# Reactive systemic vasculitis in the course of a coronavirus OC43 infection: a case report

Benjamin Jacquet, Vito Curiale, Hélène Mangeard, Émilie Ferrer, Sylvie Chaillou

Center of Gerontology Rainier III, Princess Grace Hospital, Monaco

## Abstract

This case report details a severe systemic failure following a coronavirus OC43 (HCoV-OC43) infection. A 78-year-old man, who had been vaccinated against SARS-CoV-2, was hospitalized for a flu-like infection and abdominal pain, revealing bilateral hemorrhagic adrenal infarctions with secondary adrenal failure. Imagery examinations showed adrenal necrosis and multiple ischemic cerebral strokes. A multiplex retro-transcriptase polymerase chain reaction (RT-PCR) became positive for HCoV-OC43. Cardio-vascular, infectious, and auto-immune exams were negative. A steroid medication finally allowed clinical improvement, and the diagnosis of reactional vasculitis was retained. An unknown pathogenicity of HCoV-OC43 is possible, considering that RT-PCR research is rarely made. The hypothesis of cross-reactions with SARS-CoV-2 antivaccine antibodies is also feasible. At last, the possible former virulence of HCoV-OC43 is being researched, in the event that this virus is connected to the 1889 Russian influenza pandemic. The development of multiplex RT-PCR would enable the study of other HCV-OC43 infections.

Correspondence: Benjamin Jacquet, Center of Gerontology, Rainier III Clinic, Princess Grace Hospital, 1 Avenue Pasteur, 98000, Monaco. Tel. : +377 97 98 99 00.
E-mail: benjamin.jacquet@chpg.mc

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## Introduction

Human coronaviruses (HCoVs) are RNA-enveloped viruses,[1] including α-coronavirus (229E and NL63), and β-coronavirus (OC43 and HKU1). Recently, three more β-coronavirus emerged: severe acute respiratory syndrome coronavirus, responsible for the 2003 atypical pneumonia outbreak in south-east Asia; middle east respiratory syndrome coronavirus, circulating in the Middle East since 2012; and severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) the causative agent of the COVID-19 pandemic. HCoVs are responsible for upper respiratory tract infections and flu-like syndromes. However, SARS-CoV-2 was associated with diffuse pneumonia, respiratory distress, and excess of mortality and hospitalizations. We wonder if other common HCoVs have a potential for serious illness. A case of severe and complex systemic failure following a coronavirus OC43 (HCoV-OC43) infection is reported.

## Case report

### First hospital admission

A 78-year-old man was admitted to the emergency room (ER) for abdominal right flank pain and constipation following a flu-like syndrome, with fever, dry cough, and rhinorrhea. The patient was on clopidogrel, statin, and antihypertensive agent for a previous transient ischæmic attack. He underwent a two-dose SARS-CoV-2 vaccination schedule with an RNA vaccine, the last injection being performed one month earlier. The blood test showed a white blood cell (WBC) count at 17,170 leucocytes/mm$^3$, with normal C-reactive protein (CRP). SARS-CoV-2 reverse transcriptase polymerase chain reaction (RT-PCR) on the nasopharyngeal swab was negative. A normal computed tomography scan (CT scan) with contrast allowed the patient discharge (Figure 1).

### Second hospital admission

Two days later, the patient came again to the ER, with a low-grade fever (37.5°C), despite ceftriaxone medication. Systemic inflammatory response syndrome (SIRS) appeared, with WBC

16,830 leucocytes/mm$^3$, high CRP (215 mg/L), fibrinogen (8.70 g/L), low sodium and potassium (132 mm/L, 3.2 mmol/L). SARS-CoV-2 RT-PCR was negative again. A second abdominal CT scan without contrast showed bilateral hemorrhagic adrenal infarctions (Figure 2). The patient was moved to the intensive care unit for severe hypotension (70/40 mmHg).

## Intensive care unit stay

Hemodynamic improved on normal saline and noradrenaline. Adrenal failure was treated by intravenous hydrocortisone and fludrocortisone. Nevertheless, fever and SIRS persisted (CRP 296 mg/L, procalcitonin 1,50 ng/mL, fibrinogen 8,82 g/L), and oxygen therapy was initiated (4L/min). Despite negative blood and urine cultures, a combination of piperacillin-tazobactam and linezolid was started but remained ineffective. A positron emission tomography with fluorodeoxyglucose was performed, showing a non-specific pulmonary inflammatory pattern in both lung bases and bilateral adrenal necrosis. Lupus anticoagulant was negative and thrombotic microangiopathy was ruled out.

SARS-CoV-2 infection was ruled out after three negative tests. Thus, a nasopharyngeal multiplex RT-PCR was made, detecting the RNA of HCoV-OC43.

On day 5 the patient experienced acute delirium with drowsiness, without focal neurological deficit. A cerebral magnetic resonance imaging showed a large right frontal lobe ischemic stroke, with partial hemorrhagic transformation (Figure 3) and scattered acute ischemic lesions in the vertebrobasilar territory.

The cardiovascular assessment was normal, including transesophageal echocardiogram, supra-aortic trunk Doppler ultrasound, and 48-hour Holter electrocardiography. According to neurological advice, clopidogrel was continued, with preventive-dose subcutaneous heparin treatment.

## Clinical improvement and transfer in the acute geriatric ward

On day 11, the patient's general appearance and hypotension improved, and supplemental oxygen decreased to 1 l/min on hydrocortisone and fludrocortisone therapy. For the persistence of a low-grade (38°C) fever with SIRS (CRP 121 mg/L, fibrinogen 7,56 g/L) the patient was transferred to our acute geriatric ward for a diagnostic workup.

Sepsis was ruled out due to negative blood and urine cultures and the ineffectiveness of the antibiotic trial and systemic vasculitis was considered. However, anti-neutrophil cytoplasmic antibodies, anti-nuclear antibodies, anti-native DNA, and anti-21-hydroxylase (anti-adrenals) were all negative. Lupus anticoagulant and throm-



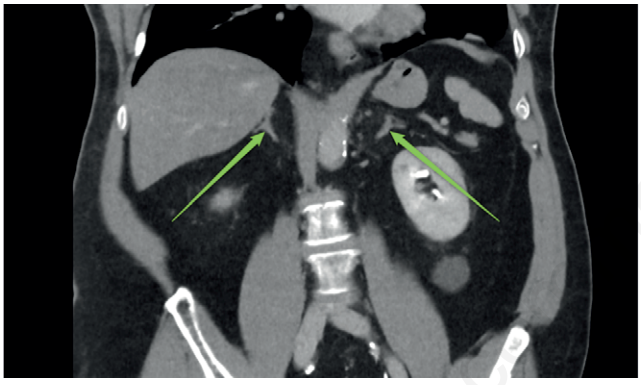

**Figure 1.** First abdominal computed tomography scan with contrast (coronal view) showing normal adrenal glands (green arrows).

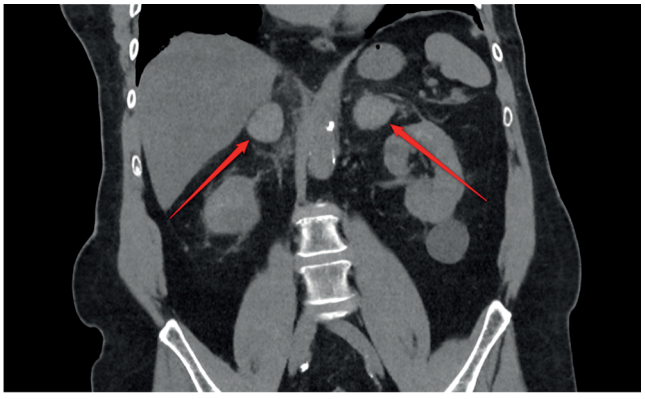

**Figure 2.** Second abdominal computed tomography scan without contrast (coronal view) showing bilateral hemorrhagic adrenal infarctions (red arrows).

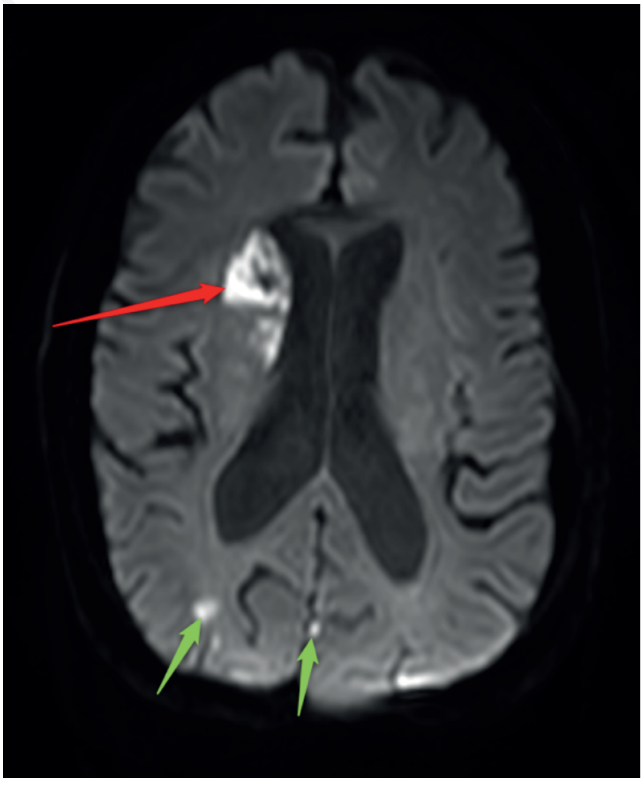

**Figure 3.** Diffusion-weighted magnetic resonance imaging (axial view), showing the right frontal acute ischemic stroke (red arrows), and other posterior acute ischemic lesions (green arrows).

botic microangiopathy were retested negative. Finally, giant cell arteritis (GCA) was suspected, even if the positron emission tomography failed to show aortic hypermetabolism. The latter hypothesis was ruled out after a normal biopsy of the temporal artery.

On day 14, CRP was still high (148 mg/L), as well as fibrinogen (7,75 g/L). As a diagnosis was lacking, we decided to switch from the association hydrocortisone and fludrocortisone to a glucocorticoid regimen with prednisone (1 mg/kg body weight). This change allowed a prompt fever extinction and a spectacular improvement in general symptoms, accordingly.

On day 19, CRP decreased to 16 mg/L, and fibrinogen to 3,85 g/L. The benefit from the glucocorticoid regimen supported the diagnosis of systemic vasculitis of unknown origin. On day 21, the patient was sent home. Since this hospitalization, he had significant improvement, and the glucocorticoid was tapered as we are used to doing in GCA.

## Discussion

The role of the HCoV-OC43 infection in the pathophysiology of vasculitis remains unclear. Three pathogenic mechanisms are hypothesized.

### Could the coronavirus OC43 trigger vasculitis?

We can argue that HCoVs, including HCoV-OC43, have a potential for systemic vasculitis but this is not widely supported in the literature. In the US, it was shown that HCoV-OC43 was associated with a higher burden of medical care, and was prevalent in hospitalized people.[2] In Canada, 11% of acute cases of pneumonia in a nursing home were due to HCoV-OC43, according to the high virulence of this subgroup.[3] The presence of HCoV-OC43 in brain tissue was found in an 11-month-old boy with viral encephalitis.[4] SARS-CoV-2 and other coronaviruses are neurotropic and thrombogenic, cause cytokinin storms and share similarities to the physiopathology of vasculitis.[5]

The mechanisms underlying OC43-induced vasculitis share some aspects with reactional cerebral vasculitis occurring in the course of different viral infections (varicella-zoster virus, other herpes viruses, parvovirus B19, arboviruses, and others).[6] The clinical role of HCoV-OC43 may be largely underestimated as the specific assay is rarely done.

### Could vasculitis be related to the severe acute respiratory syndrome coronavirus vaccination?

Our patient was fully vaccinated against COVID-19, with the second dose of RNA vaccine injected one month earlier. We can argue that vaccine-induced antibodies could be responsible for an uncontrolled immune response that, in the course of an HCoV-OC43 infection, could have triggered vasculitis using a cross-reactivity.

β-coronavirus (HCoV-OC43 and SARS-CoV-2) are similar respective to antigen structure.[7] Cross-reactivity within the β-coronavirus group has already been described in the literature. An HCoV-OC43 epidemic that occurred in 2003 was responsible for positive SARS-CoV serologies in Asia.[3] More recently, an analysis of 296 serums of COVID patients showed that serious infections were significantly more prevalent in subjects with a lower titre of a specific HCoV-OC43 antibody, the anti-nucleocapsid antibody.[8] Another study showed that severe SARS-CoV-2 infections are less frequent in adults living with young children, possibly because of repeated contact with coronaviruses, including OC43.[9] Finally, we mention a study showing a cross-reactivity among SARS-CoV-2 antibodies and OC43 and 229E subgroup antibodies in children; however, this mechanism is not found in adults.[10]

Nevertheless, the similarities between anti-vaccine and anti-HCoV-OC43 antibodies remain uncertain. Moreover, the SARS-CoV-2 RNA vaccine induces anti-spike antibody production, whereas the most cross-reactive antibody seems to be the anti-N-protein.

### Has coronavirus OC43 been able to regain its former virulence?

Formerly, the OC43 subgroup showed more virulent forms as medical historians have argued. Indeed, the 1889 Russian flu pandemic may have been due to coronavirus OC43, rather than to an influenza virus. This hypothesis is based on genomic studies, showing that HCoV-OC43 was born 130 years ago from a bovine coronavirus.[11]

The epidemic started in Saint-Petersburg in 1889 and spread following the European railway network. The Russian flu was responsible for a large number of hospitalizations and a significant excess of mortality, especially among men and old people. Severe acute cases of pneumonia were described, in some cases neurologic symptoms and finger and toe redness suggesting the occurrence of a reactive vasculitis.[12]

There were several epidemic waves of the Russian flu over about five years, before dropping out. HCoV-OC43 nowadays is associated with mild illness. We can imagine that herd immunity was acquired. A decrease in HCoV-OC43 virulence driven by spontaneous mutation and natural selection is another possible mechanism underlying the end of the pandemic, as we expect in the COVID-19 pandemic after the emergence of the less virulent Omicron Sars-CoV-2 subgroups.

The HCoV-OC43 virulence responsible for the patient's illness remains unclear: we can speculate that a mutated virus was more aggressive, but no such event has been reported before in the literature. The absence of a prior OC43 immunity is an alternative explanation, considering that, in a recent study, 22% of adults were seronegative.[8]

## Conclusions

This is the first report of reactive systemic vasculitis in the course of an HCoV-OC43 infection. Some questions still need to be answered. Do a mutated subgroup of coronavirus OC43 act as a trigger for inducing vasculitis? Is there an unknown pathogenicity of this virus, similar to that described at the time of the Russian flu? What is the possible role of SARS-CoV-2 vaccination on the inflammatory response? Is there cross-reactivity between HCoV-OC43 antibodies and those of other coronavirus subgroups?

The development of multiplex RT-PCR, supported by the SARS-CoV-2 outbreak, is supposed to help us be more accurate in detecting HCoV-OC43, allowing a better understanding of the clinical course of the infection and its consequences.

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