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Immunological Manifestations of *Helicobacter pylori* Infection: Polyserositis?

Helicobacter pylori İnfeksiyonunda Bağışıklık Yanıtı: Poliserozit

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Abstract

Polyserositis is the general inflammation of serous membranes with associated effusion. Except for tuberculosis and coxsackie virus, infections are a very rare cause of polyserositis. We describe a case of a 41-year-old woman with chronic mild thrombocytopenia that presented with polyserositis and whose investigation was negative for common causes of serosal inflammation, showing great clinical improvement after *Helicobacter pylori* eradication therapy. Besides serositis, we also discuss other immunological manifestations of *Helicobacter pylori* infection. To our knowledge, this is the first case that establishes *Helicobacter pylori* as a potential cause of serosal inflammation, thus expanding immunological manifestations of *Helicobacter pylori* infection.

Keywords: *Helicobacter pylori*, serositis, thrombocytopenia

Öz

Poliserozit seröz membranlara karşı oluşan genel yangı ile birlikte oluşan efüzyondur. Bu olgu sunumunda bir serozal yangı nedeni bulunmayan, ılımlı kronik trombositopenisi olan 41 yaşındaki kadın hastada gelişen poliserozitin, var olan *Helicobacter pylori* enfeksiyonunun tedavisinden sonra tam bir klinik iyileşme gösteren vaka sunuldu. Bu sunumda, serozit dışında, *Helicobacter pylori* enfeksiyonunun bağışıklık sistemindeki etkileri de tartışıldı. Bu olgu sunumu, bilgilerimize göre, *Helicobacter pylori* enfeksiyonunun neden olduğu gösterilen ilk serozaya karşı yangı makalesidir ve buradaki bulgular *Helicobacter pylori* enfeksiyonunun bağışıklık sisteminde meydana getirdikleri ile ilgili bilgilerimizi artırmaktadır.

Anahtar Kelimeler: *Helicobacter pylori*, serozit, trombositopeni

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Introduction

Polyserositis is defined as general inflammation with effusion of serous membranes, such as the pericardium, pleura and/or peritoneum at the same time.[1] Therefore, transudative (non-inflammatory) effusions are excluded, including heart, renal and hepatocellular failures, even though such distinction is usually only possible with analysis of serosal fluids.[2] Causes of polyserositis include autoimmune and autoinflammatory disorders, infections, tumors, drugs, hematological and endocrine disorders, as shown in Table 1. In fact, serosal involvement is frequent in both autoimmune and autoinflammatory disorders and polyserositis incorporates common classification criteria of systemic lupus erythematosus (SLE) and Familial Mediterranean fever (FMF).[3] It is also estimated that tumors are responsible for about 20% of cases and this proportion rises when peritoneum is involved.[4] In a recent retrospective study of 92 patients with polyserositis, a cause could not be established in about 42% of cases and serosal involvement was limited to pleura and pericardium in 83%.[4] Infectious causes are not common in patients with

Table 1. Causes of polyserositis

	Examples
Autoimmune and autoinflammatory disorders	Adult-onset Still's disease, celiac disease, cryopyrin-associated periodic fever syndromes, **familial Mediterranean fever**, mixed connective tissue disease, inflammatory bowel disease, IgG4-related disease, polyglandular autoimmune syndrome type II, polymyositis, rheumatoid arthritis, Sjögren's syndrome, **systemic lupus erythematosus**, systemic sclerosis, tumor necrosis factor-associated periodic syndrome
Drugs*	Amiodarone, antivirals, clozapine, everolimus, methotrexate, praziquantel, ramipril, TNF inhibitors, trimethoprim/sulfamethoxazole, tyrosine kinase inhibitors, vaccines (13-valent pneumococcal conjugate vaccine)
Endocrine disorders	**Hypothyroidism** (myxedema), panhypopituitarism
Hematological disorders	Acute intermittent porphyria, acute myeloid leukemia, allogeneic bone marrow transplant transplantation, chronic myelomonocytic leukemia, graft-versus-host disease, lymphomas, multicentric Castleman's disease (TAFRO syndrome, Castleman-Kojima disease), myelodysplastic syndromes, nasal-type T/NK-cell lymphoma, Waldenström's macroglobulinemia
Infections	Bacteria (*Bartonella henselae, Burkholderia pseudomallei, Chlamydia spp., Coxiella burnetii, Listeria monocytogenes, Mycoplasma pneumoniae, Neisseria meningitidis, Salmonella enterica, Streptococcus pneumoniae*), **tuberculosis**, viruses (adenovirus, **coxsackie**, herpesvirus, **HIV****, influenza, mumps, parainfluenza, parvovirus B19)
Neoplasms	Breast cancer, gastric adenocarcinoma, **lung cancer** (mainly adenocarcinoma), pancreatic adenocarcinoma, mucinous cystadenoma of appendix, ovarian cancer (Meigs syndrome)
Others	Camptodactyly-arthropathy-coxa vara-pericarditis syndrome

*Drug-induced lupus is commonly described with listed examples.
**Polyserositis is probably the manifestation of opportunistic infections in such patients.
Note: Common causes of polyserositis are highlighted in bold.

polyserositis except tuberculosis, *Salmonelle enterica* and rarely some opportunistic infections such as *Bartonella henselae* in immunocompromised patients.[4–6]

Helicobacter pylori has classically been associated with gastroduodenal disorders, including peptic ulcer disease, eosinophilic esophagitis, functional dyspepsia, atrophic gastritis and, possibly, negatively with gastroesophageal reflux and Barrett's metaplasia.[7] However, several extragastric manifestations of *Helicobacter pylori* infection are now well established, particularly hematological conditions such as idiopathic thrombocytopenic purpura (ITP), iron-deficiency anemia and vitamin B12 deficiency.[8] Testing for *Helicobacter pylori* is recommended in peptic ulcer disease, gastric cancer, low-grade gastric mucosa-associated lymphoid tissue lymphoma (MALToma), long-term nonsteroidal anti-inflammatory drugs or aspirin, dyspepsia, unexplained iron-deficiency anemia, ITP and after completion of eradication therapy.[9] However, *Helicobacter pylori* has also been variably implicated in many other diseases where infection appears to be more prevalent than in controls, including cardiovascular (e.g., coronary heart disease), gastrointestinal (gallstone disease, non-alcoholic fatty liver disease, pancreatitis, pancreatic cancer, colorectal cancer and hepatic encephalopathy), neurologic (increased carotid intima-media thickness, vascular dementia, cognitive impairment, Alzheimer's disease and increased severity of Parkinson's disease), respiratory (chronic obstructive pulmonary disease and adult-onset asthma, which is contrary to the protective effect seen in allergic and childhood asthma), dermatologic (chronic spontaneous urticarial, erythrosis and rosacea), uro-gynecologic (infertility, gestational diabetes and pre-eclampsia), metabolic (diabetes mellitus and metabolic syndrome), head and neck diseases (central serous chorioretinopathy, glaucoma, chronic tonsillitis, recurrent aphthous stomatitis and periodontal diseases).[10–12]

Immunological manifestations of *Helicobacter pylori* infection can involve different organs. The prevalence of *Helicobacter pylori* infection appears to be lower in patients with inflammatory bowel disease (IBD) and an inverse relationship between microscopic colitis and *Helicobacter pylori* has been described.[11] In fact, treatment for *Helicobacter pylori* infection may be associated with a significant increase in the risk of autoimmune diseases, including IBD.[13] Similarly, the same inverse relationship may also be present in other acquired autoimmune disorders where *Helicobacter pylori* exerts a protective role, including celiac disease. On the other hand, cohorts and prospective studies have suggested a positive association between *Helicobacter pylori* infection and primary biliary cirrhosis.[11] Autoimmune thyroid diseases, including Grave's disease and Hashimoto's thyroiditis, have also been

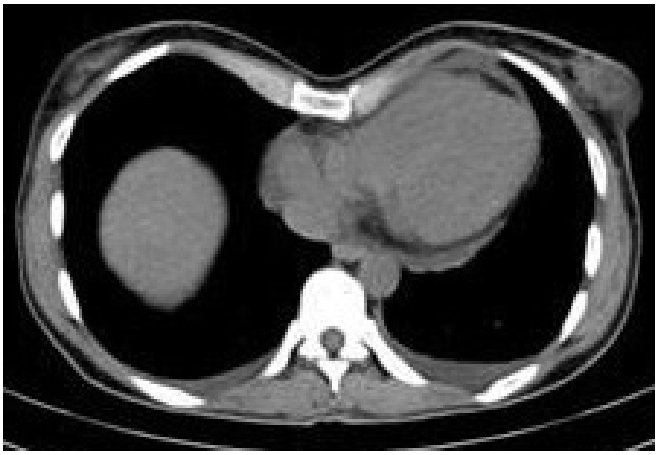

Figure 1. Computed tomography (CT) scan showing small-sized pericardial and bilateral pleural effusions.

positively associated with *Helicobacter pylori* infection, whilst eradication therapy has promoted disappearance of vitiligo manifestations in a minority of patients.[12]

We describe a case of polyserositis in a middle-aged woman whose work-up was negative for common causes of serosal inflammation, showing great clinical improvement after *Helicobacter pylori* eradication therapy. Patient consent was obtained for publication of the case report.

Case Report

A 41-year-old woman was referred to our Internal Medicine outpatient department presenting with fatigue and general discomfort, anorexia and unspecified unintentional weight loss lasting for a few months. She had no fever, nausea and vomiting, diarrhea, respiratory symptoms, arthralgia or skin rashes, but reported epigastric discomfort related to food ingestion. The obtained Glasgow Dyspepsia Severity Score (GDSS) was 14. Her relevant past history included major depression, mild chronic thrombocytopenia and a transient ischemic attack (TIA) six years before whose etiologic work-up was not known. Her gynological and obstetric history was irrelevant with no miscarriages. She was taking low-dose acetyl-salicilic acid and escitalopram daily. Physical examination was unremarkable except for epigastric discomfort on palpation. A computed tomography (CT) scan showed small-sized pericardial and bilateral pleural effusions, along with hepatic subcapsular and gallbladder wall thickening and periportal edema (see Figure 1). Laboratory workup was therefore obtained in order to clarify the cause of polyserositis: cell blood count

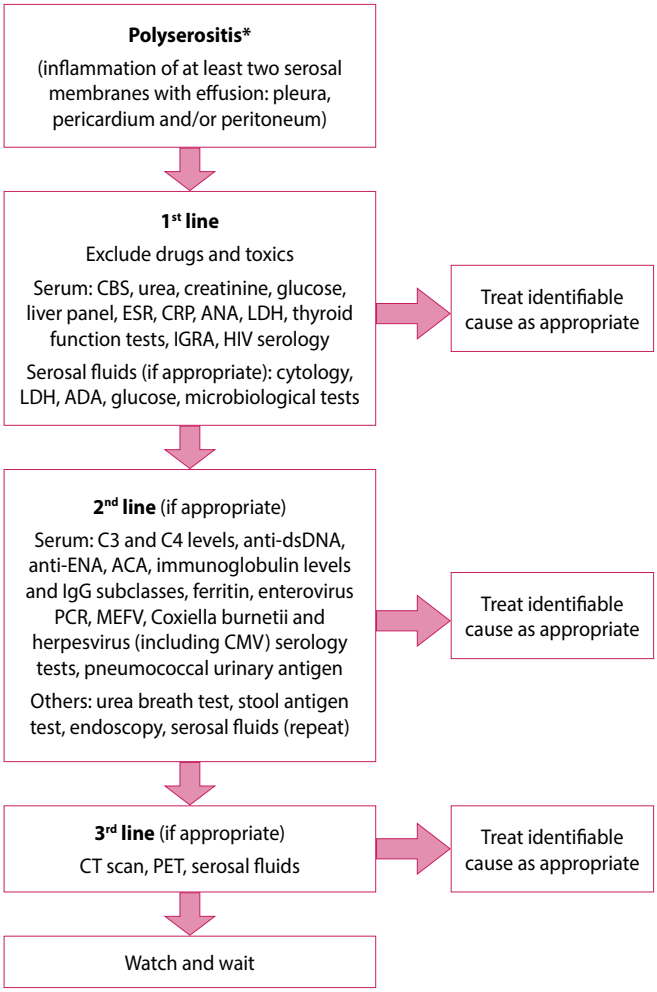

Figure 2. A workup algorithm for polyserositis.

showed only mild thrombocytopenia (platelet count of 130 x 10^9/L); acute phase reactants, electrolytes, renal and thyroid function and liver panel tests were within the normal range; immunological workup was non-conclusive, including antinuclear, antiplatelet, antiphospholipid and anti-dsDNA antibodies and extractable nuclear antigen (ENA) panel, while complement levels and serum immunoglobulins were the normal range; interferon-gamma release assay (IGRA) and human immunodeficiency virus (HIV) serology were negative and microscopic urinalysis was normal. Esophagogastroduodenoscopy revealed marked erythema in gastric antrum mucosa and first portion of the duodenum with few erosions. Biopsies were obtained and histological analysis demonstrated moderate chronic gastritis with signs of activity and no intestinal metaplasia or epithelial dysplasia in the gastric antrum (and to a lesser degree in the gastric body), along with foveolar hyperplasia. The search for *Helicobacter pylori* by Giemsa staining was highly positive in the gastric

antrum. Sequential therapy regimen for *Helicobacter pylori* eradication with esomeprazole, amoxicillin, clarithromycin and metronidazole was prescribed. After completion, the patient mentioned that all symptoms had disappeared, gaining about three kilograms one month after eradication therapy. Another CT scan was obtained three months after antibiotic treatment, showing no pleural or pericardial effusions but only minimal subcapsular thickening. At this time, urea breath test was also negative for *Helicobacter pylori* infection, while thrombocytopenia had resolved (platelet count of 211 x 10^9/L).

Discussion

ITP has been linked to several infectious agents, including *Helicobacter pylori*. Eradication therapy is able to significantly increase platelet counts even after the third or fourth-line regimen, but such response is more marked in some ethnic groups (e.g., Hispanics).[12] In adults, the 2011 American Society of Hematology practice guideline for ITP proposed that screening for *Helicobacter pylori* should be considered in patients in whom eradication therapy would be used if testing is positive, thus recommending eradication therapy in secondary (*Helicobacter pylori*-associated) ITP, which is expected to achieve an overall response (platelet count ≥30 x 10^9/L and at least doubling of the basal values) in about 50% of cases.[14] Our patient had high platelet count that followed eradication therapy. Antiplatelet antibodies were negative but both Fc receptor (FcR) clearance of antibody opsonized platelets by spleen macrophages and FcR-independent mechanisms of platelet clearance by anti-glycoprotein Ib antibodies have been recognized in ITP.[15]

Regarding the history of TIA, one should mention that *Helicobacter pylori* has been associated with anticardiolipin antibody positivity and its eradication with the disappearance of such antibodies and even of clinical manifestations of antiphospholipid syndrome (APS), although described infectious triggering factors of APS have been mostly viral.[16,17] However, the absence of typical manifestations of APS such as poor obstetric outcomes or venous thromboembolism in our patient makes the diagnosis of seronegative APS less probable than atypical ITP. To our knowledge, serositis might be a rare manifestation of secondary APS but not for primary ITP, so both serositis and thrombocytopenia may constitute immunological manifestations of *Helicobacter pylori* in this clinical scenario.[18] Non-specific activation of the immune system, as described for secondary ITP, might explain such association, but molecular mimicry and other mechanisms cannot be excluded at this point.[19]

In autoimmune serositis, autoantigens cannot be eliminated and induce cycles of injury and repair, surpassing the ability of fibrinolysis to prevent fibrosis, as it commonly occurs in SLE.[20] Mechanisms of serositis in many autoimmune disorders often include not only the activation of mesothelial cells that may lead to excessive serosal fluid production, but also microvascular injury and increased capillary permeability that may be present in serositis secondary to *Helicobacter pylori* infection.[21] However, serositis is strongly associated with autoinflammatory/inflammasome-driven disorders where the innate immune system has a central role such as FMF, and even in SLE, a prototypic autoimmune disorder, a possible link with the innate immune system has been described in relation to specific manifestations such as serositis. Specifically, reduced P2X7R expression in patients with SLE-related serositis has been associated with increased IL-6 signaling.[22] Therefore, it is possible that pathogenetic mechanisms that are responsible for serositis in *Helicobacter pylori* infection could eventually also be dependent on a primary dysfunction of the innate immune system, besides activation of mesothelial cells and/or microvascular injury. Even though lipopolysaccharides and flagellin do not efficiently activate Toll-like receptors and *Helicobacter pylori* commonly avoids many innate immune system receptor-mediated activations, it can activate neutrophils by producing neutrophil activating protein and also promote gastritis by inducing Nod1-dependent inflammatory responses; in fact, it has been demonstrated that *Helicobacter pylori* is able to counteract both T cell and innate immune responses.[23,24]

Considering the high prevalence of *Helicobacter pylori* infection in the general population, it is reasonable to include a noninvasive screening test (urea breath tests or stool antigen tests) in the workup algorithm of polyserositis (Figure 2) if such association is established. Such rationale is supported by the high proportion of idiopathic cases and the fact that *Helicobacter pylori* is a potentially treatable cause of polyserositis. A retrospective study has included 92 patients with polyserositis but only three with pleura-pericardium-peritoneum involvement, of whom only one had an identifiable cause (unknown origin adenocarcinoma).[4] To our knowledge, this is the first case

that identifies *Helicobacter pylori* as a potential etiologic agent of polyserositis, thus expanding immunological manifestations of *Helicobacter pylori* infection.

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