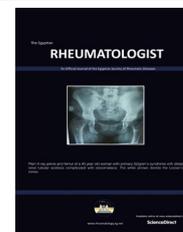




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## CASE REPORT

# Severe gastrointestinal involvement in adult-onset Henoch–Schönlein purpura associated with clarithromycin-resistant *Helicobacter pylori* infection



Guillermo Delgado-García<sup>a,\*</sup>, Ilse Mandujano-Cruz<sup>a</sup>, Kiber González-Padilla<sup>b</sup>,  
Badir Hernández-Velázquez<sup>c</sup>, Sylvia Martínez-Cabriales<sup>d</sup>,  
Jorge Ocampo-Candiani<sup>d</sup>, Miguel Ángel Villarreal-Alarcón<sup>a,b</sup>,  
Dionicio Galarza-Delgado<sup>a,b</sup>

<sup>a</sup> Department of Internal Medicine, University Hospital, Autonomous University of Nuevo León, Mexico

<sup>b</sup> Division of Rheumatology, University Hospital, Autonomous University of Nuevo León, Mexico

<sup>c</sup> Division of Gastroenterology, University Hospital, Autonomous University of Nuevo León, Mexico

<sup>d</sup> Division of Dermatology, University Hospital, Autonomous University of Nuevo León, Mexico

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### KEYWORDS

Henoch–Schönlein purpura;  
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Antineutrophil cytoplasmic antibodies

**Abstract** *Background:* Henoch–Schönlein purpura (HSP) is an uncommon vasculitis in adults. Gastrointestinal involvement is part of the classical tetrad and can present as bleeding. *Helicobacter pylori* infection in the setting of HSP has been reported a few times in the literature and may be involved in the pathogenesis of this disease as a triggering agent.

*Case report:* A 48-year-old man presented to the emergency department with 9 days of acute symmetric additive polyarthritides, 2 days of palpable purpura involving lower limbs, recent-onset intense mesogastric pain and hematochezia. *H. pylori* was detected in gastric tissue and triple therapy (clarithromycin, amoxicillin and omeprazole) was started. Gastrointestinal bleeding and other symptoms stopped 24 h after steroid initiation and he was later discharged on prednisone (1 mg/kg) and azathioprine (100 mg/day). Shortly after discharge he was readmitted with hematochezia and clarithromycin-resistant *H. pylori* infection was suspected. Bleeding stopped following reinstitution of corticosteroids and a second-line scheme (levofloxacin, amoxicillin and omeprazole) was introduced. Corticosteroids were gradually tapered and he remained on azathioprine. Nine months later he was doing fine. The pertinent literature is briefly discussed, highlighting the previous cases of concurrent diagnosis in adult patients.

\* Corresponding author at: Departamento de Medicina Interna, Hospital Universitario “Dr. José E. González”, Universidad Autónoma de Nuevo León, Av. Madero y Gonzalitos s/n, Col. Mitras Centro, 64460 Monterrey, Mexico.

E-mail addresses: [grdelgadog@gmail.com](mailto:grdelgadog@gmail.com), [guillermo.delgadogr@uanl.edu.mx](mailto:guillermo.delgadogr@uanl.edu.mx) (G. Delgado-García).

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**Conclusion:** To the best of our knowledge, this is the first report describing resistance to clarithromycin-containing triple therapy in a *H. pylori*-infected adult patient with HSP. Gastrointestinal bleeding remains one of the most feared manifestations of HSP. These patients may benefit from *H. pylori* screening, as this might positively affect their prognosis. Further studies in adults are nevertheless needed to clarify this association and its therapeutic impact.

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## 1. Introduction

Henoch–Schönlein purpura (HSP) is an uncommon vasculitis in adults, with an annual estimated incidence of 8–18 cases per million [1]. Gastrointestinal involvement is part of the classical tetrad and occurs in one in ten adult patients at disease onset and in more than half of the cases when the disease is fully established [2,3]. Hemorrhage is one of the most severe manifestations of gastrointestinal involvement [4]. *Helicobacter pylori* infection in the setting of HSP has been reported a few times in the literature, but its role in the course of this disease remains controversial [5]. Here, we describe the case of a male patient presenting with gastrointestinal bleeding, as a manifestation of HSP, in whom *H. pylori* infection was also diagnosed, and then we discuss the pertinent literature.

## 2. Case report

A 48-year-old man with a medical history notable for newly diagnosed type 2 diabetes presented to the emergency department with 9 days of acute symmetric additive polyarthritides, 2 days of palpable purpura involving lower limbs and recent-onset intense mesogastric pain. On further questioning, he revealed that he recently suffered from constipation that required manual disimpaction. Soon after that, he developed hematochezia, which was self-limited and without hemodynamic compromise. He was febrile and had a heart rate of 117 bpm. His abdomen was soft with no peritoneal irritation signs. Initial laboratory workup showed no significant alterations in complete blood count. His serum creatinine was 0.6 mg/dL and C-reactive protein 98.5 mg/dL (upper normal limit: 6 mg/dL). No abnormalities were found on urinalysis. Fecal immunochemical test was positive for occult blood. ELISA for human immunodeficiency virus, hepatitis B surface antigen and anti-hepatitis C virus were all negative. Huddleson's reaction was also negative. He was positive for perinuclear anti-neutrophil cytoplasmic antibodies (pANCA) with a titer of 1:640. Antinuclear, anti-MPO and anti-PR3 antibodies, as well as rheumatoid factor, were all negative. No lesions were found in the contrast-enhanced abdominal computerized tomography scan. Under the suspicion of vasculitic process, a skin biopsy was performed on the same admission day. He remained under observation until his second inpatient day when he had hematochezia and was thus started on prednisone (1 mg/kg).

Ringed esophagus, esophageal mucosal erythema, gastric subepithelial hemorrhage, duodenal erythema with an ulcer <1 cm were noted on upper endoscopy. Descending colonic and rectal mucosal erythema, and rectal edema and subepithelial hemorrhage were found on rectosigmoidoscopy. Histopathology of biopsy specimens revealed chronic

esophagitis compatible with reflux disease, active chronic gastritis, acute ulcerated duodenitis, focal active colitis, and edema and congestion of the rectal lamina propria. Immunofluorescence was not performed. *H. pylori* was detected in gastric tissue and he was therefore started on triple therapy (clarithromycin, amoxicillin and omeprazole).

Leukocytoclastic vasculitis was confirmed by skin histopathology and immunofluorescence demonstrated granular vascular deposits of IgA (+2), confirming the presumptive diagnosis of HSP. Bleeding and other symptoms stopped 24 h after steroid initiation and he was later discharged on prednisone and azathioprine (100 mg daily).

He skipped some doses of his medications and, shortly after discharge, was readmitted with hematochezia. Bleeding stopped following reinstitution of corticosteroid therapy. One month after finishing triple therapy, urea breath test (UBT) was performed and interpreted as positive, so we started him on a second-line scheme (levofloxacin, amoxicillin and omeprazole). He completed his treatment regimen and, four weeks later, UBT was repeated and tested negative. Corticosteroid therapy was gradually tapered and he remained on azathioprine. Nine months later, on the follow-up, he was doing fine and reported no symptoms.

## 3. Discussion

Gastrointestinal bleeding is considered a severe gastrointestinal manifestation of HSP and, in the largest unselected series to date, occurred in about 23 percent of patients, either as occult (10.3%) or overt hemorrhage (12.9%) [3,4]. However, it is worth noting that children were included in the previous figures and also that gastrointestinal involvement was more frequent in children than adults (67.3% vs 57.4%;  $p < 0.05$ ) [3]. Gastrointestinal symptoms may precede the skin involvement and have been ascribed to immune complex deposition in vessel walls which lead to edema and hemorrhage [2]. pANCA with negative ELISA-ANCA has been previously detected in HSP patients with gastrointestinal symptoms and this may indicate that the ANCA target antigens may be different in HSP. These patients had higher disease activity [6]. Gastric and duodenal endoscopic appearance of HSP was first described in a 14 year-old girl by Akdamar et al. in 1973 [7]. Colonoscopic findings have been reported more rarely and were first described in two adult patients more than a decade later by Di Febo et al. [8,9]. The main findings include redness, petechiae, erosion, nodular changes, ulceration and strictures. These lesions are predominantly distributed in the second part of the duodenum, terminal ileum and rectosigmoid colon [10,11]. Concurrent involvement of upper and lower gastrointestinal tracts may not be uncommon as long as both upper endoscopy and colonoscopy are performed [11].

**Table 1** Adult-onset HSP patients with concurrent *H. pylori* infection.

Case	Author	Country	Year	Sex	Age	GIB	Cr (mg/dL)	Proteinuria (g/d)	ANA	ANCA	H. pylori	PPI	Antibiotics	Relapse
1	Reinauer et al.	Germany	1995	F	21	Positive	1.2	1.2	Negative	Negative	UBT / Bx	Positive	Amp	No <sup>§</sup>
2	Machet et al.	France	1997	M	65	Positive	0.8	3	Negative	NR	Bx	Positive	Amp + CLR + Dap	No
3	Cecchi et al.	Italy	1998	M	62	FOBT	Normal	0.5	Negative	Negative	RUT	Positive	Amox + CLR	No
4	Novák et al.*	Hungary	2003	M	38		NR	NR	NR	NR	UBT / Bx	NR	NR	NR
5				M	53		NR	NR	NR	NR	UBT / Bx	NR	NR	NR
6				M	54		NR	NR	NR	NR	Bx	NR	NR	NR
7	Kellerman	USA	2006	M	65	Negative	3.9	6.2 <sup>‡</sup>	Negative	1:80	SAT	Positive	Amp + CLR	†
8	Grivceva-Panovska et al.	Macedonia	2008	M	29	Negative	Normal	Negative	Negative	NR	IgG serology	Positive	CLR + MTZ	No
9	Hoshino	Japan	2009	M	33	FOBT	0.89	Negative	Negative	Negative	RUT	Positive	Amox + CLR	No <sup>§</sup>
10	Hamzaoui et al.	Tunisia	2011	F	62	Positive	Normal	3.3	NR	NR	Bx	NR	NR	No
11				M	20	Negative	Normal	Negative	NR	NR	Bx	Positive	NR	No
12	Ulas et al.	Turkey	2012	M	49	FOBT	Normal	0.45	Negative	NR	RUT + Bx	Positive	Amox + CLR	No
13	Berriche et al.	Tunisia	2014	M	67	Negative	1.8	0.6	Negative	Negative	Bx	Positive	Amox + CLR	No

Patients in remission were eliminated. GIB: gastrointestinal bleeding; Cr: serum creatinine; ANA: antinuclear antibodies; ANCA: antineutrophil cytoplasmic antibodies; *H. pylori*: *Helicobacter pylori* infection; PPI: proton-pump inhibitor; FOBT: positive fecal occult blood test; NR: not reported; UBT: urea breath test; Bx: biopsy; RUT: rapid urease test; SAT: stool antigen test; Amp: ampicillin; CLR: clarithromycin; Dap: dapsone; Amox: amoxicillin; MTZ: metronidazole.

\* One of Novák's patients had GIB, but they did not specify which one.

‡ Urine protein:creatinine ratio.

† Died during this hospital stay.

§ Reinfection.

Leukocytoclastic vasculitis could be demonstrated in gastrointestinal biopsy samples, especially in severe lesions. Histopathology is also useful for the differential diagnosis [10,11]. Based on previous studies and pediatric data, Audemard-Verger et al. recently proposed an algorithm for the management of adult patients with gastrointestinal involvement. For severe manifestations, surgical evaluation and prednisone (1 mg/kg daily) are recommended. Methylprednisolone pulse therapy and/or cyclophosphamide can also be considered [13]. In this series, prognosis was not subanalyzed according to gastrointestinal involvement. Renal insufficiency, nephrotic and nephritic syndromes during the course of HSP is more commonly observed in adults than in children [3, personal communication]. In a French retrospective, multicenter cohort study, which included 250 adult patients with biopsy-proven nephritis, gastrointestinal involvement was not a risk factor for nephritis [12], personal communication. Relapses are not unexpected in adult patients [13].

Bacterial pathogens have been suspected to trigger HSP [5]. *H. pylori* has been alike implicated as a causative or triggering agent of several extradigestive diseases [14]. In the setting of HSP, *H. pylori* infection has been reported a few times in the literature (Table 1) [15–23], but this association may be underestimated because it is not deliberately sought [17,21]. Furthermore, *H. pylori* role in the natural history of HSP remains a matter of debate [5]. Directly or via immune or inflammatory processes, *H. pylori* might be involved in HSP pathogenesis [21]. Shin et al. have speculated that increased serum IgA, decreased C3 levels, and increased cryoglobulins by *H. pylori* infection might favor the formation of immune complexes and trigger the development of HSP [24]. Xiong et al. conducted a meta-analysis to assess the association between *H. pylori* infection and HSP in Chinese children. They found that children with HSP had a higher incidence of infection than control subjects (49.27% vs 23.39%, respectively). The pooled odds ratio (OR) for *H. pylori* infection among children with HSP, compared with control subjects, was 3.80 (95% CI: 2.54–5.68). Cumulative meta-analysis was also performed and confirmed this association with a narrower confidence interval (OR = 3.35, 95% CI: 2.95–3.81). Moreover, the pooled OR for *H. pylori* infection among HSP patients with predominant gastrointestinal symptoms was 4.62 (95% CI: 2.66–8.01,  $p < 0.001$ ). *H. pylori* eradication decreased the recurrence rate of HSP in infected children (RR = 0.38, 95% CI: 0.25–0.58,  $p < 0.001$ ) [25]. On the other hand, Cai et al. found no significant difference in recurrence rate with the use of triple therapy in infected children (14% vs 24%). The incidence of nephritis was, nevertheless, lower in those children who were treated with triple therapy (5% vs 33%,  $p < 0.05$ ) [14,26].

Results of the previous studies should be interpreted in light of at least two limitations. First, the age of the population studied, since prognosis may vary according to the age of onset [3]. Second, the diversity in *H. pylori* isolates from different populations, as these may differ between Chinese and non-Chinese populations [25]. In relation to the above, Novák et al. studied 11 Hungarian adult patients with HSP and found that anti-*H. pylori* IgG concentration was higher in those with acute disease ( $n = 5$ ) than in those in remission ( $n = 6$ ) ( $86 \pm 32$  vs  $32.5 \pm 23.2$  U/ml,  $p < 0.05$ ). They also had a higher concentration than control subjects ( $n = 20$ ) ( $86 \pm 32$  vs  $25.5 \pm 28.5$  U/ml,  $p < 0.05$ ). In addition, total IgA concentration was higher in patients with acute disease compared to

those in the control group ( $5.5 \pm 1.1$  vs  $2.43 \pm 1.2$  g/L,  $p < 0.05$ ) [18].

Because of the rarity of this vasculitis in a country where *H. pylori* infection is fairly prevalent among adults [27], this pathogen is probably not the sole factor involved in HSP pathogenesis. Moreover, a patient who has been treated for HSP associated with *H. pylori* infection can be reinfected without showing symptoms of HSP [21]. According to the Maastricht IV/Florence Consensus Report, the evidence available shows no clear causal association or therapeutic link between *H. pylori* and other extradigestive disorders [28], such as HSP. However, the Kyoto global consensus report strongly recommends that infected patients should be offered eradication therapy [29]. Because of its high degree of accuracy and non-invasiveness [28], UBT may be thus useful as a screening tool in HSP patients, especially in those corticoreistant, corticodependent or with predominant gastrointestinal symptoms. It is also important to confirm *H. pylori* eradication at the end of the treatment. To the best of our knowledge, this is the first report describing resistance to clarithromycin-containing triple therapy in a *H. pylori*-infected adult patient with HSP. This is of special interest as Garza-González et al. previously reported that our city is part of a region with low clarithromycin resistance (8.1%) [30]. Therefore, even in these areas, clarithromycin resistance should be considered in any *H. pylori*-infected patient with HSP who continue to deteriorate clinically despite steroid and triple therapy.

In conclusion, gastrointestinal bleeding is one of the most severe gastrointestinal manifestations of HSP. These patients may benefit from *H. pylori* screening, as this might positively affect their prognosis. Further studies in adults are nevertheless needed to clarify this association and its therapeutic impact.

#### Conflict of interest

None.

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