A Trigger for or an Exaggerated Immune Response: Vasculitis Following Viral Infection

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Abstract

Henoch-Schoenlein purpura-HSPN is nowadays called Immunoglobulin A vasculitis. It is commonly having an acute inception and progression while IgA nephropathy is frequently a long-lasting advanced kidney disorder that progressively leads to Kidney dysfunction. A retrospective case report with clinical presentations and various laboratory investigations. A young girl was admitted with painless hematuria, high blood pressure, and purpuric skin rash. The rash started over the lower limbs and then progressed to the abdomen and upper limbs. It was associated with bilateral ankle pain and swelling, abdominal pain, and inability to walk. These all happened after the COVID-19 infection eight-weeks before. She was clinically diagnosed as a Henoch-Schoenlein Purpura-HSP and hence she was restarted on steroids. She had a dramatic response to steroids within one-month, however, she developed several relapses over the next two months when the steroid was reduced to < 15mg per day. The skin biopsy revealed a leukocytoclastic-vasculitis involving the skin-palpable purpura. The immunofluorescence findings revealed a couple of superficial dermal-vessels that showed positive-staining with IgA/C3. Azathioprine (AZA) 100mg per-day was started-as a steroid sparing-agent-along with the gradual withdrawal of steroid without further relapses over the three-months period. During a further six-months of follow-up period, while on AZA 100mg per-day alone, the patient had complete-remission and without any recurrence. **Conclusion:** This finding may suggest that SARS-CoV-2 triggers autoimmune diseases.

Keywords: COVID-19 infection, Henoch-Schoenlein Purpura (HSP), Steroid dependent and AZA

Introduction

Immunoglobulin A (IgA) vasculitis, previously called Henoch Schoenlein purpura (HSP) is a self-limited, systemic, non-granulomatous, and autoimmune complex, of small vessel vasculitis, with multiorgan involvement.[1]

IgA vasculitis/HSB is the most common form of vasculitis in children with an incidence of approximately 20 in 100,000 children, with the highest frequency between 4 and 6 years old, although it can occur at any age.[2,3]

Its etiology is unclear but is associated with infections (bacterial, viral, and parasitic), medications, vaccination, tumors (non-small cell lung cancer, prostate cancer, and hematological malignancies), alpha-1-antitrypsin deficiency, and Familial Mediterranean Fever.[4] IgA vasculitis/HSP is characterized by a classic

tetrad of nonthrombocytopenic palpable purpura, arthritis or arthralgias, gastrointestinal and renal involvement, but rarely it does involve other systems (lungs, central nervous system, and genitourinary tract).[5]

In this paper, we report an IgA vasculitis /HSP case that occur after a COVID-19 infection in a young girl, who was treated as a steroid-dependent case with complete remission on Azathioprine (AZA).

Case Report

A 14-year-old girl, with a known case of chronic eczema, was admitted to a tertiary hospital with painless hematuria, high blood pressure, and purpuric skin rash. The rash started over the lower limbs, then progressed to the abdomen and upper limbs. It was associated with bilateral ankle pain and swelling, abdominal pain, and inability to walk. All these events occurred after the COVID-19 infection eight weeks back. In addition, she had noticed increased hair loss and the occurrence of oral ulcers but there were no genital ulcers. Also, she had irregular menstruation that lasted for 15 days.

The clinical examination revealed a young girl, with morbid obesity (weight 116 kg, height 160 cm, and BMI 45), high blood pressure 130/80 for her age, and she was afebrile. She had active palpable purpuric erythematous lesions on her thighs, abdomen, arms, and forearms. Also, she had tenderness and swollen ankles, wrists, and shoulder joints, with malar flush (cheeks redness upon sun exposure). She was put on lisinopril 5 mg per day and steroids 60 mg per day were started for two weeks but then stopped by the family after improvement.

Laboratory investigations revealed a total leukocyte count that was at the upper normal range level and increased urinary red blood cells count of >60, but all remaining investigations were normal including virology, immunology, and inflammatory markers.

Table 1: shows the various laboratory tests at admission.

Variables	Laboratory Results	Normal values
Hemoglobin (g/dL)	14 g/dl	11.5 - 15.5
Total leukocyte count (cells/µL)	10 x 10 3/ul	2.2 - 10
Platelets (cells/µL)	419 x10 9/l	150 - 450
INR	0.95 ratio	0.8 - 1
Serum Creatinine umol/l	58 umol/l	(53-97.2)
Serum urea	3.6 mmol/l	(2.1-8.5)
Urine protein creatinine ratio(PCR)	6.9 mg/mmol	<20
Urine RBCs	>60 cells/ul	<2
Albumin (g/dL)	36g/l	34 - 50
ESR	17mm/h	2 - 30
C-Reactive Protein (mg/L)	5 mg/l	<10 mg/l
Complement levels (C3)	1927 mg/l	850 - 1600
Complement levels (C4)	335 mg/l	120 - 360
Anti-Nuclear Antibody (ANA)	Negative	(1:80 or less)
Anti-Neutrophilic Cytoplasmic Autoantibody (ANCA)	Not reactive	(<19 AU/ml)
Immunoglobulin A -serum	Not available	>368 mg/dl
HIV 1&2 Antibodies	Nonreactive	(Not detected)
Hepatitis B surface antigen	0.32 Nonreactive ratio	(1-9 log IU/ml)
Anti-hepatitis C virus Abs	Nonreactive	(1-8 log IU/ml)
TSH	2.8 mIU/l	0.4 - 4
Free T4	14 pmol/l	11 - 18
HbA1c	5.4%	(<6.0%)
QuantiFERON TB test	Not detected	0.2-0.99 IU/ml)

One month later, she was seen by a dermatologist, and she was clinically diagnosed with a case of IgA vasculitis/HSP hence she has restarted steroids with Prednisone 60 mg per day orally. She had a dramatic response to steroids within one month but also developed several relapses over the next two months when the steroid dosage was reduced to less than 15 mg daily.

Figure 1 shows an active purpuric erythematous lesion. This acute phase shows the polymorphic Gutate un-blanch-able erythematous purpuric lesions along with large dusky purpuric lesions with hemorrhagic centers, as shown in both shins, figure 1A. Figure 1B shows the healing phase with crusted and fading purpuric lesions with others healed with **post-inflammatory hyperpigmentation.**

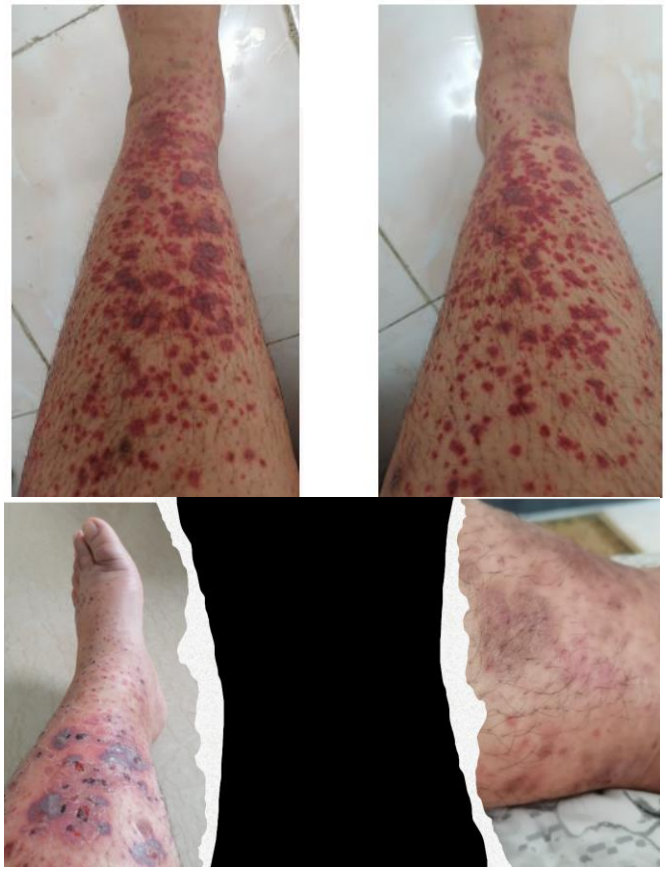

Figure 1: Active purpuric erythematous lesion on thigh, abdomen, and leg. **(a)** Acute phase of the polymorphic Gutate un-blanch-able erythematous purpuric lesions along with large dusky purpuric lesions with hemorrhagic centers. **(b)** Healing phase with crusted and fading purpuric lesions with others healed with post-inflammatory hyperpigmentation.

Figure 2 shows the skin punch biopsy findings after several relapses. It shows the histopathological changes in hematoxylin and eosin-stained slides of HSP include: superficial perivascular infiltrates of mainly neutrophils, extravasation of RBCs from vascular walls, leukocytoclasia (neutrophilic degeneration forming nuclear dust), and fibrinoid necrosis of vessels. There was a Superficial perivascular inflammatory infiltrate, as shown in Figure 2A. Also, there was an extravasation of RBCs and leukocytoclasia (nuclear dust), as shown in Figure 2B. In addition, there was a fibrinoid necrosis of the vessel, as shown in Figure 2 C.

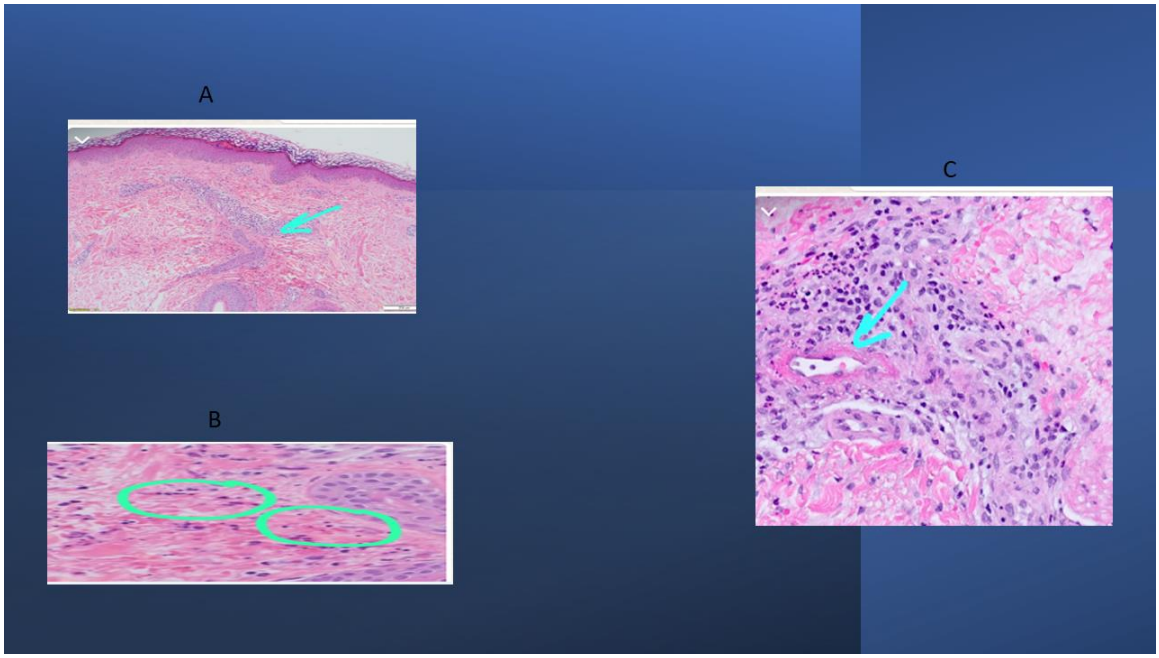

Figure 2: Skin punch biopsy findings after several relapses. (a) Superficial perivascular inflammatory infiltrate. **(b)** Extravasation of RBCs and leukocytoclasia (nuclear dust). **(c)** Fibrinoid necrosis of the vessel.

The histopathologist concluded that the microscopic finding of the skin punch biopsy revealed leukocytoclastic vasculitis, which is consistent with IgA vasculitis/HSP with no dysplasia or malignancy features.

The immunofluorescence findings revealed superficial dermal vessels with positive staining for IgA++ and C3++ but IgG and IgM were negative.

She developed frequent relapses of skin eruption and arthralgia in association with tapering of steroid dose over the next three months. Hence, azathioprine 100 mg per day was started as a steroid-sparing agent along with the gradual withdrawal of steroids without relapses over the three months period. During a further six months of the follow-up period, while on azathioprine 100 mg per day alone, the patient had complete remission and without any recurrence.

Diagrammatic summary of the events of the case from the initial development of IgA vasculitis/HSP post-COVID-19 infection till complete remission (Figure 3).

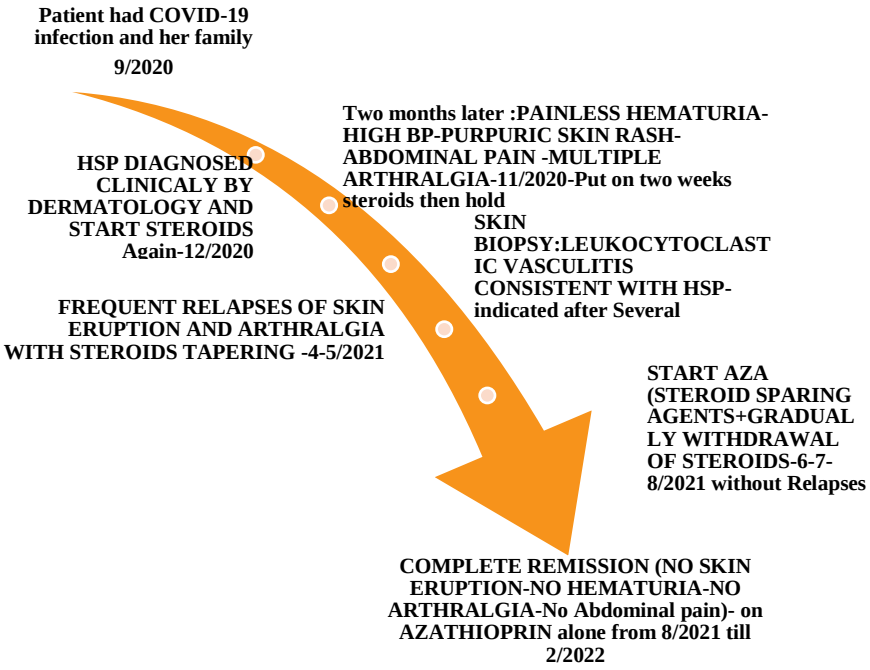

Figure 3: Diagrammatic summary of the events until complete remission.

Discussion

COVID-19 caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and the COVID-19 pandemic is currently an ongoing global problem and is known to cause vasculitis-like syndromes [~~6~~) as in the current case report. The characteristics of patients with IgA vasculitis/HSB following COVID-19 are summarized in Table 2. There were seven cases of IgA vasculitis/HSB (6-12). The median age was 23.3 years and the ratio of adults to children was 4:3. Interestingly, all cases were male. Other symptoms excluding cutaneous purpura were observed in three of seven cases with abdominal pain, and three of seven cases with nephritis. Furthermore, all nephritis cases were adults, and 75% of adult cases showed IgA vasculitis/HSB following COVID-19 infection, whereas IgA nephritis was not identified in the children.

Table 2: shows the summary of the published cases with IgA vasculitis/HSB following COVID-19.

Author	Age	Sex	Days after COVID-19 Test Positive	Involvement	Treatment
Suso, et al.[7]	78-ys	male	5 weeks later	Skin -nephritis	Steroid pulse and Rituximab
Hoskins, et al.[8]	2-ys	male	Same time	Skin - abdominal pain	Intravenous steroid
Allez et al.[6]	24-ys	male	unknown	Skin - abdominal pain	Methylprednisolone 0.8 mg/day
Sandhu et al.[9]	22-ys	male	Same time	Skin -nephritis	Prednisolone 1 mg/kg
AlGhoozi et al.[10]	4-ys	male	37 days later	Skin	Not stated

Jacobi, et al.[11]	3-ys	male	Same time	Skin - abdominal pain	Antibiotics
Li et al.[12]	30-ys	male	Same time	Skin -nephritis	Losartan 25 mg following prednisolone 40 mg for 7 days
Atris et al	14-ys Female	female	eight weeks	Skin - abdominal pain-nephritis	Lisinopril, Steroid and AZA

In comparison to the previous seven cases, the current case age was 14 years, female, who had IgA vasculitis/HSP eight weeks post COVID, which caused skin rash, nephritis, abdominal pain, and arthritis, with a good response to Prednisolone at first then several relapses occurred but complete remission was achieved after AZA was introduced.

European League Against Rheumatism/Paediatric Rheumatology International Trials Organisation/Paediatric Rheumatology European Society (EULAR/PRINTO/PRES) published new classification criteria for childhood vasculitides, including IgA Vasculitis in 2010:

• Purpura or petechiae and One of the following four criteria: ◦ abdominal discomfort ◦ arthritis or arthralgia ◦ kidney association ◦ leucocytoclastic vasculitis with predominant IgA deposits or proliferative glomerulonephritis with predominant IgA deposits (sensitivity 100%; specificity 87%).[13] The current case has developed all these criteria as stated earlier.

IgA vasculitis/HSP is usually a clinical diagnosis, therefore, a skin biopsy is rarely obtained and usually, no laboratory testing is necessary to establish a diagnosis.[14] However, chronic, or recurrent IgA vasculitis/HSP symptoms should always raise concern for alternative causes of cutaneous small vessel vasculitis, such as ANCA-associated vasculitis or systemic lupus erythematosus (SLE).[15,16]

Regarding the several relapses in the current case, various laboratory tests were done to exclude other causes and revealed that ANA, ANCA, and virology tests were all negative. Also, C-RP, Complement C3/C4, Platelets, and INR were within normal levels. In addition, clinicians decided to obtain a skin biopsy which revealed a leukocytoclastic vasculitis involving the skin (palpable purpura).

Earlier studies, performed in 2004 and 2006, including an 8-year follow-up, showed the same results, with no long-term benefit of corticosteroid treatment [17-19]. Renal manifestations, such as hematuria and proteinuria, were not resolved after 28 days of corticosteroid treatment but were reduced compared with patients receiving a placebo. At 6-month follow-up, the study found that 61% of patients had resolved kidney manifestations compared with 34% of placebo patients. This study pointed out that the usefulness was best in people over six years of age presenting with mild kidney manifestations at inclusion and recommends the possible usage of corticosteroids in mild instances to modify the course of kidney involvement.[17] The study also found statistically significant results regarding the treatment of extra-renal symptoms. In addition, less frequently, joint pain and abdominal involvements were stated uncommonly among people taking corticosteroid treatment vs. placebo. Also, there was no difference between the groups regarding skin manifestations.[18,19]

In our case, there were different relapses that occurred while on steroids alone. Hence, AZA was added along with corticosteroids. As revealed in a clinical and histopathologic study by Foster et al, AZA therapy showed a therapeutic effect on IgA nephritis/HSB with a combination of corticosteroids.[20] In steroid-dependent patients, such cases could be managed by tapering steroids within three months and continued AZA as monotherapy for six months without any relapses or with no adverse events reported. This approach is similar to what is being practiced in the management of inflammatory bowel disease.[21,22]

Conclusion

IgA vasculitis/HSP is typically a self-limited disease but in the current case, several relapses have occurred while even on steroid therapy. COVID-19 may have a role or be related to this recurrence status. This, however, will need more research to further investigate this relationship.

IgA vasculitis/HSP is usually a clinical diagnosis, therefore, a skin biopsy is rarely obtained and usually, no laboratory testing is necessary to establish a diagnosis except recurrent cases may need it for elaborate on further differential diagnosis.

This case suggests that SARS-CoV-2 could trigger autoimmune diseases. AZA appeared to be an effective steroid-sparing medication, allowing all steroid-dependent patients to be successfully tapered off steroids.

Ethics statement

Patient consent for publication was obtained.

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