

# Severe COVID-19 and long COVID in a 31-year-old woman with incontinentia pigmenti: A case report

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## Abstract

Incontinentia pigmenti is a rare genetic disease affecting the skin, microvasculature, and central nervous system, in which a hyperactive inflammatory response is observed. Due to the inflammatory phase of COVID-19 and associated cytokine storm, infection with SARS-CoV-2 in individuals with incontinentia pigmenti is a concern. Furthermore, type I interferon autoantibodies are found in life-threatening COVID-19 pneumonia and in 25% of individuals with incontinentia pigmenti. The present case report describes a 31-year-old Caucasian woman with incontinentia pigmenti and severe COVID-19. She was hospitalized for oxygen therapy, intravenous antibiotics, and corticosteroids. Eight months later, she is still symptomatic. To our knowledge, she is the first reported case of long COVID in incontinentia pigmenti. Increased autoimmunity may be implicated in both incontinentia pigmenti and long COVID. Pending evidence-based guidelines, COVID-protective measures including vaccination should be recommended to all patients with incontinentia pigmenti. Specific interferon therapy may be considered along with usual COVID treatment.

## Keywords

Infectious disease, incontinentia pigmenti, COVID-19, SARS-CoV-2, apoptosis, TNF- $\alpha$ , long COVID, type I interferon autoantibodies, autoantibodies, NEMO, inflammation

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## Introduction

Incontinentia pigmenti (IP) is a rare X-linked genetic disease affecting the skin, hair, teeth, microvasculature, and central nervous system. In the hemizygous male, the disease is usually lethal. In the heterozygous female, severity varies according to the random process of X inactivation.

IP is caused by a mutation in the *NEMO* gene (Xq28) encoding the nuclear factor-kappa-B (NF- $\kappa$ B) essential modulator (NEMO) protein. NEMO regulates cell proliferation and immune response by limiting apoptosis.<sup>1</sup> In 80% of IP cases, the mutation in the *NEMO* gene is a deletion of exons 4 to 10. The truncated NEMO molecule is devoid of activity, resulting in a complete lack of NF- $\kappa$ B activation and an acute sensitivity to tumour necrosis factor alpha (TNF- $\alpha$ )-induced apoptosis.<sup>2</sup>

Varying degrees of immunodeficiency have been observed in IP. In 1972, Honig and Miller described a possibly related immunological disorder.<sup>3</sup> In 2017, unresponsiveness to lipopolysaccharide injection was noted in two women affected by IP with immunodeficiency.<sup>4</sup> The immune

dysregulation in IP is classically linked to an exaggerated inflammatory response leading to increased apoptosis.<sup>5</sup>

Coronavirus disease (COVID-19), a SARS-CoV-2 infection, is of concern to individuals with IP, as COVID-19 can induce TNF- $\alpha$  as well as the apoptosis to which these individuals are particularly vulnerable. The compound, synergistic effect of COVID-19 and IP is therefore troubling. The following case report describes the clinical evolution of COVID-19, including severe disease and long COVID, in a patient with IP.

In the general population, COVID-19 infection may induce a severe inflammatory phase, or cytokine storm showing high serum levels of interleukins 6 and 8 (IL-6 and

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IL-8) and TNF- $\alpha$ .<sup>6</sup> The post-mortem lung analysis of fatal COVID-19 cases revealed apoptosis, necroptosis, and massive inflammatory cell infiltration, necrotic cell debris, and pulmonary interstitial fibrosis.<sup>7</sup>

Anomalies related to type I interferons, including autoantibodies, have also been found in severe COVID<sup>8</sup> (10%)<sup>9</sup> and in fatal COVID (20%).<sup>10</sup> Furthermore, those autoantibodies are more prevalent in individuals with IP (25%) than in the healthy population (3%).<sup>9</sup> The concentration of autoantibodies against type I interferons  $\alpha$  and  $\omega$  was increased with age, whereas interferon- $\beta$  autoantibodies were rarer (1.3% of critical patients and 0.9% of deceased patients) and were not age-dependent.<sup>10</sup>

## Case

### Medical history

The patient is a 31-year-old Caucasian woman affected by IP. In May 2006, she was identified as having an *NEMO* gene deletion of exons 4 through 10.

She was born at term (weight 3.57 kg and APGAR<sup>11</sup> score 8-9-9). She had typical IP skin involvement and reports skin healing delays and scars for even minor injuries. In early adulthood, she had a cholecystectomy, from which she suffered complications including dehiscence of the wound. She had staples for approximately 2 years before closing of the wound. Healing time for a cervical sprain and ligament tear were also longer than expected.

She reports six to seven infections a year, mainly initially viral and progressing to bacterial involvement requiring antibiotic therapy. Community-acquired infections would last longer (a month as compared to 7–10 days for others). Prior to COVID-19, she was never hospitalized for an infection.

The patient reports normal vision but narrow visual field and no involvement of the retina. On physical examination, she has 16 pointed teeth, including three milk teeth. Her hair is sparse. Some nails have typical striae. She reports easy bruising but has no mottled rash. Her feet and lower legs have a purplish coloration. She has been taking metoprolol for an arrhythmia since April 2020. She never smoked and was not exposed to secondary smoke.

She does not have epilepsy or mental retardation. She reports learning difficulties in school, for which she needed special help. In high school, she repeated Grade 10. She had been working as a supervisor of a daycare service while studying for a second university certificate, when she was infected with SARS-CoV-2.

### Evolution of SARS-CoV-2 infection

In Day 1, on 8 August 2020, she had fatigue and a sore throat. A nasopharyngeal swab on the same day tested positive for SARS-CoV-2 on polymerase chain reaction (PCR).

In Day 14, she consulted a COVID-19 clinic, complaining of fever (40.5°C), chills, myalgia, asthenia, headaches,

anosmia, dysgeusia, pharyngitis, dry cough, dyspnea at speech, anorexia, dizziness, diarrhoea, and facial rash. Vital signs were blood pressure 102/79 mmHg, pulse 112 bpm, saturation 93% in room air, respiratory rhythm 30 bpm, and oral temperature 38.2°C. Physical examination showed poor general state, increased work for breathing, with retractions and diffuse crackles. She was transferred to the Emergency Department and then hospitalized. She received oxygen supplementation by nasal cannula, intravenous corticotherapy, and antibiotics. She did not need intubation. She was diagnosed with bacterial pneumonia as per chest X-ray and discharged 4 days later with moxifloxacin for 7 days.

In Day 29, she consulted for relapsing cough and dyspnea. Vital signs were within normal range (blood pressure 139/88 mmHg, pulse 98 bpm, saturation 100% in room air, respiratory rhythm 20 bpm, temperature 36.4°C). Pulmonary auscultation and physical examination were normal. The chest X-ray showed an overall decrease in alveolar consolidation but persistence in the pulmonary bases and accentuation in the left inferior lobe. Doxycycline was started for 7 days, as well as a budesonide/formoterol inhalator.

In Day 50, she was diagnosed with acute otitis media. She complained of earache, hearing loss, sore throat, nasal congestion, rhinorrhea, headache, myalgia, and dizziness. She was subfebrile. The cough had improved somewhat. She received intranasal corticosteroids and a prescription for cefprozil antibiotic, from which she later developed a rash. Intramuscular ceftriaxone was planned but levofloxacin was tried first, given the rhinosinusitis symptoms.

In Day 70, symptoms persisted but without fever. Refractory rhinosinusitis was suspected; a non-steroidal anti-inflammatory drug was prescribed while awaiting sinus imaging.

In Day 86, a computed tomography (CT) angiography was ordered for coughing and slowly worsening dyspnea, as increased fatigue interfered with her capacity to perform the activities of daily living. The CT angiography showed alveolitis but no pulmonary embolism. The patient was referred to a pulmonologist. A new course of corticotherapy and antibiotics helped relieve infectious (suspected bacterial superinfection) and inflammatory symptoms.

In Month 3, symptoms persisted and now included cognitive deficits. Unable to focus attention, she quit work; academic performance dropped. She had a normal cognitive screening including a score of 28/30 on the Montreal Cognitive Assessment<sup>12</sup> (MoCA).

In Month 8, side effects of a first COVID-19 vaccination on 21 April 2021 included 40°C fever and temporary exacerbation of long-haul symptoms (headaches, dizziness, nausea, chills, myalgia, cough, and dyspnea).

In Month 9, the patient is still unable to work, with persistent severe fatigue and multiple symptoms (Table 1). She now considers adapting her lifestyle for a return to work, as she does not expect symptom resolution anytime soon, although her health is slowly improving.

**Table 1.** Persistent symptoms reported by patient – Month 9 post-infection.

|   |   |
|---|---|
| Exacerbation of symptoms during physical or mental activity | Dizziness   |
| Incapacitating fatigue (10–12 h/day sleep plus naps)        | Hair loss   |
| Continuous headaches  | Diaphoresis with exacerbation of other symptoms   |
| Attention deficit   | Sleep disorder (relieved by zopiclone)  |
| Memory deficits (anomia, loss of conversation thread)       | Intermittent chills without fever   |
| Fluctuating dyspnea   | Intermittent red eyes with pain   |
| Fluctuating cough   | Intermittent flushing   |
| Chest pain, discomfort                                      | Intermittent sore throat  |
| Arthralgia  | Exacerbation of anxiety   |
| Post-activity polypnea                                      | Depression (now resolved)   |
| Increased resting heart rate                                | Obsessive compulsive disorder (verification of door 10×/day)                              |
| Exacerbation of palpitations                                | Post-traumatic stress disorder (nightmares, worry of SARS-CoV-2 reinfection, and anxiety) |
| Back and leg pain   |   |

She has enrolled in a clinical trial based on Nepotchatykh et al.'s<sup>13</sup> profiling of circulating microRNAs (miRNAs) in myalgic encephalomyelitis/chronic fatigue syndrome, a syndrome with symptoms common to long COVID. She was assessed for miRNA levels and underwent a post-exertional stress challenge. She was also referred to a research study on long COVID and will get the battery of tests planned by the *Bio Banque québécoise de la COVID-19* (BQC19)<sup>14</sup> as well as an autoantibody panel, including autoantibodies against type 1 interferon. She will also be tested for primary immunodeficiency. Results are pending.

## Discussion

The scientific literature indicates a severe episode of COVID-19 in a patient with IP.<sup>9</sup> Several hypotheses may be advanced. The COVID-19 cytokine storm triggers, among other things, a TNF- $\alpha$  increase and possible apoptosis. Individuals affected by IP are highly sensitive to both TNF- $\alpha$  and apoptosis. Although the serum level of TNF- $\alpha$  was not measured, the combination of COVID-19 and IP could result in an exaggerated inflammatory response and magnified apoptosis.

Second, autoantibodies have been suspected to contribute to the aetiology of COVID-19 and long COVID. Autoantibodies against type I interferon were not present in asymptomatic or mild COVID cases (0/663) but were detected in 10.2% of life-threatening COVID (101/987).<sup>9</sup> Type I interferon autoantibodies are also more common in individuals with IP than in the general population, and a possible association between IP and susceptibility to autoimmunity has been raised in the scientific literature.<sup>9</sup> A study of six patients with IP showed that three had autoimmunity.<sup>15</sup> Our patient's autoantibody levels were not initially measured; detailed measures will be available as part of her current participation in two clinical trials. Other mechanisms may be involved as well, but more research is needed.

This suggests an interesting option for treatment; individuals with autoantibodies against some, but not all, interferons could potentially receive interferon- $\beta$  injections.<sup>10</sup> One patient with IP and COVID showed good clinical

results. She had antibodies against interferon- $\alpha$  and  $\omega$  but not  $\beta$ . As proposed by Bastard et al.,<sup>16</sup> individuals with IP could conceivably be screened for autoantibodies before ever getting COVID-19. If infected with SARS-CoV-2, they could then receive personalized interferon therapy.

It is noteworthy that the present patient is female and have a body mass index 33 kg/m<sup>2</sup> (height 1.65 m and weight 90.9 kg), both of which are risk factors for long COVID in the general population,<sup>17</sup> in addition to hospitalization.<sup>18</sup> Long COVID may therefore not be specific to her IP status.

The patient also presented with arrhythmia at the young age of 30 years. Arrhythmia is not usually present in IP. Another underlying medical condition may therefore complicate the clinical picture.

Finally, there may be publication bias. It is highly imperative that healthcare professionals report all COVID-19 cases complicated by IP, no matter the outcome, so as to advance knowledge in this rare disease.

## Conclusion

Considering TNF- $\alpha$ , apoptosis, and possible autoantibodies against type I interferon, it is biologically plausible that individuals with IP are at risk for severe COVID-19. More research is needed to understand the various contributory pathways and to develop specific treatment.

Furthermore, the present case shows symptoms compatible with long COVID. More case reports and research on physiopathology are needed to verify whether IP is indeed a risk factor for long COVID. To our knowledge, this is the first long COVID case report in a patient affected by IP.

While awaiting evidence-based guidelines, individuals with IP should rigorously adhere to preventive and protective measures against COVID-19, including vaccination. In addition to usual COVID treatments, specific interferon therapy should be considered in a research setting, as indicated.

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