

SHORT COMMUNICATION

Cutaneous Marginal Zone B-cell Lymphoma Evolving into Anetoderma: A Role of Matrix Metalloproteinases?

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Anetoderma is a rare disease characterised by localised atrophy of the skin due to destruction of dermal elastic fibres. It can be classified as primary or secondary: the secondary type is associated with several skin diseases, including infectious, inflammatory and neoplastic diseases (1). However, only a few cases of anetoderma secondary to cutaneous B-cell lymphoma have been described previously (2–6). Here, we describe a case of cutaneous marginal zone B-cell lymphoma evolving into anetoderma. In addition, our immunohistochemical analyses suggest that certain soluble factors including matrix metalloproteinase (MMP) produced by the infiltrating lymphocytes may play a role in the elastolytic process.

CASE REPORT

A 50-year-old Japanese man who had a 30-year history of multiple nodules and plaques in his back and extremities, visited our hospital in June 2010. Plaques were gradually evolving into anetodermic lesions. He had had no other remarkable past history. Physical examination revealed multiple brown-reddish slack plaques with atrophic skin and teleangiectasia in his back and a purplish nodule on his thigh (Fig. 1A, B). Histological examination taken from the plaque on the thigh revealed the massive infiltration of small atypical lymphocytes and plasma cells throughout the dermis and subcutaneous tissue (Fig. 1C). There was a grenz zone sparing the epidermis. The neoplastic cells had irregular nuclear contours, coarse chromatin, inconspicuous nucleoli and scant cytoplasm (Fig. 1D). Elastica-VanGieson staining showed a marked decrease of elastic fibres throughout the dermis (Fig. 1E). On immunohistochemical analyses, infiltrating lymphocytes were positive for CD20 and Bcl-2 (Fig. 1F). The plasma cells expressed CD138 and κ -chain (Fig. 1G). Monoclonal rearrangement of the immunoglobulin H (IgH) gene was detected from a skin lesion. Computed tomography of the whole body and fluorodeoxyglucose-positron emission tomography (FDG-PET) scan detected no abnormal lesions. No atypical haematopoietic cells were found in his bone marrow. He was diagnosed as having cutaneous marginal zone B-cell lymphoma with anetoderma. Plaque on the thigh regressed by the electron beam radiation therapy (Total 36Gy), and there has been no recurrence during a 1-year follow-up period.

Immunohistochemical analysis

To elucidate the pathogenesis of the loss of elastic fibres in dermis of skin lesions, we immunohistochemically examined the expression of MMP-2, MMP-3, MMP-9 and MMP-12 in the lesional skin using anti-MMP-2 antibody (1/100, AB19167, Chemicon), anti-MMP-3 antibody (1/100, SL-1 IID4, Millipore), anti-MMP-9 antibody (1/50, ab2167, Abcam) and anti-MMP-12

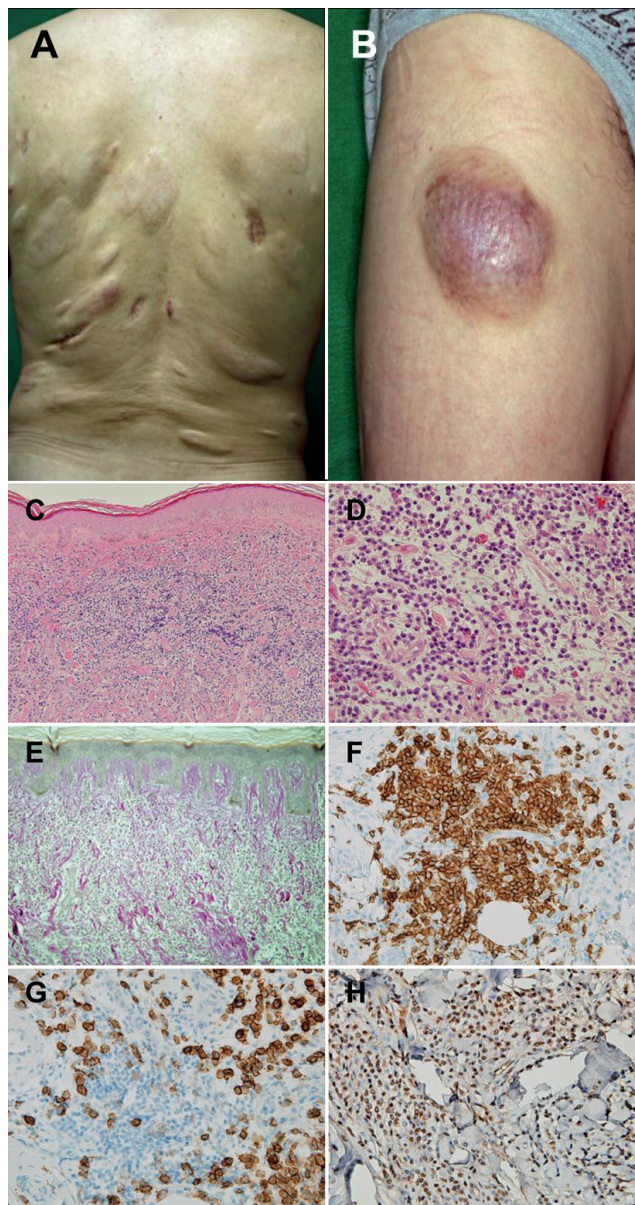


Fig. 1. (A, B) Multiple brown-reddish slack plaques with atrophic skin and teleangiectasia on back and thigh. (C, D) Histological examination of the plaque on the thigh. Massive infiltration of small atypical lymphocytes and plasma cells (H&E, original magnification $\times 200$ (C) and $\times 400$ (D)). (E) Marked decrease of elastic fibres throughout the dermis (Elastica-VanGieson, original magnification $\times 200$). (F) Proliferating lymphocytes were positive for CD20. (G) Plasma cells expressed CD138. (H) Proliferating lymphocytes were positive for MMP-9. Original magnification $\times 400$.

antibody (1/100, MABT147, Millipore). The staining of MMP-9 was observed in and around infiltrating lymphocytes in the dermis (Fig. 1H). In contrast, the staining of MMP-2, MMP-3 and MMP-12 were not observed (Fig. S1A–C¹). Control IgG staining was negative (Fig. S1D¹). These results suggest that MMP-9 might be responsible for the degradation of elastic fibres in our patient.

DISCUSSION

Secondary anetoderma is associated with several skin diseases; cutaneous infections such as herpes zoster, borreliosis, syphilis and human immunodeficiency virus; inflammatory disorders including lupus erythematosus, antiphospholipid syndrome, acne, sarcoidosis; tumours and immunocytoma including mycosis fungoides (1). The association of haematologic malignant neoplasms, such as granulomatous slack skin, and dermal elastolysis has been well recognised. However, there have been only a few cases of anetoderma secondary to cutaneous B-cell lymphoma (2–6) (Table S1¹). Sixteen cases (male:female=14:2) were reported between 1995 to 2013 and 7 cases of cutaneous marginal zone B-cell lymphoma were included.

Although a pathogenic role of antiphospholipid antibodies was recently suggested (3), the precise mechanism of anetoderma is still unknown. However, it is possible that certain soluble factors produced by the infiltrating lymphocytes may play a role in the elastolytic process. Interleukin (IL)-6, which induces the final maturation of activated B cells into immunoglobulin-producing cells, may play such a role (7). Another hypothesis is that MMPs secreted from infiltrating tumour cells might be involved in the elastolytic process.

The degradation of elastic fibres is mediated by elastases, including MMP. MMPs consist of more than 25 well-characterised members of secreted or transmembrane proteins that degrade the extracellular matrix and basement membrane macromolecules (8, 9). Four groups of the MMP family of proteinases are known to be capable of degrading elastic fibres: the gelatinases MMP-2 (gelatinase A), MMP-9 (gelatinase B), matrilysin MMP-7, and the macrophage metalloelastase MMP-12 (8, 9). MMP-9 has stronger elastolytic potential than MMP-2 in human skin (10). In previous studies, the loose skin diseases with the loss of elastic fibres, including anetoderma, mid-dermal elastolysis and blepharochalasis were associated with the over-expression of MMP-9 in inflammatory infiltrates such as leucocytes and macrophages (11–13). Furthermore, it has been reported that MMP-9 was secreted from neoplastic plasma cells in multiple myeloma, and MMP-9 degraded extracellular matrix and facilitated tumour cell invasion (14). We identified that infiltrating lymphocytes in the patient's skin lesion were positive

for MMP-9 and negative for MMP-2, MMP-3 and MMP-12. These findings suggest that MMP-9 may play a role in the development of anetoderma in our case. Interestingly, it has been reported that doxycycline inhibits MMP activity *in vitro*, independent of its antimicrobial activity (15), suggesting that doxycycline might be a therapeutic alternative.

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¹<https://doi.org/10.2340/00015555-1992>