CASE REPORT

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Urticarial vasculitis associated with post-streptococcal disease in children: a case report

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ABSTRACT

Background: Urticarial vasculitis (UV) is a rare clinicopathologic, especially among children and infants. Most urticarial vasculitis is caused by unknown etiology. Rarely has it been linked to post-streptococcal disease as a non-suppurative complication of a streptococcus infection. Treatment of urticarial vasculitis can be challenging. It is based on the clinical phenotype, systemic symptoms, and/or underlying diseases.

Case Presentation: This study reports a case of a child with an itchy but more painful and burning sensations urticarial lesion which persisted for more than 24 hours, left a residual ecchymotic hyperpigmentation lesion when resolved, and was accompanied by systemic symptoms such as joint pain, fatigue, and gastrointestinal symptoms. The symptoms were preceded by signs of pharyngitis one week before the symptoms and supported by an increase in ASO titer that raised the suspicion of a previous recent streptococcal infection. Skin biopsy revealed a leukocytoclastic vasculitis, a specific finding supporting the diagnosis of urticarial vasculitis. The combination of antibiotics, antihistamines, and corticosteroids gave our case a good clinical response and outcome.

Conclusion: A high awareness of urticarial vasculitis linked to post-streptococcal diseases is needed to establish prompt treatment and prevent further complications.

Keywords: children, post-streptococcal, urticarial vasculitis.
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INTRODUCTION

Urticarial vasculitis (UV) is characterized by long-lasting urticarial lesions that persist for more than 24 hours, which can leave dusky hyperpigmentation lesions later.[1–3] Although manifest with wheals and/or angioedema, due to their distinctly different pathophysiologic mechanisms, urticarial vasculitis is not considered a subtype of common urticaria, a mast cell-driven disease without damage of vascular.[4,5] Urticarial vasculitis is a rare clinicopathologic existence caused by inflammatory injury to the small vessels of the skin. The histopathologic examination will show leukocytoclastic vasculitis.[1–3] Urticarial vasculitis manifests as skin lesions and can extend systemically, affecting the musculoskeletal, renal, pulmonary, gastrointestinal, and ocular systems.[3] The prevalence of urticarial vasculitis is not well described due to its rarity.[3,6] In patients with chronic urticarial lesions, the prevalence is approximated from 3% to 20%, with a reasonable estimate of the prevalence around 5%.[7] Urticarial vasculitis is mentioned to be rare in children and infants; only a few pediatric cases have been reported.[7–9] Most urticarial vasculitis is caused by unknown etiology. However, it has been linked to certain drugs, infections, autoimmune connective disease, myelodysplastic disorders, and malignancies.[3,9]

Streptococcus infection has been reported to be associated with urticarial vasculitis and another infection cause.[3] Group A streptococci (GAS) are gram-positive, particularly Streptococcus pyogenes, and often colonize the pharynx and skin. GAS is reported responsible and/or related to several diseases after the infection, called post-streptococcal diseases.[10] Post-streptococcal diseases can be suppurative or non-suppurative and often occur 1 to 3 weeks after a pharyngitis or skin infection.[10–12] Several immune mechanisms have been proposed in non-suppurative post-streptococcal diseases, such as antibody-directed molecular mimicry, possible super antigen stimulation of T cells, and immune complex deposits.[10,11] Post-streptococcal vasculitis is a non-suppurative complication of GAS infections. One of the manifestations of this condition is urticarial vasculitis which is rare and not a well-recognized condition. Urticarial vasculitis is immune-complex mediated and, as such, is classified as a type III hypersensitivity reaction.[13] Complement activation system due to antibody-antigen complex leads to the cutaneous neutrophil influx, increase in vascular permeability, and mast cell degranulation followed by the release of chemokines and cytokines. Furthermore, proteolytic enzymes are released from neutrophils, leading to tissue damage and edema. The sum of these processes caused the clinical manifestation of urticarial vasculitis.[3,7,13]

The current approaches to diagnostic workup and treatment for UV in children may differ globally due to the lack of large randomized or controlled trials.[1,3] The UV approaches in children focus on determining the possible cause, underlying systemic disease, and treatment selection. Since urticarial vasculitis is rare in children and post-streptococcal urticarial vasculitis is not a well-recognized condition, a high awareness of this post-streptococcal disease is needed to establish prompt treatment and prevent further complications. The purpose of this case study is to present one case of urticarial vasculitis in children suspected to be induced by a prior recent streptococcal infection that was previously rarely reported.

CASE REPORT

A 13-year-old boy came with chief complaints of itchy dark pink wheels all over the body in the last 4 days before admission, accompanied by edema on the eyelids and lips. The parents gave him an antihistamine, then the itching was reduced, but the wheels and edema were not. He also complained of joint pain in both knees, ankle, and elbow with edema in both ankles. The symptoms followed by fever, pain, fatigue, burning sensation, and itch all over the body, which were severe at night before dawn. Day by day, the itchiness was getting worse, and the wheals were widened, darker, and more painful. When the wheals become resolved, they turn into dark plaques and leave a dusky hyperpigmentation lesion. Joint pain and edema, especially on the ankles, were also getting worse, thus making him difficult to walk. On the fourth day, he had gastrointestinal symptoms such as colicky abdominal pain, nausea and sometimes vomiting. He had a history of sore throat, cough, and fever one week before his cutaneous symptoms. He had no dyspnea and no complaints about his defecation or urination. He never had the same symptoms before, has any family history with the same symptoms, has no history of consuming medication regularly, and has no history of chronic infection, allergic diseases, malignancy, or autoimmune diseases.

The patient's physical examination showed widespread urticarial lesions that occurred more than 24 hours which were a pruritic but more painful and burning sensation. On his arms, chest, and back there were multiple urticaria lesions with classical indurated wheals, resolved with purpura or hyperpigmentation, as seen in Figure 1. There were multiple urticaria lesions on his legs and feet, with classical wheals and reddish-blue to purple, net-like cyanotic pattern resembling livedo reticularis lesions. These lesions were also resolved with purpura or hyperpigmentation, as seen in Figure 2. His vital sign was within normal limit, with no sign of anemia, no icteric, no cyanosis, or dyspnea. Breath, heart, and gut sounds were normal, with no sign of lymphadenopathy, ascites, hepatomegaly, or splenomegaly.

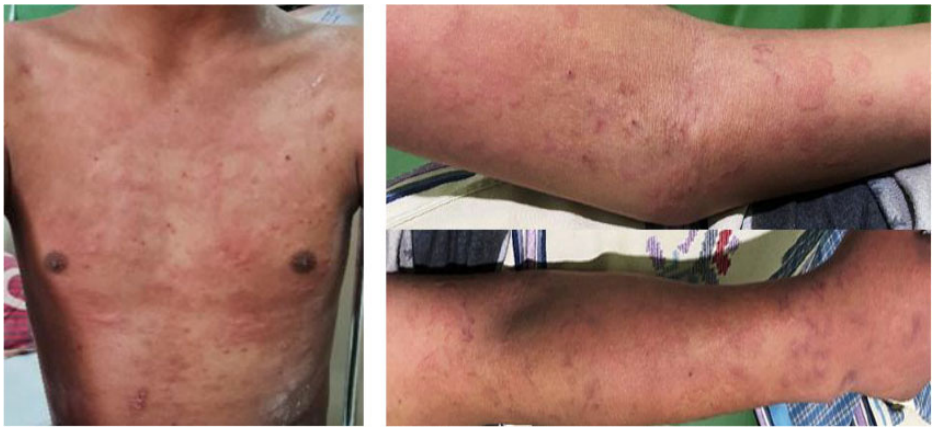

Figure 1. Multiple urticaria lesions on arms, chest, and back with classical indurated wheals were resolved with purpura or hyperpigmentation.

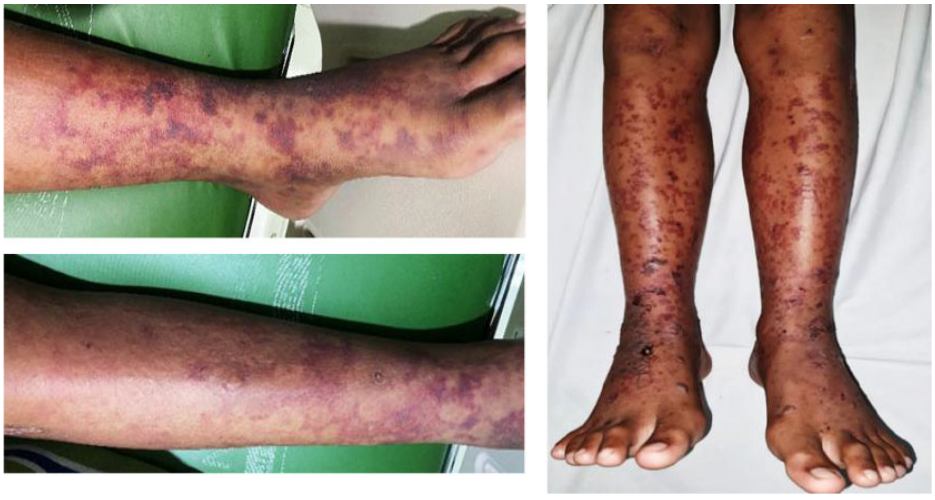

Figure 2. Multiple urticaria lesions on his legs and feet, with classical wheals and reddish-blue to purple, net-like cyanotic pattern resembling livedo reticularis lesions. These lesions were also resolved with purpura or hyperpigmentation.

Laboratory findings showed hemoglobin was 17.7 g/dL, leucocytes 5920/μL with 76% neutrophilia, thrombocytosis of 632000 platelets/μL, and erythrocyte sedimentation rate was 15 mm/hour. The CRP was increased to 6.7 mg/dL, and procalcitonin increased to 1.507 ng/mL. ANA test showed a normal limit at 14.2 AU/mL (Ref. < 40), C3 was normal at 105 mg/dL (Ref. 90-207), and C4 was also normal at 19.1 mg/dL (Ref. 17.4-52.2). Antistreptolysin O (ASO) increased at 440 IU/mL, raising the suspicion of a previous recent streptococcal infection. Covid-19 rapid antigen test showed a negative result. A urine examination revealed no proteinuria or haematuria. The renal function test, liver function test and electrolytes were within normal limits. Blood and urine cultures were sterile.

Chest X-ray and ankles X-ray showed the normal result. Echocardiography revealed mild mitral regurgitation,

mild tricuspid regurgitation, and mild pulmonary regurgitation with an ejection fraction of 68.49%, which did not meet the criteria for rheumatic valvulitis. Skin lesions punch biopsy revealed: the epidermis were spongiosis, pityriasiform vesicle foci containing neutrophils; dermal papillae were edematous with neutrophil and lymphocytic infiltration; the dermis showed neutrophilic vasculitis with extensive infiltrates of neutrophil cells of capillary vessel walls, superficial dermis to epidermis and leukocytoclastic vasculitis (LCV) was seen. These findings were consistent with urticarial vasculitis.

As initial treatment, the patient was treated with an antihistamine (cetirizine), ibuprofen, and antibiotic ampicillin injection, which was given initially and later replaced by oral erythromycin. On the 3rd day of admission, corticosteroid (prednisone 1 mg/kg/day) was started due to reappearing of an urticarial lesion on the face and chest. The next day, urticaria on his legs and feet started to fade in some areas and resolved with purpura and hyperpigmentation lesions. The joint pain, especially on the ankles, was reduced as well as pruritic and burning or painful sensations on the skin lesions. On the 8th day of admission, there were no new urticaria lesions. Joint pain became much better, the skin lesions showed improvement with no pruritic nor burning/painful sensation, along with the improvement of gastrointestinal symptoms, then the patient was discharged. Erythromycin was continued for 10 days after discharge to ensure the eradication of infection and prevent further streptococcal infection complications. One month later, the wheals, rash, and purpura disappeared, but it still left hyperpigmentation lesions. After 6 months of follow-up, there were no recurrent cutaneous symptoms of UV or other systemic symptoms. The hyperpigmentation lesions completely disappeared, and the patient was well and had no complaints.

DISCUSSION

Urticarial vasculitis is a distinct clinical entity and is different from urticaria due to its different characteristics and pathophysiologic mechanisms, even though they are both marked by the presence of hives with/without angioedema.[4] Urticaria is a mast cell-driven disease characterized by the rapid appearance of wheals and/or angioedema which are more associated with itching sensation, and returning to their normal appearance usually within 1–24 hours.[4,5,14] Meanwhile, urticarial vasculitis is considered to be a complex immune disease. The pathogenesis of UV is believed to be related to type III hypersensitivity reaction. UV is characterized by wheals that persist longer than 24 hours, leave residual hyperpigmentation, and are more associated with burning/painful sensations and constitutional symptoms.[3,8,15] As in our case, the patient complained of widespread wheals with itchy, painful, and burning sensations all over the body for the last 4 days. His wheals persisted for more than 24 hours, not responding well to antihistamines and left a residual hyperpigmentation lesion when resolved. These findings were consistent with the clinical presentation of urticarial vasculitis. Urticarial vasculitis usually presents with classical wheals, but rarely livedo reticularis, an erythema multiforme-like eruption, Raynaud's phenomenon, or even bullae may develop.[8,15] As in our case, there was urticaria with livedo reticularis lesions in his leg. Our case also presented with angioedema on the lips and eyelids and urticarial lesions. Angioedema has been reported in 42%-50% of patients with urticarial vasculitis.[3,16] Angioedema, in UV, occurs when the vasculitis affects the capillaries and postcapillary venules of deeper layers of the dermis and submucosal tissue.[15,17]

Diagnosis of urticarial vasculitis is challenging due to the various clinical presentations. Thus a lesional biopsy is considered the gold standard for diagnosis among clinicians.[1,3] Histopathological evidence of leukocytoclastic vasculitis on biopsy is crucial in establishing a definite diagnosis of UV.[1,3,8] In our case, we did the punch biopsy from the newly appeared lesion (less than 48 hours lesion), and it showed leukocytoclastic vasculitis. A definite diagnosis of urticarial vasculitis can be made. Upon confirmation of diagnosis, the patient with UV is divided based on serum complement levels and systemic manifestations. Normocomplementemic urticarial vasculitis (NUV) are patients with UV with normal complement levels; NUV generally self-limited, idiopathic, benign, and has a better prognosis with few systemic complications. Urticarial vasculitis with low levels of complement is either classified as hypocomplementemia urticarial vasculitis (HUV) when systemic involvement is only one to none or hypocomplementemic urticarial vasculitis syndrome (HUVS) when systemic involvement is significant and involves more than one organ system.[1–3,8,18] Systemic feature of UV can be varied and usually seen in hypocomplementemic patients; the common systemic feature is musculoskeletal symptoms such arthralgia and arthritis. Less common systemic features are respiratory, renal, and gastrointestinal involvement. Rare dan very rare features are cardiac, ophthalmologic, and CNS involvement, along with miscellaneous manifestations.[8] Our case was classified as Normocomplementemic urticarial vasculitis (NUV) since C3 and C4 were within normal limits but showed arthralgia, arthritis, and gastrointestinal symptoms (abdominal pain, nausea, and vomiting) as a systemic feature of UV. Since several systemic symptoms occurred, comprehensive management and closed monitoring were done for our case to prevent further complications.

In our case, there was a high possibility of association of urticarial vasculitis with the post-streptococcal disease. The patient had a sign of pharyngitis one week before the cutaneous symptoms, supported by an increase of ASO titer that rising the suspicion of a previous recent streptococcal infection. The patient had no sign of other infection, no history of other diseases nor medications as a trigger or cause of his symptoms, then only a recent streptococcal infection that related to his urticarial vasculitis symptoms condition is considered as a post-streptococcal disease. The post-streptococcal disease is described as a disease or complication related to a recent streptococcal infection.[10,11] Post-streptococcal disease usually occurs 1 to 3 weeks after a pharyngitis or skin infection,[12] as in our case, the symptoms of urticarial vasculitis started to develop in one week after suspicious streptococcal infection. The post-streptococcal disease may

manifest in several organs, such as urinary or renal, cardiovascular, musculoskeletal, central nervous, integumentary, and circulatory systems. The commonly described post-streptococcal diseases include post-streptococcal glomerulonephritis, post-streptococcal arthritis, pediatric autoimmune neuropsychiatric disorders, and acute rheumatic fever.[10,11] Post-streptococcal vasculitis, especially urticarial vasculitis, is not a well-recognized condition. It's a rare complication of post-streptococcal infection.[12] Based on our best knowledge, the prevalence/incidence of this condition was unknown due to its rarity, especially in children.

Treatment of urticarial vasculitis can be challenging due to the lack of large randomized or controlled trials evaluating the efficacy of existing therapies.[3] Moreover, no diagnostic criteria, clinical guidelines, or treatment algorithms exist. The diagnostic workup and treatment approaches of urticarial vasculitis may differ globally.[1,2] Currently used medications for treating urticarial vasculitis include antihistamines, NSAIDs, dapsone, colchicine, hydroxychloroquine, immunosuppressives agent, corticosteroids, and select biologics.[3,19] The selection and duration of therapy for UV are based on the clinical phenotype, the presence of systemic symptoms and/or underlying diseases, the clinical response of treatment, and the likelihood of relapse.[1] UV can be caused by infections, malignancy, or drugs and can resolve with withdrawal of the culprit drug or cure/ control of infection/malignancy.[2] Corticosteroids are the most commonly used drugs in UV and are effective for treating skin symptoms in more than 80% of patients.[1,2] Antihistamine is also commonly used in UV. Still, it was not effective in most patients with UV,[2] however, it can be given to help treat the angioedema and true urticaria lesions that occur in around half of the patients, and antihistamines are safe. They can be considered to treat itchy in urticarial vasculitis patients.[9] Addition of immunosuppressive or immunomodulatory agents allows corticosteroid tapering. It improves the efficacy of therapy, especially in severe cases of UV.[2] In our case, since infection is suspected as the underlying disease, we started therapy with a broad-spectrum antibiotic along with an antihistamine. This initial therapy did not respond well on the third day of therapy. The cutaneous lesions started to reappear, then a corticosteroid was added. The combination of these drugs gave a good clinical response in our case. In several commonly post-streptococcal diseases, American Heart Association (AHA) recommends continuous antimicrobial prophylaxis, such as rheumatic fever/rheumatic heart disease and post-streptococcal reactive arthritis.[20,21] In our case, the patient did not receive secondary prophylaxis since no recommendations and no carefully designed or well-controlled studies have been established for UV related to post-streptococcal disease.

Monitoring of response to treatment in UV is important; when the primary lesions, cutaneous symptoms, disappear completely during 3 months or less after the initiation of treatment, it is called complete cutaneous remission of UV. When cutaneous lesions do not resolve completely with initial therapy and additional treatment is required to control the disease, it is called partial cutaneous improvement. It is called non-responders UV if there is no improvement in skin symptoms of UV seen during or after the treatment.[2,22] In our case, although the initial presentation of UV showed several systemic manifestations, the patients showed a good response. Complete cutaneous remission was shown since all symptoms disappeared within 1 month of therapy, although it left hyperpigmentation lesions. After 6 months of follow-up, there were no recurrent cutaneous symptoms of UV or other systemic symptoms. This showed a good prognosis in our case.

The limitation of this case study is the causal relationship between streptococcal infection and urticarial vasculitis cannot be proven precisely. However, this report highlights the importance of high awareness of prior streptococcus infection in the diagnostic approach of urticarial vasculitis in children, especially when there are suspicious symptoms of this infection. Further carefully designed and well-controlled studies are needed to establish the causal relationship between UV and streptococcus infections.

CONCLUSION

We can conclude that the treatment of urticarial vasculitis can be challenging. It is based on the clinical phenotype, systemic symptoms, and/or underlying diseases. Thus, high awareness of urticarial vasculitis linked to post-streptococcal diseases is needed to establish prompt treatment and prevent further complications.

CONFLICT OF INTEREST

The authors have no conflict of interest to disclose.

ETHICAL CONSIDERATION

Informed consent was obtained from the patient based on the COPE and ICMJE protocols regarding the publication ethics before the study was conducted. Written informed consent was obtained from the parents.

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AUTHOR CONTRIBUTIONS

IBRS involved in concepting, designing, and supervising the manuscript. AMP, ZH, and AE conducted the study and analyzed the data. All authors prepare the manuscript and agree for the final version of the manuscript to be submitted to this journal.

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