Myxovirus Resistance Protein A Is a Useful Additional Histological Marker in Suspected Cutaneous Lupus Erythematosus

Wietske M. LAMBERS[1], Gilles F. H. DIERCKS[2], Femke M. HOMAN[3], Berber DOORNBOS-VAN DER MEER[1], Hendrika BOOTSMA[1], Johanna WESTRA[1] and Karina DE LEEUW[1]

Departments of [1]Rheumatology and Clinical Immunology, [2]Pathology, and [3]Dermatology, University Medical Centre Groningen, University of Groningen, Hanzeplein 1, NL-9700 RB Groningen, The Netherlands. E-mail: w.m.lambers@umcg.nl

Accepted Jun 25, 2020; Epub ahead of print Jul 3, 2020

Cutaneous lupus erythematosus (CLE) is a heterogeneous autoimmune skin disease. Since the clinical picture can be quite heterogeneous, histological confirmation is of importance. However, the typical histological features, including an interface dermatitis, are not at all specific. As CLE is an interferon (IFN)-driven disease, IFN-related markers, such as myxovirus resistance protein A (MxA), could be helpful in the diagnostic process. This can be illustrated by 2 cases.

CASE REPORTS

Case 1. A 64-year-old woman was referred to our tertiary centre with erythematous skin eruptions on the face, arms, hands, and in the neck. She reported photosensitivity. Dermatological examination revealed indurated erythematous plaques localized on the chin, forehead and over the cheeks, including the nasal bridge. Furthermore, a band-shaped alopecia was seen. The differential diagnosis included subacute cutaneous lupus erythematosus, rosacea, lichen planopilaris, rosacea papulo-pulstulosa, and frontal-fibrosing alopecia.

The histology of the eruption on the chin showed a mild perivascular and perifollicular lymphocytic infiltrate with focal basal cell vacuolization. MxA staining was performed for further differentiation, and was strongly positive in the epidermis, adnexal structures, infiltrate, endothelium and stromal cells. The final diagnosis was SCLE, and hydroxychloroquine was started.

Case 2. A 46-year-old woman, with a history of psoriasis, was referred with itching skin eruptions that appeared differently from the psoriatic lesions and were noticed since 2 years. She reported photosensitivity. On dermatological examination, annular erythematous plaques, with central aspect of poikiloderma were seen on the left upper leg and the left flank. Alternate treatment with corticosteroids class III–IV, ultraviolet B (UVB), and methotrexate, had no effect. The differential diagnosis included chronic discoid lupus erythematosus, extragenital lichen sclerosus, dermatomyositis (sine myositis), and atrophic mycosis fungoides. Histology showed a superficial band-like lymphohistiocytic infiltrate in the upper dermis with focal presence of basal cell vacuolization. There was only slight lymphocytic atypia, and no loss of T-cell markers was noted. The MxA staining showed positivity for the endothelium and some inflammatory cells, but the epidermis and skin adnexal structures were negative, making discoid lupus erythematosus very unlikely. Follow-up biopsies eventually showed a picture compatible with mycosis fungoides, and further treatment consisted of UVB therapy.

DISCUSSION

CLE is a heterogeneous autoimmune skin disease. It can appear as self-contained disease entity or as one of the clinical features of the rheumatic disease systemic lupus erythematosus (SLE). Different types are distinguished, of which acute CLE (ACLE), subacute CLE (SCLE), chronic discoid lupus erythematosus (CDLE), and lupus tumidus occur most frequently.

Histologically, ACLE, SCLE, and CDLE are characterized by a lymphocytic interface dermatitis with vacuolar degradation of keratinocytes as well as necrotic keratinocytes at the dermo–epidermal junction (1). Lupus tumidus shows perivascular lymphocytic infiltrates and mucin deposition in the papillary and reticular dermis. However, these characteristics are not at all specific.

The pathogenesis of CLE is, to a great extent, driven by inappropriate activation of type I and III IFNs (2, 3). IFNs are cytokines that can be produced by several cell types and are important for generation of antiviral effects. The pathogenic role of IFN is supported by detection of IFN-regulated chemokines in CLE lesions that are co-localized with cytotoxic lymphocytes (4). Also, type I IFN gene expression in blood and skin of patients with CLE correlates with Cutaneous Lupus Area and Severity Index (CLASI) activity score (5, 6).

MxA, a cytoplasmic GTPase, is tightly regulated by type I and III IFN expression in blood and skin and is strongly correlated with IFN gene expression (IFN signature) (7, 8). We therefore tested the diagnostic potential of skin biopsy immunostaining with MxA.

After approval from the regional Medical Ethical Board (19 March 2018, UMCG Research register number 201800245), 178 skin biopsy specimens were collected from the local pathology database. A series of 19 autoimmune and non-autoimmune skin conditions were selected. Herpes simplex skin lesions were included as positive controls and healthy controls were included as negative controls. Skin biopsies were formalin-fixed and embedded in paraffin. After stepwise deparaffinization with xylene and ethanol, antigen retrieval was performed by 1 h incubation at 90°C with Tris-HCL/EDTA buffer (pH 9.0), followed by endogenous peroxidase blocking. Skin sections were incubated with anti-MxA (R&D Systems, AF7946) in PBS with 1% FCS, at a concentration of 0.3 µg/ml and incubated overnight at 4°C. Consecutively, after incubation with 1:50 diluted rabbit anti goat immunoglobulins-HRP conjugate (Dako, 0449), sections were stained with diaminobenzidine-chromogen (Dako, K4006) and counterstained with haematoxylin.

doi: 10.2340/00015555-3587
Acta Derm Venereol 2020; 100: adv00234

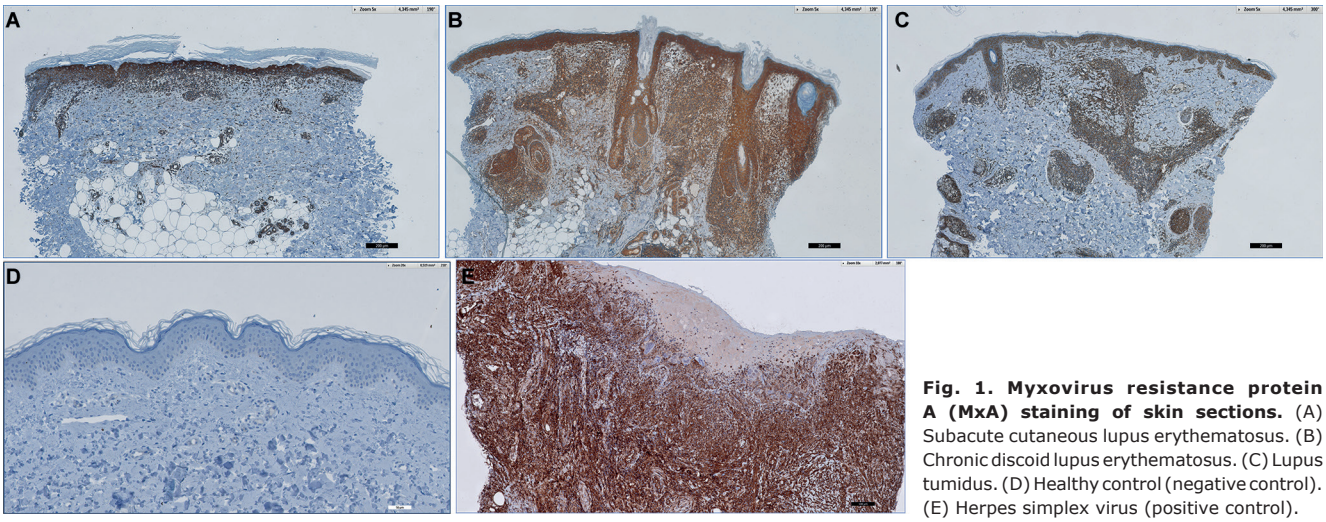

Fig. 1. Myxovirus resistance protein A (MxA) staining of skin sections. (A) Subacute cutaneous lupus erythematosus. (B) Chronic discoid lupus erythematosus. (C) Lupus tumidus. (D) Healthy control (negative control). (E) Herpes simplex virus (positive control).

The expression of MxA was scored semi-quantitatively by a dermatopathologist (GD) and a technician (BD) in respectively epidermis, skin appendages, fibroblasts, infiltrates, and endothelium (0 for no expression, 1 for moderate expression, 2 for mediate expression, and 3 for strong expression). MxA scores per biopsy were calculated based on cumulative expression of these various structures (e.g. 3 for epidermis plus 2 for endothelium, etc.), divided by the number of assessable structures.

MxA staining was strongly and consistently positive in both epidermis, skin appendages, infiltrate, fibroblasts, and endothelium in 90.3 % of CLE skin sections, except for lupus tumidus. **Fig. 1** shows representative histopathological sections with MxA staining in SCLE, CDLE, lupus tumidus, healthy control (negative control), and herpes simplex virus (positive control). Mean MxA expression, with a maximum score of 3, with 95% confidence intervals (95% CI) is shown in Fig. S1[1] for each analysed skin disease. A receiver operating characteristic (ROC) curve was constructed for CDLE, SCLE and CLE non-specified vs other skin diseases, which showed an area under the curve (AUC) of 0.90 (95% CI 0.85–0.95). The negative predicting value was 94%. The MxA expression pattern in dermatomyositis, which is also an IFN-driven autoimmune disease, was as strong as in CLE. In a number of other conditions, such as perniosis, polymorphic light eruption and graft versus host disease, high MxA expression was found in some of the cases.

In conclusion, MxA is strongly expressed in CDLE and SCLE skin. Because of the high negative predictive value, MxA staining can be useful as an additional histological marker in CLE next to routine histology and the lupus band test. Notably, the marker is sensitive, but not specific, as other (IFN-related) dermatoses also show MxA expression. As expected, addition of this marker in clinical practice results in restriction of misdiagnosis and treatment delay.

[1]https://doi.org/10.2340/00015555-3587

ACKNOWLEDGEMENTS

This work was supported by the Dutch Arthritis Foundation, project 15-1-401.

The authors have no conflicts of interest to declare.

REFERENCES

1. Kuhn A, Landmann A. The classification and diagnosis of cutaneous lupus erythematosus. J Autoimmun 2014; 48–49: 14–19.
2. Kuhn A, Wenzel J, Weyd H. Photosensitivity, apoptosis, and cytokines in the pathogenesis of lupus erythematosus: a critical review. Clin Rev Allergy Immunol 2014; 47: 148–162.
3. Sarkar MK, Hile GA, Tsoi LC, et al. Photosensitivity and type i IFN responses in cutaneous lupus are driven by epidermal-derived interferon kappa. Ann Rheum Dis 2018; 77: 1653–1664.
4. Wenzel J, Zahn S, Mikus S, Wiechert A, Bieber T, Tüting T. The expression pattern of interferon-inducible proteins reflects the characteristic histological distribution of infiltrating immune cells in different cutaneous lupus erythematosus subsets. Br J Dermatol 2007; 157: 752–757.
5. Kuhn A, Amler S, Beissert S, et al. Revised Cutaneous Lupus Erythematosus Disease Area and Severity Index (RCLASI): a modified outcome instrument for cutaneous lupus erythematosus. Br J Dermatol 2010; 163: 83–92.
6. Oh SH, Roh HJ, Kwon JE, et al. Expression of interleukin-17 is correlated with interferon-α expression in cutaneous lesions of lupus erythematosus. Clin Exp Dermatol 2011; 36: 512–520.
7. Haller O, Staeheli P, Kochs G. Interferon-induced Mx proteins in antiviral host defense. Biochimie 2007; 89: 812–818.
8. Huijser E, van Helden-Meeuwsen CG, Groot N, et al. MxA is a clinically applicable biomarker for type I interferon activation in systemic lupus erythematosus and systemic sclerosis. Rheumatology 2019; 58: 1302–1303.