

Case report

An interesting case of small vessel pathology following coronavirus infection

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SUMMARY

Vasculitis is a descriptive term for a wide variety of conditions characterised by inflammation of the blood vessels that may occur as a primary process or secondary to an underlying disease. Occlusive vasculopathy is a different clinical entity characterised by skin changes and ulceration of the lower extremities because of thrombosis of the small vessels of the dermis and is usually associated with pre-thrombotic conditions. Both conditions can be confirmed or excluded by skin biopsy. We report the case of a 63-year-old woman presenting with upper and lower respiratory tract symptoms followed by a vasculitic rash on both legs. The patient underwent extensive radiological and laboratory investigations that were negative apart from positive coronavirus OC43. A biopsy of the skin was performed. Considering the clinical presentation and the investigations performed, the diagnosis of small vessel vasculopathy following coronavirus OC43 has been suggested by the authors.

BACKGROUND

Numerous microbial agents, including bacteria, viruses, protozoa and fungi, have been described in association with vasculitis.¹ This strong causality is well evidenced with certain types of infection such as hepatitis B virus-related polyarteritis nodosa (PAN) and hepatitis C virus-related cryoglobulinaemia,^{2,3} while this association between infection and vasculitis is less robust with a wide variety of other infectious pathogens. The work-up for vasculitis is, therefore, extensive and aims to exclude other possible aetiologies of malignancy, autoimmune diseases and other infections.

Vasculopathy is associated with risk factors predisposing to thrombosis. Coronaviridae are reported to be associated with thrombotic events.⁴

This is a case that demonstrates potential association of coronavirus OC43 with vascular pathology that the authors believe is post-immune inflammation, but the diagnosis of vasculopathy has been also suggested by experienced clinicians.

CASE PRESENTATION

A 63-year-old woman presented with a 5-day history of coryza, sore throat, dry cough and vomiting. She developed painful leg swelling and a rash 2 days after the emergence of initial symptoms. She denied mouth ulcers, joint pains or eye symptoms. On further systemic enquiry, she described episodes of visual hallucination, which had fully

resolved by the time of hospital attendance, and a couple of self-limiting episodes of epistaxis of no haemodynamic significance. She denied haemoptysis and haematuria, and she felt systemically well. She denied any recent drug ingestion apart from her regular medications, which include mirtazapine and quinine sulphate.

Her medical history was significant for subarachnoid haemorrhage 20 years ago. She stated that she had a similar rash 1 year ago also associated with coryzal symptoms, but in contrast to the current rash, symptoms had resolved spontaneously within 3 days.

Examination revealed purple discolouration of the toes of both feet with non-blanching purpuric lesions on both legs (figure 1). Blisters and haemorrhagic bullae were seen on the medial aspects of both legs and the soles of the feet (figure 2). Both feet were tender and warm to the touch with pedal pulses intact bilaterally and no sensory deficit. Chest, abdominal, cardiac and neurological examinations were normal.

INVESTIGATIONS

Full blood count revealed a mild normocytic, normochromic chronic anaemia (baseline haemoglobin 100×10^9 g/L), normal total and differential white cell counts and low platelets of 68×10^9 /L. A blood film revealed thrombocytopenia, which gradually normalised during the hospital admission. Coagulation screen remained normal, including activated partial thromboplastin time (APTT),



Figure 1 Image on admission showing purple discolouration of the toes.



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Figure 2 Image on admission showing blisters and haemorrhagic bullae on the medial aspects of the leg.

prothrombin time (PT) and fibrinogen levels. C reactive protein was mildly elevated (27 mg/L). Renal and liver function, folate and B₁₂ levels were all within normal limits. Urine dipstick was normal.

CT angiography was obtained for whole aorta and bilateral lower limbs, with concurrent CT of the chest, abdomen and pelvis to investigate for arterial thrombus, lymphadenopathy or malignancy. Both scans were normal and excluded mechanical causes for this patient's presentation.

The patient underwent an extensive vasculitis work-up to further investigate the rash. Autoimmune profile (rheumatoid factor, antineutrophil cytoplasmic antibodies, antinuclear antibodies, anti-dsDNA, chromatin level, lupus anticoagulant antibody, anticardiolipin antibody, anti-B₂ glycoprotein-1 antibody, anti-Ro antibody, anti-La antibody, anti-Sm antibody, anti-ribonucleoprotein antibody, anti-Jo-1 antibody, ribosomal autoantibody, anticentromere antibody and extractable nuclear antigen Scl70 antibody), complement levels, cryoglobulins, cryofibrinogen, Bence-Jones protein, protein electrophoresis and immunoglobulins were normal (please see [table 1](#)).

Viral screen was only positive for coronavirus OC43. Influenza PCR, hepatitis B and C antibodies, HIV, cytomegalovirus, Epstein-Barr virus and parvovirus B19 serology were all negative. Screening for *Legionella*, *Mycoplasma* and *Pneumococcus* was negative (please see [table 2](#)).

Although the score according to Duke's criteria was 1, infective endocarditis was excluded by normal echocardiography and serial negative blood cultures. A skin punch biopsy was obtained and demonstrated necrosis in the small vessels with inflammatory cells.

DIFFERENTIAL DIAGNOSIS

The differential diagnosis for this case would be between a vasculitic process and a veno-occlusive vasculopathy.

The initial clinical presentation was typical of a small vessel vasculitic process, but the skin biopsy was taken after steroid initiation and the results were not diagnostic of small vessel vasculitis. A confirmed preceding coronavirus OC43 infection

Table 1 Autoimmune screen

Investigation	Result	Reference range
Rheumatoid factor	<10 IU/mL	0–15 IU/mL
Serum antinuclear antibodies (ANA) screen	Negative	
Serum anti-dsDNA	<1 k[IU]/L	0–8 k[IU]/L
Serum chromatin level	<0.2 AI	0.0–0.9 AI
Serum Ro-52 antibody	<0.2 AI	0.0–0.9 AI
Serum Ro-60 antibody	<0.2 AI	0.0–0.9 AI
Serum La antibody	<0.2 AI	0.0–0.9 AI
Serum Sm IgG antibody	<0.2 AI	0.0–0.9 AI
Serum Sm/ribonucleoprotein IgG antibody	<0.2 AI	0.0–0.9 AI
Serum ribonucleoprotein-A antibody	<0.2 AI	0.0–0.9 AI
Serum ribonucleoprotein-68 antibody	<0.2 AI	0.0–0.9 AI
Serum ribosomal autoantibody screen	<0.2 AI	0.0–0.9 AI
Serum anti-centromere antibody	<0.2 AI	0.0–0.9 AI
Serum extractable nuclear antigen Scl70 antibody	<0.2 AI	0.0–0.9 AI
Serum Jo-1 antibody	<0.2 AI	0.0–0.9 AI
Serum anticardiolipin level	3 GPLU/mL	0–19 GPLU/mL
Serum anti-B ₂ glycoprotein-1 antibody level	3 GPLU/mL	0–19 GPLU/mL
Lupus anticoagulant screen	Not detected	
Serum proteinase 3 antineutrophil cytoplasmic antibody	<0.2 AI	0–0.9 AI
Serum myeloperoxidase antineutrophil cytoplasmic antibody	<0.2 AI	0–0.9 AI
Serum cryoglobulin	No detectable precipitate after 7 days	
Complement C3	1.6 g/L	0.90–1.80 g/L
Complement C4	0.32 g/L	0.10–0.40 g/L
Serum protein electrophoresis	No evidence of a monoclonal band (paraprotein)	
Serum IgG level	11 g/L	6.0–16.1 g/L
Serum IgA level	4.0 g/L	0.8–4.0 g/L
Serum IgM level	1.4 g/L	0.5–2.0 g/L

characterised by coryzal symptoms raised the suspicion of a post-viral, ANCA-negative vasculitis. The normalisation of inflammatory markers and thrombocytopenia without any specific intervention lends support to this hypothesis. Extensive negative workup for vasculitis has excluded any other causative pathology.

Vasculopathy is an important differential diagnosis that is sometimes difficult to distinguish from vasculitis. Clinically, the raised palpable purpura was in favour of vasculitis in contrast to the reticular pattern that is usually seen with vasculopathy.⁵ Histologically, there was no evidence of vessel lumen occlusion to suggest occlusive non-vasculitic vasculopathy. However, in this context, we should acknowledge that differentiation is not always possible because vessel wall infiltration may occur with late occlusive vasculopathy and intravascular thrombosis may complicate vasculitis.⁶

TREATMENT

While in hospital the patient remained systemically well and afebrile, and the respiratory symptoms and the rash on both ankles resolved quickly, the ischaemic changes on the feet worsened daily despite oral calcium channel blockers, intravenous iloprost therapy and sildenafil. Drugs used were oral nifedipine modified release 40 mg two times per day and oral sildenafil 25

Table 2 Microbiology screen

Investigation	Result
Adenovirus	Not detected
Coronavirus 229E	Not detected
Coronavirus HKU1	Not detected
Coronavirus NL63	Not detected
Coronavirus OC43	Reactive
Human metapneumovirus	Not detected
Human Rhin/enterovirus	Not detected
Influenza A	Not detected
Influenza B	Not detected
Parainfluenza virus 1	Not detected
Parainfluenza virus 2	Not detected
Parainfluenza virus 3	Not detected
Parainfluenza virus 4	Not detected
Respiratory syncytial virus	Not detected
<i>Bordetella parapertussis</i>	Not detected
<i>Chlamydia pneumoniae</i>	Not detected
<i>Mycoplasma pneumoniae</i>	Not detected
HIV-1 and HIV-2 antibody and HIV p24 antigen screen	Not detected
Hepatitis C antibody level	Not detected
Hepatitis B surface antigen screen	Not detected
Hepatitis B core antibody screen	Not detected
Epstein-Barr virus IgG screen (blood)	Reactive
Epstein-Barr virus IgM screen (blood)	Not detected
cytomegalovirus IgG screen (blood)	Not detected
cytomegalovirus IgM screen (blood)	Not detected
Parvovirus B19 IgM level (blood)	Not detected
Parvovirus B19 IgG level (blood)	Reactive

mg three times per day. Iloprost infusions were abandoned after a 3-day trial due to ineffectiveness. The patient presented with pain and was managed with regular paracetamol, codeine and gabapentin with oral morphine for breakthrough pain.

OUTCOME

Nine days into admission with no clinical improvement, oral steroids were introduced (prednisolone 30 mg once daily). While the vasculitic rash on the ankles responded well, the steroid therapy did not halt disease progression. The process continued to progress, with the distal parts of the feet becoming more dusky and painful. Fifteen days into admission, the patient's toes were black and necrotic with no evidence of wet gangrene and were physiologically amputated (figure 3).

DISCUSSION

Vasculitis is characterised by inflammation of the blood vessel wall with reactive injury of mural structures, leading to tissue ischaemia and necrosis due to loss of vascular integrity and luminal compromise. Vasculitis may occur as a primary process or may be secondary to another underlying aetiology (eg, infection, drugs and malignancy). Microbes, including bacteria, viruses, protozoa and fungi, have been incriminated in the pathogenesis of vasculitis.¹ The causal link between HCV and cryoglobulinaemic vasculitis (CV), and HBV and PAN and CV are well established.² These two entities are included as 'vasculitis associated with probable aetiology' in the 2012 Chapel Hill Consensus Conference on the Nomenclature of Vasculitides.³



Figure 3 Image after 2 weeks of admission showing dusky and necrotic toes.

Other reported associations between viruses and post-immune vasculitides are less robust and often anecdotal or controversial.

The pathogenesis of most vasculitides caused by viruses is incompletely understood and differs depending on the causative organism. Both direct endothelial invasion and indirect autoimmune mechanisms have been postulated.¹

Coronaviruses (CoVs) are of the Coronaviridae family and are enveloped viruses with a single strand of RNA. Under electron microscopy, the virions appear as spike-like projections from the virus membrane giving the appearance of a crown. Human CoVs (HCoVs) were first described in the 1960s and are now known to comprise a large family of viruses, including 229E, NL63, OC43, HKU1, MERS-CoV, SARS-CoV-1⁷ and SARS-CoV-2 (COVID-19).⁸ CoVs predominantly affect the respiratory tract; however, there is evidence linking them to systemic disease. COVID-19 infection has been implicated in the pathogenesis of Kawasaki disease.⁹ HCoV-OC43 and HCoV-229E were detected more frequently in brain tissue from multiple sclerosis patients compared with healthy individuals.¹⁰

Our patient has been exhaustively investigated for known causes of vasculitis. Normal imaging and laboratory investigation has excluded malignancy, and the skin biopsy, although not diagnostic of vasculitis, was taken after steroid initiation and failed to reveal any specific histology, though a vasculitic process could not be excluded. The recent COVID-19 pandemic has revealed the particularly vasculopathic activity of some coronaviruses and there is well-documented evidence of COVID-19-associated vasculitis.^{11 12} Infection, including with viruses known to have strong association with vasculitis such as HCV, HBV and HIV, has also been investigated. The patient had a similar vasculitic rash 1 year ago, but this had been resolved spontaneously and had never been investigated. Therefore, it is difficult to say whether that rash was associated with a similar coronavirus OC43 infection or was related to another pathology. Though we do not have diagnostic histology of vasculitis, we believe this to be a case of small vessel vasculitis caused by coronavirus OC43 infection. Further research is needed to provide more robust evidence for this potential association.

Learning points

- ▶ Infection plays an important role as an aetiology or a trigger of certain types of vasculitis and should be included as a part of an extended vasculitis work up.
- ▶ Despite being predominantly respiratory tract viruses, coronaviruses have been described in association with other systemic diseases.
- ▶ This case suggests a potential association between coronavirus OC43 and small vessel pathology.

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