer: 1/200) with negative tying. - negative antithyroid, anti-phospholipid, and anti-transglutaminase antibodies[a].	Autoimmune hypoparathyroidism	Calcium Carbonate (4 g per day) Alfacalcidol (0.5 µg per day)	Good evolution
Case 5 (Figs. 2 and 3)	Male	55	8	- COVID-19 infection in 2022 - type 2 diabetes (since 2009), diabetic nephropathy (since 2020), and arterial hypertension (since 2021)	INN-insulin human Furosemide, Acetylsalicylic acid	- bilateral myalgia and paresthesia. - diffuse edema of all the right inferior limbs with glossy cardboard skin, associated with complete anesthesia, and a motor deficit of the right leg and foot muscles on clinical examination	- Positive ANA (AC-4, titer: 1/20) with negative typing. - line-blot myositis[c]: positive anti-Mi2. - radiological testing (computed tomography and magnetic resonance imaging): presence of a collection depending of the biceps femoris muscles, which was associated with a local myositis (right thigh), a compression of the sciatic	Necrotizing autoimmune myositis [2003 European Neuromuscular Center (ENMC)]	Chirurgical intervention antibiotherapy rehabilitation	Clinical recovery

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Table 1 (*continued*)

Case No	Gender	Age (year)	Delay between AIM and the last COVID-19 infection (Week)	Associated conditions	Medications	Clinical manifestations	Investigations	Diagnosis (Criteria used)	Treatment	Evolution
							nerve, and a specific interstitial lung disease. - Anatomopathological analysis (thigh muscle biopsy): presence of myositis with a local necrotizing fascitis.			
Case 6	Female	41	8	- COVID-19 infection in 2022 - cholecystectomy in 2018		- dysphagia, sicca syndrome, polyarthralgia	- Complete blood count: leukopenia (white cells: 3170 cells/mm^3) and lymphopenia (1000 cells/mm^3). - Erythrocyte sedimentation rate: 23 mm/1st hour (cut-off: 15 mm/1st hour). - positive ANA (AC-1, titer: 1/400) with anti-dsDNA and anti-nucleosome on typing. - salivary glands biopsy: chronic lymphocytic sialadenitis grade 3 of schisholm.	Sjögren Syndrome [2003 American colleague of rheumatology/ european alliance of associations for rheumatology (ACR/EULAR)]	Corticotherapy (0.5 mg/kg/day) Hydroxychloroquine (200 mg 2 pills/day)	Good evolution
Case 7	Male	67	8	- COVID-19 infection in 2021 - chronic obstructive pulmonary disease	Terbutaline	- fever, polyarthralgia, polyarthritis, polyseritis and a worsening dyspnea	- Erythrocyte sedimentation rate: 100 mm/1st hour (cut-off: 15 mm/1st hour). - C-reactive protein: 120 mg/L (cut-off <6 mg/L). - ANA and IgM-rheumatoid factor[a]: negative. - positive anti-citrullinated cyclic peptides[a]: 27 RU/mL (cut-off <5 RU/mL). - knees, ankles, and hip X-rays: normal.	Rheumatoid arthritis [2010 American colleague of rheumatology/ european alliance of associations for rheumatology (ACR/EULAR)]	Cortcosteroids (0,5 mg/Kg/day) Metotrexate (4 pills per week)	Good evolution
Case 8	Female	54	8	- COVID-19 infection in 2020, February then April 2022 - hypertension since 2020	Ipproton losartan	- polyarthralgia (hips and ankles) - polyarthritis (the right and left metacarpals and the interphalangans of the right and left second fingers)	- Erythrocyte sedimentation rate: 100 mm/1st hour (cut-off: 15 mm/1st hour). - positive ANA (AC-4, titer: 1/180), negative typing. - positive IgM-rheumatoid factor: 122 RU/mL (cut-off: 20 RU/mL). - anti-citrullinated cyclic peptides: negative. - ankles' X-rays: erosions.	Rheumatoid arthritis [2010 American colleague of rheumatology/ european alliance of associations for rheumatology (ACR/EULAR)]	Metotrexate (4 pills per week)	Good evolution
Case 9	Male	12	6	- COVID-19 infection in 2021		- achilles tendon pain - arthritis muscle pain deformity of the left	- Positive ANA (AC-1, titer: 1/800), typing: anti-nucleosomes and anti-DFS70.	Peripheral juvenile ankylosing spondylarthritis	Corticosteroids (16mg/day) methotrexate (3 pills per week)	Clinical improvement.

(*continued on next page*)

Table 1 (*continued*)

Case No	Gender	Age (year)	Delay between AIM and the last COVID-19 infection (Week)	Associated conditions	Medications	Clinical manifestations	Investigations	Diagnosis (Criteria used)	Treatment	Evolution
						lower limb and -tendonitis (enthesis) on clinical examination	- HLA-B27 typing[d]: positive			
Case 10 (Fig. 4)	Female	32	4	- COVID-19 infection in 2023		- gait disorder, vesicosphincter disorder, visual blurring, and progressive worsening of walking - ataxic walking, an unstable standing position, a motor deficit and hypoestesis in both lower limbs on clinical examination	- Positive ANA (AC-1, titer: 1/180), negative typing. - anti- neutrophil cytoplasmic antibodies, anti-aquaporin 4 antibodies and anti-myelin oligodentrocytes glycoprotein: negative[c]. - radiological testing (fundus, brain and spinal magnetic resonance imaging): bilateral papilledema stage 2 and intermediate uveitis, diffuse high T2 signal throughout the cervical, thoracic, and lumbosacral cord, and enhancement of the entire spinal cord after gadolinium injection	Acute myelitis	Intravenous methylprednisolone (1 g per day for 5 days)	Clinical improvement.
Case 11	Female	37	2	- COVID-19 infection in 2020		- heaviness in both lower limbs and paresthesia - distal muscle deficit and tactile and thermoalgesic hypoesthesia at C3–C4 level on clinical examination	- ANA and anti-aquaporin 4 antibodies: negative. - cerebral/medullary magnetic resonance imaging: diffuse high T2 signal throughout the cervical cord.	Acute myelitis	Corticoides for 5 day (1g per day)	Clinical improvement
Case 12 (Fig. 5)	Male	43	1 et half	- COVID-19 infection in 2021		- four-limb paresthesia - heel gait walk with toe flexion, a discrete distal deficit, and diminished osteotendinous reflexes in both upper limbs on clinical examination	- Cerebro-spinal-fluid: normal proteinorachia and glycorachia. - ANA and anti- neutrophil cytoplasmic antibodies: negative. - EMG: sensorimotor polyradiculoneuropathy with a demyelinating mechanism.	Guillan barré syndrome (Brighton criteria)	Symptomatic treatment	Clinical improvement
Case 13	Male	60	1 et half	- COVID-19 infection in 2021 - double valve replacement	Acenocoumarol since 2017	- four-limb paresthesia, heaviness, weakness and slurred speech and mastication. - walking with assistance, flaccid tetraparesis, abolished osteotendinous reflexes	- Cerebro-spinal-fluid: normal proteinorachia and glycorachia. - ANA: negative. - EMG: neurogenic electrical patterns.	Guillan barré syndrome (Brighton criteria)	Corticosteroids (bolus: 1g/day) rehabilitation	Good evolution

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Table 1 (*continued*)

Case No	Gender	Age (year)	Delay between AIM and the last COVID-19 infection (Week)	Associated conditions	Medications	Clinical manifestations	Investigations	Diagnosis (Criteria used)	Treatment	Evolution
						in the lower limbs and weak reflexes in the upper limbs, and facial diplegia predominantly on the right on clinical examination				
Case 14	Female	64	1	- COVID-19 infection in 2021 - diabetes type 2, hypertension and stentated Coronary patient	InsulinC aptoprilA cetylsalicylic acid	- heaviness and paresthesia in the four limbs. - possible walk with bilateral help, motor deficit of the four limbs, and superficial and deep hypoesthesia on clinical examination	- Cerebro-spinal-fluid: normal proteinorachia and glycorachia. - ANA and anti- neutrophile cytoplasmic antibodies: negative. - EMG: inflammatory polynevritis of secondary axonal demyelinating mechanism.	Guillan barré syndrome (Brighton criteria)	Rehabilitation	Clinical spontaneous recovery
Case 15	Male	67	2	- COVID-19 infection in 2022 - diabetes type 2, hypertension	InsulinC aptopril	- heaviness in both lower limbs and paresthesia in all four limbs. - impossible gait, a sensory and motor deficit in the four limbs, abolished osteotendinous reflexes in the lower limbs, and superficial hypoesthesia with deep sensory disturbance on clinical examination.	- Cerebro-spinal-fluid: albumino-cytological dissociation. - positive ANA (AC-4, titer = 1/180), negative typing. - positive anti-neutrophil cyto-plasmic antibodies (cANCA), negative typing[c]. - EMG: inflammatory polynevritis of secondary axonal demyelinating mechanism.	Guillan barré syndrome (Brighton criteria)	IV immunoglobulins (0.4 g/kg/day)	Good evolution
Case 16 (Fig. 6)	Female	47	8	- COVID-19 infection in 2021		- diarrhea, dysphagia and edematous fingers	- Positive ANA: (AC-3, titer = 1/800), anti-Sm/RNP and anti-centromere antibodies on typing.	Non specific immune stimulation	Symptomatic treatment	- Disappearence of clinical symptoms - Persistance of ANA (AC-3, titer = 1/180)

AIM: autoimmune manifestations, COVID-19: coronavirus disease 2019, SLE: systemic lupus erythematosus, SS: Sjögren syndrome, ANA: antinuclearantibodies, RTSH: anti-thyroid stimulating hormon receptor antibodies, ds: double-stranded, EMG: electromyography, MPO: anti-myeloperoxydase, PR3: anti-proteinase 3.

[a] ELISA: Euroimmun, Germany.

[b] turbidimetric SPA PLUS, Binding Site.

[c] line-blot: Euroimmun, Germany.

[d] complement-dependent cytotoxicity, Lagitre.

[e] IIF: Euroimmun, Germany.

specific physical signs. Additionally, targeted laboratory and imaging evaluations, and potentially physiological or histological analyses were performed. Upon physician request, immunological investigations were initiated, including antinuclear antibodies (ANA) screening by indirect immunofluorescence (IIF) on *HEp-2* cells, ANA typing using either ELISA (Biosystems, Spain) or line-blot assay (Euroimmun, Germany), and specific autoantibody assessments with regard to the clinical context. The confirmation of AID was based on established international criteria and expert opinions. The ethical review process was initiated after observing a cluster of potentially documentable and publishable post-COVID-19 AIM cases. It followed a two-phase approach: obtaining approval from the local ethics committee and securing informed consent (verbal or written) from each participating patient.

3. Results

Data from 16 patients with AIM after post-COVID-19 infection were collected. The mean age was 44.6 ± 15.5 years (range: 12–67 years). There were eight men and eight women (sex ratio = 1).

AIM appeared 1 week to three months after the COVID-19 infection. Fifteen patients had a moderate COVID-19 presentation (no need for hospitalization or oxygen therapy) and one patient had an asymptomatic COVID-19 form, with fortuitous RT-PCR after the infection of the husband (case 16). AIM appeared after the first infection in all cases except for case 2 (second infection) and case 8 (third infection). Since Tunisia began vaccination in March 2021, all infected cases before this date were unvaccinated (Cases 1, 5, 7, 9, 11, 12, 13, and 16). The policy of our country was to vaccinate on the first step people over 60 years old by age groups (decreasing: ≥75 years, 65–74 years, then 60–64 years), and health professionals in contact with COVID-19 patients. Thus, cases 2, 3, 6, and 10 were infected before COVID-19 vaccination. Cases 4, 8, and 14 were infected more than 1 year after the COVID-19 vaccination, and case 15 refused the vaccine.

Based on specific international criteria, 15 patients were diagnosed with AID [Guillain-barré syndrome (GBS: cases 12, 13, 14, 15), Graves'diseases (GD: cases 1 and 2), Rheumatoid arthritis (RA: cases 7 and 8), acute myelitis (AM: case 10 and 11), type 1 diabetes (D1: case 2), Hashimoto's thyroiditis (HT: case 3), autoimmune hypoparathyroidism (AHPT: case 4), necrotizing autoimmune myositis (NAM: case 5), Sjögren syndrome (SS: case 6), and juvenile ankylosing spondylarthritis (jAS: case 9), one case each] and they were treated with specific treatments. The diagnoses retained for the other case was non-specific stimulation of the immune system (case 16) with improvement under symptomatic treatment.

All the data related to the cases are presented in Table 1.

4. Discussion

Following the emergence of the SARS-CoV-2 pandemic, the potential association between this virus and autoimmunity has become the subject of ongoing investigation [22]. However, owing to conflicting findings, a definitive conclusion regarding the capacity of this virus to unveil or induce autoimmune disorders remains elusive [23–25].

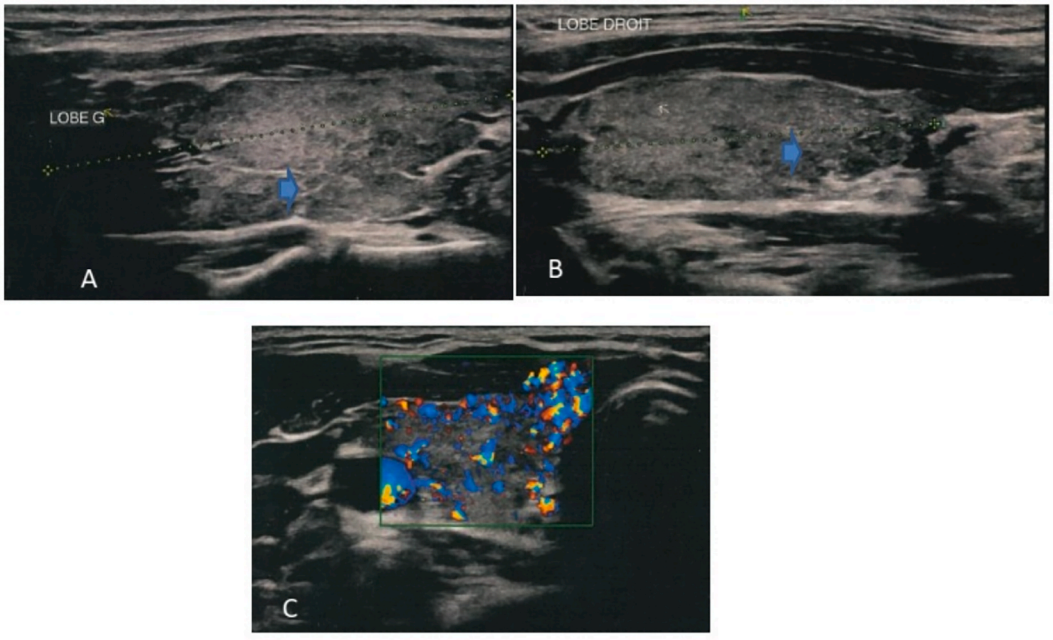


Fig. 1. Case 1: Thyroid gland ultrasound on longitudinal scan (A: left lobe, B: right lobe) showing heterogenous parenchymal echostructure with steaky lines (blue arrow); C: right lobe thyroid gland color doppler ultrasound on transversal section showing diffuse parenchymal hyperhemia.

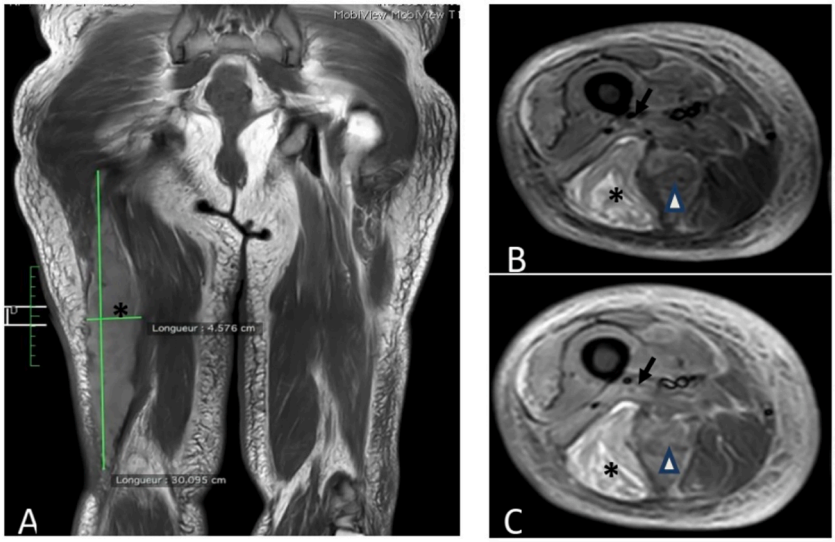


Fig. 2. Case 5: MRI of the thighs in T1 (A) coronal sections, and axial STIR (B) and T1 Fat Sat with Gadolinium injection (C): Fusiform (asterisk) collection well limited developing in the intermuscular fascia between the two heads of biceps femoris muscle, in heterogeneous hyper signal STIR and T1 (measuring 30 × 4.5 × 6 cm). It is associated with an infiltrated aspect of the surrounding fasciomuscular soft parts, particularly of the biceps femoris muscular body (Arrowhead). The collection comes in contact with the right sciatic nerve (arrow) to the middle third of the thigh. Fine collection under the fascia of the extensive lateral muscle dissecting the muscle mass of its fascia. Bilateral fatty degenetation oh the thigh muscles predominant on the right.

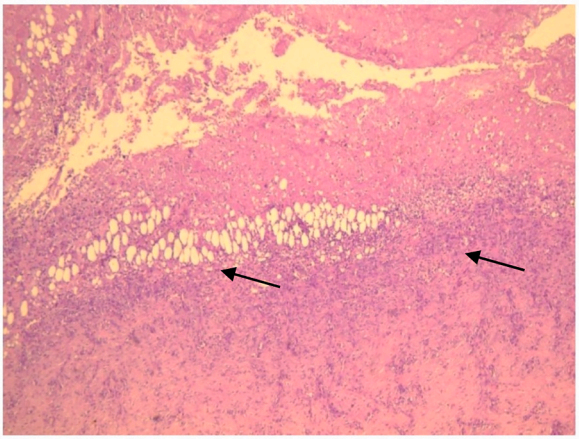


Fig. 3. Case 5: Thigh muscle biopsy showed a myositis with a local necrotizing fascitis (black arrow).

Herein, we report a series of AIM that developed after SARS-CoV-2 infection. The concept of virus-induced autoimmunity has been a longstanding hypothesis [26], supported by the observation of AIM following viral infections and the detection of viral genetic material (DNA or RNA) or specific antibodies targeting the virus in patients with AID [27]. Evidence further strengthens this concept, with the demonstration of autoantibody production after viral infection [28], and molecular mimicry, bystanding activation, and epitope spreading being the leading proposed mechanisms [29].

Our case series demonstrates a diverse spectrum of AIM, encompassing both clinical symptoms and laboratory abnormalities. Notably, a significant proportion of patients exhibited co-occurrence of multiple AIM, facilitating the diagnosis and classification of autoimmune disease (AID) according to internationally established criteria (ENMC for NAM, ACR/EULAR for SS and RA, Amor criteria for jAS, and Brighton criteria for GBS). Importantly, a thorough review of medication history excluded drug-induced autoimmunity as a potential contributor because none of the reported medications are known to induce autoimmune reactions [30–34].

Some of our cases were vaccinated against SAR-CoV-2 one year or more before the infection. Knowing that the timeline of AIM onset post-COVID-19 vaccination reported in the literature are ranging from a few hours to two months post-COVID-19 vaccination

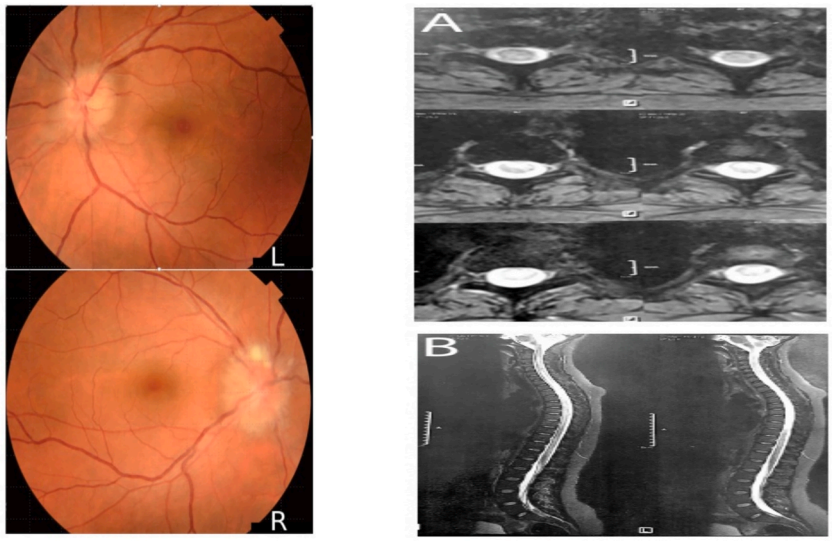
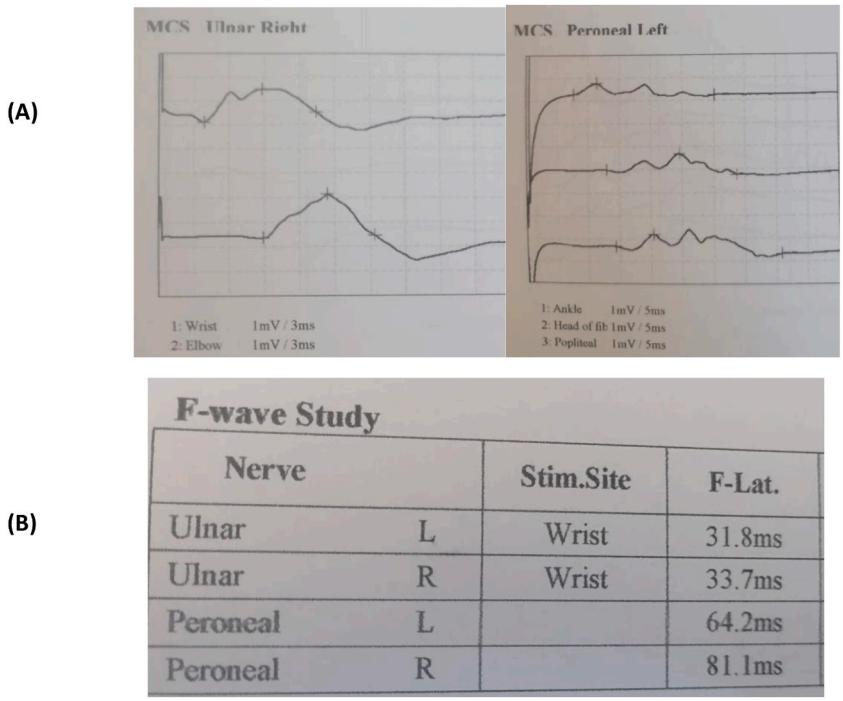


Fig. 4. Case 10: I. Funds examination showing bilateral papillary edema stage 3; II. Sagittal (A) and axial (B) T2 Weighted MRI showing highsignal intensity throughout the cervical, thoracic and lumbosacral cord.



Nerve		Stim.Site	F-Lat.
Ulnar	L	Wrist	31.8ms
Ulnar	R	Wrist	33.7ms
Peroneal	L		64.2ms
Peroneal	R		81.1ms

Fig. 5. Case 12: Electromyography shows: **(A)** a lengthening of latencies and temporal dispersion in the upper limb (ulnar nerve right) and in the lower limb (peroneal nerve left), **(B)** a clear reduction in the speed of sensitive conduction potentials in upper and lower limbs with F wave elongation.

[35], It is unlikely that AIM reported in our series were related to the COVID-19 vaccination.

The mean age in our series was 44.9 ± 11.5 years, with a sex-ratio = 1 and AIM that appeared 1 week to 3 months after COVID-19 infection. Two large studies on the incidence of AID following COVID-19 infection reported that the mean age of patients with AID post-COVID-19 infection was 51.1 years (20–89 years) and 52.2 years (15–55 years), with 64.3 % and 50.5 % of female patients, respectively [23,36]. The delay between the onset of COVID-19 infection and AIM was estimated to be 19 ± 11.4 to 44 ± 16 days [37]

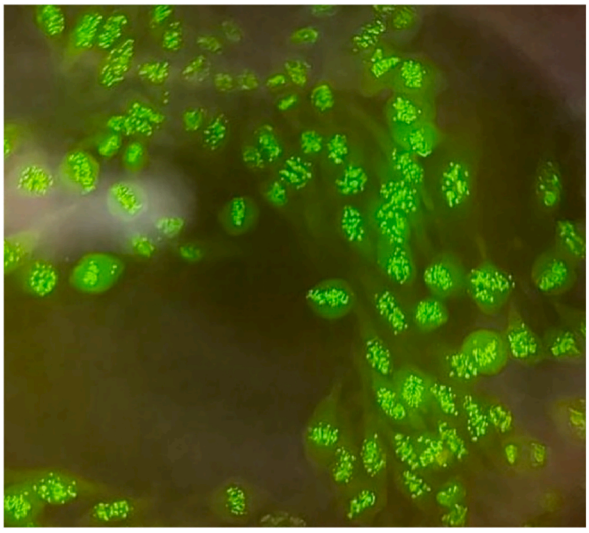


Fig. 6. Case 16: Centromere pattern on Indirect Immunofluorescence assay.

or between 14 and 112 days [23].

Our study reported six patients with post-COVID-19 infection neurological involvement, comprising four cases of GBS (cases 12, 13, 14, and 15) and two cases of AM (cases 10 and 11). In fact, many cases of GBS associated with COVID-19 infection have been reported [38]. Our GBS patients, aged between 43 and 67 years, were predominantly male (3 out of 4). This aligns with the existing literature reporting a male predominance in GBS following COVID-19 infection, with a median age of 61 years [39], possibly due to the increased susceptibility of male neurological cells to SARS-CoV-2 spike protein binding via angiotensin-converting enzyme 2 receptors [40]. Our patients presented a moderate form of COVID-19, and only one patient required intravenous immunoglobulin (IVIG). In fact, two large studies on patients who developed GBS post-COVID-19 infection showed that 85 % of these patients presented with a moderate presentation of COVID-19, and 25 % were treated with IVIG [41]. The mechanism of GBS post-COVID-19 infection is hypothesized to involve molecular mimicry between viral epitopes and those of the nervous system [40]. AM is also a frequent spinal cord disease observed after COVID-19 infection [42]. Both AM patients in our series were female, aged 32–37 years, presented a moderate form of the infection, and were treated with corticosteroids. Our case records fall within the findings of the largest review of spinal cord diseases post-COVID-19, which reported that patients with AM post-COVID-19 infection were aged between 3 and 67 years and most of them (17/18) presented a moderate form of the infection and were treated with corticotherapy [43]. Molecular mimicry is also thought to be the primary autoimmune mechanism underlying AM development in this context [44].

Our case series also included four patients with autoimmune endocrine disease post-COVID-19 infection. This included one case of GD (case 1), one case of GD co-occurring with D1 (case 2), one case of HT (case 3), and one case of AHPT (case 4). Both GD post-COVID-19 infection diagnoses in our series occurred in relatively young patients (29 and 39 years) who presented a moderate form of COVID-19 and were treated with specific treatment (selenium, …). Although GD following COVID-19 infection has been documented, with reported cases ranging from 21 to 53 years of age, mostly presenting a moderate form of the infection and treated as in our cases, it remains a relatively rare occurrence [45]. Molecular mimicry is a proposed mechanism for GD post-COVID-19 development [46]. A 23-year-old female patient with a moderate form of COVID-19 was also diagnosed with HT in our study; another infrequently reported AID post-COVID-19 with a moderate form of infection in the majority of reported cases [45]. Similar to GD post-COVID-19 infection, molecular mimicry is likely the underlying autoimmune process [46]. Our case series also identified a 39-year-old male with D1, preceded by a moderate form of COVID-19. Indeed, the largest systematic review of COVID-19 induced D1 reported only five adults (aged 19–33 years) who developed this disease after a moderate form of infection [47]. The proposed mechanisms for this association are molecular mimicry and bystander activation [48]. To our knowledge, this study presents the first documented case of combined D1 and GD following COVID-19 infection, although a similar association has been reported in rare cases following COVID-19 vaccination [49]. To the best of our knowledge, our case (44-year-old) with a new AHPT post-COVID-19 infection is the fourth case reported after three previous patients aged 43, 46, and 53-year-old [50]. Unlike in our case, these three patients developed new AHPT post-severe forms of COVID-19. However, all patients had a good outcome (recovery). The autoimmune mechanism leading to AHPT post-COVID-19 infection remains unknown.

Three patients in our study were diagnosed with a connective tissue disease post-COVID-19 infection. There were two seropositive cases of RA (case 7:67-year-old and case 8:54-year-old) and one case of SS (case 6:41-year-old) post-mild COVID-19. RA post-COVID-19 infection has not been rarely described [16], and the age of the reported cases ranged between 25 and 65 years, with most presenting a moderate form of the infection [51]. However, SS post-COVID-19 infection remains very rare [4]. Molecular mimicry is the probable mechanism leading to these two diseases post-COVID-19 infection [52].

In our series, we reported one case of peripheral juvenile AS post-mild-COVID-19 infection (case 9: 12-year-old). SA in general and peripheral SA after COVID-19 infection has been reported previously [4,16]. The ages of the few reported cases ranged between 20 and

60 years [53]. To the best of our knowledge, this is the first reported case of juvenile SA post-COVID-19 infection. Molecular mimicry is thought to be the principal mechanism underlying autoimmune and auto-inflammatory rheumatic diseases [52].

We identified a 55-year-old patient (case 5) diagnosed with NAM post-mild-COVID-19 infection. Three cases only were reported with an age ranged between 51 and 60 years, and in whom two cases had severe COVID-19 [36,54]. Molecular mimicry and bystander activation may be the mechanisms involved in triggering NAM post-COVID-19 infection [55].

A female patient (case 16) in our series showed persistent ANA-positivity post-asymptomatic-COVID-19 infection associated with clinical signs of localized scleroderma. ANA positivity after COVID-19 infection has been previously described [56,57]. Women showed greater persistence of ANA than men [58]. Similar to our case, Marutori et al. found that some patients had an ANA pattern suggestive of antibodies related to scleroderma without developing the disease [59].

In conclusion, this study describes a series of 16 patients who developed a variety of AIM following COVID-19 infection. While a temporal association between infection and AIM onset was observed, pre-existing asymptomatic autoimmunity remains a possibility. Therefore, a definitive conclusion regarding COVID-19's role in triggering or unmasking autoimmunity cannot be established. Further investigations are warranted to elucidate the potential mechanisms underlying the development of autoimmune diseases in the context of COVID-19.

CRediT authorship contribution statement

Mourad Elghali: Conceptualization, Data curation, Formal analysis, Methodology, Software, Supervision, Validation, Visualization, Writing – original draft. **Mariem Mhiri:** Investigation, Writing – review & editing. **Imen Chaabene:** Investigation, Writing – review & editing. **Ines Bayar:** Investigation, Writing – review & editing. **Bilel Ben Amor:** Investigation, Writing – review & editing. **Imen Jaziri:** Data curation, Writing – original draft. **Maha Changuel:** Data curation. **Rihab Ben Dhia:** Data curation. **Narjes Gouta:** Data curation. **Jamel Saad:** Data curation. **Rym Hadhri:** Data curation. **Ahmed Zrig:** Data curation. **Soumaya Boudokhane:** Investigation, Writing – review & editing. **Hela Marmouche:** Investigation, Writing – review & editing. **Mahbouba Jguirim:** Investigation, Writing – review & editing. **Nabil Sakly:** Conceptualization, Methodology, Project administration, Supervision, Validation, Visualization, Writing – original draft.

5. Ethical approval

The study was conducted according to the guidelines of the Declaration of Helsinki. The ethics committee of the hospital of the hospital of Fattouma Bourguiba Monastir confirmed that no ethical approval is required.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author upon reasonable request.

Funding

Not applicable.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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