Case report

Psoriasis vulgaris and digestive system disorders: Is there a linkage?

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Abstract: Psoriasis is well-known immune-mediated skin disease often associated with co-morbidities, including dyslipidaemia and obesity. Few reports imply that the disease might be also related to pathology of mucosal surfaces, especially that of the digestive system. The authors present a case of psoriasis and concurrent digestive system abnormalities, and review the literature regarding the topic. A 40-year-old man suffered from an exacerbation of exudative psoriasis for about 6 months. Topical antipsoriatics proved ineffective and the disease gradually progressed to a severe disseminated form. Subsequent detailed examinations revealed persistent gastroduodenitis due to *H. pylori* infection, pancreatic dysfunction and fatty change of the liver, although the patient denied any gastrointestinal symptoms. As a result appropriate treatment of the diagnosed digestive system disorders was added to topical antipsoriatic therapy. Within 2 weeks of treatment clinical symptoms and laboratory signs showed a marked trend to normalisation. The presented medical history seems to suggest that there may be some kind of interplay between psoriasis and digestive system disorders.

Key words: psoriasis; digestive system; gastritis, pancreatitis; chronic liver disease

Introduction

Psoriasis is an immune-mediated disease of skin and joints often precipitated by infection. Cutaneous involvement is always the predominant feature. However, a couple of reports suggest that there might be also a connection between psoriasis and other organ disorders, including that of the digestive system [1].

A relationship between *Helicobacter pylori* infection and skin disease, especially chronic urticaria, have been documented. *Helicobacter pylori* eradication appears to be beneficial in patients with lichen planus, prurigo, Sjögren's syndrome, Henoch-Schönlein purpura, and rosacea [2,3]. Moreover, there are hypotheses implicating the pathogen in triggering psoriasis [3]. There are also data concerning concurrent presentation of psoriasis and gastritis, duodenitis, celiac disease or inflammatory bowel disease [4-6]. A few authors have related psoriasis and disturbances of the incretory and excretory pancreatic functions and even acute pancreatitis [7-9]. Single reports on liver dysfunction or chronic liver disease in psoriatic individuals have been published, including hepatic cirrhosis or psoriasis being a cutaneous sign of hepatocellular carcinoma [10-14].

Disposition to psoriasis is primarily genetic, but some dysmetabolic changes, such as obesity, dyslipi-

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Fig. 1. Patient's lower extremities before (**a**) and after 2 weeks of treatment (**b,c**). Detailed description in text.

daemia, hyperuricaemia, impaired glucose tolerance or insulin resistance, may increase the risk for psoriasis as well as for some of the digestive system disorders, especially liver diseases [10-11]. On the other hand, pro-inflammatory factors upregulated in psoriasis, especially interleukin (IL) 18, are likely to increase risk of the metabolic syndrome [15]. Previous reports have endorsed an association between psoriasis and the metabolic syndrome or lipid abnormalities [6,16,17]. Furthermore, psoriasis is believed to be an independent risk factor for subclinical atherosclerosis [6]. At present the lipid profile, lipoprotein, apolipoprotein, brain (B-type) natriuretic peptide (BNP) and its metabolite, N-terminal pro-B-type natriuretic peptide (NT-proBNP), levels are considered to be good predictors of cardiovascular disease and may be useful markers of cardiovascular risk in psoriatics [6,18].

The association between psoriasis and digestive system disorders remains unclear. The current report present a case of psoriasis associated with multiple digestive system disorders and review the literature regarding the topic.

Case presentation

A 40-year-old man presented with signs and symptoms consistent with severe and disseminated exudative psoriasis. The patient had been diagnosed as having psoriasis at 8 years of age, and for 32 years he had been presenting with only few small skin plaques with no need for systemic treatment or hospitalisation. Approximately 6 months preceding admission he suddenly developed a severe exacerbation of the disease. He was treated with various topical corticosteroid preparations, such as fluticasone, clobetasol or betamethasone with salicylic acid ointments (subsequently), and short-term oral doxycycline (2×100 mg/d; 10 days) and niacin (3×200 mg/d). However, the treatment proved ineffective and his skin condition gradually worsened, especially following a flu-like illness 2-3 weeks prior to the admission. On admission the patient suffered from intense pruritus within the involved skin and malaise. He made no other complaints; he denied any prior or current gastrointestinal symptoms. His medical history included hypertension for more than 3 years, and his daily medication consisted of perindopril (1×5 mg/d). However, due to normal blood pressure values (mean 135/70 mmHg) for more than 2 months, the antihypertensive drug had been withdrawn. The patient did not have any history of blood transfusion or habitual alcohol consumption, and had not ingested alcohol or any drugs known to induce pancreatitis or liver damage prior to the admission. There was substantial tobacco consumption habit, up to 30 cigarettes per day. A family history of psoriasis was apparent; the patient's mother suffered from the disease since childhood. Of

note, the patient had neither familial nor personal history of gastrointestinal disorders.

On the admission psoriatic lesions covered approximately 40% of the cutaneous surface, including the scalp, trunk, buttocks, and upper and lower extremities, but not the face, neck, palms and soles. There were a large number of patches, ranging in size from 1 to 10 cm in diameter and having a tendency to confluence. The most prominent lesions were present on the right shin, involving the entire anterior and lateral aspect of the limb. They were very distinctive, full red colour with a violaceous tint and covered with fine scales (Fig. 1a). The psoriatic plaques on medial aspect of the left shin, as well as the lesions on medial surfaces of both arms and forearms displayed the trend to coalesce into large patches, up to man's hand size. Small water drop-shaped or coin-shaped plaques up to large patches covered with medium scales were observed on the other involved areas. The thighs were the exception with the lesions inflamed, thick and multilayered associated with overlapping scales resembling rupees. The PASI score was estimated at 28.7. Physical examination demonstrated overweight, body mass index was calculated at 29.76 kg/m^2. There was no evidence of any bacterial or viral infection.

Laboratory data (Table 1) revealed a remarkable elevation of serum lipase and amylase activity and abnormal liver function tests. The levels of total cholesterol and LDL cholesterol were slightly increased, whereas the serum concentrations of triglyceride and HDL cholesterol were within normal range. More detailed analysis disclosed abnormal ApoB/ApoA-I ratio. In addition, there were significant increases in serum level of CRP (C reactive protein) and NT-proBNP. All virologic and serologic markers for hepatitis B and C virus were negative. An abdominal ultrasound revealed slight hepatomegaly and inhomogeneous fatty change of the liver (Fig. 2). No stones or sludge of the gallbladder and of the common bile duct were detected. The pancreas was homogeneous and measured 25 mm at the head, 26 mm at the body, and 29 mm at the tail. An upper gastrointestinal tract endoscopy displayed no macroscopic pathology of the oesophagus, stomach or duodenum. *H. pylori* infection was diagnosed with a biopsy check during endoscopy with a rapid urease test. Histological examination of gastric and duodenal mucosa biopsies disclosed significant inflammatory changes (Fig. 3). Despite remarkable disturbances of serum lipid profile, there were no significant abnormalities on cardiological examination. The transthoracic echocardiography revealed only negligible dilatation of the left atrium and ventricle and slight left ventricle hypertrophy, but there were no changes of the left ventricle ejection fraction.

Initially topical treatment for psoriasis consisted of dexpanthenol aerosol. Subsequently it was continued

Fig. 2. Liver ultrasound scan. Inhomogeneous increase of the liver echogenicity within the segment 4 of the right lobe (arrowheads), the segment 7 of the right lobe and the segments 2 and 3 of the left lobe. Hepatomegaly; the liver size in the anterior axial line was 146 mm; in the midclavicular line, 119 mm; and in the sternal line, 84 mm.

with corticosteroid preparations, including hydrocortisone ointment, betamethasone with salicylic acid ointment and then fluticasone cream, combined with 0.125-0.25% cignolin, cholesterol, urea with salicylic acid, salicylic acid sulfur soap, or sulfur salicylic acid ointments. In addition, oral antihistamine therapy with clemastine (2×1 mg/d) for 10 days and subsequently with fexofenadine (1×180 mg/d) was introduced. Therapeutic measures for gastrointestinal disorders included appropriate diet and pancrelipase (10,000 IU per meal or snack; 3×/d), as well as hepatoprotectants, such as thiazolidine-4-carboxylic acid (3×200 mg/d) and essential phospholipids, especially 3-sn-phosphatidylcholine (2×300 mg/d). The patient received vitamin E (3×100 mg/d), and ascorbic acid combined with rutoside (3×200+50 mg/d) as well. Moreover, with the *H. pylori* infection diagnosis the standard treatment for the pathogen eradication was initiated, consisting of amoxycillin (2×1 g/d; 10 days) and clarithromycin (2×500 mg/d; 14 days) combined with omeprazole (2×20 mg/d; 14 days). Within 2 weeks of the treatment a considerable clinical improvement was achieved. The itching subsided. The skin lesions started to remit gradually. At the time of discharge psoriatic scales persisted only on the skin of knee-joints and right shin, at the other sites previously covered with lesions there were distinct post-inflammatory hyperpigmentations (Fig. 1b, c). Simultaneously trend to normalisation of the pancreas and liver function parameters was observed (Table 1).

Table 1. Clinical characteristic of the patient (normal reference ranges are given in parentheses; * for individuals younger than 75 years).

		On admission	During treatment	At discharge
PASI score		28.70		19.20
Peripheral blood				
Red blood cell count (M/mm^3)	(4.00-5.70)	3.94		
Haematocrit level (%)	(40-54)	40.60		
Haemoglobin (g/dL)	(13-18)	13.30		
MCV (fL)	(80-100)	103		
White blood cell count (K/mm^3)	(4-10)	7.70		
Thrombocyte count (K/mm^3)	(120-400)	341		
Serum chemistry				
CRP (mg/dL)	(0-10)	23.70		21.50
Total bilirubin (mg/dL)	(0.20-1.10)	0.72		
Glucose (mg/dL)	(65-100)	92		
Uric acid (mg/dL)	(3-7)	4.28		
Total cholesterol (mg/dL)	(120-200)	238		194
HDL cholesterol (mg/dL)	(35-60)	45		34
LDL cholesterol (mg/dL)	(70-135)	173		127
Triglyceride (mg/dL)	(40-160)	100		164
ApoA-I (g/L)	(1.10-2.10)	1.15		0.81
ApoB (g/L)	(0.50-1.40)	1.31		1.11
ApoB/ApoA-I	(~0.50)	1.13		1.37
NT-proBNP (pg/mL)	(110-125)*	660		752
Homocystein (μmol/L)	(5-12)			8.43
Pancreatic Lipase – EC 3.1.1.3 (IU/L)	(7-60)	319	75	66
α-Amylase (U/L)	(20-80)	135		67
ALT (IU/L)	(10-40)	62		27
AST (IU/L)	(10-40)	151		53
γ-GTP (IU/L)	(11-50)	559	390	144
Sodium (mmol/L)	(135-148)	143		138
Potassium (mmol/L)	(3.40-5.50)	4.03		3.80
Calcium (mmol/L)	(2.10-2.60)	2.19		
Chlorine (mmol/L)	(94-105)	110		103
Virus markers				
HBs-Ag			absent	
HCV-Ab			absent	
Urinalysis		normal	normal	normal

ALT – alanine transferase; ApoA-I – apolipoprotein A-I; ApoB – apolipoprotein B; AST – aspartate transferase; CRP – C reactive protein; γ-GTP – γ-glutamyl transpeptidase; HBs-Ag – hepatitis B surface antigen; HCV-Ab – hepatitis C virus antibody; HDL – high density lipoprotein; IU/L – international units/liter; LDL – low density lipoprotein; MCV – mean corpuscular volume (i.e. average red blood cell size); NT-proBNP – N-terminal pro B-type natriuretic peptide; PASI – Psoriasis Area and Severity Index.

Discussion

Little is known about the potential relationship between psoriasis and gastrointestinal, pancreas and liver dysfunction. However, the digestive system disorders are speculated to be involved in the psoriasis pathology. The presented case, consistently with a few published reports, appears to suggest that *H. pylori* infection may be related to psoriasis. Nevertheless, the
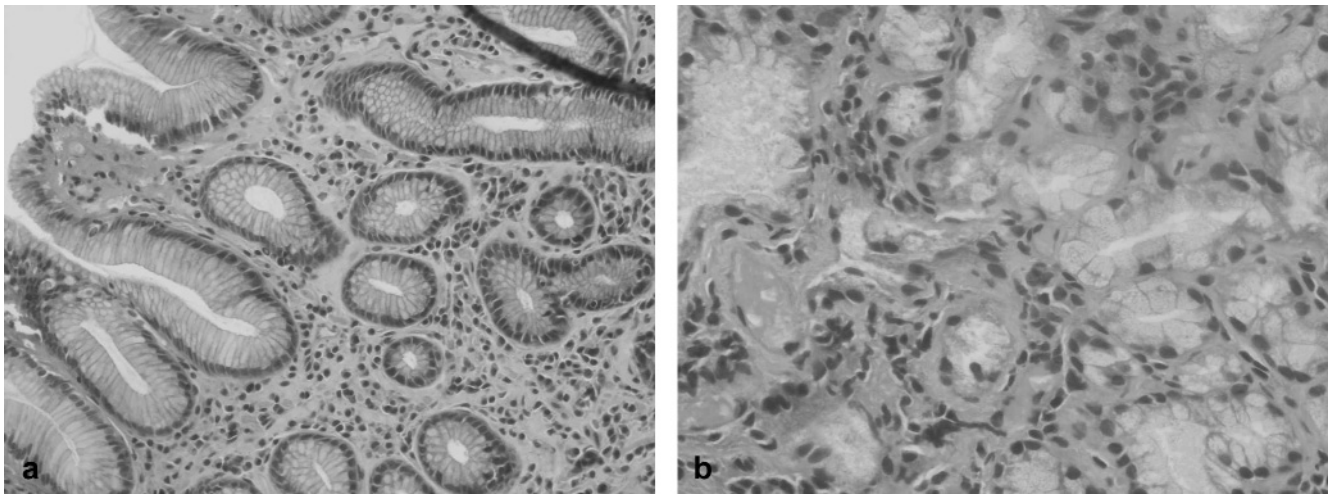
Fig. 3. Histological examination of gastric (**a**) and duodenal (**b**) biopsies (H+E). (**a**) Gastric mucosa with hyperaemia, oedema and moderate infiltration with plasma cells and lymphocytes as well as single eosinophils and neutrophils (original magnification, ×20). (**b**) Duodenal mucosa with considerable hyperaemia and oedema, most prominent within stroma of the duodenal papilla. Moreover, there is moderately increased cellularity of the mucosa with lymphocytes and plasma cells, and single neutrophils and eosinophils (original magnification, ×40). The histopathological examination is consistent with persistent gastritis and duodenitis, respectively.

existing literature data are conflicting. Some authors described marked improvement and/or remission of the refractory disease following proven bacteria eradication [19,20], whereas others consider the approach to be of no benefit to psoriatic individuals [21]. For example, Dauden *et al.* [21] observed no improvement of psoriatic lesions, despite successful *H. pylori* eradication. Potential cutaneous pathology of *H. pylori* remains unknown, but it may be associated with a superantigen effect of the bacteria or their products, increased mucosal permeability of the gastrointestinal tract, various autoimmune mechanisms, or impairment of vascular integrity [2]. Recently, a hypothesis of superantigen-mediated pathogenicity has became a focus for research on psoriasis [22]. This new concept of psoriasis pathophysiology, defining it as a Th-1-mediated disorder, implicates superantigens in triggering the disease. As they bind MHC class-II molecules, not only constitutively expressed HLA-DR molecules on professional antigen-presenting cells, including macrophages and dendritic cells, but also cytokine-induced HLA-DR molecules on nonprofessional antigen-presenting cells, such as keratinocytes, without any prior processing, superantigens easily prime large number of resting T cells. Superantigen-induced T cells are likely to produce large amounts of inflammatory cytokines, including TNF-α and -β, IL-2 or INF-γ [2,22]. It is enticing to speculate that some of unique virulence factors developed by *H. pylori* to survive and proliferate in the stomach may act as superantigens (i.e. immunostimulatory molecules acting as Vβ-restricted extremely potent polyclonal T cell mitogens). These may include the urease, flagellar proteins, an H-gated urea transporter, several adhesins, and espe-

cially multifunctional vacuolating cytotoxin A (VacA) and the cytotoxin-associated gene pathogenicity island (cag-PAI). Of note, expression of the cag-PAI is responsible for the building of a secretion apparatus delivering some bacterial proteins, such as an immunodominant antigen cag A, directly into the cytosol of host cells [2,23]. However, preliminary study of Dauden *et al.* [23] indicated that cag A status was not associated with type, severity and duration of psoriasis. Another factor probably linking *H. pylori* infection and the psoriasis pathophysiology is increased mucosal permeability of the stomach and intestine. Abnormalities of gastric or intestinal epithelium structure and function might result in a greater exposure to alimentary antigens or toxins, including microbial factors. These may leak into circulation, evoke specific immune response and eventually may be deposited along the skin basement membrane zone, which is believed to be the first step of their percutaneous elimination. If microbial antigens share structural homologies with skin components (molecular mimicry), the additional result may be the development of antigen-antibody complexes, cross-reactive antibodies or specific T cells cross-reacting against epidermal autoantigens [24,25]. For example, molecular mimicry between *H. pylori* antigens and keratin 17 may result in activation of autoreactive T cells and augment keratinocyte hyperproliferation [22]. Moreover, some *H. pylori* products or structural proteins may cross-react with such extragastrointestinal epitopes as Lewis antigens [26,27], sialylated glycoconjugates [28] or sialic residues of laminin [29]. Humbert *et al.* [30] findings seem to support the hypothesis. Increased mucosal permeability of the stomach and intestine has

been demonstrated in *H. pylori*-infected subjects as well [31]. Vascular impairment is considered to be another important component of the most skin diseases linked to *H. pylori* infection. Animal studies demonstrated that the bacteria disrupted interstitial and intravascular cell to cell interactions, leading to marked microvascular dysfunction [32]. Furthermore, it is probably associated with increased levels of fibrinogen [33], and platelet activation and aggregation [34], other processes implicated in the microvascular dysfunction and inflammatory-cell recruitment.

Presented medical history may also signal the relationship between psoriasis and pancreas disorders. Intriguingly, no clinical signs or symptoms of pancreatitis were reported; especially the patient denied abdominal pain, which is a dominant feature of the disease. Literature data indicate that asymptomatic abnormalities of pancreatic enzymes are not infrequent in patients with inflammatory bowel diseases, or positive for chronic hepatitis B or C virus, or HIV infection. Most of these patients do not develop clinical pancreatitis and usually do not require specific therapy [35,36]. Only few reports regarding the pancreas dysfunction in psoriasis have been published [7,8]. Pietrzak *et al.* [7] demonstrated higher serum levels of pancreatic lipase in male psoriatics compared to healthy controls. Khardikova *et al.* [8] observed impaired exocrine and endocrine pancreas function in psoriatic individuals, the latter finding may account for higher prevalence of diabetes mellitus in psoriasis [37]. Recently recurrent acute pancreatitis over the course of psoriatic arthritis has been described [9]. In the case presented here interpretation may be biased by the patient's hypertension history and perindopril administration. One should remember that some systemic as well as topical medications were sporadically linked to acute pancreatitis [38-41] including angiotensin-converting enzyme inhibitors (i.e. perindopril) [42,43]. However, the patient had not presented with any signs and symptoms within prior three-year antihypertensive treatment, and due to normal blood pressure values, he had not been taking the compound for more than 2 months preceding the diagnosis of pancreatitis. Other pancreatitis causes, including mechanical obstacle or current heavy drinking, were excluded with the use of various gold-standard techniques. Possible relationship between psoriasis and pancreatitis remains an enigma. A noteworthy hypothesis could be that of intestinal barrier dysfunction, all the more since some authors reported increased intestinal permeability in patients with acute pancreatitis [44,45]. There is, however, another possibility. Some clinical and experimental evidence suggests that the immune system and pro-inflammatory cytokines play a key role in the pathogenesis of acute pancreatitis, with IL-18 being one of the pivotal mediators of inflammation [46]. One

should appreciate that IL-18 is believed to be involved in psoriasis development and is up-regulated in psoriatic individuals [47,48].

At the end of the list of digestive system pathology observed in the presented case, but not least, are liver abnormalities. The literature analysis revealed a couple of reports of recurrent cholestatic jaundice related to generalised pustular psoriasis. The jaundice episodes were of unclear pathogenesis, but some neutrophilic cholangitis was documented on liver biopsy. It raised the question whether the organ was the subject to the same disorder as the skin, inasmuch accumulation of neutrophils in the epidermis is one of the vital histological features of pustular psoriasis [12,13]. Apart from biliary involvement in the course of pustular psoriasis, nonalcoholic steatohepatitis was linked to psoriasis vulgaris [10,11]. The fatty liver change related to psoriasis vulgaris were noted in the "POLI.ST.E.N.A." study, being a prospective survey on the nonalcoholic fatty liver disease (NAFLD) [10]. The conditions coexisted in overweight or obese young adults with a central-type body fat distribution. Of note, not only is obesity believed to be associated with NAFLD, but also it has been reported to be a separate risk factor for more severe psoriasis [6,49,50]. Given the current trends in systemic therapy of psoriasis, especially the usage of drugs of well documented hepatotoxicity, e.g. methotrexate, the association of the disease and even modest liver damage might be of great clinical importance [51]. The pathogenetic link between psoriasis, obesity and NAFLD remains unclear. However, evolving research suggests that the chronic inflammatory nature of psoriasis itself may be an important factor for the mentioned relationships. Psoriasis is characterised by a Th1 cytokine preponderance, and these factors have pleiotropic effects on a large variety of processes, including angiogenesis, insulin signalling, adipogenesis, lipid metabolism, immune cell trafficking, or epidermal proliferation. Therefore, pro-inflammatory cytokines (*e.g.* TNF, IL-6, IL-18) are not only implicated in the psoriasis pathogenesis, but might cause inflammation in other organs as well [15]. For example, IL-18 was significantly upregulated in subjects with NAFLD and according to Vecchiet *et al.* [52] the factor might be even an important marker of liver diseases. In turn enhanced expression of TNF and IL-6 has been detected in the adipose tissue, which may implicate it in the local and systemic inflammatory responses [53].

The association between psoriasis and the metabolic syndrome gives rise to particular concern, due to a possible increase of cardiovascular risk. Indeed epidemiological studies revealed high prevalence of cardiovascular co-morbidity among psoriatic patients [6,54]. Refractory dyslipidaemia and other lipid profile abnormalities, especially abnormal ApoB/ApoA-I

ratio and NT-proBNP level (heart failure marker), observed in the presented case seem to confirm described relationships and may signal the very onset of atherosclerotic vascular disease. The root cause of NT-proBNP level increase in the current case is unclear, but it may indicate the presence of cardiac dysfunction, in spite of insignificant cardiac examination. Of course, one should not overlook potential confounding factors that might significantly contribute to NT-proBNP elevation, including smoking, hypercholestrolaemia or drugs (e.g. angiotensin-converting enzyme inhibitors). Importantly, literature data demonstrated unchanged hepatic degradation of NT-proBNP in cirrhosis and no correlation was found between the marker levels and the hyperdynamic circulatory changes in cirrhotic subjects [55]. On the other hand, the levels of BNP and NT-proBNP tend to be lower in obese people, and hepatic steatosis is rather associated with low levels of NT-proBNP [56,57].

The findings of this case seem to suggest some kind of interplay between psoriasis and digestive system disorders. Further studies are needed to establish if the pathogenic links exists and elucidate a possible chain of cause and effect as well as time relationships between specific disorders.

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