We report here a case of a 52-year-old woman with erythema gyratum repens-like lesions appearing during anti-p200 pemphigoid, probably induced by oral penicillin. The diagnosis of anti-p200 pemphigoid was made by the presence of in vivo bound and circulating IgG anti-basement membrane zone auto-antibody reactive with the dermal side of salt-split skin and with 200 kDa protein in dermal extract on Western immunoblot. Laser scanning confocal microscopic study disclosed the localization of IgG at the lamina lucida-lamina densa border. Skin lesions responded poorly to high dose of prednisone and the combination of prednisone and dapsone. When methotrexate was added, skin lesions healed within 3 weeks. To our knowledge, erythema gyratum repens-like lesions have not been described previously in this disorder. Thus, we have expanded the clinical morphological spectrum of patients with anti-p200 pemphigoid and first described a patient whose disorder was probably drug-induced. Key words: pemphigoid; anti-p200 pemphigoid; erythema multiforme bullosum; erythema gyratum repens; laser scanning confocal microscopy.

(Cliped from original)
Because of the atypical clinical presentation and its poor response to a high dose of systemic corticosteroids, additional studies were performed. Using laser scanning confocal microscopic (LSCM) study we compared the localization of in vivo bound IgG to the localization of various BMZ markers: monoclonal antibody directed against β4-integrin (upper part of lamina lucida marker), laminin-5 (lamina lucida-lamina densa border marker) and collagen IV (lamina densa marker). Immunoglobulins were visualized by labelling with fluorescein isothiocyanate (FITC)-conjugated goat anti-human IgG antibody, whereas BMZ markers were labelled with Cy5-conjugated anti-mouse antibodies. Immunofluorescence images were overlaid by an image processing system integrated in the LSCM and photographed (10). LSCM study disclosed the presence of in vivo bound IgG below the localization of β4-integrin, above the localization of collagen IV and co-distributed with laminin-5 (Fig. 2). Indirect immunofluorescence showed reactivity of circulating IgG anti-BMZ antibody with the dermal side of the salt-split skin (Fig. 3). Western immunoblot analysis performed on the dermal extract showed serum reactivity with 200 kDa protein (Fig. 4). Histology showed subepidermal blisters and the inflammatory infiltrations in the dermis consisted mostly of neutrophils (not shown).

A final diagnosis of anti-p200 pemphigoid was made and the treatment was modified. After adding methotrexate 12.5 mg/week to corticosteroids 40 mg/day, the skin lesions healed in 3 weeks. At this time there was post-inflammatory hyperpigmentation but no scarring on the skin. During the next 3 months prednisone was tapered and withdrawn. During the ensuing 4 months’ treatment with methotrexate 5 mg a week, the patient was in remission, following which the treatment was discontinued. The skin lesions did not reappear in 3 months’ follow-up and repeated serum study for the presence of anti-BMZ antibody was negative.

**DISCUSSION**

Several cases of drug-induced autoimmune bullous diseases, especially pemphigus foliaceus and BP have been described (11–14). The development of bullae 1–3 months after the introduction of an offending drug strongly suggests the diagnosis of drug-induced BP (13). In most of the patients, stopping the suspected medication improved the eruption, but in some with severe disease this was not the case (13). We report here the first patient with anti-p200 pemphigoid probably provoked by oral intake of penicillin given because of prolonged cough. Oral and skin lesions started 5 days after the beginning of therapy and were initially diagnosed as bullous erythema multiforme. Skin lesions disappeared in 2 weeks on corticosteroid treatment, but reappeared one week after steroid was tapered, this time resistant to corticosteroids.
Immunopathological studies showed the presence of in vivo bound and circulating IgG anti-BMZ antibody reactive with the dermal side of salt-split skin and 200 kDa protein on dermal extract by immunoblot. The bullous erythema multiforme preceded the onset of drug induced anti-p200 pemphigoid, which started 5 days after drug intake. During hospitalization the skin eruptions evolved into lesions clinically resembling erythema gyratum repens, which has not been previously reported in anti-p200 pemphigoid. Laboratory investigations did not reveal internal malignancy.

The majority of published cases with anti-p200 pemphigoid were younger than our patient’s 52 years, while BP normally affects older patients. Differential diagnosis are inflammatory types of epidermolysis bullosa acquisita (EBA) (15), bullous systemic lupus erythematosus (15), anti-laminin-5 cicatricial pemphigoid (16) and anti-p200 pemphigoid (1).

A precise diagnosis of autoimmune, subepidermal bullous diseases has significant implications for both prognosis and treatment. In patients with anti-laminin-5 cicatricial pemphigoid it is necessary to exclude the presence of internal cancer, in EBA – the presence of inflammatory bowel diseases or/and endocrinopathies or lymphoma/leukaemia, whereas anti-p200 pemphigoid has no recognized systemic associations and seems to be linked only with psoriasis vulgaris (8). In our case of anti-p200 pemphigoid there was no evidence or history of either internal malignancy or other skin diseases.

This is the first study on the localization of in vivo bound IgG to the localization of different BMZ markers. It is of special value in diagnosing cases not detectable via circulating antibody (10).

Interestingly, there is a discrepancy between the localization of 200 kDa antigen and in vivo bound IgG determined by direct immunoperoxidase electron microscopy, which shows the presence of immunodeposits throughout the entire lamina lucida and lamina densa (1). In our patient in vivo bound IgG was localized below β4-integrin, above collagen IV and co-distributed with laminin-5, which corresponds with their ultrastructural localization at the border of lamina lucida-lamina densa. This finding reflects the ultrastructural localization of the target antigen (6). The lack of co-localization of in vivo bound IgG and β4-integrin indicates the absence of immunodeposits in the upper part of lamina lucida. This suggests the diffusion of peroxidase marker from site of reaction to the upper part of lamina lucida observed in immuno-electron microscopic study.

It has been postulated recently that combined therapy consisting of corticosteroids and sulfones might give a sustained response in patients with anti-p200 pemphigoid (9). Our patient was treated for 2 weeks with prednisone and dapsone without success. When methotrexate was added, there was an improvement. Thus, one might consider low-dose methotrexate in those patients who respond poorly or cannot tolerate dapsone.

To our knowledge, this is the first description of a patient with anti-p200 pemphigoid who presented erythema gyratum repens-like lesions. In addition, we believe this to be the first report of a patient in whom this disorder was probably drug induced.
ACKNOWLEDGEMENT

This work was supported by a grant from the Polish Scientific Research Committee (KBN No. 2 PO5B 176 29 and KBN No. 2 PO5B 065 30).

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