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Single Case

A Case of Lamina Lucida-Type Linear IgA Disease Complicated by Colon Polyposis and Rectal Adenocarcinoma

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Keywords
Colorectal carcinoma · Diaphenylsulfone · Linear IgA disease · Multiple colorectal polyps · Myelodysplasia syndrome

Abstract
Linear IgA disease (LAD) is a rare autoimmune bullous disease characterized by IgA deposition in the basement membrane zone (BMZ). A 66-year-old male was treated for myelodysplastic syndrome at our hospital for 5 years, during which his condition remained stable. He visited our department because of erythema with itching, which appeared 1 year ago and gradually exacerbated with the development of blisters and erosions. During the first visit, multiple erythemas with erosions and crusts on their periphery were observed on the trunk and lower limbs. Histopathological examination revealed subepidermal blisters with inflammatory cell infiltration, mainly constituting of neutrophils, eosinophils, and lymphocytes. Direct and indirect immunofluorescence showed linear IgA deposits in the BMZ and IgA anti-BMZ antibodies, respectively, while immunoblotting using a concentrated culture supernatant of HaCaT cells detected IgA antibodies reactive to 120-kDa LAD-1. Accordingly, the patient was diagnosed with lamina lucida-type LAD. Subsequent colonoscopy revealed multiple colorectal polyps and rectal adenocarcinoma (Tis, N0, and M0). Multigene panel test showed an *ATM* variant of unknown significance but did not detect any pathogenic variants associated with intestinal polyposis syndrome. The skin lesions quickly resolved with oral diaphenylsulfone 50 mg/day and resection

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of the colorectal polyps and adenocarcinoma. To our knowledge, this is the first reported case of LAD associated with multiple colorectal polyps and rectal adenocarcinoma. Additionally, we also analyzed reported cases of LAD associated with malignancy from the literature.

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Introduction

Linear IgA disease (LAD) is a rare autoimmune bullous disease which shows histopathologically subepidermal blisters and immunologically linear IgA deposits in the basement membrane zone (BMZ) [1]. LAD is subdivided into major lamina lucida (LL)-type and minor sublamina densa-type, which react with epidermal and dermal sides, respectively, by IgA indirect immunofluorescence using 1M NaCl-split skin. IgA antibodies in LL-type LAD patients react with the 97-kDa LABD97 and 120-kDa LAD-1 [2]. LAD has been reported to be a risk factor for various malignancies [3]. Here, we report a case of LAD complicated by multiple colorectal polyps and rectal adenocarcinoma. We also performed a literature survey to characterize the reported cases of LAD associated with malignancy.

Case Report

The patient was a 66-year-old Japanese man who referred to our department for itchy erythema on the trunk, which had appeared 1 year ago, exacerbated by the development of blisters and erosions. He had been receiving oral vitamins K2 and D3 for myelodysplastic syndrome (MDS) for 5 years and had no history of medications that could induce autoimmune bullous diseases, nor a family history of gastrointestinal polyposis or colorectal cancer. He had not undergone routine cancer screenings in the past.

Physical examination revealed multiple erythemas with tense blisters and erosions on their periphery, as well as pigmentation of the trunk and extremities (Fig. 1a). No mucosal lesions were observed. Although laboratory tests revealed abnormalities related to MDS (leukocytes, 3,740/μL; hemoglobin, 8.1 g/dL; platelet count, 19.4 × 10^4/μL; and reticulocyte count, 12.6 × 10^4/μL), blasts, markers of leukemia transition, anti-desmoglein 1/3, and anti-BP180 antibodies were absent. Tests for *HLA-DQA1* and *HLA-DQB1* allelic variations and IgA anti-epidermal transglutaminase antibodies, disease markers for celiac disease, yielded negative results. Histopathological examination of a skin biopsy specimen from a bullous erythematous lesion on the back revealed subepidermal blisters and infiltration of neutrophils, eosinophils, and lymphocytes into the blisters and superficial dermis (Fig. 1b).

Direct immunofluorescence revealed a linear deposition of IgA and punctate deposition of C3 in the BMZ (Fig. 1c, d), while indirect immunofluorescence using normal human skin tissue revealed IgA anti-BMZ antibodies at a 10× dilution (Fig. 1e). Additionally, indirect immunofluorescence performed using 1M NaCl-split-skin showed IgA reactivity on the epidermal side (Fig. 1f). Finally, immunoblotting using a concentrated culture supernatant of HaCaT cells as substrate revealed strong IgA reactivity with the 120-kDa LAD-1 in the patient serum (Fig. 1g), which was consistent with the diagnosis of LL-type LAD.

The patient underwent concurrent examination for bullous disease and malignant tumors. Furthermore, upper gastrointestinal endoscopy was performed and revealed no abnormalities. Colonoscopy revealed >100 pedunculated polyps, <20 mm in size, in the

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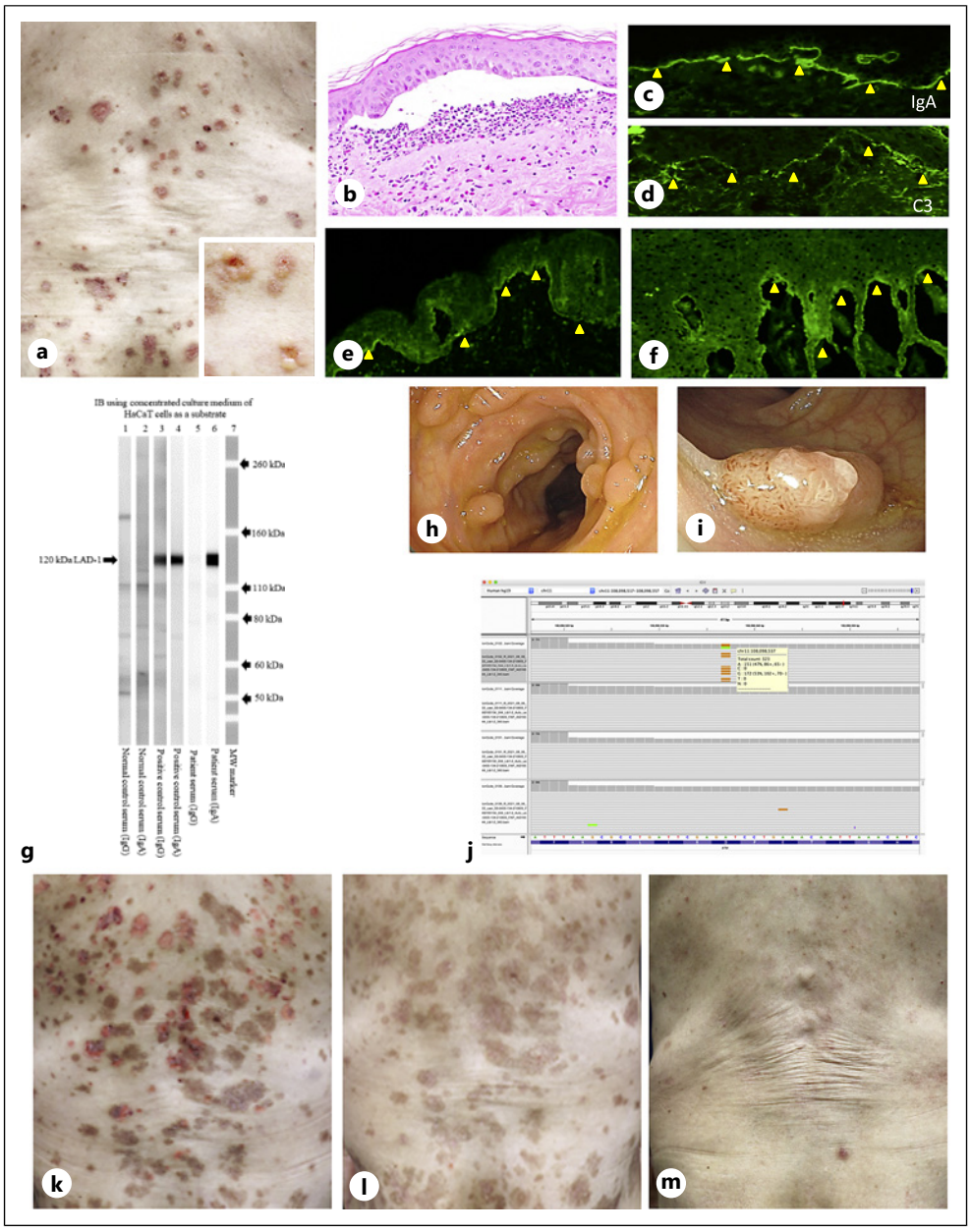

Fig. 1. Clinical, histopathological, and immunological characteristics of the patient. **a** Clinical features of the trunk at the first visit. **b** Histopathological findings of the biopsy specimen of a vesicle on the back (hematoxylin and eosin staining, original magnification ×200). **c**, **d** Direct immunofluorescence staining for IgA (**c**) and C3 (**d**). **e** Indirect immunofluorescence using normal human skin. **f** Indirect immunofluorescence using 1M NaCl-split-normal human skin. **g** Immunoblotting (IB) using concentrated culture supernatant of HaCaT cells as a substrate revealed strong IgA reactivity with the 120-kDa LAD-1 in the patient serum (lane 6); the supernatant, also reacted with IgG and IgA positive control sera (lanes 3 and 4). Lane 7 indicates the molecular weight markers. **h**, **i** Colonoscopy revealed multiple colorectal polyps (**h**) and adenocarcinoma (**i**). **j** Results of the panel sequencing. The identified rare variant, *ATM*:c.107A>G/p.Asp36Gly is shown by Integrative Genomics Viewer (IGV; Broad Institute), indicated with a red arrow. **k** Clinical features 1 month after the first visit without significant improvement. **l** Clinical features after 3 months of treatment. **m** Clinical features after 2 years of follow-up.

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colorectum (Fig. 1h, i). Subsequent histopathological examination of the biopsy specimens confirmed the diagnosis of tubular adenoma, two of which were rectal adenocarcinomas (Tis, N0, and M0). Suspecting familial adenomatous polyposis, *MUTYH*-associated polyposis, and other hereditary polyposis diseases, we performed a multigene panel test consisting of 59 genes to detect intestinal polyposis and hereditary colorectal cancer [4]. Although no pathogenic genetic alterations in the germline were found that could explain the development of multiple colorectal polyps, we identified a missense variation, *ATM* (NM_000051.3): c.107A>G/p.Asp36Gly (dbSNP:rs1488019755), Chr11:108,098,537 (on Assembly GRCh37), which corresponded to an *ATM* variant of uncertain significance (Fig. 1j). This variant is not registered at the Genome Aggregation Database (gnomAD) (PM2). Multiple in silico analyses predicted deleterious effects of the missense variant on the ATM protein, including PolyPhen-2, probably managing; PROVEAN, deleterious; and UMD-Predictor, pathogenic (PP3). Based on the ACMG/AMP guidelines, the variant was classified as uncertain significance. In addition, this variant was registered in the Clin Var database as a pathogenicity of uncertain significance, with a review status of two stars.

For approximately 1 month, the patient did not respond to initial treatment with oral antihistamines and topical corticosteroids (as shown in Fig. 1k). Thus, 1 month following the first visit, after confirming of LAD, treatment with oral diaphenylsulfone (DDS; 50 mg/day), antihistamines, and topical steroids was initiated. Additionally, 1 month prior to LAD diagnosis, the diagnosis of colorectal cancer was confirmed during the initial endoscopic mucosal resection. Thereafter, endoscopic mucosal resection for multiple colorectal polyps was performed several times after treatment initiation with DDS. Within 3 months, the bullous erythematous skin lesions rapidly resolved (Fig. 1l), and no recurrence was observed during the 2 years of follow-up (Fig. 1m).

Discussion

In 1901, for some cases that had been diagnosed as dermatitis herpetiformis (Duhring's disease), Chorzelski and Jablonska [5] proposed a new disease entity: linear IgA bullous dermatosis. In linear IgA bullous dermatosis, also called as LAD, linear IgA deposits in the BMZ are observed and the disease is not associated with gluten supersensitivity. In 2021, Hashimoto et al. [6] verified the previous reports of this condition and proposed the term LAD as more suitable name, mainly because some cases do not show blister formation.

It has been indicated that LAD might be triggered by viral or bacterial infection, medication, or malignant tumors, including lymphoproliferative disease (e.g., Hodgkin's lymphoma or B-cell lymphoma) [3]. There are also reports of LAD in association with visceral malignancy, including bladder, esophageal, breast, thyroid, and colorectal cancers [3]. Therefore, LAD may have a tendency to be associated with malignancies. A previously reported LAD case associated with colorectal cancer did not have polyposis [7].

We performed a literature survey after 2000 and collected 8 cases of LAD associated with malignancy, including the present case (Table 1) [7–13]. All the patients were males. Three patients had hematopoietic malignancies and five had visceral malignancies. Two patients developed LAD several months after the malignancies appeared, while 6 patients were found to have malignancies by systemic examinations at the onset of LAD; the malignancies in three of these cases were progressive. Finally, oral administration of DDS or prednisolone was effective in patients with benign tumors but not in those with progressive cancers.

In the present case, multiple colorectal polyps with rectal cancer were observed, along with *ATM* alteration. While germline pathogenic *ATM* variants have been reported to moderately increase the risk of colorectal cancer, the evidence for this is not well established

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Table 1. Characteristics of LAD associated with malignancy

Reference	Age, sex	Type of malignancy	Onset of LAD from the diagnosis of malignancy	The treatment of LAD	Rash after the treatment of malignancy and LAD	Prognosis after admission
Lai-Cheong et al. [7], 2007	74 M	Metastasized colonic adenocarcinoma (palliative treatment)	Simultaneous	PSL40 mg/day, MMF1.5 g/day	Not improved	ND
Colmant et al. [8], 2020	72 M	AITL (chemotherapy)	Simultaneous	mPSL	Improved by the treatment of LAD	Died after 2 months
van der Waal et al. [9], 2001	50 M	Metastasized renal cell carcinoma (palliative treatment)	Simultaneous	PSL100 mg/day, DDS100 mg/day	Improved by the treatment of LAD	Died after 2 months
Yhim et al. [10], 2011	54 M	Non-Hodgkin's lymphoma (chemotherapy, aPBSCT)	9 months later	mPSL2mg/kg, DDS100 mg/day, IVIg	Improved by the treatment of LAD	ND
Adamic et al. [11], 2008	86 M	Advanced pancreatic carcinoma (palliative treatment)	Simultaneous	mPSL 32 mg/day, DDS100 mg/day	Improved by the treatment of LAD	Died after 1 month
Keller et al. [12], 2003	54 M	Renal cell carcinoma (surgery)	Simultaneous	DDS100 mg/day	Improved by the treatment of LAD and malignancy	ND
Tiger et al. [13], 2015	46 M	Chronic lymphocytic leukemia (chemotherapy)	6 months later	None	Improved by the treatment of malignancy	ND
Present case	66 M	Colonic adenocarcinoma (surgery)	Simultaneous	DDS 50 mg/day	Improved by the treatment of LAD and malignancy	Alive

AITL, angioimmunoblastic T-cell lymphoma; mPSL, methylprednisolone; PSL, prednisolone; DDS, diaphenylsulfone; aPBSCT, autologous PBSC transplantation; ND, not described; MMF, mycophenolate mofetil.

[14]. Furthermore, although an association between multiple colorectal polyps, colorectal cancer, and the development of LAD has been suggested, further studies involving similar cases are required to confirm this relationship.

In conclusion, we report the first case of LAD associated with colon polyposis and rectal adenocarcinoma during MDS treatment. We speculated that, in our case, DDS treatment rapidly improved the skin lesions, while the combination of endoscopic mucosal resection and oral DDS possibly suppressed recurrence during the follow-up period. The patient provided

written informed consent to publication of this case. The CARE Checklist has been completed by the authors for this case reports, attached as online supplementary material (for all online suppl. material, see https://doi.org/10.1159/000532104).

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Statement of Ethics

Ethical approval is not required for this study in accordance with local or national guidelines. Written informed consent was obtained from the patient for publication of this case report and any accompanying images.

Conflict of Interest Statement

The authors have no conflict of interest to declare.

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Author Contributions

Akiko Miyazaki and Saori Itoi-Ochi were the main contributors, acquired and analyzed patient data, and wrote and submitted the manuscript. Mami Hayashia and Asako Ota analyzed patient data. Shinya Inoue and Kengo Nagai contributed to the examination and treatment of the patient. Naohiro Tomita, Hidetaka Eguchi, Yasushi Okazaki, and Hideyuki Ishida performed multigene panel testing and the analysis of pathogenic genetic alterations. Takashi Hashimoto supervised the writing of the manuscript.

Data Availability Statement

All data generated or analyzed during this study are included in this article and its online supplementary material. Further inquiries can be directed to the corresponding author.

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