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Life-threatening COVID-19 in a thymoma patient with anti-interferon-α autoantibodies

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ABSTRACT

Neutralizing anti-interferon (IFN)-α autoantibodies can lead to immune dysregulation, potentially resulting in critical coronavirus disease 2019 (COVID-19). We report a case presenting with severe COVID-19 who was subsequently diagnosed to have thymoma and neutralizing anti-IFN-α autoantibodies.

1. Background

Interferon (IFN)-α is a member of the type 1 interferons, which are essential for antiviral immunity. Neutralizing anti-IFN-α and anti-IFN-ω are anti-cytokine autoantibodies that can predispose to severe viral infections, most notably COVID-19 but also influenza, Middle-East Respiratory Syndrome (MERS), West Nile virus and various herpesviruses.[1] Patients with thymoma are also known to be more susceptible to viral infections such as cytomegalovirus (CMV), Epstein-Barr virus (EBV), and herpes simplex virus (HSV),[2] possibly due to Good's syndrome, a rare immunocompromised status featuring thymoma and hypogammaglobulinemia, or dysregulated negative thymic selection and subsequent production of anticytokine autoantibodies. Here we present a case who developed life-threatening COVID-19 despite being fully vaccinated against SARS-CoV-2, and was subsequently found to have underlying thymoma and anti-IFN-α autoantibodies.

2. Case presentation

An 80-year-old-woman with independent activities of daily living presented to the emergency department with lip cyanosis and shortness of breath. In the preceding week, she had experienced sore throat, followed by a productive cough. She was a retired florist, and had a history of pemphigus vulgaris, last treated with rituximab 12 years and 8 years before this visit. Two years prior to this presentation, she had received two doses of mRNA-1273 SARS-CoV-2 vaccines, followed by two booster doses with mRNA-1273.211 bivalent vaccines at six monthly intervals, with the last dose six months prior to this presentation. On arrival, the patient's vital signs were as follows: clear consciousness, a respiratory rate of 28 breaths/min, a temperature of 36.4 °C, a pulse of 86 beats/min, a blood pressure of 118/57 mmHg, and a peripheral oxygen saturation (SpO2) of 94 % under non-rebreathing mask. Physical examination revealed lip cyanosis, bilateral lung crackles, and diffuse wheezing. The patient's white blood cell count was 17780 (cells/μL) with predominant neutrophils 89.9 %, and her C-reactive protein (CRP) level was 18.14 mg/dL. Her nasopharyngeal swab tested positive for SARS-CoV-2 antigen. Chest X-ray showed a mediastinal mass and bilateral pulmonary infiltrates (Fig. 1 panel A). Subsequent chest computed tomography (CT) revealed a 9.7-cm anterior mediastinal mass morphologically suggestive of thymoma, along with ground glass opacities bilaterally (Fig. 1 panel B). She received immediate treatment with remdesivir, dexamethasone, and tocilizumab.

Despite prompt diagnosis and management, her respiratory distress worsened, necessitating intubation within 24 h due to hypoxemic respiratory failure. Nine days after intubation, she was successfully weaned from mechanical ventilation and extubated. Her repeat nasopharyngeal sample tested negative for SARS-CoV-2 antigen on the day of extubation.

A biopsy of the anterior mediastinal tumor was performed on the fifteenth day of admission; histopathology confirmed a lymphocyte-rich thymoma (WHO type B). Laboratory examinations showed hypogammaglobulinemia, with immunoglobulin G (IgG) level at 387.6 mg/dL, and low circulating B-cells and natural killer cells. Anti-acetylcholine

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receptor antibody testing revealed a weak positive result, but the patient did not have clinical signs or symptoms suggestive of myasthenia gravis. Given the combination of thymoma and hypogammaglobulinemia, Good's syndrome was suspected to be the cause of rapid progression of her SARS-CoV2 infection. However, she had no prior history of recurrent sinopulmonary infections or other opportunistic infections. This was her first hospitalization. She also tested positive for IgG against CMV, HSV, varicella-zoster virus (VZV), and SARS-CoV-2. Her SARS-CoV2 antigen test turned negative on day 10 after COVID-19 diagnosis, and no viral rebound or persistent viral shedding due to hypogammaglobulinemia occurred. Laboratory testing for anti-cytokine autoantibodies revealed the presence of neutralizing anti-IFN-α, which provided a plausible explanation for the patient's critical COVID-19 despite vaccination and satisfactory viral clearance. Simultaneous screening for neutralizing anti-interleukin (IL)-23, anti-IL-17, and anti-IFN-γ autoantibodies yielded negative results.

One month after admission, the patient underwent thymectomy. Her post-operative course was uneventful. Pathology of the entire tumor led to a revised subtyping of the thymoma to a WHO type AB. She was discharged and returned to her baseline independent activities of living. The laboratory follow-up after one year showed persistent hypogammaglobulinemia, B lymphocytopenia and neutralizing anti-IFN-α autoantibodies (Fig. 1 Panel C). However, the patient did not have any recurrent admissions for infections.

3. Discussion

Type 1 interferons exert diverse effects in response to viral infections, including inducing anti-viral responses in cells, enhancing the function of T cells and NK cells and promoting the ability of dendritic cells to

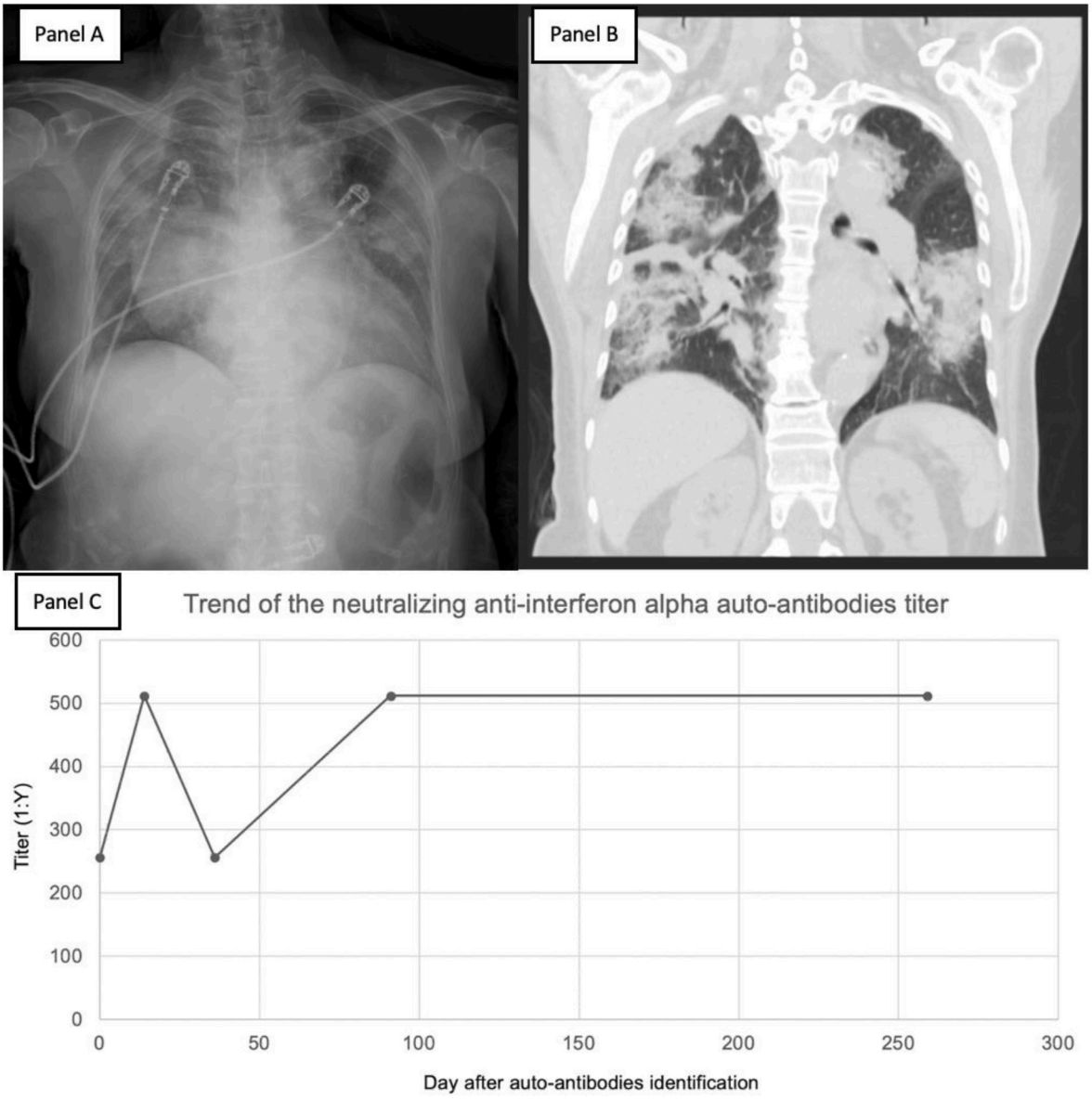

Fig. 1. The initial radiologic findings of this patient (Panel A), and the computed tomography of chest (Panel B), at the admission and the trend of the neutralizing anti-interferon-alpha autoantibodies titer (Panel C)
Panel A. The chest plain film displayed a well demarcated mass with smooth border at right chest and infiltration at bilateral lung fields.
Panel B. The computed tomography showed ground glass opacity at bilateral lung fields.
Panel C. The anti-interferon alpha autoantibodies titer was evaluated in serial dilution and documented as the first dilution of plasma which no longer inhibit 1 ng/mL of recombinant human interferon alpha STAT1 signaling. The day when the presence of autoantibodies was first identified, shortly after critical COVID-19 was day 0. The titer was followed up on day 14, day 36, day 91 and day 259. The titer did not decrease during convalescence nor after thymectomy.

stimulate effector T cells. Therefore, the presence of autoantibodies against type 1 interferons impaired her antiviral immune responses, and in conjunction with her advanced age, hypogammaglobulinemia and space-occupying anterior mediastinal mass, increased the severity of COVID-19.[3]

Autoantibodies against type 1 interferons have been associated with approximately 10 % of critically-ill patients with COVID-19. This case highlights severe COVID-19 as an index presentation of thymoma associated with neutralizing autoantibodies against IFN-α. Initially, the coexistence of thymoma and hypogammaglobulinemia raised the suspicion of Good's syndrome. However, the absence of other infections before or after this admission, and the presence of specific antibodies, notably raised against SARS-CoV-2 nucleocapsid, did not support this diagnosis. Subsequent testing identified anti-IFN-α autoantibodies, that are also commonly found among thymoma patients.[4] The patient also did not suffer from prolonged viral shedding or require intravenous immunoglobulin (IVIG) as typical for patients with hypogammaglobulinemia due to Good's syndrome or rituximab-induced B-cell depletion. Previous studies reported that the type 1 interferon autoantibodies could be induced by the COVID-19 mRNA vaccine.[5] Since there was no past history of recurrent infection, the autoantibodies were potentially induced by the vaccination. However, with the absence of antibodies against spike protein, the effects of vaccine immunization might be limited. Whether the autoantibodies were stimulated by the vaccine remained unclear.

Impaired type 1 interferon response increases susceptibility to severe viral infections, as observed in this case with critical COVID-19.[6] Thymoma, known for its impact on lymphocyte function, likely exacerbated immune dysfunction, including T and B lymphocyte impairment and autoantibody production neutralizing type 1 interferons, thus contributing to severe COVID-19 outcomes.[7] Despite limited studies linking thymoma directly to severe COVID-19, this case underscores the need for further investigation.

Patients with autoantibodies against type 1 interferons were more susceptible to other viral infections including influenza and to complications of live-attenuated vaccines, such as yellow fever vaccine due to inadequate protective effect against virus strain of the vaccine.[8,9] Identification of such patients is crucial for avoiding vaccine-related adverse effects and managing potential severe viral infections effectively. We suggest evaluating the presence of autoantibodies against type I interferon once the patient diagnosed with thymoma and patients with recurrent or severe infections without known etiology including critical COVID-19 despite vaccination.

Vaccination against SARS-CoV-2 and influenza, especially in patients with thymoma or elderly patients who may harbor autoantibodies against Type 1 interferon autoantibodies. Though there is risk to develop autoantibodies against type 1 interferon, following mRNA vaccination, the possibility is low and the benefit still outweighs the risk. Treatment strategies for patients with anti-IFN-α autoantibodies include supplementing with interferon lambda or IFN-β, although evidence supporting this approach is anecdotal or currently in clinical trials.[10]

Limited studies exploited whether the titer of autoantibodies against type 1 interferon decrease after thymectomy. In this patient, the follow-up antibody titer after 8 months did not decrease, while the clinical significance remains to be explored.

4. Conclusion

The relationship between thymoma and severe SARS-CoV-2 infection remains ambiguous. Given the predisposition of thymoma patients to develop autoantibodies, assessing their presence in cases of severe COVID-19 could inform clinical management, potentially guiding interventions like cytokine supplementation and vaccine precautions. This report presents a case exemplifying these complexities, emphasizing the need for tailored approaches in managing thymoma-associated immune dysregulation and severe viral infections.

CRediT authorship contribution statement

Yu-Shan Shih: Writing – original draft, Conceptualization. **Wan-Ting Tsai:** Writing – review & editing. **Bei-Chia Guo:** Methodology. **Aristine Cheng:** Writing – review & editing, Supervision, Resources, Methodology, Formal analysis, Data curation, Conceptualization. **Jann-Tay Wang:** Writing – review & editing.

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List of abbreviations

CMV	cytomegalovirus
COVID-19	coronavirus disease 2019
CRP	C-reactive protein
CT	computed tomography
EBV	Epstein-Barr virus
HSV	herpes simplex virus
IFN	interferon
IgG	Immunoglobulin G
IL	interleukin
IVIG	intravenous immunoglobulin
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SpO2	oxygen saturation
VZV	varicella-zoster virus
WHO	World Health Organization

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jmii.2025.02.002.

References

1. Fernbach S, Mair NK, Abela IA, et al. Loss of tolerance precedes triggering and lifelong persistence of pathogenic type I interferon autoantibodies. *J Exp Med*. 2024;221(9), e20240365.
2. Chang R, Duan S, Li S, et al. Viral infection in thymoma and thymic tumors with autoimmune diseases. *Thorac Cancer*. 2021;12(22):2971–2980.
3. McNab F, Mayer-Barber K, Sher A, Wack A, O'Garra A. Type I interferons in infectious disease. *Nat Rev Immunol*. 2015;15(2):87–103.
4. Shiono H, Wong YL, Matthews I, et al. Spontaneous production of anti-IFN-alpha and anti-IL-12 autoantibodies by thymoma cells from myasthenia gravis patients suggests autoimmunization in the tumor. *Int Immunol*. 2003;15(8):903–913.
5. Xu W, Wen X, Cong X, Jiang W. COVID-19 mRNA vaccine, but not a viral vector-based vaccine, promotes neutralizing anti-type I interferon autoantibody production in a small group of healthy individuals. *J Med Virol*. 2023;95(10), e29137.
6. Bastard P, Rosen LB, Zhang Q, et al. Autoantibodies against type I IFNs in patients with life-threatening COVID-19. *Science*. 2020;370(6515).
7. Cheng A, Holland SM. Anti-cytokine autoantibodies: mechanistic insights and disease associations. *Nat Rev Immunol*. 2024;24(3):161–177.
8. Zhang Q, Pizzorno A, Miorin L, et al. Autoantibodies against type I IFNs in patients with critical influenza pneumonia. *J Exp Med*. 2022;219(11).
9. Bastard P, Michailidis E, Hoffmann HH, et al. Auto-antibodies to type I IFNs can underlie adverse reactions to yellow fever live attenuated vaccine. *J Exp Med*. 2021;218(4).
10. Ryoo S, Koh DH, Yu SY, et al. Clinical efficacy and safety of interferon (Type I and Type III) therapy in patients with COVID-19: a systematic review and meta-analysis of randomized controlled trials. *PLoS One*. 2023;18(3), e0272826.