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Necrotizing Vasculitis Post COVID 19: About A Series of 5 Cases

Chaymaa Nasmi[1*], Amal Tbatou[1], Khadija Mouaddine[1], Abdelilah Bentahila[1], Bouchra Chkirate[1]

[1]Paediatric Rheumatology's Department, Children's Hospital, Rabat, Morocco

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***Corresponding author:** Chaymaa Nasmi
Paediatric Rheumatology's Department, Children's Hospital, Rabat, Morocco

Abstract **Original Research Article**

Post-covid19 necrotising vasculitis is a recently introduced pathological entity, representing one of the rare extra-respiratory covid 19 infections that can threaten vital and functional prognosis. Our series included 5 children, three girls and two boys. The average age of our patients was 6 years. The median time between exposure to the SARS Cov2 virus and the onset of clinical symptoms was 4.5 weeks. The clinical expression of post-covid vasculitis was polymorphic, including mainly skin lesions with cyanosis in 60% and necrotic purpura in 40% of cases. Cardiac anomalies were noted in only one patient presenting myocarditis with pulmonary arterial hypertension. No renal or ocular anomalies were observed in any of our patients. The PCR COVID 19 was positive in only one patient, associated to positive SARS Cov2 IgM and IgG serology. The other four patients had only positive IgG serology. The diagnosis of necrotising vasculitis was confirmed by histological study of skin biopsies. On the basis of all the clinical, biological, radiological and histological criteria, the diagnosis of acute necrotising vasculitis post SARS COV 2 infection was set, since all the biologic tests were normal apart from the recent coronavirus infection. Our patients received medical treatment including oral corticosteroids and anticoagulants, with a good clinical and biological outcome, except for two children who underwent amputation of both legs.

Keywords: Vasculitis, inflammation, ischemia, necrosis, child, SARS COV-2, COVID 19.

INTRODUCTION

In December 2019, a new infection called coronavirus 2019 (COVID-19) emerged in Wuhan, China. The pathogen responsible for COVID-19 is "severe acute respiratory syndrome coronavirus 2" (SARSCoV-2), an RNA virus in the Coronaviridae family [1]. Respiratory manifestations were initially the most frequant. However, it has become clear that the virus can affect any organ, including the circulatory system, directly via tissue tropism or indirectly via immune and inflammatory responses. The most common vascular anomaly was Kawasaki vasculitis, as well as vasculitis-like skin lesions and systemic arterial lesions or venous thromboembolism [2]. The aim of this study is to describe the clinical, paraclinical and therapeutic aspects of SARS COV2's vasculitus through the observations of 5 cases of necrotising vasculitis reported in the paediatric rheumatology's department of Children's Hospital, and to compare the results with data in the literature.

MATERIEL AND METHODS

It's a retrospective study of five cases of post-covid 19 necrotising vasculitis diagnosed in our department since the begining of the pandemic from 30 March 2019 to 30 September 2022. For each patient, we collected the epidemiological, clinical, paraclinical, therapeutic and evolution particularities.

RESULTS

Our series include 5 children, three girls and two boys. The average age of our patients is 6 years, with extremes ranging from 1 to 15 years. No pathological antecedents were noted, particulary no history of autoimmune pathologies and no history of drugs use. The median time between exposure to the SARS Cov2 virus and the onset of clinical symptoms was 4.5 weeks, although this interval could not be precisely determined in two patients. The clinical expression of post-covid vasculitis was polymorphic in our series, and was dominated by skin lesions, with cyanosis and oedema in 60% of cases and necrotic purpura in 40%. The necrotic lesions initially affected mainly the lower limbs, with a bluish appearance of the toes, oedema and coldness, extending to the tip of the nose and pinna (Figure 1). Systemic signs such as arthralgia were present in 40% of cases, with a deterioration in general condition in 60% of cases, and fever in 80% of cases. Digestive signs were

noted in only one patient, with abdominal pain, diarrhoea and vomiting. Cardiac anomalies were found in only one patient, presenting myocarditis with pulmonary arterial hypertension. No renal, cerebral or ocular anomalies were observed. Immunologic tests ans viral serologies were normal. The PCR COVID 19 was positive in one case, associated to positive SARS Cov2 IgM and IgG serology. The other four patients had only serology IgG positive. A significant biological inflammatory syndrome was noted in all patients. Doppler ultrasound of the venous and arterial vascular axes was pathological in two patients. Histological study of skin biopsies, was performed mainly leukocytoclastic vasculitis in two patients (40% of cases), acute haemorrhagic oedema (AHEI) in one case, IgA vasculitis in one patient and vasculitis classified as undetermined in one patient. On the basis of all the clinical, biological, radiological and histological criteria, the diagnosis of acute necrotising vasculitis post SARS COV 2 infection was set, since all the biologic tests were normal apart from the recent coronavirus infection. Our patients received medical treatment including oral corticosteroids and anticoagulants, with a good clinical and biological outcome, except for two children who underwent amputation of both legs.

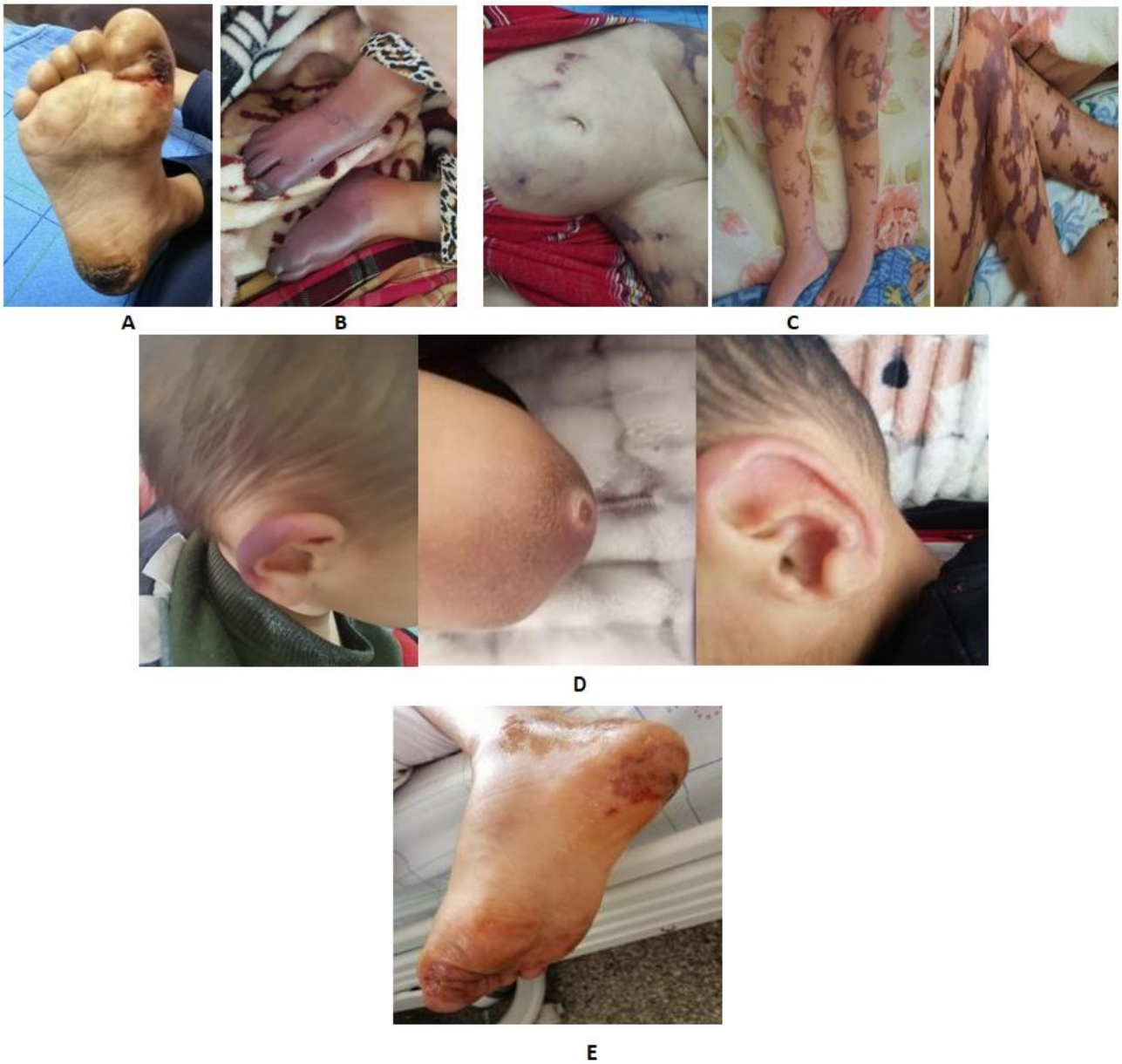

Figure 1: Acroischaemic and necrotizing lesions of post-covid vasculitis in 19 patients in our series; A: oedema and cyanosis of the feet, ecchymotic purpura of the heels/ ulcerations with necrosis of the heel and toes (case n1); B: Necrotic purpura with painful oedema of both feet extending to the ankles (Case n2); C: Purpuric ecchymotic lesions on both lower limbs extending to the abdomen (case n3); D: Cyanosis of the upper end of the right auricle/ Knots in the elbow and auricle (case n 4); E: Trophic disorders of the 2 feet , necrosis of the 5 toes of the right foot then ischemia of the 2 legs (Case n5)

Table 1: Clinical, paraclinical and therapeutic characteristics of patients in our series

Case n 5	Case n 4	Case n 3	Case n 2	Case n 1	
15 years F	1 year F	4 years F	19 months M	7 years M	**Age/ sex** **M-F**
PCR positive /serology covid IgM positive IgG positive	PCR negative/ serology covid IgM negative IgG positive	PCR negative/ serology covid IgM negative IgG positive	PCR negative/ serology covid IgM negative IgG positive	PCR negative/ serology covid IgG positive	**Exposure to SARS Cov2** **PCR SARS COV2/ COVID serology**
2 weeks	Non determined	2 months	Non determined	1 month	**Time between exposure to SARS Cov-2 and clinical symptoms**
Fever and asthenia Functional total impotence of the 2 lower limbs	Fever and viral prodromes (cough and rhinorrhoea) Abdominal pain Diarrhoea and vomiting	Fever and asthenia arthralgias in the 2 lower limbs with total functional impotence	Fever and asthenia	Polyarthralgia Asthenia No fever	**Systemic signs**
Trophic disorders of the 2 feet cyanosis, swelling and coldness in both feet necrosis of the 5 toes of the right foot then ischemia of the 2 legs	Purpura ecchymotic and necrotic at the tip of the nose and on the 2 legs knots on elbow and pinna	ecchymotic purpuric lesions in the two lower limbs then extending to the abdomen	- Necrotic purpura with painful oedema of both feet extending to the ankles. - Cyanosis of the upper end of the right auricle	-Edema and cyanosis of the feet, ecchymotic purpura of the heels -Ulcerations on the 5th toe, elbow, auricle and extension side of the 3rd MCP of both hands	**Skin lesions**
non	no	no	No	Cardiac anomaly: Myocarditis with pulmonary arterial hypertension	**Other clinical anomalies**
Indetermined vasculitis	leukocytoclastic vasculitis	IgA vasculitis	Acute haemorrhagic oedema (AHEI)	leukocytoclastic cutaneous vasculitis	**Histological type of vasculitis**
Demodulation of flow in the middle segments of the leg bilaterally, with no flow distally	normal	Arterial Doppler of the IMs: In favour of demodulated flow in the vascular axes of both MI No visible stenosis	Partial narrowing of the distal part of the popliteal vein with reduced vascular flow	normal	**Doppler ultrasound**
Anticoagulants then amputation of both legs	Anticoagulants Oral corticosteroids	anticoagulants Antiplatelet agents corticosteroid bolus then oral corticosteroids	Oral corticosteroid therapy Amputation of both legs	Anticoagulants Oral corticosteroid therapy Parenteral antibiotics	**Treatment**

DISCUSSION

Coronavirus 2019 (COVID-19), caused by SARS-CoV-2, has opened a new era in paediatric rheumatology practice, as it has been associated with inflammatory complications such as vasculitis and arthritis.

Paediatric vasculitis associated with COVID-19 (excluding Kawasaki like vasculitis associated with a multisystem inflammatory syndrome) is very rare. Only 41 cases have been reported so far in littérature [3]. It is essential to analyse the pathophysiological mechanisms responsible for this condition in the light of available scientific data in order to set standardised strategies in the management of these patients.

The cause-effect relationship between COVID 19 and vasculitis remains poorly elucidated. The direct effects of the virus (via viral replication) and the damage caused by the immune response against the virus are probably the most important and are possibly intertwined in the pathogenesis of COVID-19-associated vasculitis. SARS-CoV-2 directly damages the endothelium and causes "endotheliitis" [2]. Viral inclusions in endothelial cells and increased endothelial apoptosis have been demonstrated in histopathological studies including patients with COVID-19. These phenomena lead to micro and macroangiopathy resulting in acute ischaemia and necrosis [4]. Immunothrombosis and microemboli particularly affect organs that receive a relatively high proportion of cardiac output, such as the brain. In fact, thrombi and thrombotic microangiopathy were demonstrated in the biopsy of an adolescent with COVID-19-associated CNS vasculitis [5].

The endothelium acts as a barrier between platelets and collagen/tissue factor (TF). The exposure of the basal membran triggers the thrombotic cascade via interactions between platelets, TF and collagen, with dysregulated endothelial cells releasing pro-inflammatory cytokines (interleukins IL1, IL6) that contribute to inflammation of the vascular wall. In addition to endothelial damage, pro-inflammatory cytokines such as interleukin 6 cause alterations in IgA glycosylation, with the formation of immune complexes that lead to IgA vasculitis [6].

In normal states, angiotensin-2-converting enzyme converts angiotensin II (ATII) into AT1-7, which stimulates endothelial cells to produce nitric oxide (NO). As well as maintaining vascular homeostasis and modulating vasodilation, NO prevents inflammation by returning macrophages to an anti-inflammatory state. When SARS-CoV-2 binds and deregulates CEA2, the balance shifts in favour of ATII antithrombin, leading to decreased NO, vasoconstriction, reduced blood flow and ischaemia in target tissues/organs [7]. Other pathophysiological mechanisms that have been elucidated include neutrophil activation and cell apoptosis with the release of extracellular traps (NETs) containing neutrophil granule proteins and host nuclear material. Torres-Ruiz *et al*., recently demonstrated that anti-NET antibody positivity correlated with antinuclear antibody and ANCA positivity in COVID-19 [8].

A more recent cohort study by Batu *et al*., [3], published in November 2022, was carried out in 14 centres in 6 countries. 41 children with vasculitis associated with SARS Cov 2 infection documented using the same inclusion criteria, studied the clinical, paraclinical, therapeutic and evolutionary characteristics of these patients. The most common subtype of vasculitis was IgAV/HSP (n = 30). The median time between exposure to SARS-CoV-2 and onset of vasculitis was 13 days. Skin (92.7%) and gastrointestinal (61%) involvement were the most common manifestations of vasculitis. Most patients (68.3%) received glucocorticoids, and 14.6% also received additional immunosuppressive drugs. Remission was achieved in all patients. All IgAV/HSP patients in this cohort had skin manifestations, while 18 (60%) had gastrointestinal involvement and 13 (43.3%) had renal involvement.

A systematic review of the English literature was conducted using Pubmed/MEDLINE and Scopus, with a total of 25 articles describing 36 patients with COVID-19-associated paediatric vasculitis, including data on patients with onset of vasculitis at an age younger than 18 years, evidence of exposure to SARS-CoV-2, and evidence of diagnosis of vasculitis (imaging, histopathological evidence, specific diagnostic/classification criteria). Patients with Kawasaki disease-type vasculitis associated with multisystem inflammatory syndrome in children (MIS-C) were excluded [9].

The median age of patients with COVID-19-associated paediatric vasculitis in the literature was 13 years (1.1-17) with a male predominance (M/F: 2.3). The median time between exposure to SARS-CoV-2 and vasculitis was 17.5 (2-150) days and this time interval was only reported for 10 patients (but not certain in some cases). The duration was ≤1 week in four patients (3 IgAV/HSP patients and 1 AAV patient) while it was 2-5 weeks in five patients (2 IgAV/HSP patients, 2 AAV patients, 1 CNS patient). One patient with retinal vasculitis had a latency of five months. The most common manifestations of vasculitis were skin (58.3%), kidney (30.5%), gastrointestinal (GIS, 13.8%), CNS (13.8%) and lung (11.1%) anomalies.

The clinical expression of post-covid vasculitis is mainly characterised by cutaneous eruptions secondary to the systemic consequences of COVID-19 localised to the extremities, such as peripheral cyanotic lesions, acro - ischaemic micro-thrombotic lesions progressing to necrosis and gangrene. Cutaneous manifestations are considered to be an uncommon presentation of COVID-19. Acroischaemic lesions, observed in severe or critical COVID-19 patients, take

the form of peripheral cyanotic lesions, reticulated livedos, sometimes with bullous lesions which may progress to dry gangrene [10].

The histological types of post-covid vasculitis found were mainly IgAV/HSP vasculitis (25%), frostbite (19.4%), ANCA-associated vasculitis (AAV) (13.8%) including 3 associated with anti-PR-3 ANCA and 2 associated with anti-MPO ANCA, central nervous system (CNS) vasculitis (11.1%), retinal vasculitis (5.5%), urticarial vasculitis (5.5%), cutaneous leukocytoclastic vasculitis (2.7%), and acute haemorrhagic oedema of childhood (AHEI, 2.7%). Biopsy results from 18 patients were consistent with a diagnosis of vasculitis (frostbite in 7 cases, AAV in 5 cases, CNS vasculitis in 3 cases, IgAV/HSP in 2 cases and cutaneous leukocytoclastic vasculitis in 1 case). The SARS-CoV-2 virus was detected in the biopsy of seven patients (38.8%) [11].

Urticarial vasculitis has been found in two patients with COVID-19. The cutaneous manifestations are exanthems similar to those of chickenpox, petechial eruptions similar to those of dengue fever and urticaria, characterised histologically by deposits of immunocomplexes [12]. Clinically, lymphocytic vasculitis presents as purpuric skin lesions on the toes, feet, heels and hands. Histologically, there is dermatitis with vascular degeneration of the basal layer of the epidermis, endotheliitis with lymphocytic infiltration of dermal vesicles and arterioles, and microthrombosis of papillary dermal capillaries. Immunohistochemistry revealed an inflammatory infltrate composed mainly of mature T cells with a predominance of helper T lymphocytes. Cytoplasmic granular positivity for the SARS-CoV-2 spike protein is present in the endothelial cells of capillary and post-capillary vesicles [13].

All patients with frostbite, retinal vasculitis and AHEI improved without any therapeutic intervention. The majority of patients diagnosed with vasculitis post COVID 19 received corticosteroids (40%), while rituximab (14.2%) and cyclophosphamide (11.4%) were the most frequently used immunosuppressive drugs. Remission was achieved in 23 of the 28 patients. Five patients (4 with central nervous system vasculitis; 1 with ANCA-associated vasculitis) died. No outcome was reported in 8 patients [9].

Comparing treatment response and outcome in COVID19-associated paediatric vasculitis versus paediatric vasculitis not associated with COVID-19, relatively good clinical outcomes were found when patients were treated with corticosteroids and immunosuppressive drugs. Antiplatelet or anticoagulant therapy could also be considered in cases of severe COVID-19-associated vasculitis, such as ANCA-associated vasculitis or CNS vasculitis [14].

Treatment of IgA vasculitis associated with COVID-19 was consistent with our current practice, with a good outcome similar to that seen in IgAV/HSP not associated with COVID-19. Corticosteroids were used in the treatment of five (55.5%) IgAV/HSP patients while NSAIDs were the only drug used for the remaining IgAV/HSP patients (n=4). Complete remission was achieved in all nine IgAV/HSP patients. In patients with AAN-associated vasculitis (AAV), extensive immunosuppressive therapy with rituximab or cyclophosphamide was introduced in addition to corticosteroids. Antithrombotic treatment was prescribed only for patients with vasculitis (AAV) and venous thrombosis. Only one patient received antiplatelet therapy and anticoagulants for her myocardial infarction. Of the five patients with ANCA VAA-associated vasculitis, only one died despite treatment with immunosuppressants such as RTX, CYC, mycophenolate mofetil (MMF) and azathioprine (AZA) [15].

Ongoing studies are looking at targeted therapies targeting one or more proteins in signalling pathways specific to the vascular system, in particular angiopoietin-2 (NCT04342897), VEGF. These biomarkers include vascular endothelial growth factor A, vascular endothelial growth factor receptor type 1, Syndecan-1 (a marker of glycocalyx degradation) and VWF [16].

CONCLUSION

Although COVID-19-associated paediatric vasculitis is very rare, awareness of this rare entity is important to ensure early diagnosis and treatment. The clinical features of the subtypes of COVID-19-associated paediatric vasculitis are similar to those of paediatric vasculitides not associated with COVID-19. Functional prognosis may be preserved if positive diagnosis and treatment are promptly initiated. While conservative measures are sufficient for patients with certain types of vasculitis such as IgA vasculitis (HSP), isolated cutaneous vasculitis and AHEI, corticosteroids and immunosuppressive treatments are necessary for other subtypes of vasculitis such as ANCA-associated vasculitis and CNS vasculitis.

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