Subacute cutaneous lupus erythematosus due to proton pump inhibitor intake: case report and literature review

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Submitted: 5 December 2010
Accepted: 9 June 2011

Arch Med Sci 2012; 8, 4: 743-747
DOI: 10.5114/aoms.2012.30300

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Patients with lupus erythematosus (LE) frequently require systemic corticosteroid therapy and some of them also take non-steroidal anti-inflammatory drugs for arthritis or aspirin for thrombosis prevention. However, these drugs, especially if taken concomitantly, may significantly increase the risk of peptic ulcer, and proton-pump inhibitors (PPIs) are currently considered as first line prophylaxis to reduce this risk. The PPIs induce a pronounced and long-lasting reduction of gastric acid production, being the most potent inhibitors of acid secretion available today. In general, PPIs are well tolerated, although some recent reports have raised concerns about the possibility of LE induction due to intake of PPIs [1-6].

Here, we present an additional patient with lansoprazole-induced LE and summarize current literature data on that subject.

A 57-year-old Caucasian woman was admitted to our department with a 2-month history of development of extensive annular, confluent erythemas on the entire body. Three months before skin lesion appearance the patient initiated therapy with lansoprazole due to chronic duodenitis diagnosed on endoscopy. She had no other concomitant diseases and did not take any other drugs.

On admission the patient demonstrated prominent confluent annular erythemas located on the trunk, face, both extremities and V-neck area (Figures 1 A-B). No other abnormalities were found on physical examination. The patient was in good general condition, but complained of significant fatigue lasting for the last 2 months. Laboratory examinations revealed slight leucopoenia (3.840 leucocytes/μl), decreased level of C3 complement component (0.816 g/l, normal range: 0.9-1.8 g/l), slightly elevated activity of aminotransferases in the serum (aspartate aminotransferase 40 U/l, alanine aminotransferase 37 U/l) as well as leukocyturia (500 cells/μl) and erythrocyturia (250 cells/μl). Based on the indirect immunofluorescence on HEp cells, circulating antinuclear antibodies with homogeneous and granular pattern of fluorescence were detected and identified using Western blot as anti-Ro (SS-A) antibodies. Rheumatoid factor was negative. The direct immunofluorescence of the lesional sun-exposed and non-lesional sun-unexposed skin showed scant granular IgM deposits at the dermo-epidermal junction. The histology showed features of interface dermatitis with focal vacuolar degeneration of the basal layer of the epidermis and perivascular lymphocytic infiltrate in the dermis. Subacute cutaneous lupus erythematosus (SCLE) was diagnosed and lansoprazole was suggested as a triggering drug due to a time relationship between the lansoprazole intake and disease outbreak. The drug was discontinued and prednisone 0.5 mg/kg/day

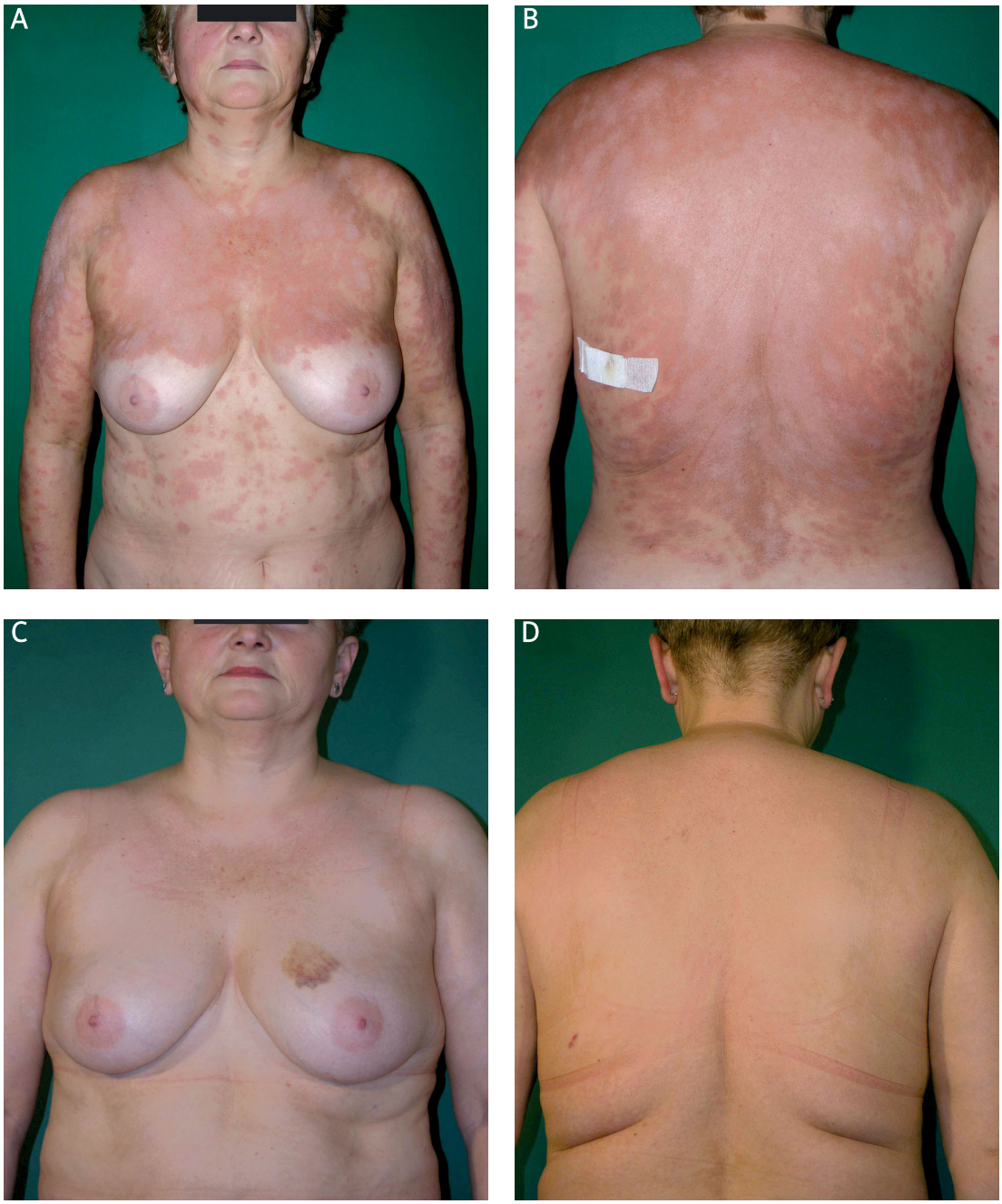

Figure 1. Extensive, confluent annular erythemas, located predominantly on the trunk (**A, B**). The same patient: complete remission 2.5 months later (**C, D**)

with ranitidine 150 mg bid was started. The therapy was continued for 4 weeks and then the corticosteroid dose was stepwise tapered. Complete clearance of skin lesions was noted within 4 weeks of the treatment. Two months later the patient was followed up in our department and neither clinical nor laboratory abnormalities were found. One year after the disease outbreak the patient still remains in complete remission, receiving no medicines.

Only 13 patients with PPI-induced LE (including our patient) have been described in the literature to date (Table I). However, we suspect that the prevalence of this PPI-related adverse effect may be much higher, as most physicians are not aware of such possibility. This suggestion may be supported by the fact that even within LE reported in the literature, some of them were in fact diagnosed retrospectively to be PPI-induced [3].

Table I. Characteristics of all patients reported in literature as having lupus erythematosus due to proton pump inhibitor intake

Case no. [ref]	Age/sex	Responsible drug	Time to disease occurrence	Lupus criteria	Circulating antibodies	Skin histology	Direct immunofluorescence of the skin biopsy	Course (time to remission after accused drug discontinuation)
1[1]	73/F	Pantoprazole	8 days (phototoxic reaction); 14 months (discoid lesions)	Photosensitivity Discoid lesions ANA	ANA: Anti-Ro, RF	Features of discoid lupus erythematosus (n.o.s.)	IgM deposits	Significant improvement on hydroxychloroquine therapy
2[2]	69/F	Lansoprazole	3 months	Photosensitivity ANA	ANA (speckled pattern): anti-Ro	A dense perivascular lymphocytic infiltrate in the dermis with keratinocyte necrosis, exocytosis and vacuolar degeneration of the basal layer	Sparse deposits of C3 and C1q	Complete remission (3 weeks)
3[2]	63/F	Lansoprazole	3 months	ANA	ANA (speckled pattern): anti-Ro RF	Superficial perivascular infiltrate in the dermis with epidermis atrophy, keratinocyte necrosis and vacuolar degeneration of the basal layer	No data	Complete remission (4 weeks)
4[3]	63/F	Pantoprazole	3 days*	Photosensitivity ANA	ANA (speckled pattern): anti-Ro	Lymphocytic interface dermatitis with vacuolar degeneration of basal layer, keratinocyte necrosis and perivascular lymphocytic infiltrate	Negative	Complete remission (4 weeks)
5[3]	57/M	Lansoprazole	4 weeks	Photosensitivity ANA Anti-dsDNA antibodies	ANA (speckled pattern): anti-Ro and anti-dsDNA RF Lupus anticoagulant	CLE	IgG and C3 deposits	Active disease until death 2 years later (the drug was not discontinued)
6[3]	61/F	Lansoprazole	3 weeks	Discoid lesions ANA	ANA (speckled pattern): anti-Ro RF	CLE (n.o.s.)	Positive (n.o.s.)	Complete remission (12 weeks)
7[3]	50/F	Omeprazole	7 weeks	Malar rash Arthritis Proteinuria Seizures Psychosis ANA Anti-dsDNA antibodies	ANA (homogeneous pattern): anti-dsDNA	Not done	Not done	Complete remission (4 weeks)

Table I. cont.

Case no. [ref]	Age/sex	Responsible drug	Time to disease occurrence	Lupus criteria	Circulating antibodies	Skin histology	Direct immunofluorescence of the skin biopsy	Course (time to remission after accused drug discontinuation)
8[3]	51/F	Pantoprazole	4-8 weeks	Photosensitivity ANA	ANA (speckled pattern) RF	Erythema multiforme-like CLE (n.o.s.)	Negative (n.o.s.)	Active disease until death (the drug was not discontinued)
9[4]	61/F	Lansoprazole	4 weeks	Photosensitivity Lymphopenia ANA	ANA: anti-Ro	Extensive follicular plugging, patchy basal layer degeneration, epidermal atrophy and interface dermatitis with superficial perivascular lymphocytic infiltration	Not done	Complete remission (8 weeks)
10[5]	60/F	Omeprazole	4 months	ANA Anti-dsDNA antibodies	ANA: anti-Ro and anti-dsDNA	Interface dermatitis with keratinocyte apoptosis and a chronic inflammatory cell dermal infiltrate	Not done	Complete remission (4 weeks)
11[6]	85/F	Omeprazole	About 3 months	ANA	ANA: anti-Ro	Follicular plugging, epidermal atrophy, basal layer vacuolar damage and necrotic keratinocytes with band-like inflammatory cell infiltrate at the dermo-epidermal junction	Negative	Complete remission (4 weeks)
12[6]	78/F	Omeprazole	3 months	ANA	ANA: anti-Ro and anti-La	Keratinocyte necrosis, vacuolar degeneration of the basal layer with lichenoid lymphocytic infiltrate at the dermo-epidermal junction	Negative	Complete remission (12 weeks)
13[current case]	57/F	Lansoprazole	3 months	Leucopenia Leukocyturia Erythrocyturia ANA	ANA (homogeneous and granular pattern): anti-Ro	Epidermal atrophy, patchy vacuolar damage of the basal layer and perivascular lymphocytic infiltrate in the upper dermis	Granular IgM deposits	Complete remission (4 weeks)

The history of the first reported patient with PPI-induced (pantoprazole) LE differs significantly from the other described subjects, as initially (8 days after initiation of pantoprazole) phototoxic lesions were noted that cleared over a period of one month upon discontinuation of pantoprazole, but after another thirteen months discoid lupus erythematosus developed in the areas of the most intense phototoxic lesions [1]. Remarkably, the patient was proven to be anti-Ro positive at the time of phototoxic reaction [1].

Importantly, all other patients demonstrated features of SCLE on the skin and only 3/12 have extracutaneous symptoms, usually of mild intensity. Interestingly, one patient with pre-existing systemic LE developed cutaneous lesions typical for SCLE upon exposure to PPI (Table I).

Although we could not exclude that the described patients only represent an accidental coexistence of SCLE with PPI intake, several features favor a causal relationship between these two events. Firstly, a close temporal relationship between the introduction of the suspended drug and onset of SCLE lesions ranging from 3 weeks to 4 months was observed in the majority of patients. Such delay of clinical symptom appearance is typical for drug-induced SCLE. In one patient SCLE developed as early as 3 days after pantoprazole intake, but it could be assumed that rapid skin lesion development might be related to the re-challenge of PPIs, despite previous history of pantoprazole-induced SCLE [3]. Furthermore, even with substantial immunosuppression no improvement could be achieved unless the accused drug was discontinued. Upon discontinuation of PPIs a rapid complete remission was usually noted (Table I). Only in patient 1 with discoid lesions did some residual skin symptoms remain [1].

Interestingly, none of the reported subjects was positive for anti-histone antibodies, which are linked to drug-induced SLE. On the other hand, most of the patients (11/13) had anti-Ro antibodies. Taking this phenomenon into account, we would like to support the proposal by Bracke *et al.* [2], who suggested the need to modify the criteria for drug-induced SCLE by changing "the presence of anti-histone antibodies" to "the presence of anti-Ro antibodies".

In conclusion, currently available data indicate that PPIs may induce LE in predisposed patients. However, this warning is only based on case reports. Therefore, prospective studies should be performed in the future to reliably assess the true relationship and prevalence of this PPI-related phenomenon.

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