

# Henoch–Schönlein purpura in the setting of COVID-19 infection: Two pediatrics cases and review of the literature

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#### Abstract

Henoch–Schönlein purpura (HSP) is the most common systemic vasculitis in children, often following a viral infection. Various types of rashes attributed to COVID-19 infection have been described in the literature; however, HSP has rarely been reported. We report two children with HSP associated with acute COVID-19 infection with a review of the available literature. We highlight the clinical presentation, medical management, outcome and age-related difference of reported patients. A limitation of this article is the retrospective nature, limiting full patient history and associated conditions. The findings of this review show that HSP in the setting of COVID-19 is more common in children than adults, with a male predominance, involving various body systems creating a constellation of presentations. Given that HSP can have long-term morbidity from renal disease if untreated, this review may help guide the practitioner's approach to HSP and recognition in the setting of COVID-19 infection.

Keywords: Case report, coronavirus disease 2019, Henoch-Schönlein purpura

# Introduction

The dermatologic findings described in Coronavirus disease 2019 (COVID-19) patients are myriad, including exanthem, vesicular lesions, urticaria, purpura, chilblains, violaceous macules, livedo, eruptive cherry angioma and erythematous rashes.<sup>[1-6]</sup> In the largest series to date, skin lesions were found in 2 (1.5%) of 150 COVID-19-infected patients.<sup>[2]</sup>

Henoch–Schönlein purpura (HSP) has rarely been reported in patients with COVID-19 infection.<sup>[7-30]</sup> HSP is a small vessel, IgA-mediated vasculitis that is the most common systemic vasculitis in children.<sup>[31]</sup> The diagnosis of HSP is based on

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**Revised:** 02-04-2023

Published: 30-09-2023

**Received:** 04-01-2023 **Accepted:** 19-04-2023

Access this article online
Quick Response Code:

Website:
http://journals.lww.com/JFMPC
DOI:
10.4103/jfmpc.jfmpc\_26\_23

clinical criteria including the presence of palpable purpura in the absence of thrombocytopenia and one or more of the following supporting criteria – acute abdominal pain, arthritis or arthralgia, renal involvement (hematuria or proteinuria), and biopsy evidence of leukocytoclastic vasculitis or proliferative glomerulonephritis with IgA deposits.<sup>[31]</sup> We report two children with HSP due to COVID-19 and review the literature regarding this association. We objectively summarized the beneficial or harmful interventions useful for clinicians when encountering a patient with HSP triggered by COVID-19 infection.

#### **Case Histories**

#### Case 1

An 8-year-old male presented to the pediatric emergency department with a one-week history of pain in his ankles, knees, and hands and poorly characterized abdominal pain. Two days

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How to cite this article: Zumbro C, Davidson S, Daley WP, Camacho SM. Henoch–Schönlein purpura in the setting of COVID-19 infection: Two pediatrics cases and review of the literature. J Family Med Prim Care 2023;12:1790-5.

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prior to presentation, he developed bilateral upper extremity edema and a rash on his shins described as "tiny bruises". His family initially thought he had experienced trauma during baseball practice; however, the edema and rash worsened, coalescing into palpable purpura on his shins, thighs, and buttocks prompting evaluation. His history was significant for COVID-19 infection three weeks prior to presentation characterized by nasal congestion and cough. Examination was significant for normal heart rate and blood pressure. He was well hydrated without icterus. Lung examination revealed good air movement throughout without any adventitious breath sounds. Heart examination revealed a regular rhythm without murmur, gallop, or rub. The abdomen was soft, nontender, and free of hepatosplenomegaly. He had nonpitting edema of his ankles, hands, and forearms. There were diffuse, nonblanching purpura on the lower extremities [Figure 1]. Laboratory investigation revealed normal values for urinalysis, complete blood count (CBC), renal panel, hepatic panel, creatinine kinase, troponin-T, proBNP, TSH, fibrinogen, ANA, c-reactive protein (CRP), partial thromboplastin time (PTT), and prothrombin time-international normalized ratio (PT-INR). There was elevation of the erythrocyte sedimentation rate (ESR, 21 mm/h; upper limits of normal = 10 mm/h) and D-dimer (3007 ng/mL; upper limit of normal = 500 ng/mL). He was diagnosed with HSP and admitted for treatment with corticosteroids. The edema and arthralgia improved and he was discharged on a steroid taper. At follow-up 9 months following discharge, he had resolution of all symptoms with no interval development of hypertension or renal disease.

#### Case 2

A 4-year-old male presented to the pediatric emergency department with a 2-day history of abdominal pain and vomiting. His physical examination was normal except for tenderness to palpation in the right lower quadrant (RLQ). Laboratory investigation revealed normal values for urinalysis, CBC, renal panel, hepatic panel, ESR, and CRP. Abdominal ultrasound revealed prominent lymph nodes in the RLQ, but a normal appendix and no evidence for intussusception. He was diagnosed with mesenteric adenitis and discharged home. He re-presented to the pediatric emergency department 3 days later with worsening abdominal pain, vomiting, and decreased oral intake. Examination revealed mild tachycardia with normal blood pressure. He was ill-appearing with dry mucous membranes. Lung examination revealed good air movement throughout without any adventitious breath sounds. Heart examination revealed a regular rhythm without murmur, gallop, or rub. The abdomen was soft, nondistended, free of hepatosplenomegaly, but with tenderness to palpation in the RLQ. His extremity exam was normal, without edema. He had no cutaneous rashes. Urinalysis was significant for elevated specific gravity, ketonuria, and proteinuria. COVID-19 polymerase chain reaction testing was positive. Further laboratory investigation revealed normal values for CBC, renal panel, hepatic panel, ESR, CRP, lactate, and proBNP. Repeat abdominal ultrasound showed a normal appendix. Computed tomography (CT) scan of the abdomen and pelvis was significant for thickened jejunal bowel loops with prominent enhancement consistent with enteritis. He was admitted due to dehydration, for which he was given intravenous fluids. Abdominal pain, vomiting, and poor oral intake persisted, necessitating continued intravenous hydration. Two days after admission, he developed blood-tinged diarrhea, determined to be due to Campylobacter jejuni for which azithromycin was started. The following day he developed petechiae and purpura on his hands, forearms, wrists, buttocks, feet, and shins [Figure 2a and b]. He also began to complain of pain in his knees and feet. CBC, PTT, and PT-INR were normal. Due to the constellation of clinical features, he was diagnosed with HSP and systemic steroids were started due to worsening abdominal pain and bloody diarrhea. After the initiation of steroids (prednisone 1 mg/kg/day), there was a gradual resolution of abdominal pain, joint pain, and diarrhea. Repeat urinalysis on three occasions was normal. He was discharged home eight days following admission on an oral prednisone taper and a proton-pump inhibitor for ulcer prophylaxis.

Figure 1: Palpable purpura on the lower extremities





Figure 2: Palpable purpura on the lower portion of the legs and feet (a) and elbow (b)

but persistent small intestinal wall thickening. Prednisone was increased back to 1 mg/kg/day with improvement in symptoms. He was discharged home after five days.

He re-presented to the emergency department three days later with a return of severe abdominal pain and worsening of rash. Laboratory abnormalities on admission included mild hypoalbuminemia (3.1 g/dL), mild normocytic anemia (HGB = 9.1 g/dL), proteinuria (200 mg/dL), and mild elevation in cystatin-C (1.01 mg/dL; upper limits of normal = 0.95 mg/dL). Abdominal ultrasound was normal. A subsequent 24-h urine collection showed significant proteinuria (765 mg/24 hours). Nephrology recommended a renal biopsy, which showed focal proliferative and necrotizing glomerulonephritis with IgA immune complex deposition [Figure 3a-c]. He was given high-dose methylprednisolone (250 mg Qday) for 3 days, followed by oral prednisone (2 mg/kg/day). He had prompt improvement in symptoms and was discharged after seven days on a prednisone taper. At follow-up two months after discharge, he was asymptomatic and doing well off steroids.

#### Discussion

The cases presented above meet the diagnosis of HSP with the presence of a diffuse nonblanching purpural rash, absence of thrombocytopenia, abdominal pain, arthralgia, and kidney involvement (proteinuria), and to include into the HSP diagnosis; Case 2 also showed glomerulonephritis with IgA deposition. HSP is the most common systemic vasculitis in children, with a worldwide annual incidence ranging from 3.4 to 22/100,000 in adults and children.<sup>[32]</sup> HSP arises due to a complex interaction of chemokines, cytokines, leukocytes, and vascular epithelium resulting in complement activation, endothelial injury, and IgA deposition, suggesting a dysregulated IgA-mediated immune response to an antigen.<sup>[33]</sup> Triggering agents include medications, cancers, vaccines, and infectious agents, including parasites, bacteria, and viruses, particularly infectious agents responsible for upper respiratory infections.<sup>[34]</sup> Both cases presented above had HSP triggered by COVID-19, whereas Case 2 had overlapping bacterial enteritis.

A novel virus, severe acute respiratory syndrome coronavirus 2, entered clinical medicine in 2019 as the respiratory disease referred to as COVID-19. In a small, retrospective study (n = 14)

of COVID-19 patients with cutaneous manifestations, the causes were equally divided between inflammatory lesions [including exanthem (28.6%), vesicular (14.3%), and urticaria (7.1%)] and vascular lesions [including purpura (14.3%), chilblains (14.3%), violaceous macules (7.1%), livedo (7.1%), and eruptive cherry angioma (7.1%)].<sup>[6]</sup> While most information regarding dermatologic findings in COVID-19 infection are derived from single case reports, larger case series have been reported. In the largest series to date, skin lesions were found in 2 (1.5%) of 150 COVID-19-infected patients.<sup>[2]</sup> In a smaller case series (n = 88), 20% of COVID-19 patients manifested skin findings, which included erythematous rashes (78%), urticaria (17%), and vesicular lesions (5%).<sup>[5]</sup> Among the varied presentations of COVID-19 is vasculitis, which arises from the virus binding to endothelial cells resulting in vascular inflammation and dysfunction.[35]

To date, 29 patients have been reported with HSP in the setting of COVID-19 infection,<sup>[7-30]</sup> including the children we report [see Table 1]. The association of HSP and COVID-19 has been reported as slightly more common in children (51.7%) than in adults (48.3%), although previous smaller cases reported a higher frequency in adults.<sup>[26]</sup> There is a marked male (89.3%) predominance, with ages ranging from 23 months to 87 years.

Thirteen patients (44.8%) developed HSP within 2–37 days (average  $\pm$  SD, 18.2  $\pm$  11.7 days) of having COVID, whereas 15 (51.7%) were diagnosed with COVID at the time of presentation with HSP; in one patient, the interval was not mentioned. The most common presenting symptom of HSP was a purpuric rash, seen in 27 (93.1%) reported patients. One patient presented with abdominal pain but developed a rash within two days of presentation.

Other symptoms important in the clinical diagnosis of HSP that were reported include abdominal pain (62.1%), arthralgia or arthritis (59%), renal involvement (37.9%), and hematochezia (24.1%). Arthralgia or arthritis was reported in 42.8% of adults and in 73.3% of children. Five patients (17.2%) had symptoms involving four organ systems, twelve patients (41.4%) had symptoms involving three organ systems, and seven patients (24.1%) had two organ systems involved.

Elevated CRP and ferritin, markers of inflammation, have been associated with the cutaneous inflammatory process associated



Figure 3: Kidney biopsy showing glomerulus with fibrinoid necrosis of the capillary tuft taken at ×200 magnification (a), glomerulus with very focal endocapillary hypercellularity taken at ×400 magnification (b), and positive IgA immunofluorescence noticed for IgA complex deposition taken at ×200 magnification (c)

	Ia	the setti	ng of COVIL	-19							
Ref#	Age	Sex	COVID	Rash	Gastrointestinal	Joint	Renal	Biopsy	CRP	Treatment	Outcome
	(yr)		(days)								
						Α	dults				
7	59	М	35	Purpuric*				Skin (LCV)	Nm	Steroids	Nm
8	71	F	0	Purpuric*				Skin (LCV)	Elevated	Betamethasone	Nm
9	83	Μ	0	Purpuric*				Skin (LCV)	Elevated	Steroids	Nm
10	29	М	30	Purpuric*	Abdominal pain Hematochezia			Skin (LCV)	Nm	Steroids	Improved
11	78	М	21	Purpuric*		Arthritis	Proteinuria hematuria	Kidney (IgAN)	Elevated	Steroids rituximab	Improved
12	24	Μ	0	Purpuric*	Abdominal pain	Arthralgias		Skin (LCV)	Elevated	Steroids	Improved
13	49	Μ	14	Purpuric*				Skin (LCV)	Nm		Improved
14	22	М	0	Purpuric*	Abdominal pain, nausea, vomiting	Arthralgias	Proteinuria	Skin (LCV) kidney (IgAN)	Normal	Steroids mycophenolate	Improved
15	30	М	0	Purpuric*	Abdominal pain	Arthralgias	Proteinuria hematuria	Skin (LCV) kidney (IgAN)	Elevated	Steroids	Improved
16	62	М	10	Purpuric*	Abdominal pain hematochezia		Proteinuria hematuria	Skin (LCV)	Nm	Steroids	Improved
17	84	М	15	Purpuric			Proteinuria hematuria	Skin (negative LCV) kidney (IgAN)	Nm	Steroids mycophenolate	Improved
17	87	М	nm	Purpuric*			Proteinuria hematuria	Skin (LCV)	Nm	Steroids	Full recovery
18	70	М	0	Purpuric*	Abdominal pain hematochezia	Arthralgias	Proteinuria hematuria	Skin (LCV) kidney (IgAN)	Normal	Steroids	Improved
19	66	М	15	Purpuric*	Abdominal pain	Arthralgias		Skin (LCV)	Elevated	Steroids	Nm
				1	1	Ch	ildren	. ,			
20	2	М	0	Purpuric*	Abdominal pain hematochezia			Skin (LCV)	Nm	Steroids	Full recovery
21	4	nm	0	Purpuric*	Abdominal pain GI bleeding	Arthralgias			Nm	Steroids	Improved
22	4	М	37	Purpuric*	or steering	Arthralgias			Normal		Full recovery
23	3	М	0	Purpuric*	Abdominal pain				Nm	Steroids	Improved
24	8	М	7	Purpuric*	The second se	Arthralgias			Normal		Full recovery
25	13	М	28	Purpuric*				Skin (negative IgA)	Normal	Steroids	Improved
26	5	F	0	Purpuric*	Abdominal pain*	Arthritis			Elevated	Steroid	Full recovery
27	16	М	2	Purpuric*	Abdominal pain hematochezia		Proteinuria hematuria		Elevated	Steroids	Improved
28	13	F	0	Purpuric*	Abdominal pain	Arthritis			Elevated		Full recovery
29	3	М	0	Purpuric*	Abdominal pain	Arthritis	Proteinuria hematuria		Elevated	NSAID	Improved
30	4	М	0	Purpuric*		Arthritis			Normal	Steroid	Full recoverv
30	23 m	М	0	Purpuric*	Abdominal pain, hematochezia*	Arthralgias			Normal	Steroid	Nm
30	4	М	0	Purpuric*	Abdominal pain* Diarrhea*	Arthritis			Nm	Steroid	Nm
case-1	8	М	21	Purpuric*	Abdominal pain	Arthralgias	Proteinuria hematuria		Normal	Steroids	Full recovery
case-2	4	М	2	Purpuric	Abdominal pain* hematochezia	Arthralgias	Proteinuria	Kidney (IgAN)	Normal	Steroids	Full recovery

Legend: \*, presenting symptom; nm, not mentioned; LCV, leukocytoclastic vasculitis; IgAN, IgA nephritis

with COVID-19.<sup>[1]</sup> Nineteen of the reported patients had CRP documented, of which ten (52.6%) had elevated levels. These inflammatory markers are not specific and can be elevated in other syndromes related to COVID-19, such as multisystem inflammatory syndrome (MIS).<sup>[36]</sup> The presented Case 2 had normal CRP despite having infectious enteritis secondary to *Campylobacter jejuni*; he did not meet the criteria for MIS.

The severity of COVID-19 varied among those reported, without any correlation between disease severity and skin findings.<sup>[5]</sup> Skin biopsies were obtained in 15 patients (51.7%), and 13 (86.7%) showed leukocytoclastic vasculitis. Adult patients more commonly underwent skin biopsy (92.9%) compared to children (13.3%) for the diagnosis of HSP. The increased rate of skin biopsies in adults might reflect the need to rule out other

causes of vasculitis, as HSP is less common in adults. Vasculitis is often associated with a fatal disease that requires prompt recognition, including autoimmune/rheumatologic disease, malignancies, medications or drugs, and chronic infections like hepatitis.<sup>[37]</sup> A detailed history should guide the diagnosis.<sup>[31,37]</sup> Renal biopsies were obtained in six patients (20.7%), all showing IgA nephropathy. Jedlowski and Jedlowski<sup>[18]</sup> reported a positive skin biopsy direct immunofluorescence for IgA in 50% of cases compared to 100% of kidney biopsies.

HSP is self-limited with good prognosis and treatment is supportive.<sup>[32]</sup> Corticosteroids are first-line therapy in patients with classic HSP for complications such as nephritis, severe abdominal pain, and gastrointestinal bleeding.<sup>[32]</sup> Both patients, cases 1 and 2, received steroids due to severe abdominal pain; Case 2 re-presented to the ER with intussusception, a well-known complication of HSP,<sup>[33]</sup> that resolved spontaneously. Treatment with corticosteroids was started on 24 (82.8%) of the reported patients, resulting in amelioration of rash, renal disease, and abdominal symptoms. Outcomes were documented in 23 patients with full resolution occurring in nine (39.1%) and improvement after a short follow-up in 14 (60.8%).

The limitations of this article are related to the retrospective nature, including missing data from the patient's past medical history. This systematic review was limited to the number of cases identified in the database and the definition of HSP, all cases were compiled for descriptive analysis, and a larger sampling is needed to assess a statistical analysis. Also, as COVID-19 is a newly emerging disease, the long-term consequence is lacking, including the recurrence of HSP due to COVID-19.

In conclusion, we report two children with HSP associated with COVID-19 infection. Further, we review the available literature on clinical presentation, medical management, and outcome in patients with HSP-associated COVID-19. The findings of this review show that HSP in the setting of COVID-19 is more common in children than adults, with a male predominance, involving various body systems creating a constellation of presentations. Given that HSP can have long-term morbidity from renal disease if untreated, this review may help guide the practitioner's approach to the rare patient with HSP in the setting of COVID-19 infection in children and adult patients.

Informed consent statement: Informed consent was given by the parents and the patient's identity was protected.

## **Declaration of patient consent**

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

#### Acknowledgements

We are so grateful for Dr. Michael Nowicki and his guidance during the preparation of this report.

#### Financial support and sponsorship

Nil.

# **Conflicts of interest**

There are no conflicts of interest.

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