IgA negative immunofluorescence in diagnoses of adult-onset Henoch-Schönlein purpura

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ABSTRACT

We describe two cases of young adult men presenting with diffuse petechial rash and gastrointestinal disturbances. They were found to have leukocytoclastic vasculitis without immunoglobulin A findings under direct immunofluorescence on skin biopsy histopathology performed over a week after the appearance of lesions. Henoch Schönlein purpura (HSP) was diagnosed based upon the clinical presentation as well as the leukocytoclastic vasculitis biopsy findings.

KEYWORDS Direct immunofluorescence; Henoch Schönlein purpura; immunoglobulin A; leukocytoclastic vasculitis

Henoch Schönlein purpura (HSP) is a systemic disease in which antigen-antibody complexes activate the complement system, causing inflammation and small-vessel vasculitis. Although HSP, also called immunoglobulin (Ig) A vasculitis, is classically associated with IgA deposition on direct immunofluorescence, this finding is unnecessary to make the diagnosis.

CASE DESCRIPTIONS

Two white men presented with a chief complaint of petechial rashes on the trunk, bilateral arms, and legs, which later spread all over the body to the forearm, sparing the palms and soles (*Table 1*). Both patients had nausea, vomiting, and several episodes of diarrhea for a few days before the presentation. The first patient reported blood streaks in the stool, abdominal pain, and fever. He subsequently developed joint pain in bilateral knees, ankles, and wrist joints. Computed tomography of the abdomen showed inflammation of the duodenum and ileum, and endoscopy showed a mucosal nodule, but the biopsy was unremarkable. Both patients denied chest pain, shortness of breath, abdominal pain, headache, photophobia, neck rigidity, dry eyes, and oral ulcers. Laboratory tests in the first patient showed leukocytosis of $20.5/\text{mm}^3$, with a C-reactive protein level of 101.2 mg/L. This prompted us to rule out an infectious

source, and tests for HIV, hepatitis, Lyme disease, syphilis, chlamydia, and gonorrhea were negative. A stool infectious workup was also negative. An autoimmune panel for anti-nuclear antibodies (ANA), anti-neutrophil cytoplasm antibodies (ANCA), rheumatoid factors (RF), complements, and IgA was unremarkable. Similarly, an infectious and rheumatological workup was unremarkable for our second patient, as were his inflammatory markers (white blood cell count of $6.9/\text{mm}^3$, erythrocyte sedimentation rate of 17 mm/h, and C-reactive protein of 18.2 mg/L). Skin biopsy of both patients showed leukocytoclastic vasculitis, although direct immunofluorescence was negative for IgG, IgM, and IgA. Both patients were started on steroids for a vasculitic rash with high suspicion for HSP, after which the rashes improved. HSP was clinically diagnosed in both patients, and they were discharged with rheumatology follow-up.

DISCUSSION

HSP is a systemic autoimmune small-vessel vasculitis having a quartet presentation of palpable purpura, arthralgia, gastrointestinal involvement, and renal involvement. Most commonly it occurs in children between the ages of 3 and 15 years.¹ The precise etiology of HSP is unclear. It is believed that IgA antibody immune complexes formed as a result of infection, malignancy, immunization, certain drugs, or autoimmune conditions deposit

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Received April 4, 2020; Revised May 12, 2020; Accepted May 14, 2020.

Table 1. Similarities and differences in two white men with adult-onset Henoch-Schönlein purpura

Variables	Case 1	Case 2
Age (years)	32	25
Rash	Petechial	Petechial
Fever	Yes	No
Nausea/vomiting	Yes	Yes
Abdominal pain	Yes	No
Diarrhea	Bloody	Nonbloody
Joint pain	Yes	No
White blood cell count (mm ³)	20,000	6900
C-reactive protein (mg/L)	101.2	18.2
Erythrocyte sedimentation rate (mm/h)	12	17
Skin biopsy	Leukocytoclastic vasculitis	Leukocytoclastic vasculitis
IgA immunofluorescence in skin biopsy	Negative	Negative

in small vessel walls and activate complement pathways, which lead to perivascular and interstitial infiltration of neutrophils. Histologically, these events occurring in a purpura site biopsy are named leukocytoclastic (leukocyte clastic), which means destruction of leukocytes. Using immunofluorescence staining, IgA deposition is observed in the epidermis or dermoepidermal junction.

HSP is diagnosed largely by clinical criteria. The European League Against Rheumatism/Pediatric Rheumatology International Trials Organization criteria for HSP diagnosis, published in 2010, consist of palpable purpura as a mandatory criterion, with at least one of the following findings: (a) diffuse abdominal pain; (b) leukocytoclastic vasculitis with predominant IgA deposits on skin biopsy; (c) arthralgia/arthritis in any joint; or (d) renal involvement (hematuria/proteinuria).² IgA deposition is found in 75% to close to 100% of clinically confirmed cases of HSP.^{3,4} However, it has been repeatedly acknowledged that a subset of HSP cases exists in which vascular IgA deposition in the skin appears to be negative.^{4,5} Indeed, one important study calculated that a lack of IgA positivity has a negative predictive value of only 81%.⁴

The minority of cases in which IgA is absent may reflect variation in the duration of the lesion, as some of the instigating IgA deposition may have dissipated before the time of biopsy.⁴ This explanation is supported by observations that direct immunofluorescence IgA positivity is increased when the biopsy is taken closer to the onset of the lesions and declines with the progression of time. One study showed that in suspected HSP, the direct immunofluorescence positivity is around 85% when the

biopsy is performed within 7 days of onset of skin lesions, but drops to around 15% if more time elapses before a biopsy is taken.⁴ Utilizing the timing explanation for negative IgA findings in a minority of HSP cases, we can explain why the direct immunofluorescence for case 1 yielded negative IgA results. The onset of lesions for this patient occurred at least 2 weeks before his skin biopsy. However, in case 2, the onset of lesions was noticed only 7 days before the date of skin biopsy, and yet direct immunofluorescence IgA was still negative.

Placed in historical perspective, HSP was identified and diagnosed early in the 19th century many years before the discovery of IgA immunoglobulin in the 1960s.⁶ In 1994, the Chapel Hill Consensus Conference included IgA-dominant immune deposition in their definition of HSP. However, their definition was not intended to function as a set of required diagnostic criteria.² The more recent criteria included “predominant IgA deposits on skin biopsy” as a nonessential criterion. Thus, the absence of IgA on immunofluorescence does not exclude a diagnosis of HSP.

In conclusion, although HSP is largely seen in children, it is a disease to be considered in adults presenting with non-thrombocytopenic purpura with arthralgias, abdominal complaints, and/or hematuria. These cases highlight that although HSP is classically associated with deposition of IgA within vessel walls, the disease can be diagnosed even with a negative IgA immunofluorescence biopsy based upon clinical findings alone. If a biopsy is desired for extra confirmation of clinical suspicion, it may be more useful to perform the biopsy closer to the onset of symptoms.

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