

CASE REPORT

HENOCH-SCHÖNLEIN PURPURA IN AN ADULT PATIENT: EXTRAGASTRIC, CUTANEOUS MANIFESTATION OF HELICOBACTER PYLORI INFECTION

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Abstract: Today there is evidence that *Helicobacter pylori* has a critical role in different extragastric diseases. The discovery of a number of other new *Helicobacter* species has stimulated research into different extragastric diseases, in which an infectious hypothesis is plausible. Enterohepatic *Helicobacter* species have been hypothesized to play a role in different disorders including the extragastric manifestations of *H. pylori* infection. The authors present a case of Henoch-Schönlein purpura in an adult patient with *Helicobacter pylori* infection and disease regression after triple anti-*Helicobacter* eradication therapy. The patient was monitored, over a follow-up period of almost 9 years after eradication of *Helicobacter pylori* presence, by clinical examination as well as serological findings. There was no disease recurrence during the follow-up period and no markers of *Helicobacter pylori* reinfection. Since disease recurrence occurs throughout weeks to months, the authors conclude that Henoch-Schönlein purpura is a possible extragastric, cutaneous manifestation of *Helicobacter pylori* infection.

Key words: Henoch-Schönlein purpura, *Helicobacter pylori* infection

Introduction

Today there is evidence that *Helicobacter pylori* has a critical role in different extragastric diseases. The discovery of a number of other new *Helico-*

bacter species has stimulated research into different extragastric diseases, in which an infectious hypothesis is plausible. Enterohepatic *Helicobacter* species have been hypothesized to play a role in different disorders.

Concerning the extragastric manifestations of *H. pylori* infection, based on the current data idiopathic thrombocytopenic purpura and sideropenic anaemia are the diseases in which the pathogenic link appears to be strongest.

Henoch-Schönlein purpura (HSP) is an immunoglobulin (Ig) A-mediated small-vessel vasculitis that predominantly affects children. HSP is a subset of necrotizing vasculitis characterized by fibrinoid destruction of blood vessels and leukocytoclasia.

Heberden first described the disease in 1801 in a 5-year-old child with abdominal pain, haematuria, haematochezia, and purpura of the legs. In 1837, Johann Schönlein described a syndrome of purpura associated with joint pain and urinary precipitates in children. Eduard Henoch, a student of Schönlein's, further associated abdominal pain and renal involvement with the syndrome. Frank proposed the term "anaphylactoid purpura" in 1915. This followed from the reasoning that the pathogenesis probably involved a hypersensitivity reaction to an inciting agent.

Clinical manifestations include palpable purpura, arthralgia or arthritis, abdominal pain, gastrointestinal (GI) bleeding, and nephritis. The most serious long-term complication from HSP is progressive renal failure, which occurs in 1–2% of patients.

Two major classification systems are used to make a diagnosis of HSP. The first, from the American College of Rheumatology, requires two or more of the following to be present: Patient age younger than 20 years; Palpable purpura; Abdominal pain or GI bleeding; Extravascular or perivascular granulocytes on biopsy.

The second classification system, from the Chapel Hill Consensus Group, primarily uses nonclinical criteria and requires only the presence of small-vessel vasculitis with IgA deposition.

Two additional sets of criteria have been suggested for the diagnosis of HSP. Helander *et al.* [1] proposed that three or more of the following be present: Direct immunofluorescence (DIF) results consistent with vascular IgA deposition; Patient age younger than 20 years; GI involvement; Upper respiratory tract infection (URI) prodrome; Mesangioproliferative glomerulonephritis with or without IgA deposition

Michel *et al.* [2] proposed criteria to differentiate HSP from hypersensitivity vasculitis, requiring three or more of the following be present to diagnose HSP: Palpable purpura; Bowel angina; GI bleeding; Haematuria; Patient age at onset younger than 20 years; No medications as a precipitating agent.

Case report

We present patient I.G., a male aged 29 years upon admission, presenting at the out-patient ward of the Department of Dermatology in the early spring months, with symptoms of palpable purpura, afebrile, with mild joint symptoms, mild to moderate abdominal discomfort and a general feeling of weakness. The symptoms started as erythematous macular lesions, progressing to palpable purpura, 2–10 mm in diameter.

The first episode similar to this had occurred 10 years ago, with identical lesions in crops that faded after several days. The recurrence occurred on the same sites as previous lesions.

The lesions were symmetrical and distributed predominantly in the perimaleolar and in the lower legs (extensory).

The face, palms, soles, and mucous membranes were unaffected.

There was no recognizable detectable exogenous factor that might coincide with the onset of the illness.

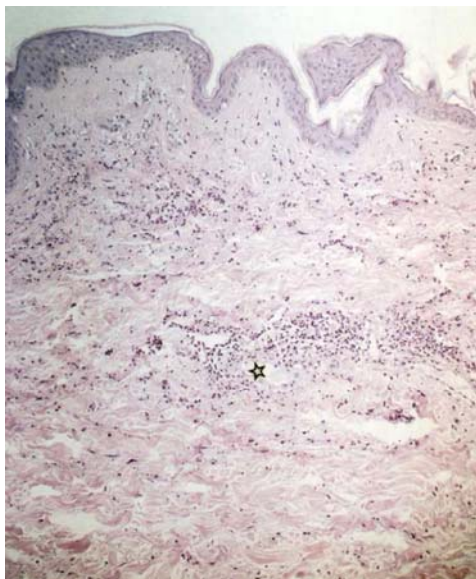


*Figure 1 – Numerous skin lesions
– pretreatment*
*Слика 1 – Многубројни кутани
промени – пред лекување*



*Figure 2 – Status after
H. Pylori therapy*
*Слика 2 – Состојба по спроведена
– анти H. Pylori терапија*

The patient had previously been treated with antibiotics and non steroid anti-inflammatory drugs and was refractory to the administered therapy. It was suggested a distinction be made between Sarcoidosis cutis, Lymphoma cutis and above all an unclear *casus pro diagnosis*. A skin biopsy was done, indicating cutaneous vasculitis.



*Figure 3 – Leucocytoclastic vasculitis in the upper and mid-dermis.
The asterisk marks the area of higher magnification*

*Слика 3 – Vasculitis leucocytoclastica во горниот и среден дермис. Астериксот
укажува на зоната на зголемување*

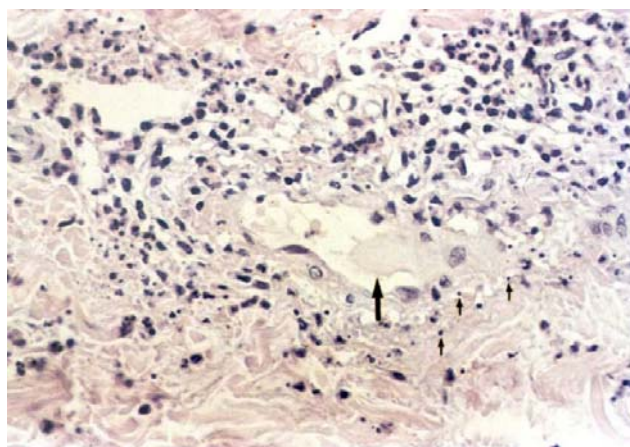


Figure 4 – Leucocytoclastic vasculitis. Fibrin thrombi (large arrow) in the lumen of the vessel featuring a destroyed wall. Note the nuclear dust in a perivascular arrangement (small arrows)

*Слика 4 – Vasculitis leucocytoclastica. Фибрински тромби (голема стрелка)
во луменот на крвниот сад. Периваскуларна нуклеарна прашина
(мали стрелки)*

The skin biopsy demonstrated fibrinoid necrosis of arteriolar and venular walls in the superficial dermis, with neutrophilic infiltration of the walls and perivascular regions. Associated fragments of inflammatory cells with nuclear debris were seen with extravasated erythrocytes.

DIF of skin biopsy sections demonstrated IgA deposition in affected vessel walls.

Gastrointestinal ultrasound was done due to the presented complaints; however, the findings were normal, as well as in the ultrasound of kidneys.

Biochemical findings showed normal levels (within laboratory range). Serum markers of inflammation CRP and RF as well as Antistreptolysine titer were within normal range. Urine findings were normal; there was neither macroscopic nor microscopic haematuria. Antinuclear antibody findings were normal.

Microbiological findings (nasal and throat swabs) showed no presence of pathogenic bacteria. However, serum levels of anti *Helicobacter pylori* IgG antibodies were highly elevated (214 IU/mL) by EIA.

Stool culture: negative. There was no occult GI bleeding.

The patient was fully examined physically and no presence of organ involvement was detected.

Medical history showed no history of recent drug ingestion and food consumption, since reports exist of medication-associated and food-associated HSP.

Neurological examination showed no focal deficits.

X-ray excluded pulmonary nodules or hilar adenopathy suggestive of malignancy (primary or metastatic) or lymphoma, which have been associated with HSP.

Upper GI endoscopy was performed in the patient due to mild epigastric pain. Esophagogastroduodenoscopy (EGD) demonstrated no lesions or diffuse erosive lesions. The CLO test was positive.

Treatment

The patient was treated by triple eradication anti *Helicobacter* therapy, consisting of Clarythromycine, Metronidazole and proton pump inhibitor (as in the relevant Maastricht Consensus). Cutaneous symptoms diminished in 3 days, with a complete cessation in 5 days.

Follow-up

The patient was carefully monitored by clinical examination as well as serological findings over a period of almost 9 years after the eradication of

Helicobacter pylori presence. There was no disease recurrence during the follow-up period and no markers of *Helicobacter pylori* reinfection. Since disease recurrence occurs throughout weeks to months in adults and children (study by Allen *et al.*, according to a study of 57 adults with HSP, exacerbations may be seen for 6 months). Thus the authors consider the follow-up period as an indicator of successful resolution of the disease.

Discussion

Knowledge concerning the exact mechanisms by which the immune complexes implicated in the pathogenesis of HSP are formed is lacking. Similarly, factors that predispose certain patients to development of the disease are poorly understood.

The etiology of HSP is unknown but involves the vascular deposition of IgA immune complexes composed of IgA1 and IgA2 and produced by peripheral B lymphocytes. These complexes are probably formed in response to an inciting factor. The circulating complexes activate complement, most likely by the alternative pathway (presence of C3 and properdin and the absence of the first component of complement in biopsies).

Polymorphonuclear leukocytes are recruited by chemotactic factors and cause inflammation and necrosis of vessel walls with concomitant thrombosis. This leads to extravasation of erythrocytes from haemorrhage in the affected organs and is manifested histologically as leukocytoclastic vasculitis.

The histology of the involved skin reveals polymorphonuclear cells or cell fragments around small dermal blood vessels. Immune complexes containing IgA and C3 have been found in the skin, kidneys, intestinal mucosa and joints, which are the major organ sites involved in HSP.

Clinical manifestations of HSP reflect small-vessel injury. Abdominal pain, present in as many as 65% of patients, is secondary to vasculitis-induced submucosal and subserosal haemorrhage and oedema, with thrombosis of the microvasculature in the gut. Haematuria and proteinuria occur in HSP-associated nephritis. Renal manifestations range from minimal change to severe crescentic glomerulonephritis.

Etiology is secondary to the mesangial deposition of IgA predominantly, but IgG, IgM, C3, and properdin deposition may also occur. These deposits can also occur in the subendothelial and subepithelial glomerular spaces. Both HSP nephritis and IgA nephropathy (Berger's Disease), which are the most common causes of glomerulonephritis throughout the world, might be different clinical presentations of the same disease process.

Dermatologic manifestations in HSP occur secondarily to immune complex deposition (IgA, C3) in vessels of the papillary dermis, resulting in vessel injury, extravasation of RBCs, and clinically observable palpable purpura. This tends to occur in dependent body regions, such as the lower legs, buttocks, back, and abdomen.

Several agents have been implicated, including group A streptococci, varicella, hepatitis B, Epstein-Barr virus, parvovirus B19, Mycoplasma, Campylobacter, and Yersinia. Less commonly, other factors have been associated as inciting agents in the development of HSP. These include drugs, malignancy, foods, pregnancy, familial Mediterranean fever, and exposure to cold. HSP has also been reported following vaccinations for typhoid, measles, yellow fever and cholera.

HSP incidence is seasonal (greatest in the spring, autumn and winter months).

Male-to-female predominance ranges from 1 : 5–2 : 1.

Most patients (75%) are children aged 2–14 years. The median age of onset is 4–5 years. Although one of the criteria for the diagnosis of HSP as published by the American College of Rheumatology is "age less than 20 years," the disease can occur from infancy to the ninth decade.

A study by Allen *et al.* shows that the clinical manifestations of HSP vary with age. Children younger than 2 years have less renal, GI, and joint involvement but more subcutaneous oedema.

The presenting history varies with each patient. The hallmark of the disease is the characteristic palpable purpura, which is seen in almost 100% of patients. HSP tends to occur on the buttocks and upper thighs in younger children and on the feet, ankles, and lower legs of older children and adults. Patients often present with low-grade fever and malaise in addition to more specific symptoms. Purpura may be the presenting sign. As many as 50% of children present with symptoms other than purpura. The eruption is often preceded by arthralgia or arthritis, abdominal pain, or testicular swelling. Although it may be present initially, renal disease often develops up to 3 months after initial presentation.

Infections may stimulate immune responses by different mechanisms. These include shared epitopes between pathogens and host, upregulation of heat shock proteins, and stimulation of lymphocytes by factors such as peptidoglycan, protein A, CpG motifs in bacterial DNA, and superantigens. Superantigens are extremely potent activators of lymphocytes. Stimulation of T cells is dependent on the presence of MHC class II molecules on antigen-presenting

cells. In contrast to classical T-cell antigens, processing of the superantigens is not needed.

Superantigens bind to MHC class II molecules on antigen-presenting cells and to conserved regions of T-cell receptor V-beta chains. Virtually all T cells expressing a superantigen-binding V-beta chain proliferate. After proliferation, activated T cells undergo apoptosis. Furthermore, repetitive stimulation may induce anergy, a process that is possibly dependent on stimulation of CD4+ regulatory T cells. Superantigens may induce autoimmunity by stimulation of autoreactive cytotoxic T cells and/or by T cell-dependent activation of antigen-specific B cells.

Reported associated factors are listed as follows. Infections: Bacteria - Group A beta haemolytic streptococci, *Campylobacter jejuni*, *Yersinia* species, *Mycoplasma pneumoniae*, and *Helicobacter pylori* (reported in one patient prior to our case report); Viruses - Varicella, hepatitis B, Epstein-Barr virus and parvovirus B19; Drugs; Medication-associated HSP - more frequent in adults than children (although reported in both populations); Drugs associated with HSP - Ampicillin penicillin, erythromycin, quinines and chlorpromazine; Neoplasm - Leukemia Lymphoma; Solid tumours - Ductal carcinoma of the breast, Bronchogenic carcinoma, Adenocarcinoma of the prostate, Adenocarcinoma of the colon, Renal cell carcinoma, Cervical carcinoma, Melanoma; Foods - Sensitivity to foods containing salicylates and azo dyes; Other - Pregnancy, familial Mediterranean fever, and cryoglobulinaemia.

HSP is usually self-limited, and treatment is primarily supportive to ensure adequate hydration and replacement of excessive blood loss. A search for the underlying or predisposing factors is a key to successful treatment. Controversies concerning the use of corticosteroids in the treatment of HSP exist with regard to whether or not they can [1] reduce the severity or duration of the disease, [2] decrease the risk of glomerulonephritis, and [3] increase the rate of relapses of the disease. An editorial that reviews these issues has recently been published [4].

Rosenblum and Winter reported more rapid improvement in abdominal pain (within 24 h) in 50% of patients when corticosteroids were initiated [4], compared with 14% in those not receiving corticosteroids. Niaudet and Habib, in a prospective uncontrolled study of 38 children with glomerulonephritis, found that corticosteroid use should be limited to patients at risk of progression of renal disease [5]. The issue of whether corticosteroids can increase the rate of disease relapse has recently been addressed. In an Italian cohort of 150 children reported by Trapani *et al.*, disease relapse was significantly more frequent in those treated with corticosteroids [6]. However, this may have been due to "confounding by indication," which means that it may have been the fact that

these patients had a more severe disease that led to their tendency to relapse, rather than treatment with corticosteroids (which were initiated because of the more severe disease). [7]

Dapsone, azathioprine, and intravenous immunoglobulin therapies have been tried with varying success, as has plasmapheresis.

Nonsteroidal anti-inflammatory drugs (NSAIDs) may be used to treat arthralgia associated with HSP. Oral corticosteroids may be of benefit in treating painful subcutaneous oedema [8].

The clinical manifestation of *Helicobacter pylori* infection is determined by a complex interaction between the bacterium and the host. The main bacterial factors associated with pathogenicity comprise outer membrane proteins, including BabA, SabA, OipA, AlpA and AlpB, the vacuolating cytotoxin VacA and the products of cagPAI. The multitude of putative virulence factors makes it extremely difficult to test the contribution of each individual factor. Interaction between bacterial factors such as CagA and host signal transduction pathways seems to be critical for mediating cell transformation, cell proliferation, invasion, apoptosis/anti-apoptosis, and angiogenesis. An animal model pathology due to *H. pylori* infection similar to that in humans can be used to evaluate virulence factors including CagA, host responses, and environmental factors [9, 10].

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Резиме

HENOCH-SCHÖNLEIN PURPURA (HSP) КАЈ ВОЗРАСЕН ПАЦИЕНТ: ЕКСТРАГАСТРИЧНА, КУТАНА МАНИФЕСТАЦИЈА НА HELICOBACTER PYLORI ИНФЕКЦИЈА

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Постојат многубројни публикувани трудови кои укажуваат дека *Helicobacter pylori* има критичка улога во различни екстрагастрични болести. Откривањето на многубројни нови *Helicobacter* специеси ги стимулира истражувањата кај различни екстрагастрични болести, кај кои е применлива инфективната хипотеза. Се претпоставува дека ентеропатските *Helicobacter* специеси имаат улога во различни екстрагастрични заболувања, вклучително екстрагастрични манифестации на *Helicobacter* инфекцијата. Авторите прикажуваат возрасен пациент со Henoch-Schönlein purpura и комплетна регресија на болеста по спроведување на трипла ерадикациона анти *Helicobacter* терапија. Пациентот беше следен во текот на речиси 9 години по спроведената ерадикација, по пат на контролни клинички прегледи и серолошки.

Во текот на следењето не дојде до релапс на болеста, ни до појава на маркери за *Helicobacter pylori* реинфекција. Поради фактот дека релапсите не се јавуваат во текот на неколку недели до месеци, авторите заклучуваат Henoch-Schönlein purpura е можна екстрагастрична, кутана манифестација на *Helicobacter pylori* инфекцијата.

Клучни зборови: Henoch-Schönlein пурпура, *Helicobacter pylori* инфекција.

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