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Colloidal Silver Ingestion Associated with Leukocytoclastic Vasculitis in an Adolescent Female

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Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
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Patient: Female, 19
Final Diagnosis: Leukocytoclastic vasculitis
Symptoms: Fatigue • joint • pain • muscle • pain • pruritis • rash
Medication: —
Clinical Procedure: —
Specialty: Dermatology

Objective: Unexpected drug reaction

Background: Leukocytoclastic vasculitis is a disease of the small vessels and is uncommon in children. In this case report, we present an adolescent case of leukocytoclastic vasculitis associated with the ingestion of colloidal silver, a naturopathic drug. This report highlights the rarity of the patient's presentation and inducing agent.

Case report: A 19-year-old female presented in the Emergency Department with severe rash on the face, and neck, and then continued to spread in a craniocaudal fashion during the day of presentation to involve trunk, back, upper and lower extremities. There was no recent travel, no pets and a negative family history for rheumatologic or autoimmune diseases. Her home medications included colloidal silver for "internal cleansing" for 4 weeks prior to Emergency Department presentation. Once the clinicians were aware of the continued ingestion of colloidal silver, the patient was advised to discontinue the drug. The patient was started on methylprednisolone with preliminary diagnosis of vasculitis, as well as concurrent therapy with colchicine. The rash was noted to be receding from the face within 24 hours. Over a hospital course of 5 days, the patient's rash and pruritus continued to slowly improve.

Conclusions: The ingestion of a naturopathic drug, colloidal silver, caused vast leukocytoclastic vasculitis in our patient warranting hospitalization due to the extent of the disease. The symptoms resolved after discontinuation of colloidal silver ingestion. Due to unknown safe ingestion concentrations and potential side effects, use of colloidal silver should be discouraged.

MeSH Keywords: Adolescent • Homeopathy • Vasculitis, Leukocytoclastic, Cutaneous

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Background

Leukocytoclastic vasculitis is a disease of the small vessels, specifically post-capillary venules involving the superficial dermis and less commonly involving the visceral organs including the renal and gastrointestinal systems (<10%) [1,2]. The histological diagnosis of this disease is described as small vessel damage from nuclear debris due to infiltrating neutrophils and neutrophil fragmentation (leukocytoclasia/nuclear dust), with fibrinoid deposition in the vessel wall, endothelial swelling, and subsequent red blood cell extravasation [1].

In general, leukocytoclastic vasculitis is an uncommon disease in the pediatric population. A retrospective population-based study in Minnesota, USA found that leukocytoclastic vasculitis had an incidence rate of 4.5 per 100 000 person-years, adjusted for sex and age; the study also found the diagnosis of leukocytoclastic vasculitis increased significantly with age [2]. However, of the 84 patients diagnosed histologically, only 6 patients were younger than 20 years of age [2]. The incidence rate between males and females was similarly reported, with some studies identifying a slight female predominance [2,3]. Systemic manifestations, malignancies, and connective tissue diseases are much more common in adults than in adolescents and children [2].

The classic presentation of leukocytoclastic vasculitis is predominantly palpable purpura distributed most commonly over the lower extremities. Patients usually present with symptoms of itching, burning, and pain in their lower limbs, with up to one-third of patients having upper extremity and/or trunk involvement [3]. Organ involvement, while rare, may also occur and can involve the kidneys, lungs, liver, heart, and brain [1,2].

The most common cause of leukocytoclastic vasculitis remains idiopathic. Well-documented diseases that are associated with leukocytoclastic vasculitis include autoimmune conditions, connective tissue disease, neoplasia, and a wide array of infections including, hepatitis C, beta-hemolytic streptococcus A, mycobacterium, chlamydia, Neisseria infection, tuberculosis, and HIV/AIDS [2,4]. Certain drug ingestions have been associated with the development of leukocytoclastic vasculitis including warfarin, naproxen, and trimethoprim–sulfamethoxazole [5–7].

In this case report, we present an adolescent case of leukocytoclastic vasculitis associated with the ingestion of colloidal silver, a naturopathic drug. This report highlights the rarity of the patient's presentation and inducing agent. The patient's condition was successfully treated with the discontinuation of colloidal silver as well as initiation of steroids and colchicine throughout a 5-day hospital course.

Case Report

The patient was a 19-year-old female with significant past medical history of abdominal migraines and psoriasis who presented to the Emergency Department (ED) with a complaint of a rash for 2 days prior to presentation. The rash was first noticed on her face and neck then continued to spread craniocaudally during the day of presentation to involve her trunk, back, and upper and lower extremities. The rash spared the palms, soles, and mucous membranes. Initially, the patient sought care from a dermatologist 1 day prior to her presentation to the ED, when the rash had spread diffusely, and she developed pruritus. The patient was prescribed triamcinolone topically. She used the topical steroid for 1 day with limited relief and no improvement in the appearance of the rash.

The rash was described as mildly irritating and pruritic. The patient also endorsed some fatigue, and mild muscle and joint pain, along with subjective fever. She had had no recent travel, no pets, and family history was negative for any rheumatologic or autoimmune diseases. Her home medications included colloidal silver for 4 weeks prior to her ED presentation, in addition to the recently prescribed topical triamcinolone.

On arrival to the ED, the patient was found to be febrile to 39.3°C, with all other vitals stable. The physical examination was significant for a raised and diffuse maculopapular rash with discrete and coalescing areas (Figure 1). The remainder of physical examination was within normal limits.

Based on her lack of symptoms of an obvious etiology, an initial, broad workup was conducted, including white blood cell (WBC) 4.3 k/uL (normal range; 4.5–11 k/uL), manual differential significant for neutrophilia of 81.8% (normal range; 45–70%), C-reactive protein (CRP) of 22 mg/dL (normal range; <2.5 mg/dL), erythrocyte sedimentation rate (ESR) of 7 mm/hour (normal range; 0–29 mm/hour for females), protein: creatinine ratio 0.23 (<0.15), basic metabolic panel (BMP) was within normal limits, rheumatoid factor was within normal limits (<10.0 IU/mL), and negative HIV-1/HIV-1 antibody screen, negative antinuclear antibody (ANA), negative anti-dsDNA, negative treponemal antibody, and negative Lyme disease antibody. A urine analysis was conducted, which was within normal limits.

The patient was then admitted to the general pediatric floor for general management and further workup. Benadryl, hydroxyzine, intravenous fluids, and antipyretics were used for the management of symptoms. A wide range of differential diagnoses were initially considered for the rash including those of infectious and rheumatic/autoimmune etiology.

Consults were obtained from the pediatric infectious disease specialist, and from the rheumatologist. The clinical decision

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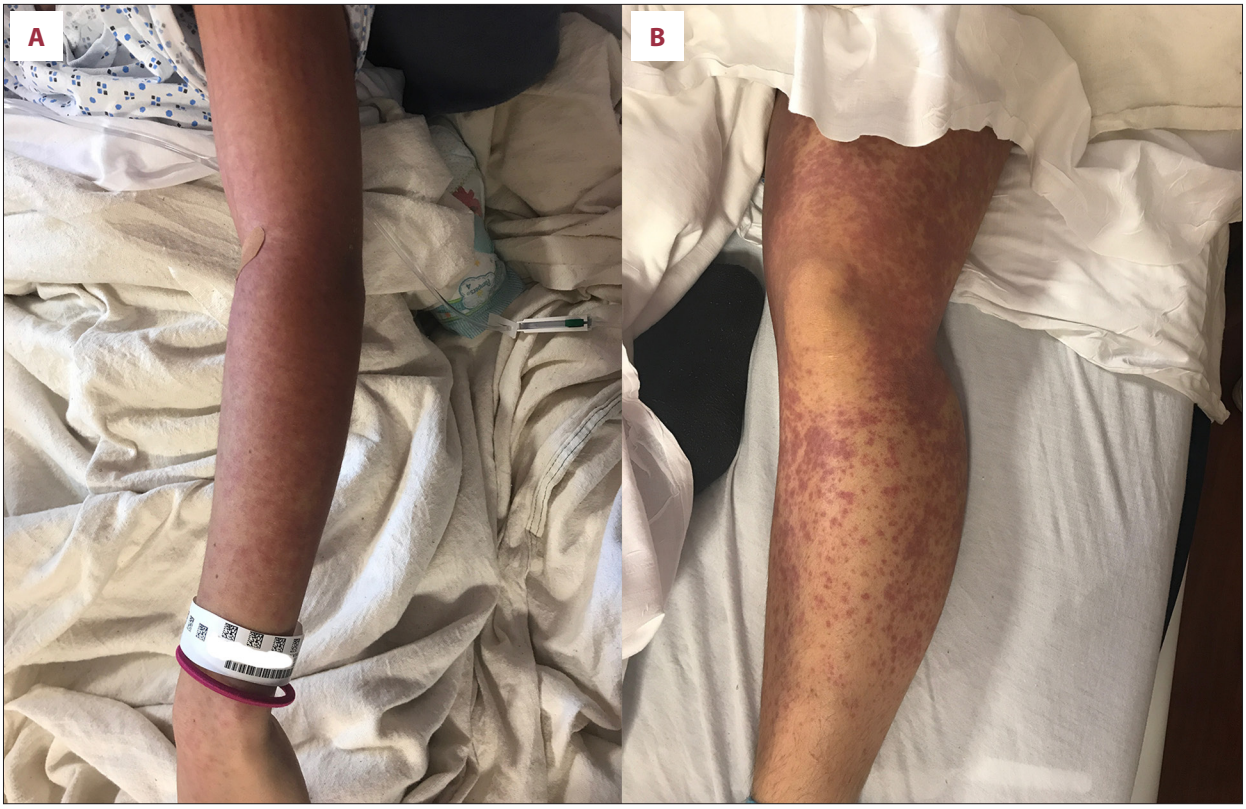

Figure 1. (**A, B**) Pruritic palpable diffuse purpura on the arm and leg.

was made to continue investigating the cause of the rash. Additional laboratory tests were in the normal range, including urine protein/creatinine ratio of 0.23 (<0.15), complement C3 was 124.0 mg/dL (normal range; 90.0–180.0 mg/dL), C4 was 24.0 mg/dL (normal range; 10.0–40.0 mg/dL), hepatitis B surface antigen was negative, hepatitis B surface antibody was positive, hepatitis C antibody was negative, total protein was 6.7 g/dL (normal range; 6.4–8.2 g/dL), cryoglobulin was negative, protein electrophoresis was normal, proteinase antibody was <1.0, myeloperoxidase antibody was <1.0, and IgA was 237.0 mg/dL (normal range; 70.0–400.0 mg/dL). Other causes of vasculitis were ruled out with normal serum quantitative immunoglobulins and negative ANA.

During the first evening of hospitalization, the patient continued to take the naturopathic supplement of colloidal silver. Once the clinicians were aware of the continued ingestion of silver colloidal, the patient was advised to discontinue the drug. The patient was then started on methylprednisolone 40 mg every 8 hours with preliminary diagnosis of vasculitis, as well as concurrent therapy with colchicine 0.6 mg daily. The rash was noted to be receding from the face within 24 hours. Over the hospital course of 5 days, the patient's rash and pruritus continued to slowly improve. The patient had no end organ dysfunction and her laboratory tests were not indicative of any autoimmune or infectious disease.

The patient was discharged on colchicine, which was discontinued once the rash completely resolved. She was also prescribed prednisone, to complete a taper schedule of 20 mg for 3 days, 15 mg for 3 days, 10 mg for 3 days, 5 mg for 3 days, then to be discontinued. The patient was followed up in the rheumatology clinic 3 weeks later, and the repeat laboratory tests conducted included ESR, CRP, and BMP, which were normal. The rash continued to diminish after discharge.

Discussion

We present a unique case of a naturopathic drug induced leukocytoclastic vasculitis in an adolescent female. Studies have shown that drug induced acute onset leukocytoclastic vasculitis cases respond to the removal of the inciting agent [8–10]. Upon discontinuing colloidal ingestion, our patient had marked improvement in pruritus and irritation over areas of her rash, as well as receding areas of skin involvement. Initiation of steroid and colchicine treatment further amplified her recovery. No indication for skin biopsy or histopathologic confirmation of disease was evident for our patient case. Clinical diagnosis of leukocytoclastic vasculitis was made based on presentation and response to interventions [3].

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Literature highlights drugs that induce leukocytoclastic vasculitis include antibiotics, especially beta-lactams, tumor necrosis factor (TNF) inhibitors, propylthiouracil, levamisole-adulterated cocaine, warfarin, hydralazine, minocycline, indomethacin, and most recently trimethoprim- sulfamethoxazole [5,7,8]. Some rare cases of leukocytoclastic vasculitis induced by anti-tuberculoid therapy have been reported in the pediatric population with ethambutol and rifampicin therapy in Japan [11], and with rifampicin and pyrazinamide therapy in India [12]. Reported cases of leukocytoclastic vasculitis induced by anti-coagulants dabigatran and rivaroxaban have also been reported [13,14]. Naproxen has also been linked to the development of leukocytoclastic vasculitis, with a severe case requiring amputation described in the Journal of Medical Case Reports [6]. The link between naturopathic drugs and supplements with leukocytoclastic vasculitis is not well studied or reported.

Our patient was ingesting a colloidal silver supplement in liquid (warm tea) form multiple times a day with the goal of "internal cleansing" as described by the product distributor website. Although not well studied, the frequency of silver colloidal use is rampant amongst naturopathic and alternative medicinal treatments. Silver colloidal is a suspension of submicroscopic silver particles in colloid base. The drug is not approved by the Food and Drug Administration for the use or treatment of any condition; however, it is used as homeopathic therapy for conditions including cancers, diabetes, and arthritis, among many more. Silver colloidal use has neither been proved to be safe, nor effective for these conditions. Upon review of the product distributor website, we found no mention of side effects with taking this drug. It has been reported that prolonged use, and in toxic amounts, silver colloidal can cause argyria (skin deposition of silver producing a blue-gray discoloration of the skin, especially in skin areas exposed to the sun) and argyrosis (deposits in the eye) which are irreversible side effects [15]. However, our literature search did not show any association between silver colloidal and leukocytoclastic vasculitis.

A case report by Rezyk et al. published in BMC Nephrology in 2016 presented a patient with T cell lymphoma, who used silver colloidal as an alternative therapy for her condition, and subsequently developed pauci-immune crescentic glomerulonephritis [16]. The authors suggested that the silver deposition triggered a cellular immune-mediated process, potentially mediated by lymphomatous T cells directed at the glomerular basement membrane. Similar to our patient, the serological tests, including ANA, anti-dsDNA, and anti-neutrophilic cytoplasmic antibody (ANCA), were all negative, and complement levels C3 and C4 were normal.

The prognosis of cutaneous leukocytoclastic vasculitis is favorable, especially in the absence of systemic disease, as seen in our patient. Drug induced leukocytoclastic vasculitis is usually noted to be confined as a localized disease manifested only by cutaneous symptoms, and resolving upon withdrawal of the inducing drug. The International Journal of Clinical Rheumatology states that the chronicity of leukocytoclastic vasculitis is predicted by the presence of arthralgias and cryoglobulins, and the absence of fever [17].

Treatment guidelines as published in the International Journal of Clinical Rheumatology in 2013 indicate that treatment depends on 2 main factors: the etiology and the extent of the disease. Should there be systemic involvement, then treatment should be determined by the most severe organ involved, with therapy including a steroid and an immunosuppressive drug used in tandem [17].

Symptomatic treatment is always recommended in cutaneous leukocytoclastic vasculitis, including analgesics, antihistamines, nonsteroidal anti-inflammatory drugs, compression stockings, and elevation of legs. Dapsone and colchicine are 2 drugs used for dermatoses, specifically those that are chronic or relapsing, and are sometimes found to be effective in treating leukocytoclastic vasculitis. Corticosteroids potentially reduce the incidence of severe renal insufficiency in children, as confirmed in several studies [18]. More research is needed on how to properly treat and manage the condition of leukocytoclastic vasculitis. There are currently no large, randomized prospective trials on the effective therapy and management of this disease from any etiology, and no studies guiding treatment of patients with unknown etiology, and with chronic, recurrent symptoms.

Many patients with leukocytoclastic vasculitis present with no history of medication intake, however, due to many over-the-counter supplements being marketed as "safe" and with "no side effects", the likelihood of patients disclosing this information during a medical history taking is low. Safety profiles, including potential side effects of over-the-counter supplements, should be discussed with patients during routine evaluation.

Conclusions

In our case, the ingestion of a naturopathic drug, colloidal silver, with the intention of "internal cleansing" caused vast leukocytoclastic vasculitis warranting hospitalization due to the extent of disease and required further clinical and medical history investigation. Symptoms resolved upon discontinuation of the ingestion of colloidal silver. Due to unknown safe ingestion concentrations and potential side effects, use of colloidal silver should be discouraged.

Conflict of interest

None.

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