RESEARCH LETTER

Characterization of the Gut Microbiota in Patients with Erythroderma

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To the Editor,

Erythroderma is a severe syndrome characterized by widespread erythema and scaling, which may arise from various aetiologies (1). Erythrodermic cutaneous T-cell lymphoma (ECTCL) represents the most aggressive manifestation within this spectrum, frequently associated with systemic involvement and a poor prognosis (1). Conversely, another extremity of this spectrum may stem from prior inflammatory dermatoses, such as atopic dermatitis and psoriasis (1). Previous studies have paid limited attention to the gut microbiome in the context of erythroderma. Therefore, our study aimed to characterize the gut microbiota profiles of patients with erythroderma, particularly focusing on the specific signatures of the gut microbiome associated with ECTCL.

We conducted a cross-sectional analysis of the gut microbiota from 16 erythrodermic atopic dermatitis (EAD) patients, 12 ECTCL patients, and 14 healthy controls. The diagnoses of EAD and ECTCL were based on integrated clinical-pathological criteria and laboratory findings. The exclusion criteria included use of systemic immunomodulators or antibiotics, extreme diets (e.g., strict ketogenic, pure vegan, and extreme macronutrient diets), pregnancy, and intake of prebiotics or probiotics in the previous 4 weeks. Microbial 16S ribosomal RNA genes from the collected stool samples were analysed using third-generation PacBio sequencing technology (2). Differences in intragroup diversity (β-diversity) and taxonomic composition among the groups were assessed using Kruskal–Wallis and Wilcoxon tests. Additionally, the gut microbiota signatures of ECTCL and EAD were established by linear discriminant analysis effect size (LEfSe) and random forest model analysis.

The mean ages of the ECTCL group, EAD group, and control group were 50.6 ± 17.4 years, 59.2 ± 15.5 years, and 55.9 ± 11.8 years, respectively (**Table I**). No significant differences were found in terms of age, sex, or body mass index among the groups. Analysis of the β-diversity index showed that the ECTCL group exhibited significantly lower intragroup diversity compared with both the control and EAD groups ($p < 0.001$). Moreover, the non-metric multidimensional scaling (NMDS) plot illustrated a reduced dispersion of the ECTCL group relative to the other 2 groups (**Fig. 1**A). *Bacteroides* emerged as the most prevalent genus among all participants (Fig. 1B). The abundance of *Faecalibacterium* tended to be lower in all erythroderma patients (Control: 14.0%, EAD: 8.6%, ECTCL: 9.2%; EAD vs Control: $p > 0.05$, ECTCL vs Control: $p > 0.05$). Importantly, the relative abundance of the *Christensenellaceae R.7 group* was significantly higher in ECTCL patients than in both control and EAD patients ($p < 0.05$).

LEfSe analysis (Fig. 1C) indicated that *Roseburia inulinivorans* and *Roseburia intestinalis* were the predominant bacterial species in healthy controls. Additionally, the species *Alistipes onderdonkii*, *Parabacteroides merdae*, *Alistipes putredinis*, *Bacteroides caccae*, *Alistipes finegoldii*, and *Bacteroides eggerthii* were significantly enriched in ECTCL, most of which are associated with the development of gastrointestinal cancer (3). To further identify ECTCL-specific microbial biomarkers, a random forest model analysis was conducted (Fig. 1D). In total, 5 bacterial genera – *Faecalibacterium*, *Alistipes*, *Ruminococcus*, *Klebsiella*, and *Prevotella 9* – were selected for differentiating ECTCL from EAD, yielding an area under the curve of 0.792.

Our results indicated a non-significant decreasing trend in beneficial gut microorganisms, including *Faecalibacterium*, in both EAD and ECTCL. Although this trend did not reach statistical significance, lower abundances of *Faecalibacterium* have previously been associated with dysregulated cytokine signatures characteristic of AD and colorectal cancer (CRC) (4). Moreover, *Roseburia intestinalis*, which was not prevalent among patients with EAD and ECTCL, has been shown to regulate barrier homeostasis, immune cell function, and cytokine release, primarily through its metabolite butyrate (5). Given that

Table I. Demographic characteristics of the study cohort

Item	Control ($n = 14$)	EAD ($n = 16$)	ECTCL ($n = 12$)	p-value
Age, mean ± SD	55.9 ± 11.8	59.2 ± 15.5	50.6 ± 17.4	0.22
Sex, *n* (%)				0.34
Male	8 (50.0)	11 (68.8)	9 (75.0)	
Female	8 (50.0)	5 (31.2)	3 (25.0)	
BMI, median (range)	23.3 (17.6, 27.5)	24.3 (20.7, 29.8)	23.0 (17.0, 30.1)	0.37
Clinical stage				NA
IIIA			3 (25.0)	
IIIB			2 (16.7)	
IVA1			4 (33.3)	
IVA2			3 (25.0)	
Smoking status				
Nonsmoker	10 (71.4)	12 (75.0)	9 (75.0)	1.00
Smoker	4 (28.6)	4 (25.0)	3 (25.0)	

EAD: erythrodermic atopic dermatitis; ECTCL: erythrodermic cutaneous T-cell lymphoma; SD: standard deviation; BMI: body mass index; NA: not applicable.

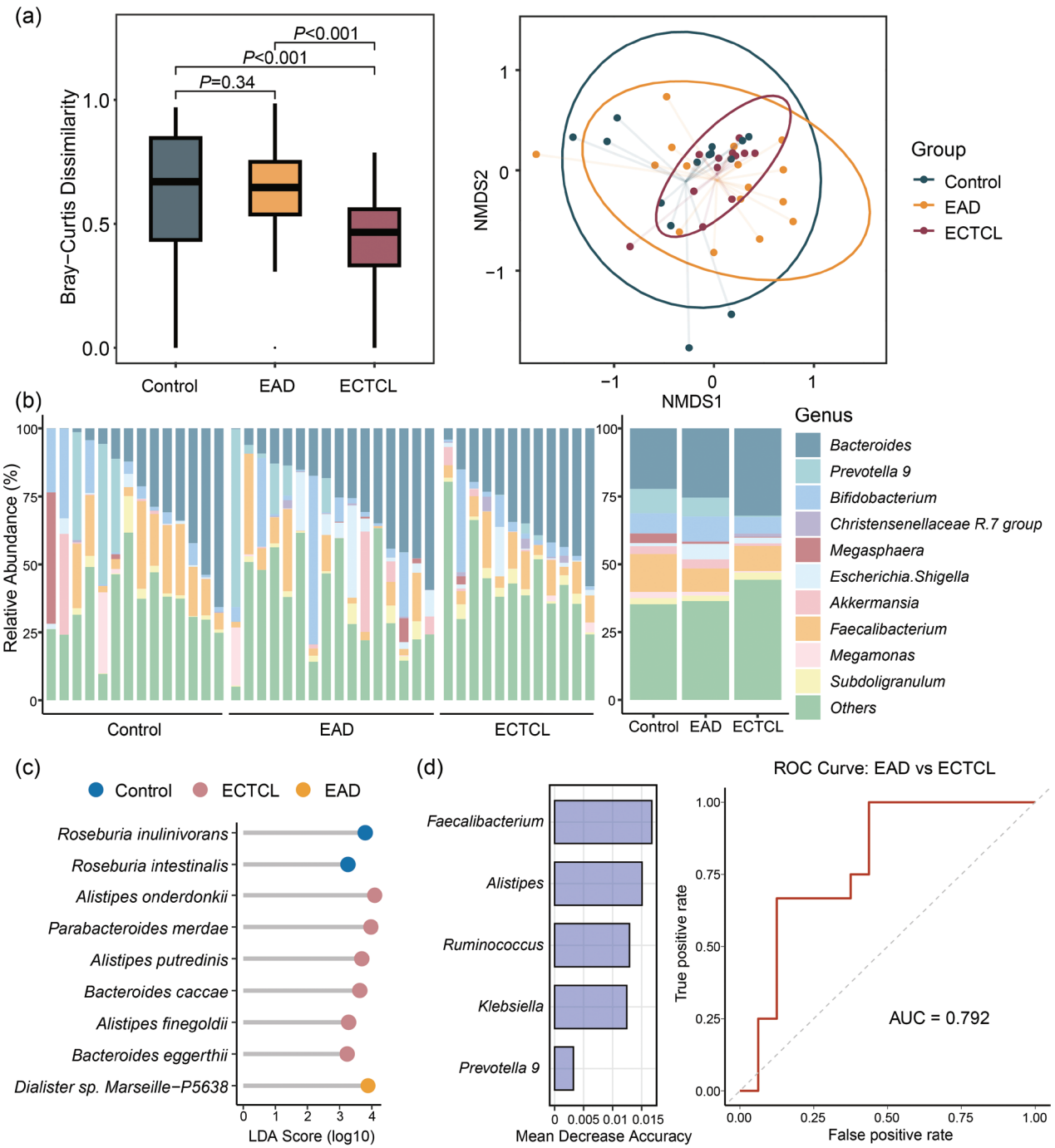

Fig. 1. Features of the gut microbiota in patients with erythroderma and healthy controls. (A) Multidimensional scaling (MDS) plot of gut microbial communities based on Bray–Curtis dissimilarity analysis at the genus taxonomic level revealed significant differences between erythrodermic cutaneous T-cell lymphoma (ECTCL) patients and healthy controls (or erythrodermic atopic dermatitis [EAD] patients). (B) Relative abundance (%) of the 10 most abundant genera in gut microbial communities among healthy controls, EAD patients, and ECTCL patients. (C) LEfSe analysis identified differentially abundant bacteria species among the healthy controls, EAD patients, and ECTCL patients. (D) The mean decreased accuracy (MDA) of the top 5 bacterial genera and receiver operating characteristic (ROC) curves were plotted to discriminate ECTCL from EAD.

ECTCL and EAD are characterized by T helper 2-predominant cytokine profiles, the dysbiotic signatures may be attributed to the complex interactions between the gut microbiome and the immune milieu (6).

ECTCL exhibited distinct malignant signatures in the gut microbiota compared with EAD. Certain bacterial subpopulations are known to be associated with oncogenesis or influence oncogenesis through immune modulation. The *Christensenellaceae R.7* group was predominant in ECTCL and has been reported to be abundant in the gut microbiota of lung cancer patients resistant to therapy (7). Furthermore, *Alistipes* has been implicated as a potential pathogen in the pathogenesis of CRC (3). Moschen et al. demonstrated that *Alistipes*

finegoldii promotes right-sided colorectal cancer via the IL-6/STAT3 pathway (8). However, further research into the influence of these bacterial subpopulations on the progression of CTCL is warranted.

To our knowledge, this study is the first to characterize the gut microbiome in patients with erythroderma, particularly highlighting the unique malignant signature of gut dysbiosis associated with ECTCL. Given that both EAD and ECTCL exhibit similar clinical manifestations and immune profiles, our findings offer a non-invasive approach for helping differentiate ECTCL from EAD through machine learning techniques based on gut microbiome analysis. However, due to the limited sample size, validation in larger, multicentre cohorts is essential for future investigations.

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The authors have no conflicts of interest to declare.

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