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Case Report

Paraneoplastic Syndrome and SARS-CoV-2—Incremental Effect of 2 Thrombogenic Conditions?

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ABSTRACT

We present the case of a patient with a nonbacterial thrombotic aortic valve endocarditis experiencing severe thromboembolic complications and an acute right internal carotid artery occlusion in the context of a paraneoplastic syndrome and an asymptomatic severe acute respiratory syndrome coronavirus-2 infection, despite treatment with different and overlapping anticoagulant medications. Patients with increased thrombogenicity due to an underlying disease might be at increased risk for thrombotic events during a severe acute respiratory syndrome coronavirus-2 infection.

RÉSUMÉ

Nous présentons le cas d'un patient atteint d'endocardite thrombotique non bactérienne de la valve aortique et présentant des complications thromboemboliques graves et une occlusion aiguë de la carotide interne droite dans le contexte d'un syndrome paranéoplasique et d'une infection à coronavirus du syndrome respiratoire aigu sévère 2 (SRAS-CoV-2) asymptomatique, malgré différentes anticoagulothérapies se chevauchant. Les patients présentant une thrombogénicité accrue en raison d'une affection sous-jacente pourraient courir un plus grand risque d'événement thrombotique en cas d'infection à SRAS-CoV-2.

Case

A 66-year-old male patient was transferred from another hospital due to a non-ST-elevation myocardial infarction with mildly persisting chest pain for 5 hours.

Six weeks prior to this event, the patient had suffered from a *Vena saphena magna* thrombosis. Diagnostic testing in the referral hospital revealed a non–small cell lung cancer with histology suggestive of an adenocarcinoma on transbronchial biopsy. Due to lymphatic and contralateral lung metastases (cT4, cN3, cM1a), palliative chemotherapy was recommended but had not been instituted. The venous thrombosis was treated with rivaroxaban 20 mg once daily, which had been taken continuously except for the day of transbronchial biopsy.

On presentation, the electrocardiogram was unremarkable, and transthoracic echocardiography revealed moderate pericardial effusion, a normal left ventricular ejection fraction without regional wall motion abnormalities, but thickened aortic valve cusps and moderate aortic regurgitation. Coronary angiography showed a 50% stenosis of the *Ramus interventricularis anterior* without hemodynamic impact, as assessed by the resting full-cycle ratio (0.93; Video 1, view video online). The resting full-cycle ratio is a non-hyperemic index that scans diastole and systole for the largest drop in pressure over the entire cardiac cycle. A value $\leq$0.89 indicates a hemodynamically relevant stenosis.

To investigate for other potential reasons for the myocardial infarction, transesophageal echocardiography was performed and showed oscillating masses on the native aortic valve up to 12x6 mm in size, which involved all 3 cusps, predominately affecting the right coronary cusp (Fig. 1A; Video 2, view video online). There was no patent foramen ovale, left atrial appendage thrombosis, or large and mobile aortic atheroma. The patient was afebrile, inflammatory markers were not significantly increased (leucocytes 9.6 Gpt/L [3.6-10.5 Gpt/L], C-reactive protein 18.8 mg/L [< 5.0 mg/L], procalcitonin 0.12 µg/L [< 0.05 µg/L]), and repeated blood cultures were negative, suggesting that bacterial infective endocarditis was unlikely, although serologic tests were not performed. Tests of hemostasis were unremarkable except for a slightly increased international normalized ratio (INR) under factor-Xa inhibition. There were no significant abnormalities in fibrinogen (2.3 g/L [1.8-3.5 g/L]) or complement factors C3 (1.66 g/L [0.90-1.80 g/L]) and C4 (0.33 g/L

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See page 219 for disclosure information.

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Novel Teaching Points

- Nonbacterial thrombotic aortic valve endocarditis is a rare but devastating complication in the context of a paraneoplastic syndrome.
- SARS-CoV-2 infection might increase the risk for thrombotic complications in patients already at increased risk for thrombotic complications, owing to underlying disease.
- The optimal anticoagulation regime is uncertain; however, well controlled unfractionated heparin might be the therapy of choice in the acute setting.

[0.10-0.40 g/L]). Cardiolipin IgM (12 U/ml [< 10 U/ml]) was borderline elevated, however ß2-glycoprotein-I IgM (< 0.9 U/ml [< 7 U/ml]) and −IgG (0.6 U/ml [< 7 U/ml]), as well as other autoimmune disease−related antibodies, was not elevated, suggesting the absence of an antiphospholipid syndrome. However, a relative lymphocytopenia (16.1% [20%-44%)) and increased lactate dehydrogenase activity (9.01 µkat/L [<4.2 µkat/L]) led to a nasopharyngeal swab for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) 9 days after the admission for myocardial infarction, which revealed a positive polymerase chain reaction for the E-gene, indicating SARS-CoV-2 infection. The patient never displayed typical symptoms for SARS-CoV-2 infection prior to or during his hospitalization.

Intravenous heparin was started (partial thromboplastin time: 60-80 seconds), and oral anticoagulation with a vitamin k antagonist was initiated. Transesophageal echocardiography 6 days later demonstrated regression of the thrombotic formations (Fig. 1B; Video 3 , view video online). We administered heparin for 11 days and stopped it after therapeutic INR was documented for 2 consecutive days. At the day of stopping heparin and 4 days after the diagnosis of SARS-CoV-2 infection, the patient experienced a stroke with a left-sided hemiparesis and diplopia. The INR was therapeutic at this time point (2.39). Cerebral computed tomography excluded intracranial hemorrhage, and cerebral magnetic resonance tomography revealed multiple cerebral infarcts in the mesencephalon, with expansion into the thalamus region, the cerebellum, and in the precortical *gyrus precentralis,* suggesting a cardio-embolic origin (Fig. 1C). Neurologic symptoms initially improved; however, despite a persisting therapeutic INR, the patient developed an acute thrombotic occlusion of his right internal carotid artery with complete left-sided hemiparesis 4 days after the first neurologic event (Fig. 1D). The patient was transferred for cerebral mechanical thrombectomy therapy, which led to complete reperfusion (Fig. 1, E and F). The patient currently remains with left-sided hemiparesis in a specialized stroke unit. At the time of the second cerebrovascular accident, 2 swabs for SARS-CoV-2 performed 7 and 8 days after the first one were negative.

Discussion

This case describes a patient with nonbacterial thrombotic aortic valve endocarditis that developed despite treatment with a factor-Xa-inhibitor and who subsequently suffered a myocardial infarction and 2 strokes within a short period of time in the context of a paraneoplastic syndrome and asymptomatic SARS-CoV-2 infection. We hypothesize that the myocardial infarction and the first stroke originated from thromboembolism, in particular due to the diffuse pattern of lesions detected by cerebral magnetic resonance tomography. The second stroke was caused by an acute right internal carotid artery occlusion, hypothetically triggered by spontaneous local thrombosis; however, embolism of a big thrombus cannot be excluded.

Paraneoplastic syndromes are often linked to increased thrombogenicity; however, nonbacterial thrombotic aortic valve endocarditis is rare even in the situation of cancer. Adenocarcinoma seems to be associated with increased rates of this condition, and the aortic valve is most often affected.[1] Current guidelines recommend anticoagulation with unfractionated or low−molecular weight heparin or a vitamin k antagonist, although there is limited evidence to support this strategy. The use of factor-Xa-inhibitors or direct thrombin inhibitors has not been evaluated.[2] Some authors suggest that a vitamin k antagonist not be used in patients with malignancy-associated nonbacterial thrombotic endocarditis, as recurrent thromboembolic events while on warfarin are common, although this was observed 30 years ago.[1] In our case, the patient developed the thrombosis under the treatment with a factor-Xa-inhibitor; therefore, we decided to use an overlapping anticoagulation with unfractionated heparin and a vitamin k antagonist.

SARS-CoV-2 infection is also associated with a high rate of thrombotic complications occurring even under prophylactic therapy.[3] Large-vessel stroke, including partial carotid artery occlusion, has been described in younger patients suffering from coronavirus disease 2019 (COVID-19).[4] Others found a low risk of acute cerebrovascular events in patients hospitalized with COVID-19, with most patients presenting with classical vascular risk factors and traditional stroke mechanisms, although a substantial number of patients had new positive antiphospholipid antibodies.[5] Hypercoagulation during SARS-CoV-2 infection has been linked to cerebral embolism in several cases.[6,7]

In our case, the patient was asymptomatic, and therefore, the duration of infection remains unknown. However, a second test performed 7 days after the positive one was already negative, thus suggesting that infection occurred earlier. The median duration of viral shedding was 20 days in survivors of COVID-19, according to a Chinese study.[8] Remarkably, native aortic valve thrombosis and its consequences occurred despite oral anticoagulation, highlighting a possible incremental effect of 2 thrombogenic conditions. Both cancer-associated thrombosis and COVID-19-related thrombotic events share common features, such as coagulopathy and endothelial dysfunction secondary to systemic inflammation or potential local infection. The prothrombotic effect of SARS-CoV-2 coronavirus infection is thought to be mediated by binding to angiotensin-converting enzyme 2 receptors on the surface of endothelial cells, which leads to endothelial dysfunction and thrombosis.[8] As heart valves are lined with endothelial cells, SARS-CoV-2 infection might hypothetically induce dysfunction of the protecting valve surface. Anticoagulation in COVID-19 seems to be beneficial; however, the best strategy is still uncertain.[3]

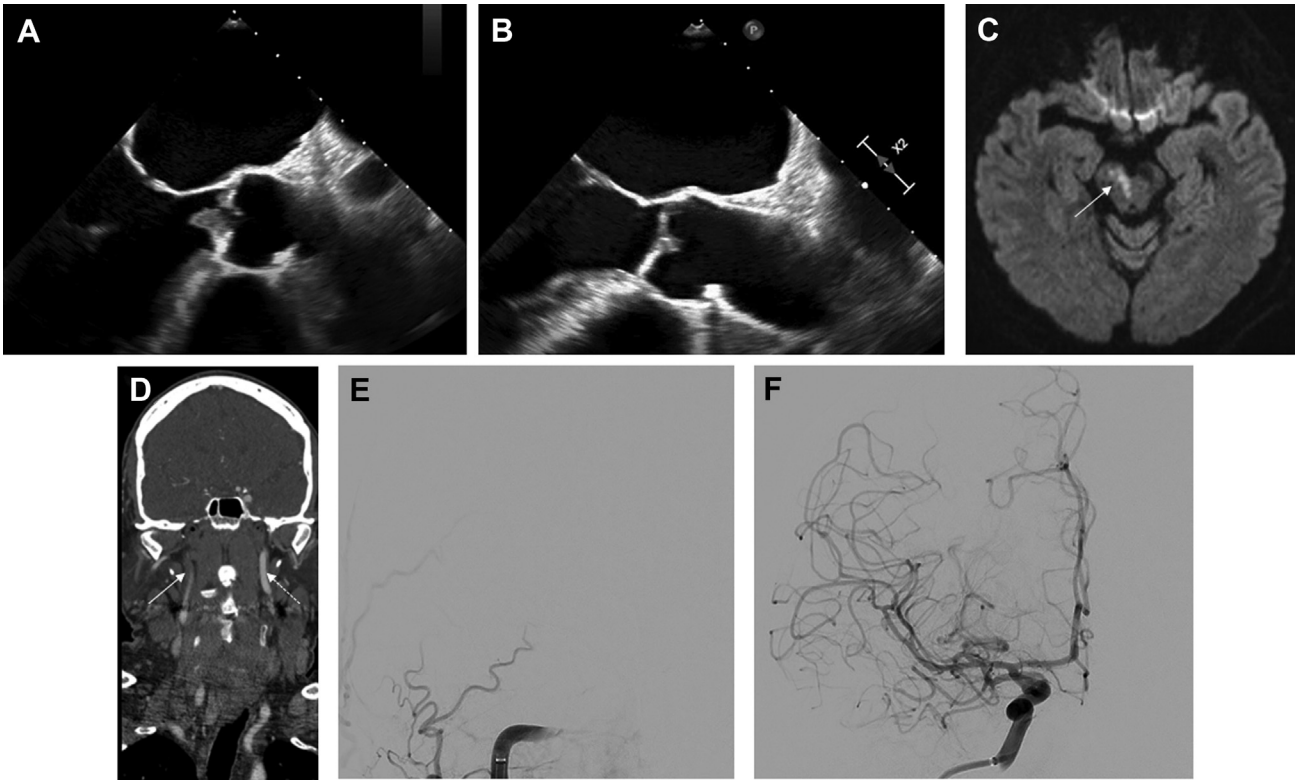

Figure 1. (**A**) Oscillating thrombotic masses on the native aortic valve (**B**) with regression in a control 6 days after initiation of antithrombotic therapy. (**C**) Acute cerebral embolism to the mesencephalon (**white arrow**). (**D**) Thrombotic closure of the right internal carotid artery (**solid arrow**), whereas the left one is well perfused (**dotted arrow**). (**E, F**) Selective angiography of the right internal carotid artery (**E**) before and (**F**) after successful interventional therapy.

This case highlights the many-sided effects of paraneoplastic syndromes and SARS-CoV-2 infection in patients who are already at increased risk for thrombotic complications, owing to underlying disease. The treatment of those patients includes several medical disciplines that should be on alert and prepared to treat SARS-CoV-2 and its thrombotic complications. Although the optimal anticoagulation regime is uncertain in such a case, well controlled unfractionated heparin might be the therapy of choice in the acute setting.

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Supplementary Material

To access the supplementary material accompanying this article, visit *CJC Open* at https://www.cjcopen.ca/ and at https://doi.org/10.1016/j.cjco.2020.10.010.