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CASE REPORT

Henoch-Schönlein purpura and crohn's disease: Expanding the range of association in pediatric patients

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Abstract

The association of new onset Henoch-Schönlein purpura (HSP) and inflammatory bowel disease (IBD) has been reported in the setting of concomitant anti-TNF-α treatment. We present two pediatric IBD cases who developed new onset HSP without such association. These cases add to the literature by suggesting an association between HSP and IBD in pediatric population. We discuss possible underlying pathophysiological mechanisms, suggesting some commonality with IgA nephropathy. Increased awareness for HSP in pediatric IBD patients regardless of anti-TNF- α therapy involvement is important for timely recognition and appropriate multi-disciplinary management.

Keywords Inflammatory bowel disease · Henoch-Schönlein Purpura · Crohn's disease · Ulcerative colitis

Introduction

Henoch-Schönlein purpura (HSP) is a multi-system small vessel vasculitis characterized by perivascular IgA deposition. HSP classically presents with tetrad of palpable purpura/petechiae, abdominal pain, arthralgia/arthritis, and renal involvement, along with histopathology displaying leukocytoclastic vasculitis (LCV) or glomerulonephritis with IgA deposition. Recognized triggers of HSP include viral/bacterial infection and certain drugs, but up to 50% do not have a clear cause. There is a reported rare association between inflammatory bowel disease (IBD) patients undergoing anti-TNF-α treatment and new onset HSP as a potential complication of therapy [1]. However, there are three reported pediatric IBD cases who developed HSP without such active immunotherapy [2–4] and we present two more cases to further affirm these findings. We discuss possible underlying pathophysiological mechanisms by drawing parallels to IBD-associated IgA nephropathy (IgAN) to suggest an association between IBD and HSP in pediatric population.

Case #1

A 15-year-old Caucasian female with ileal Crohn's disease (Paris classification: A1bL1B2B3G_0) was managed with monthly intravenous infliximab. After four treatments, she developed diffuse abdominal pain due to small bowel obstruction (SBO) caused by ileal stricture. Infliximab was stopped and patient underwent ileocolectomy with primary stapled anastomosis 3 months later. The ileal stricture was as a complication of her Crohn's disease despite treatment. Pathological findings of the resected ileocolic specimen showed active chronic Crohn's ileocolitis with stricture and fistula at the ileocecal valve with several mesenteric lymph nodes showing sinus histiocytosis. Histology showed diffuse chronic ileal mucosal inflammation, focal transmural fibrosis, disorganized hypertrophy of the muscularis mucosae, and focal transmural lymphoid infiltrates at the area of the stricture. Proximal ileal segment to the stricture showed linear ulcer while the distal cecal segment showed mucosal glandular architectural distortion with submucosal fibromuscular hypertrophy.

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She developed a fever of 38.7 °C on post-operative day (POD) 4. She was managed with ceftriaxone and metronidazole for 3 days. Blood cultures, urinalysis, respiratory viral panel, and chest X-ray were unremarkable. CT of abdomen and pelvis showed intact anastomosis without adjacent inflammation or fluid collection and post-operative inflammatory changes in the ascending colon.

On POD6, she developed non-blanching, erythematous, edematous, tender, and palpable purpura on her lower extremities (Fig. 1). She also reported mild abdominal pain and arthralgia in her distal metacarpals. Her urinalysis showed hematuria. A skin punch biopsy was performed, which showed leukocytoclastic vasculitis with a perivascular neutrophilic and eosinophilic infiltrate (Figs. 2,3). A separate punch biopsy for direct immunofluorescence detected IgA antibodies surrounding superficial dermal vessels, confirming the diagnosis of HSP. She was treated with prednisone and discharged on POD8 with near resolution of the rash. When followed up a month after discharge, the rash fully resolved without re-occurrence. There is no family history of HSP or IBD.

Case #2

A 13-year-old Caucasian male with Crohn's disease (Paris classification: A1aL3L4bB1G_1) had persistent inflammation despite treatment with methotrexate and infliximab for 2 years. During colonoscopy, his sigmoid colon perforated, and he underwent exploratory laparotomy, resection of the sigmoid colon, and creation of a diverting ileostomy. His

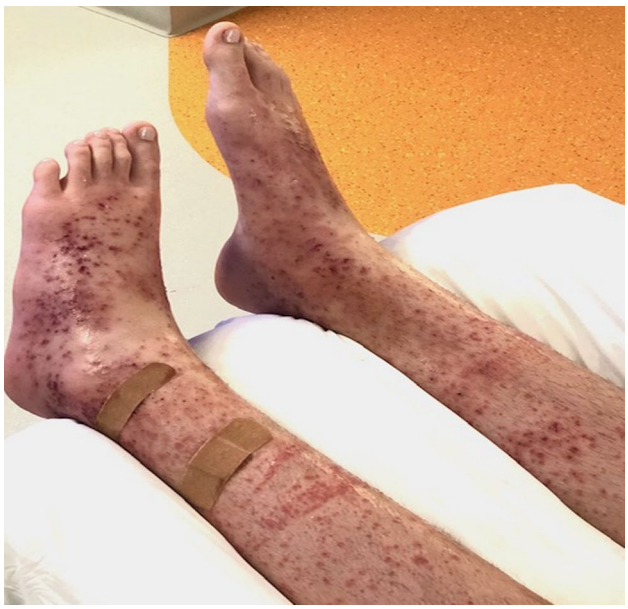

Fig. 1 Bilateral lower extremities with erythematous to purpuric macules, edematous plaques, and palpable purpura that extend from dorsal foot to mid-shin

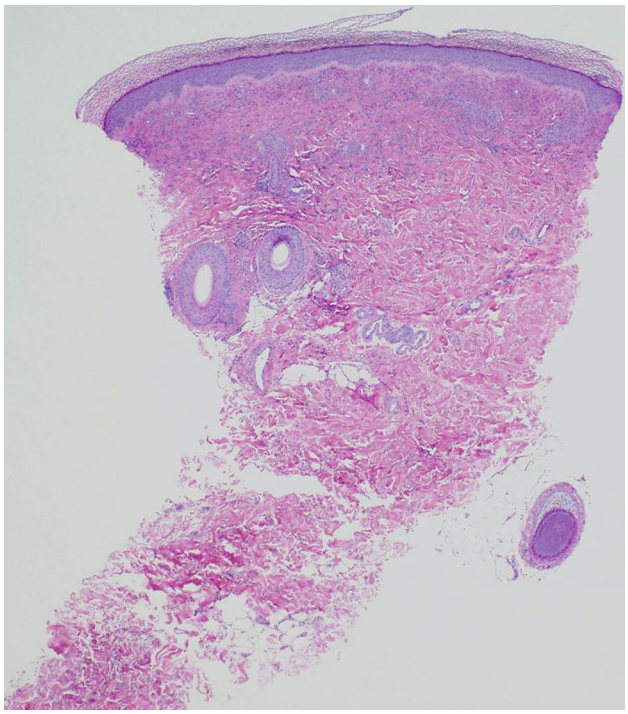

Fig. 2 A punch biopsy at low power highlights a perivascular and interstitial infiltrate within the superficial and mid-dermis (Hematoxylin–eosin stain, original magnification × 40)

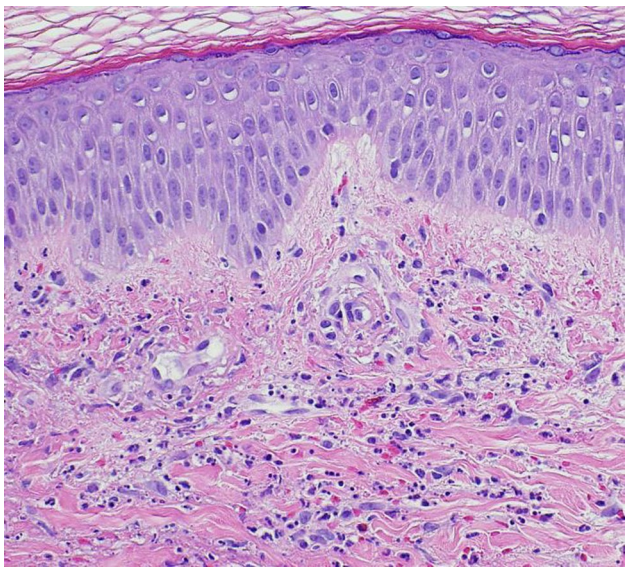

Fig. 3 High power shows neutrophils and eosinophils with admixed karyorrhectic debris and extravasated erythrocytes. There are fibrin deposits in the vessel walls (Hematoxylin–eosin stain, original magnification × 400). These are characteristic features of leukocytoclastic vasculitis

sigmoid colon was found to be a disease-specific lesion with histological findings suggestive of severely active chronic colitis, causing the perforation. The resected specimen showed extensive surface ulceration, multiple deep fissuring ulcers extending into muscularis propria, acute cryptitis, crypt abscesses, basal lamina propria lymphoplasmacytosis, and glandular architectural irregularities.

Diversion of the fecal stream brought about the remission of the inflammation and immunosuppressive therapy was not restarted after his discharge. On follow-up appointments with pediatric surgery and gastroenterology, he was still noted to be in remission with ileostomy calprotectin ranging from 20 to 40 µg/mg and mucous fistula from 10 to 20 µg/mg without any symptoms. He was not restarted on any medication.

Eleven months after the surgery, he developed bilateral ankle and distal metatarsal pain and swelling with presumed diagnosis of cellulitis. He was treated with 8-day course of cephalexin; however, he developed palpable purpura in his legs and knees upon antibiotic completion. There was no preceding illness or symptomatic changes. His urinalysis was notable for microscopic hematuria and proteinuria, supportive for a diagnosis of HSP. His Crohn's disease was still noted to be in remission as the calprotectin levels from the ileostomy and mucous fistula were still in the range mentioned above without any symptoms. He received prednisone for two months with resolution of the rash at day 10 and proteinuria after 2 months. There is no family history of HSP, IgA-related diseases, or IBD.

Discussion

As is often the case, no clear trigger for HSP was identified. Both had received antibiotics and had intra-abdominal surgeries but none of the antibiotics they received and any type of surgery, including intra-abdominal procedures, have been associated with HSP. The first case had a febrile illness with an unclear source and may be a post-surgical complication with residual inflammation.

New onset of HSP in IBD patients have been reported mostly in the setting of concomitant anti-TNF-α treatment. Of the eight published reports, only two involve pediatric subjects: one with ulcerative colitis treated with adalimumab and the other with Crohn's disease treated with both infliximab and adalimumab [1]. In both cases, HSP resolved with cessation of anti-TNF-α treatment without recurrence. Three reports refer to new onset HSP in pediatric age IBD patients while not receiving anti-TNF-α treatment [2–4]. In our two cases, palpable purpura developed when infliximab had been stopped for 3 and 11 months, respectively. It seemed possible that the first case is somehow associated with anti-TNF-α treatment given the short interval of 3 months; however, this is unlikely since the half-life of infliximab is about 14 days [8]. Interestingly, Park and Shin hypothesized that a shift from Th1 to Th2 phenotype induced by anti-TNF-α therapy can lead to eosinophilia contributing to HSP pathogenesis [5]. The patient of the first case showed eosinophilia from 4 to 5% only during the onset of HSP and eosinophils in the punch biopsy, hinting at intrinsic pathogenic eosinophilic involvement in HSP and IBD that may predispose patients for both conditions to occur simultaneously. This is further bolstered by a genetic association of HLA-DRB1, which was found in both HSP and IBD [9].

The rarity of the association between HSP and IBD has been recognized but the mechanism is still poorly understood. While HSP is IgA/immune complex mediated, IBD is thought to be predominantly T-cell driven. However, the link between T-cell- and IgA-mediated immunity has been studied in secondary IgAN due to hepatic and intestinal inflammation. Wang et al. documented this point in a study with transgenic mice that T-cell mediated mucosal immunity was crucial for intestinal mucosal inflammation and subsequent IgAN pathogenesis via IgA overproduction from gut-associated lymphoid tissue [6]. It is possible that chronic mucosal inflammation, loss of antigenic exclusion and tolerance, and dysregulated IgA production/transport results in the defining dermatopathological and glomerular HSP findings as well [4, 7]. Given strikingly similar pathophysiology between IgAN and HSP with indistinguishable renal histopathologic findings, we speculate that there is also an association between HSP and IBD that warrants further study.

Chance association between HSP and IBD in our patients cannot be ruled out; however, IgAN was found to be more prevalent among IBD patients in a recent study, suggesting a direct link and nineteen cases of IBD-associated IgAN have been reported [7]. Furthermore, higher prevalence of HSP in children may be inadequate to conclude a chance association. Epidemiological, clinical, and immunogenetic differences between pediatric and adult IBD must be taken into consideration. For example, very-early-onset IBD is associated with monogenic defects and primary immune deficiencies compared to polygenic involvement in adults [10]. In addition, pediatric ulcerative colitis is more likely to display pancolitis and more severe disease status/progress than adults [10], and higher disease severity in IBD has been associated with increased risk for autoimmune diseases [11]. Pediatric and adult IBD may encompass different immunopathogenetic processes due to immature development of mucosal immunological defenses in pediatric age that subsequently undergoes substantial changes over time [12]. This may help to explain our reported findings of new onset HSP without further immunomodulation by anti-TNF-α treatment in pediatric population.

The two presented cases add to the literature by confirming HSP occurs in IBD patients in the absence of immunosuppressant therapy. This suggests that there may be underlying immunological or genetic factors that predisposes patients to exhibit both conditions concurrently, leading to observed association. There should be increased vigilance for HSP in pediatric IBD patients whether or not anti-TNF- α therapy is involved for timely recognition and appropriate multi-disciplinary management.

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Authors Contribution John Gee Hong, MD is responsible for conception of the work, drafting, and revising it critically, and agrees to be accountable for all aspects of the work. Joseph Levy, MD is responsible for conception of the work, revising it critically for important intellectual content, and final approval of the version to be published. Evan Stokar MS, MD is responsible for acquisition of appropriate data/images for the work, revising it critically for important intellectual content, and final approval of the version to be published.

Compliance with ethical standards

Conflict of interest John G. Hong, Joseph Levy, and Evan Stokar declare that they have no conflict of interest

Human/animal rights All procedures followed have been performed in accordance with the ethical standards laid down in the 1964 Declaration ofHelsinki and its later amendments.

Informed consent Informed consent was obtained from all patients for being included in the study.

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