Psoriasis, gut and microbiome

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Linked Article: Hidalgo-Cantabrana et al. Br J Dermatol 2019; 181:1287–1295.

‘All disease begins in the gut’, the phrase attributed to Hippocrates, may sound like an overstatement but empirical evidence has linked many chronic metabolic and immune disorders to gut malfunction. It is increasingly recognized that the microbiome can change or switch on a wide range of diseases including cancer, cardiometabolic diseases, allergies, skin diseases and obesity. This is not surprising because recent advances in microbiome research have revealed that microbial cells outnumber human cells in our body by a ratio of around 10:1.

In this issue of the BJD, Hidalgo-Cantabrana et al. report on lower bacterial diversity and different relative abundance of bacterial taxa in patients with psoriasis. They further suggest that gut microbiota dysbiosis could be one of the triggers in the manifestation of psoriasis in genetically predisposed individuals. The microbiome of patients with psoriasis has been explored and reported in earlier studies. The advantage of this study is the inclusion of a healthy cohort from the same geographical area to minimize the environmental impact. While the presence of gut dysbiosis appears to be common in most studies of psoriasis, the relative abundance/decrease of different genera varies, most likely due to sequencing methodologies and computational analysis.

Essentially, the 16S rRNA gene sequencing of gut microbiome represents only the first step of a scientific journey to reveal what kind of bacteria are in our gut; it provides a solid foundation for further scientific exploration and knowledge building. However, the clinical significance of organisms identified solely by 16S rRNA gene sequencing is unclear. In addition to viable cells, dormant and dead bacteria, as well as extracellular DNA, are targeted. The next essential step is to map the presence and quantity of live bacteria. This analysis may not necessarily yield the same results as 16S rRNA gene sequencing. Another limiting factor in this study is enrolling a patient cohort with established disease and a long clinical history (average of 25 years), making it difficult to establish any meaningful cause–effect relationship.

The ultimate goal of any clinical research is the translation of clinical discoveries into new diagnostics, treatment and preventive approaches. The gut microbiome is an attractive therapeutic target because, theoretically, there is good amenability of the gut microbiome. Therapies could be based on environmental changes, diets, drugs or probiotic supplements. Evidence suggests that changing a diet dramatically leads to relatively quick gut microbiome changes, in which around 30–40% of the bacterial strains vary in their abundance. The big vision is to modulate or even prevent diseases via the microbiome alone or with other life factors. In this way, microbiome research is moving from an isolated offside position to become a beacon of hope with a lot of potential and possibilities.

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CD8+ mycosis fungoides: a wolf in sheep’s clothing?

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Linked Article: Doerschner et al. Br J Dermatol 2019; 181:1296–1302.

In this issue of the BJD, Doerschner and colleagues report on a case of mycosis fungoides (MF) with involvement of the central nervous system (CNS). Complete and ongoing remission of CNS lesions for 17 months was achieved with systemic chemotherapy and autologous stem-cell transplantation (SCT). Interferon (IFN) alfa-2a was used successfully to treat the subsequent relapse confined to the skin.

Initially, the patient was timely diagnosed with advanced-stage MF of 5 months’ duration restricted to the skin. Of note, the Prospective Cutaneous Lymphoma International Prognostic Index (PROCLIPPI) study has demonstrated a median diagnostic delay of 36 months in early-stage MF between first symptoms and initial diagnosis. However, in the face of currently lacking biomarkers for predictable disease progression it is debatable whether patients will benefit from early diagnosis. Moreover, accurate patient education on their prognosis is challenging with 5-year survival rates ranging from 88% to 30% dependent
on the clinical stage. The PROCLIP study aims to fill these significant gaps in the management of patients with MF, highlighting the project’s importance. The T-cell phenotype of MF is usually CD4+/CD8+. The 2018 update of the World Health Organization–European Organization for Research and Treatment of Cancer classification for primary cutaneous lymphomas emphasizes that clinicopathological correlation is essential to differentiate among CD8+ cutaneous T-cell lymphomas (CTCL). Indolent primary cutaneous acral CD8+ T-cell lymphoma and aggressive epidermotropic CD8+ CTCL are distinct entities whereas CD8+ cases of MF are considered as disease variants. At present, it is unclear whether the atypical expression of CD8 in MF correlates with an unfavourable clinical course. Interestingly, CD4+ to CD8+ immunophenotype switching reported in a single case of MF was associated with intraocular and CNS involvement. A hypothesis implies that CNS disease spread of MF is caused by direct extension through nerves based on confirmed optical nerve involvement. However, CNS involvement in MF is a rare, fatal complication and has been observed in early- and advanced-stage disease as well as in various subtypes of MF. Immediate neurological examination and imaging is needed when patients with MF present with either neurological or psychiatric symptoms. Diagnosis of CNS involvement can be suspected on the basis of cerebrospinal fluid analysis but for definitive diagnosis a brain biopsy is necessary. Fortunately, a complete remission of the CNS lesions was achieved in this patient due to high-dose chemotherapy followed by autologous SCT. In line with this, high-dose chemotherapy with autologous rescue has resulted in complete responses in the majority of reported patients. However, these responses were short-lived in almost all cases in contrast to long-term survival in selected patients after allogeneic SCT. Autologous SCT in CTCL is no longer regarded as a (curative) treatment option and therefore not included in the current treatment recommendations for MF. Of note, the limited cutaneous relapse together with the long-term response to IFN alfa-2a in this patient gives hope for a sustained benefit. This remarkable case provides a thought-provoking impulse about the clinical relevance of CD8 positivity in MF. The question of whether CD8 expression plays a crucial role in MF will hopefully be answered by results from the PROCLIP study in the future.

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Severe childhood psoriasis: need for safety and efficacy data on long-term treatment with biologics

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Linked Article: Thaci et al. Br J Dermatol 2019; 181:1177–1189.

Psoriasis starts in childhood or adolescence in about one-third of patients. Most children with psoriasis have mild-to-moderate disease, which is amenable to topical therapies or phototherapy, but some, with more severe disease, need systemic therapy. The availability of safe and effective systemic treatments in children with psoriasis is important, particularly given the increased risk of comorbidities (metabolic and cardiovascular diseases) and psychosocial impact that are present not only in adults, but also in children. However, while many systemic therapies are officially approved in adult patients with psoriasis (i.e. methotrexate, ciclosporin, retinoids and a certain number of biologics), the

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