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# Autoimmunity in context of exposure to SARS-Cov2 virus

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**Abstract**

**English:**

***Introduction:*** *The immune response in patients with SARS-CoV2 infection is an incompletely elucidated pathophysiological challenge. There are more and more cases in which COVID-19 vaccination induces autoimmune side effects, of course, in a selected population. What are the criteria that induce such a response? How can it be prevented? These are questions that the medical world must answer.*

***Material and Methods:*** *A 28-year-old male patient presented with repeated small hemoptysis accompanied by pleuritic pain, which started suddenly 2 days prior. From the patient's history, we note autoimmune thyrotoxicosis triggered by the administration of the second dose of the anti-SARS-CoV2 vaccine, but also a recent COVID-19 episode. At the time of hospitalization, slightly elevated serum values of D-dimers were noted, and the CT examination identified multiple unilateral filling defects in the middle and small right pulmonary arteries, accompanied by a ground-glass opacity suggestive of a pulmonary infarction and possible bilateral stenosis of the subclavian arteries. The extended immunological panel was negative, but genetic tests have identified two thrombophilic gene mutations. Functionally, a discrete decrease in lung volumes and a slight impairment of alveolo-capillary diffusion was observed. The clinical, imaging and functional evolution was favorable under anticoagulant treatment.*

***Discusions:*** *The predisposition for thrombosis in COVID-19 is determined by at least two distinct processes, subsegmental and segmental vessel occlusion and microvascular in situ immunothrombosis. Pulmonary thromboembolism occurs more frequently in the first weeks after diagnosis, but cases farther from the acute moment have also been reported in literature, including in patients with mild forms of the disease.*

*Certain adjuvant components of the vaccines, as well as the SARS-CoV2 virus itself, can trigger autoimmune reactions in genetically predisposed individuals.*

***Conclusion:*** *Patients with active or recently recovered COVID-19 should be considered at an increased risk of pulmonary embolism when they present with specific symptoms, even without the existence of other risk factors.*

**Keywords**

*SARS-CoV2 vaccine • COVID-19 • immunothrombosis • Basedow-Graves thyroiditis • pulmonary thromboembolism*

# Autoimunitatea în contextul expunerii la virusul SARS-CoV-2

**Rezumat**

**Romanian:**

***Introducere:*** *Răspunsul imun la pacienții infectați cu SARS-CoV2 reprezintă o provocare fiziopatologică încă neelucidată în totalitate. Tot mai multe cazuri evidențiază efecte secundare autoimune ale vaccinării împotriva COVID-19, desigur, într-o populație selectată. Care sunt criteriile care induc un astfel de răspuns? Cum poate fi prevenit? Acestea sunt întrebări la care comunitatea medicală trebuie să răspundă.*

***Material și Metoda:*** *Un pacient de sex masculin, în vârstă de 28 de ani, s-a prezentat cu hemoptizie mică recurentă însoțită de dureri pleurale, care au început brusc cu 2 zile înainte. Din istoricul pacientului, reiese tirotoxicoza autoimună declanșată de administrarea celei de-a doua doze a vaccinului anti-SARS-CoV2, dar și un episod recent de COVID-19. La momentul spitalizării, s-au notat valori ușor crescute serice de D-dimeri, iar examenul CT a identificat multiple defecte de umplere unilaterale în arterele pulmonare mici și mijlocii din dreapta, însoțite de o opacitate de sticlă mată sugestivă pentru un infarct pulmonar și o*

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*posibilă stenoză bilaterală a arterelor subclaviculare. Panelul imunologic extins a fost negativ, dar testele genetice au identificat două mutații genetice trombofilice. Din punct de vedere funcțional, s-a observat o scădere discretă a volumelor pulmonare și o ușoară afectare a difuziunii alveolo-capilare. Evoluția clinică, imagistică și funcțională a fost favorabilă sub tratament anticoagulant.*

***Discuții:*** *Predispoziția la tromboză în COVID-19 este determinată de cel puțin două procese distincte, occluderea vaselor subsegmentare și segmentare și imunotromboza microvasculară in situ. Tromboembolismul pulmonar apare mai frecvent în primele săptămâni după diagnostic, dar au fost raportate și cazuri mai târzii, inclusiv la pacienții cu forme ușoare ale bolii. Anumite componente adjuvante ale vaccinurilor, precum și virusul SARS-CoV2 în sine, pot declanșa reacții autoimune la persoanele predispuse genetic.*

***Concluzie:*** *Pacienții cu COVID-19 activ sau recuperați recent ar trebui să fie considerați cu risc crescut de embolie pulmonară atunci când prezintă simptome specifice, chiar fără existența altor factori de risc.*

**Cuvinte-cheie**

*Vaccin SARS-CoV2 • COVID-19 • imunotromboză • tiroidită Basedow-Graves • tromboembolism pulmonar*

## Introduction

The immune response in patients with severe acute respiratory syndrome coronavirus 2 **(**SARS-CoV2) infection is an incompletely elucidated pathophysiological challenge. Exposure to the virus, both in the context of vaccination (1) as well as associated with the infection itself (2), is very commonly associated not only with the onset or reactivation of numerous autoimmune pathologies, including vasculitis and Basedow-Graves thyroiditis, but also with a systemic prothrombotic state which can greatly increase the risk of thrombosis and tissular infarction.

## Case Report

A 28-year-old white male, is presenting to the emergency room complaining of repeated small hemoptysis accompanied by pleuritic pain and hardly productive cough, which started suddenly, during the night, about 2 days before presentation. From the patient's history, we note autoimmune thyrotoxicosis triggered by the administration of the second dose of the messenger ribonucleic acid (mRNA) type of anti-SARS-CoV-2 vaccine, but also a recent coronaviral disease (COVID-19) episode – less than a month before.

At the moment of presentation, the clinical exam was normal. Bloodwork showed slight non-specific immune response, D-dimer values 3.5 greater than normal (normal value interval, n.v., 0-243 ng/mL) and a thyroid panel with values corresponding to mild glandular hyperfunction (TSH 0.01 uIU/mL – n.v. 0.3-4.5 uIU/mL, free T4 26.8 pg/mL – n.v. 8.9-17.2 pg/mL (see *Annex 1* for a more thorough breakdown of the evolution in time of the thyroid function). Functionally, a discrete decrease in lung volumes and a slight impairment of alveolo-capillary diffusion was observed, with a forced vital capacity (FVC) of 76.3% of the expected normal value, forced expiratory volume in the first second (FEV1) of 60.5% and diffusing capacity of the lungs for carbon monoxide (DLCO) of 61.9% (see *Annex 2*). The electrocardiogram failed to show any significant changes of morphology or rhythm.The plain chest X-ray (*Fig.1*) performed revealed no pathological parenchymal changes. However, due to the sudden occurrence of hemoptysis in an otherwise healthy young male, a CT scan of the lungs was ordered, which identified multiple endoluminal thrombus filling defects in the medium and small arteries (*Fig.2*), on the right side, associated with microthromboses at the segmental and subsegmental level (*Fig.3.*), on the same side, accompanied by multiple ground-glass areas (*Fig.4*) suggestive of a pulmonary infarction. Injection of the contrast substance was impeded bilaterally, possibly by stenosis or partial thrombotic blockage of both subclavian veins (*Fig.5*).

During his hospitalization, the patient received anticoagulant treatment, with a low molecular weight heparin (LMWH) (Dalteparinum 5000IU, twice a day, subcutaneous), accompanied by antitussive medication (Codeine 15 milligrams, thrice a day, per mouth), pain-relieving medication, with a rapidly favorable evolution and no reoccurrence of hemoptysis.

Due to the patient's young age, male gender and non-smoking status a hereditary component of the prothrombotic

**Annex 1.** Detailed evolution of the patient's thyroid function

1. At the time of first diagnosis of Basedow-Graves thyroiditis (June 2021)
2. After stabilization of the disease, about 18 months after debut (February 2023)
3. Immediately after the SARS-CoV2 infection (August 2023)
4. At admission for suspicion of pulmonary trombembolism (September 2023)
5. One month after discharge (October 2023)

**Annex 2.** Detailed spirometry values and evolution in time under anticoagulant treatment

| EVOLUTION OF PULMONARY FUNCTION PARAMETERS | | | |
|---|---|---|---|
| **AT TIME OF ADMISSION** | | **ONE MONTH FOLLOW-UP** | |
| FEV1 | 60.5% | FEV1 | 87.9% |
| FVC | 76.3% | FVC | 102.4% |
| DLCO | 61.9% | DLCO | - |

| EVOLUTION OF THYROID FUNCTION PARAMETERS | | | | | | |
|---|---|---|---|---|---|---|
| | **DEBUT OF THYROIDITIS** | **BEFORE SARS-CoV2 INFECTION** | **IMMEDIATELY AFTER INFECTION** | **CURRENT ADMISSION FOR HEMOPTYSIS** | **ONE MONTH FOLLOWUP** | ***NORMAL VALUES*** |
| *TSH* | < 0.0083 | 1.531 | 0.0016 | 0.007 | < 0.005 | *0.3-4.5 mIU/mL* |
| *Free T4* | 1.35 | 0.93 | 25.56 | 26.8 | 13.3 | *8.9-17.2 pg/mL* |
| *ATPO* | 119.92 | 78.8 | - | - | 355.5 | *< 5.61 IU/mL* |
| *TRAb* | - | - | 5.61 | - | - | *< 1.75 IU/mL* |

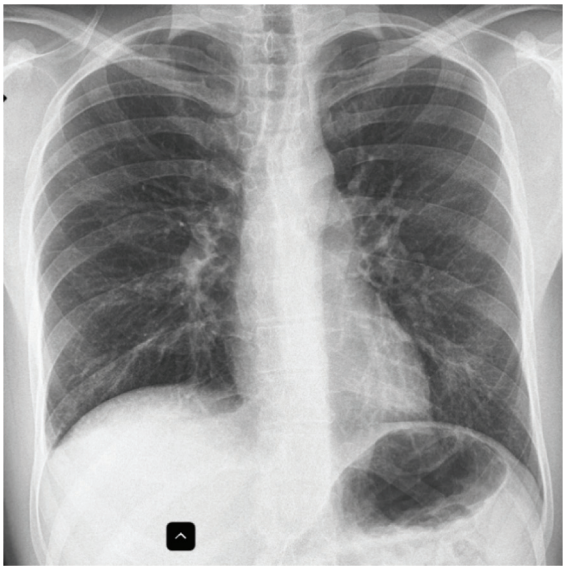

**Figure 1.** Plain chest film.

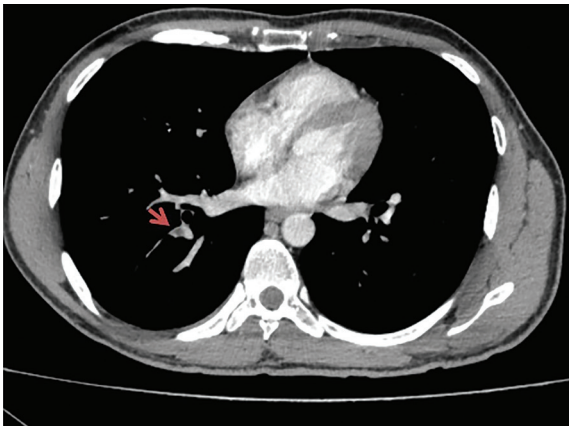

**Figure 2.** Contrast CT scan of the thorax showing a vascular filling defect due to endoluminal trombus.

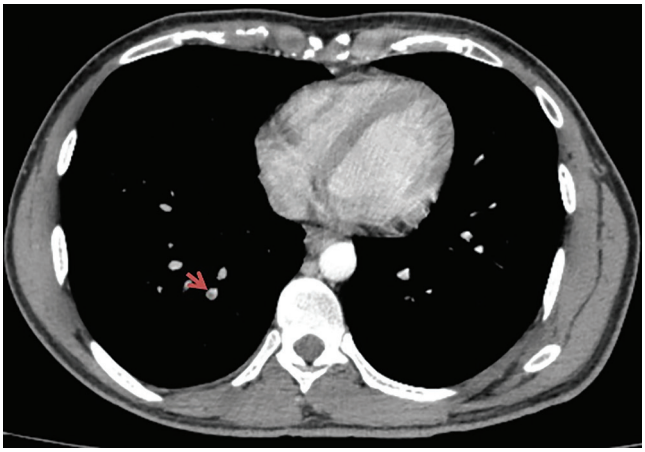

**Figure 3.** Small endolumenal thrombus.

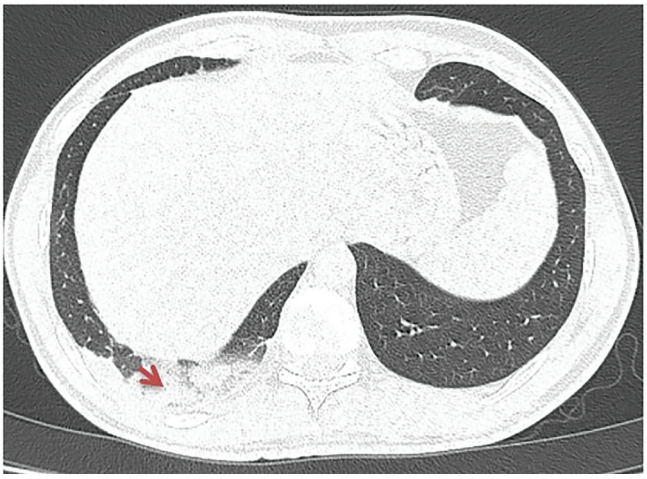

**Figure 4.** Ground-glass opacity highly sugestive of a pulmonary infarction.

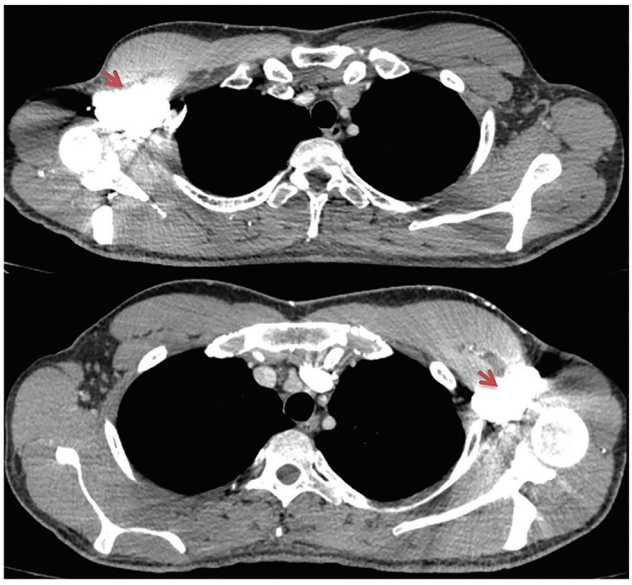

**Figure 5.** Radiopaque tracer stagnating at the subclavian level, bilaterally, penetrating with great difficulty into the rest of the vascular bed (scans done 30 minutes apart).

**Annex 3.** Detailed immunological panel

| IMMUNOLOGICAL PANEL | | |
|---|---|---|
| **HOMOCISTEIN** | 8.7 | NEGATIVE |
| **ANTI-dsDNA ANTIBODIES** | 5.4 | NEGATIVE |
| **ANTI NUCLEAR ANTIBODIES (AAN)** | 0.3 | NEGATIVE |
| **ANTI-CARDIOLIPIN ANTIBODIES** | 1.7 | NEGATIVE |
| **ANTI-PROTEINASE 3 ANTIBODIES (cANCA)** | 2.5 | NEGATIVE |
| **ANTI-MIELOPEROXIDASE ABTIBODIES (pANCA)** | 0.7 | NEGATIVE |
| **LUPIC ANTICOAGULANT** | 36.5 | NEGATIVE |

**Annex 4.** Detailed hematological panel

| HEMATOLOGICAL PANEL | | |
|---|---|---|
| **ANTITHROMBIN** | 104.7% | NEGATIVE |
| **C PROTEIN** | 115.1% | NEGATIVE |
| **S PROTEIN** | 116.6% | NEGATIVE |
| **ANTI-GLYCOPROTEIN ANTIBODIES** | <20 u/mL | NEGATIVE |
| ***MTHFR GENE MUTATION*** | *C677T*<br>A1298C | *HETEROZYGOUS POSITIVE*<br>NEGATIVE |
| **LEIDEN FACTOR V** | - | NEGATIVE |
| ***PROTHROMBIN FACTOR II*** | *G20210A* | *HETEROZYGOUS POSITIVE* |

status was suspected and the hematological revealed further genetic tests relating to both acquired and hereditary prothrombotic mutations as well as an immunological

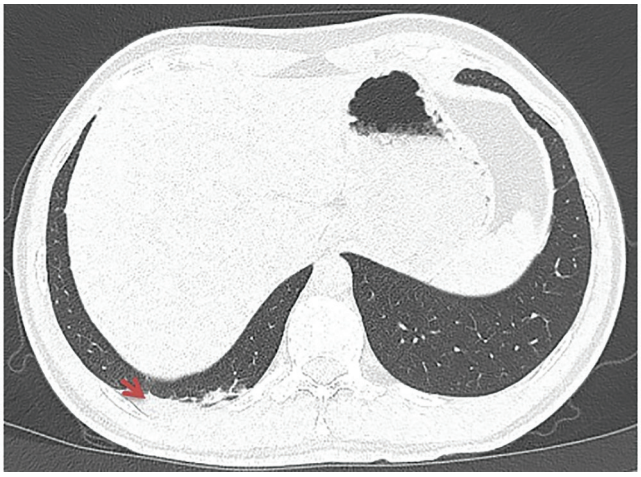

**Figure 6.** Follow-up pulmonary CT examination after one month, showing the marked regression of the ground-glass opacity, with no new or outstanting vascular filling defects being identified.

panel to be performed. The extended immunology panel (see *Annex 3*) was negative, but genetic tests (see *Annex 4*) identified heterozygous mutations in both prothrombin factor II and methylenetetrahydrofolate reductase (MTHFR) genes. Diabetological consultation found no sign or symptoms of pancreatic impairment due to the autoimmune thyroiditis. A cardiologist evaluated the patient and preformed an echocardiography, which found no pathological changes, thus recommending a switch in oral anticoagulant treatment (Apixabanum 5mg twice a day).

*FOLLOW UP*

A month after the hospital discharge the patient was reevaluated both clinically, functionally and thorough imaging. A moderate improvement in pulmonary volumes was observed, of 26.1% in FVC and 27.4% in FEV1 (see *Annex 2*.). The 6-minute-walk-test was also performed, the patient traveled 71.2% of the predicted distance, with no desaturations or other complications.

The second chest CT examination identified a marked regression of the lesions previously recorded, with some small areas reticular interstitial densification remaining in the postero-basal region of the right lung (*Fig.6*). No thrombi were identified during this scan.

In another clinic, the patient was reevaluated cardiologically and a venous and arterial Doppler echography was performed, which didn't find any sign of vascular thrombosis or hemodynamically significant stenoses, including in the territory of both subclavian veins.

The clinical, imaging and functional evolution was thus favorable under anticoagulant treatment.

## Discussion

We've searched in the medical databases PubMed, Google Scholar, Web of Science, Scopus and UpToDate using the terms "coronavirus", "COVID-19", "SARS-COV2", "thrombosis", "pulmonary embolism", "subclavian vein trombosis", "autoimmune", "Basedow Graves" and "immunothrombosis") including only full, free access articles published in the last 5 years (2019-2023).

The predisposition for thrombosis in COVID-19 is determined by at least two distinct but interdependent processes, subsegmental and segmental vessel occlusion, due to thrombi, and microvascular in situ immunothrombosis, due to excessive activation of the coagulation cascade as well as the innate immune system (3).

The prothrombotic state in COVID-19 is associated with an isolated increase in the levels of D-dimers without important changes to other serum coagulation parameters (4). This coagulation abnormality is mainly due to the compounding effects of both local endotheliopathy and endotelitis due to the direct infection of endothelial cells via the angiotension-2 (ACE-2) receptor (4, 5) as well as systemic inflammation due to the cytokine storm triggered by an uncontrolled release of proinflammatory cytokines in response to an exaggerated activation of the innate immune system (6). The main cytokines involved in the process are interleukins (ILs) IL-2, IL-6 and interferon-y (IFN-y), contributing to inflammation by increasing the production and membrane expression of tissue factor in endothelial cells and decreasing fibrinolysis (7, 8).

Immunothrombosis is defined as the dysregulation of hemostasis leading to aberrant clot formation triggered by acute and chronic inflammation. It can have a multitude of causes, such as sepsis, disseminated intravascular coagulopathy, thromboembolism and subsequent tissular infarctions as well as many infectious processes, one of them being COVID-19 (7). The main pathogenic mechanism behind immunothrombosis seems to be the exposure tissular factor on the membrane of infected endothelial cell, leading to the activation of the cascade of coagulation (7,8). Immunothrombosis is a stand-alone pathological process, being completely unrelated to embolism from deep vein thrombosis in the lower extremities (8).

Pulmonary thromboembolism occurs more frequently in the first weeks after diagnosis (9, 10, 11, 12), and is generally proportional with the severity of the disease, but cases farther from the acute moment have also been reported in literature (13, 14, 15), including in patients with mild forms of the disease.

A large-scale meta-analysis conducted by *Knight et al.* (9) investigated 48 million adult patients, with and without SARS-CoV2 infection, and determined that the presence of COVID-19 led to an important increase in the number of both arterial and venous thromboses, a number which rose sharply in the first few weeks then declined rapidly in the next two weeks. Severe cases of COVID-19 that required hospitalization were associated with a higher incidence of thrombotic events than patients who received ambulatory treatment. Another large-scale meta-analysis (10) calculated the incidence rate of pulmonary embolism (PE) in patients infected with the coronavirus to be about 13% and rising up to 19% for patients needing intensive care (ICU). The SARS-CoV2 infection rate associated with venous thromboembolism is much higher than for other acute infections, thus raising the mortality rates by about 74% (10). Other large scale meta-analyses (11, 12) found much more modest values for the incidence rate for PE, 7.1% (11) and 7.8% (12) respectively, and also confirmed frequency of adverse events for patients admitted to ICUs.

According to *Hobohm et al.* (13) PE was diagnosed in 1.9% of COVID-19 diagnoses, being responsible for a 3.1-fold increase in mortality. However, other studies (14, 15) found much more modest rates of PEs in COVID-19 patients, 0.7% (14) and 0.48 % (15) respectively (although the sample size for these later two studies was much smaller compared to the previous meta-analyses), or outright failed to find any correlations between coronaviral infection and thromboembolic events, compared to other infectious diseases (16).

Although some cases of PE after the acute phase of COVID-19 have been identified, large scale studies have failed to find a statistically significant risk of a PE episode at a distance of more than two weeks from onset of the initial symptoms. *Vechi et al.* (17) compiled a series of five clinical cases very similar to our own case, patients with mild COVID-19 treated in an outpatient setting who developed PE three to four weeks after the initial diagnosis, with no signs or symptoms suggestive of lower limb thrombosis. Few other case reports highlight cases of PE in the convalescent phase of mild COVID-19 (18, 19, 20). *Joseph et al.* (21) identified three patients who developed PE symptoms soon after being diagnosed with a mild form of COVID-19.

In the case at hand, the pulmonary infarction occurred in an otherwise healthy young male, with seemingly no personal or hereditary risk factors for clotting disorders but with a known history of an autoimmune disorder triggered by exposure to the SARS-Cov2 mRNA vaccine. A more in-depth investigation identified two key heterozygous mutations, relating to prothrombin factor II and the MTHFR (methylenetetrahydrofolate reductase) gene.

The prothrombin G20210A gene mutation is the second most commonly inherited thrombophilia after Factor V Leiden and is typically associated with both deep vein thrombosis and pulmonary embolism, being responsible for a 3 to 4-fold increased risk of thrombosis (22). MTHFR is an enzyme involved in the metabolism of homocysteine, and such a

mutation in this gene leads to an increased risk for massive and submassive PEs (23).

While extremely uncommon, upper limb deep vein thromboses (DVT) in SARS-CoV2 infection (24, 25) and vaccination (26, 27, 28) were both reported, and thus may explain the difficulty encountered during the injection of the contrast agent. Unfortunately a phlebography or a venous Doppler ultrasound could not be performed at the time of admission due to the lack of a dedicated cardiology service and the patient was examined with Doppler technology 13 days after discharge, but no significant vascular stenoses or thromboses were found. Unlike the patients noted during the browsing of literature (24, 26, 27, 28), our patient had no symptomatology pertaining to any upper or lower limb DVTs, and had no provoking condition such as the presence of an intravascular catheter or a history of vascular interventions.

While the SARS-CoV2 vaccine has been linked to adverse thromboembolic events the incidence rates were much lower than those associated with the infection itself (29).

Certain adjuvant components of the vaccines, as well as the SARS-CoV2 virus itself, can trigger autoimmune reactions in genetically predisposed individuals (30). The pathophysiological process at hand seems to be the triggering of the adaptive immune response with production of autoantibodies and proinflammatory cytokines in response to contact with certain vaccine adjuvants, the SARS-CoV2 spike glycoprotein or the viral RNA itself, most likely due to the phenomena of molecular mimicry (31, 31). While the predisposition towards such immune disfunction in the context of the novel coronavirus infections is mostly hereditary, there are certain risk factors that have been shown to increase the likelihood of developing autoimmune diseases, such as the severity of the COVID-19 episode, female gender, older age, higher body mass index (BMI) and pre-existing allergic or autoimmune disorders (33).

The SARS-CoV2 vaccine has been theorized to be the catalyst for both de-novo cases of Basedow-Graves thyroiditis (32, 34, 35, 36, 37, 38, 39, 40, 41) as well as relapses (34, 42) of already diagnosed disease. Some more in-depth studies that compiled several tens of patients with this pathology (29, 31, 32) came to the conclusion that most of cases were of young, otherwise healthy, females, with the onset of symptoms occurring in a matter of days after both the first and second immunization, with mostly favorable evolution under conventional treatment. The presence of the ACE-2 receptor in the membrane of thyroid cell leading to their direct infection (39), cross-reactivity between normal thyroid cells or the thyroid peroxidase peptide and SARS-CoV2 spike protein (39, 43), are believed to be the responsible for the thyroid injury. Our patient experienced both the sudden onset of hyperthyroidism after the administering of the second dose of the SARS-CoV2 vaccine as well as a mild relapse of his Basedow-Graves after coronavirus infection, necessitating a slight increase in dosage of his medication.

## Conclusions

Thromboembolic events are a redoubtable complication of SARS-CoV2 infection, regardless of the severity of the disease itself or the amount of time since the debut of symptoms, even if other risk factors for thrombosis are not present. In hospitalized, suspected or confirmed, COVID-19 cases a basic coagulation profile should be drawn and repeated at least every 2-3 days, keeping close watch to the value of D-dimers. Likewise, the risk of developing a secondary autoimmune disorder after exposure to the novel coronavirus should not be ignored, especially if the patient has already been diagnosed with another autoimmune disease.

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## Institutional Review Board Statement

Not applicable

## Informed Consent Statement

Informed consent of the patient was obtained.

## Data Availability Statement

Data used to support the findings of this study are available from the corresponding author upon request.

## Conflicts of Interest

The authors declare no conflict of interest.

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