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SMALL VESSEL VASCULITIS IN THE ERA OF COVID-19: CASE SERIES OF 5 PATIENTS FROM INDIA

[1]Dr Agnes Varshini, [2]Dr Vivekanandh [3] Dr Nivin Simon, [4]Dr AJS Pravin

1.,Junior resident,2. Associate Professor,3 Assistant Professor,4.Professor.Dept of Dermatology ,Sree Mookambika Institute of Medical Sciences,Kanyakumari,TamilNadu,India.

Corresponding Author: Dr Vivekanandh* ,Associate Professor , Dept of Dermatology Sree Mookambika Institute of Medical Sciences,Kanyakumari,TamilNadu India. Email id : Dr.vivekanandh@gmail.com Contact No:8778734109

Abstract:

The COVID-19 pandemic has presented a myriad of clinical manifestations, including rare complications such as vasculitis. There is a dearth of any formal study or case series in this subject. Only few reports have shown its association with COVID-19. Here we have reported case series of five patients from India who have developed vasculitis in the context of COVID-19 infection and vaccination. In this case series, all patients had palpable purpura involve primarily the lower legs. Our case series aims to provide a comprehensive overview of the clinical presentations, diagnostic approaches and management strategies employed in a case of COVID-19 induced vasculitis. Awareness of these manifestations facilities early identification and contribute to optimal care of patients as representative data on the same is limited in literature. Further research is essential to elucidate the mechanisms involved in the development of vasculitis in the context of COVID-19 and improve patient outcomes.

Keywords: COVID-19, COVID-19 vaccination, small vessel Vasculitis.

Introduction:

The COVID-19 pandemic has led to millions of cases and deaths worldwide, with vasculitis being a significant concern[1]. Vasculitis, which involves inflammation of blood vessels, can be triggered by infections, autoimmune disorders, drugs and trauma. In COVID-19 patients, specific types of vasculitis have been observed, such as IgA vasculitis (IgAV), leukocytoclastic vasculitis (LCV), and Kawasaki disease-like vasculitis[2]. These types typically affect children but can also affect adults. Treatment mainly involves supportive care, while IgA vasculitis is small-vessel and characterized by palpable purpura, arthritis, and abdominal pain[3]. Leukocytoclastic vasculitis is immune complex-mediated and often affects adults, presenting with skin lesions on the lower extremities and buttocks. Kawasaki disease is medium-vessel and primarily seen in young children. Prompt treatment is crucial to prevent complications[4].

Medications like corticosteroids, immunosuppressive drugs, and immunoglobulin therapy are typically used to treat vasculitis. However, COVID-19-associated vasculitis presents unique challenges in treatment. Furthermore, COVID-19 has been associated with various vascular complications, including cutaneous vasculitis and thromboembolic events. These complications can have a severe impact on patients and are thought to result from immune dysregulation, complement activation, direct endothelial infection, and other mechanisms[5].

ANCA-associated vasculitis is a systemic autoimmune disease characterized by mononuclear cell infiltration and blood vessel destruction, often leading to renal failure. Most common forms of vasculitis reported were Kawasaki disease Vasculitis, IgA vasculitis and Leucocytoclastic Vasculitis with symptoms being predominantly skin limited[6]. COVID-19 has been associated with the

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presentation or exacerbation of autoimmune diseases, including vasculitis. This case series explores the potential link between COVID-19 infection and the development of ANCA-associated vasculitis.

Materials and methods:

Study Design

This study is a retrospective case series involving five patients who developed small vessel vasculitis in the context of COVID-19 infection or vaccination. The cases were collected from the dermatology and internal medicine departments of a tertiary care hospital in India. The study was conducted between January 2021 and December 2022.

Inclusion criteria:

1. Patients who presented with palpable purpura primarily involving the lower legs.
2. Patients who had a history of recent COVID-19 infection or vaccination within the last four weeks.
3. Patients who provided informed consent for participation in the study.

Exclusion criteria included:

1. History of vasculitis unrelated to COVID-19.
2. Known autoimmune disorders not linked to the current presentation.

Data Collection

Data was collected through patient interviews, clinical examinations, laboratory tests, and skin biopsies. Information on demographics, clinical presentations, COVID-19 infection or vaccination history, treatment regimens, and outcomes was systematically recorded.

Clinical Evaluation

A detailed dermatological examination was performed on each patient to document the nature, distribution, and progression of skin lesions. The presence of palpable purpura, petechiae, bullae, necrosis, and ulcers was noted. Systemic involvement was assessed through patient history and relevant clinical examinations.

Laboratory tests included:

Complete blood count (CBC),Erythrocyte sedimentation rate (ESR) C-reactive protein (CRP),Renal function tests,Liver function tests,Antineutrophil cytoplasmic antibodies (ANCA) testing,Serum IgA levels.

Skin Biopsies

Skin biopsies were performed on representative lesions. The specimens were processed and examined histologically to confirm the diagnosis of vasculitis. Features such as neutrophilic infiltration, fibrinoid necrosis, and the presence of immune complexes were evaluated.

Treatment Protocols

Patients received treatments based on the severity of their conditions:Systemic corticosteroids were the primary treatment for reducing inflammation and controlling vasculitic processes,Supportive treatments included analgesics, antihistamines for pruritus, and wound care for skin ulcers.

Follow-Up

Patients were followed up at regular intervals to monitor clinical response to treatment, side effects of medications, and overall progression of the disease. Follow-up durations ranged from two weeks to six months, depending on the patient's recovery and clinical needs.

Ethical Considerations

The study was conducted in accordance with the Declaration of Helsinki. Ethical approval was obtained from the institutional review board of the participating hospital. Written informed consent was obtained from all patients or their legal guardians.

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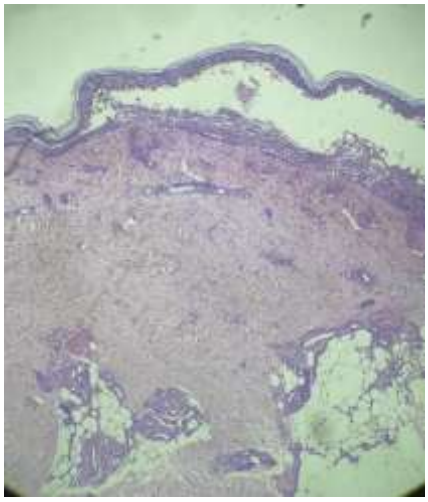
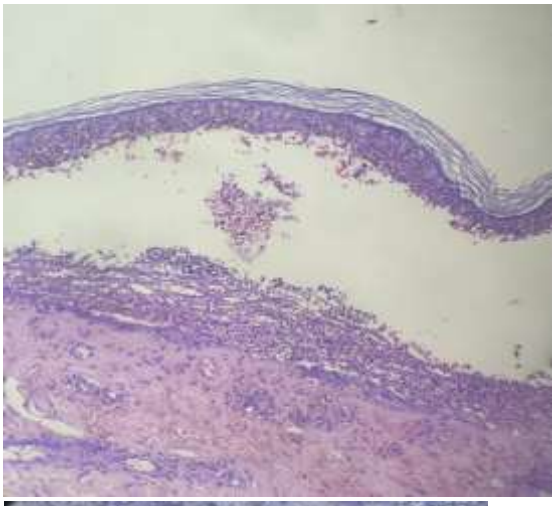
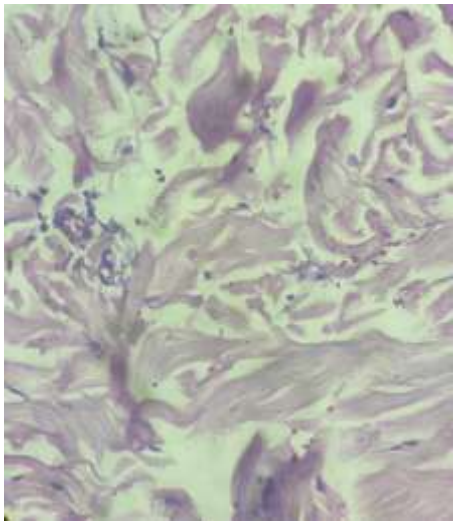
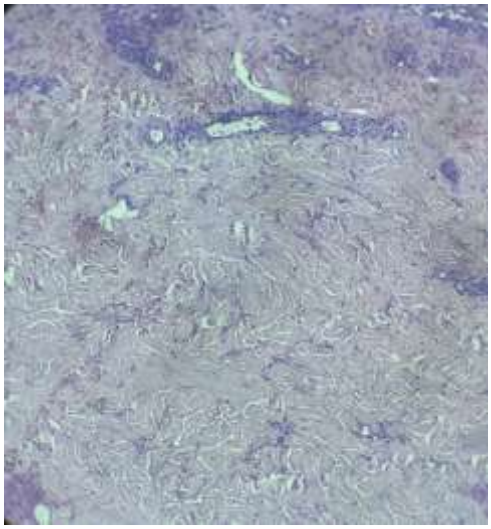
Case history:

Case:1 A 59-year-old male with skin lesions on both lower limbs presented to the dermatology department with respiratory symptoms and a suspected COVID-19 infection. Treatment with hydroxychloroquine and azithromycin led to recovery. Two weeks later, rashes appeared on legs resembling insect bite reactions, progressing through the thighs. Multiple purpuric lesions, flaccid bullae, erosions, necrosis, and small ulcers were present. A skin biopsy revealed mild hyperkeratosis of the epidermis, moderate neutrophilic infiltration, extravasated red blood cells, and lymphocytes around superficial and mid dermal vessels. Cutaneous leukocytoclastic vasculitis was confirmed. The patient was managed with corticosteroids and immunosuppressive agents to control inflammation and vasculitic processes. Regular monitoring of the patient's clinical response and medication side effects was conducted. The patient showed gradual improvement in skin lesions, reduced pain and itching, and edema and associated symptoms subsided with treatment.

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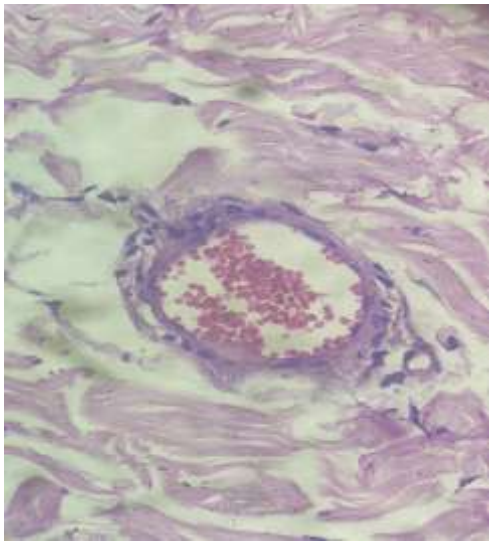

Figure: 1 (a-e)

Case:2

A 33-year-old woman with a 1-week history of skin rashes on both legs was admitted to the emergency department. The rash was petechial, purpuric, and non-pruritic, with no previous history of similar rashes. She had a COVID-19 infection four weeks prior to the rash onset. She was kept in home isolation and treated symptomatically with antipyretics and anti-tussives. Skin examination revealed rashes involving the lower extremities, with multiple scattered non-blanching round palpable petechiae and macular skin rashes. A clinical diagnosis of Leukocytoclastic vasculitis was made, and she was discharged home in satisfactory condition. However, the rashes persisted, and a skin biopsy suggested small vessel neutrophilic vasculitis. The patient was managed with corticosteroids to control inflammation and vasculitic processes, and she showed gradual improvement in skin lesions and reduced petechiae.

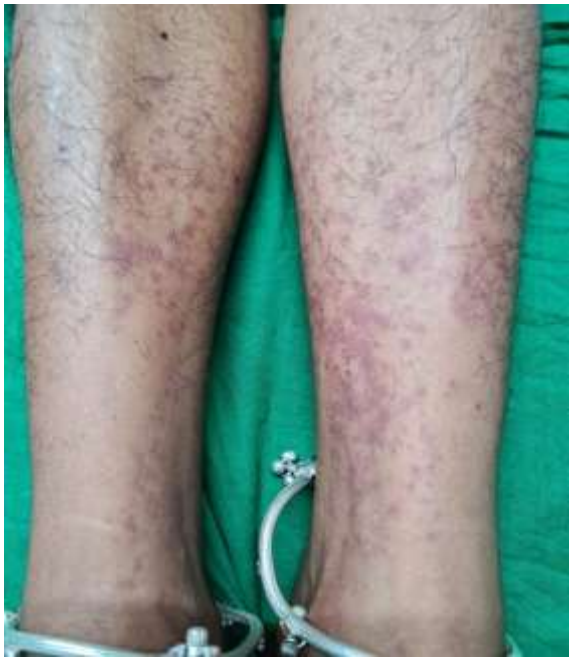

Figure: 2

Case: 3

A 28 year old women presented to the DVL OPD with a 5 day history of rashes over B/L legs, which was gradual in onset initially over the medial malleolus and gradually progressed to involve the entire legs. The rash was discrete non blanchable petechial lesions ranging from 1-4 mm in size. No h/o

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similar lesions in the past. The patient was diagnoses with COVID 19, ten days ago for which she was treated symptomatically with anti pyretic, following which she was tested negative. Following which the petechial lesions developed. It was associated with mild pruritus. No other significant co morbidities in the patient. A clinical diagnosis of Cutaneous small vessel vasculitis was made and was treated with Systemic corticosteroids to control the vascular inflammation. The patient was reviewed after 2 weeks and showed drastic improvement of the lesions.

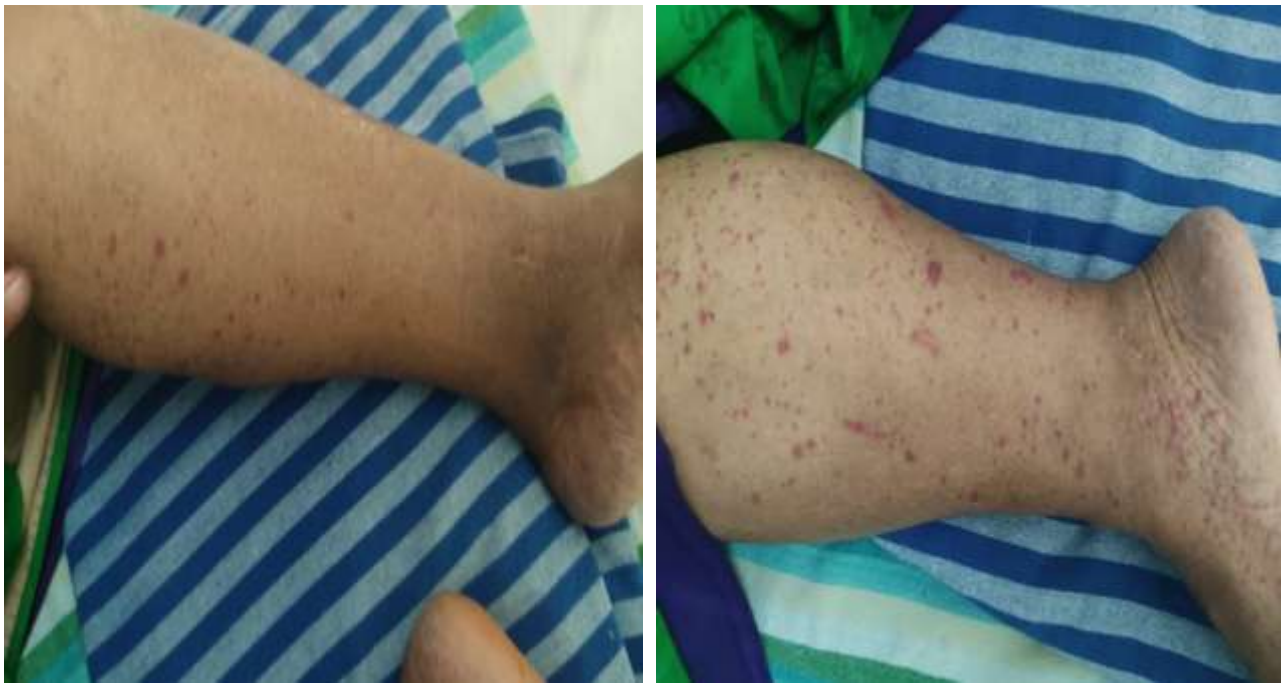

Figure:3 (a-b)

Table:1 Summary of findings of case series

Case	Age	Sex	Onset of skin lesions	h/o COVID infection/vaccination	Pulmonary infection	h/o allergy	Treated with	Prognosis
1	59	M	2-3 days	2 weeks before	No	No	hydroxychloroquine and azithromycin	Good
2	33	F	1 week	4 week before	Yes	No	Corticosteroids	Better
3	28	F	5 days	10 days before	No	No	Corticosteroids	Good
4	42	F	7 days	2 weeks before	Yes	No	Corticosteroids	Good
5	26	M	4 days	1 weel before	Yes	No	Cortiocosteroids	Better

Discussion:

The presented case series highlights several instances of vasculitis occurring in individuals in the context of COVID-19 or COVID-19 vaccination. These cases demonstrate the diverse clinical manifestations of vasculitis and its potential association with viral infections or vaccination. We will discuss each case in detail and provide insights into the implications and potential mechanisms involved.

Cutaneous leukocytoclastic vasculitis (CLV) is a small vessel vasculitis primarily affecting the skin, causing inflammation of blood vessels. Symptoms include palpable purpura, petechiae, and

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ecchymosis, which are non-blanching. CLV can be triggered by infections, medications, autoimmune diseases, and systemic vasculitis. Diagnosis is typically made through clinical evaluation, skin biopsy, and laboratory tests. Treatment depends on the underlying cause, with autoimmune diseases or infections being the primary focus. For idiopathic cases, corticosteroids or immunosuppressive medications may be used to reduce inflammation and control symptoms. Lifestyle changes may be recommended. CLV is typically self-limited, resolving within weeks to months. Recurrent episodes can occur, and treatment can alleviate symptoms and prevent complications. CLV may also be associated with systemic involvement, leading to complications in other organs. Therefore, a thorough evaluation is essential to rule out systemic vasculitis[7,8].

In a case report by Ehsan Rahmanian et al[9], in 2022, a 55-year-old woman with a nine-year history of controlled sarcoidosis developed vasculitis after receiving the Sinopharm COVID-19 vaccine (BBIBP-CorV). The patient was subsequently diagnosed with mononeuritis multiplex based on EMG-NCV findings. Treatment involved methylprednisolone and cyclophosphamide pulse therapy for 5 days, followed by continued prednisolone and a monthly pulse of cyclophosphamide. This case highlights a potential association between COVID-19 vaccination and vasculitis in individuals with underlying medical conditions like sarcoidosis.

In a systematic review conducted by Kalai Wong et al[2]. in 2022, the association between COVID-19 and vasculitis was examined. The study reviewed 8 relevant studies, including 7 case reports and 1 case series, which collectively reported 9 cases of vasculitis secondary to COVID-19. The patients had a mean age of 29.17 years, ranging from 6 months to 83 years, with a male-to-female ratio of 4:5. Common manifestations included maculopapular, violaceous, papular, and erythematous rashes. Treatment approaches for COVID-19-associated vasculitis varied and included heparin (in 2 cases), corticosteroids (specifically methylprednisolone in 6 cases), and intravenous immunoglobulin (in 4 cases). The study noted significant clinical improvement in 8 out of 9 patients, while one patient unfortunately passed away during treatment. This systematic review highlights the recognition of vasculitis as a complication of COVID-19. It discusses the pathophysiology, clinical presentation, and management of COVID-19-associated vasculitis based on the analyzed cases in the literature.

In a study by M. Allez and colleagues[3] in 2020, they reported a case of IgA vasculitis in a 24-year-old man with Crohn's disease who was admitted to the hospital with symptoms including skin rash, severe asymmetric arthralgia, periarticular swelling, and abdominal pain. Notably, this case was associated with COVID-19, confirmed by positive PCR testing for the virus. The patient had elevated levels of serum IgA and was positive for IgA on COVID-19 serologic testing. The patient had been receiving adalimumab for Crohn's disease, and his condition was considered to be in remission. Despite not having respiratory symptoms or fever, the patient tested positive for COVID-19, and his symptoms were consistent with IgA vasculitis. He was treated with low molecular weight heparin and intravenous steroids (methylprednisolone 0.8 mg/kg) and discharged with oral steroids and enoxaparin after seven days. The study suggests a potential association between COVID-19 and the development of IgA vasculitis, particularly with elevated levels of serum IgA and positive IgA serologic testing. It also highlights the complex interactions between COVID-19 and various autoimmune responses, including vasculitis.

In a case report by K. Gulati et al[10]. in 2021, a 61-year-old South Asian woman presented with COVID-19 symptoms in early April 2020 during the first peak of the pandemic. She experienced acute onset dry cough, dyspnea, fever, and myalgia. Initial laboratory tests indicated COVID-19 infection, with elevated markers such as a high neutrophil-to-lymphocyte ratio, increased platelet count, elevated CRP, high D-dimer levels, raised ferritin levels, and elevated troponin levels. The diagnosis was confirmed by SARS-CoV-2 PCR testing. The patient received supportive care for COVID-19 and gradually recovered over the following 14 days. This case is notable because the

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patient had ANCA-associated vasculitis and was receiving immunosuppression, yet she experienced a COVID-19 reinfection during the early phase of the pandemic.

These cases highlight the potential association between COVID-19 infection and the development of ANCA-associated vasculitis. The prompt diagnosis and referral for specialized treatment were crucial in managing the autoimmune disease effectively. It underscores the importance of considering autoimmune diseases in patients with prolonged or worsening symptoms following COVID-19 infection, as timely intervention can prevent disease progression. The mechanisms underlying the development of vasculitis in the context of COVID-19 require further investigation, as SARS-CoV-2 may trigger autoimmunity and autoimmune diseases.

Conclusion:

In summary, these cases contribute to our evolving understanding of the intricate relationship between viral infections, vaccination, and vasculitis. They underscore the importance of vigilance, early intervention, and individualized treatment strategies in managing vasculitis in the context of COVID-19 and related scenarios. Continued research and clinical observations are essential to unravel the complexities of these interactions and improve patient outcomes.

Declaration of patient consent: nil

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Conflicts of interest: nil

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