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A GUT Connection in Mucous Membrane Pemphigoid (MMP): Insights into the Role of the Microbiome

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The role of gut microbiota in the pathogenesis of ocular inflammatory conditions is an emerging research field with the potential for developing novel therapies for these disorders. We recently encountered an interesting patient whose clinical case raised important questions about the influence of gut microbiota and its interaction with the pathophysiology of ocular surface inflammatory conditions. The particular patient, a 68-year-old male, had developed signs of ocular mucous membrane pemphigoid (MMP) approximately five years after being diagnosed with ulcerative colitis (UC), prompting us to examine the association between the two. The diagnosis of MMP was made based on characteristic symblepharon formation and scarring as well as a conjunctival biopsy, which showed linear deposits of IgA, IgG and C3 at the basement membrane zone (BMZ) with IgA predominance. The patient did not have any classical extra-ocular manifestations of MMP. The bowel and conjunctival inflammation proved difficult to control despite multiple systemic therapies including mycophenolate, prednisone, balsalazide, azathioprine, doxycycline, levofloxacin and metronidazole. Ultimately, the patient underwent a colectomy; after which the conjunctival inflammation completely subsided within 4 months. The patient's ocular disease has continued to remain quiescent for the last 3 years without any medications, and he has subsequently undergone surgical repair of his entropion.

UC is a chronic intestinal inflammatory condition characterized by diffuse inflammation in the epithelium of the colon.[1] The etiology of UC is complex and likely involves both genetic and environmental factors; accumulating evidence suggests a role for the intestinal microbiota with subsequent change in the mucosal immunity, that result in chronic inflammation.[2] Normally, the intestinal microbiota are closely involved in the regulation of the host immune system and vice versa. Disturbances to the gut microbiota (dysbiosis) can result in hyperactive immune reactions that could induce mucosal inflammation. UC is

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linked with many ophthalmic manifestations, the most common of which are keratopathy, episcleritis, scleritis and uveitis. UC-associated cicatrizing conjunctivitis has been recorded in only three case reports, but a causative relationship between the two was never proven.[3–5] Several theories have been proposed to explain the observed association between UC and MMP. UC and MMP, both linked with a dysregulated immune system, could be simply conditions associated with an autoimmune state in susceptible individuals. The second possibility is that UC and its disturbance of the gut barrier leads to a systemic inflammatory response predisposing to extra-colonic conditions such as MMP. The latter theory is more consistent with our observation that ocular disease activity was alleviated after the colectomy.

How colonic inflammation in the setting of UC could result in ocular surface inflammation in MMP is unclear. Sotiriou et al.[5] hypothesized that colonic inflammation stimulates an antibody reaction against colonic antigens with subsequent cross-reactivity against BMZ antigens. Interestingly, there are several complimentary reports describing complete resolution of Linear IgA bullous dermatosis after complete proctocolectomy.[6] These reports considered alongside ours offer strong evidence for the potential causative role of the intestinal immunological disturbance in the pathophysiology of autoimmune diseases, such as MMP.

While microbiota composition is well linked to the individual's lifestyle (i.e., diet)[7], genetic factors also could affect microbiota, reflecting the inter-individual heterogeneity in the colonic and extra-colonic manifestation among UC patients with seemingly similar environmental exposures. For example, human leukocyte antigen (HLA) molecules shape gut microbiota which in turn may induce inflammation in individuals who are genetically susceptible to certain HLA types.[8 9] Lin et al.[10] found that HLA-B27 transgenic rats have altered gut microbiota in comparison to normal healthy rats. To further support the causality between microbiota and colonic and extra-colonic inflammation, HLA-B27 transgenic rats do not develop gastrointestinal inflammation and arthritis when raised in a germ free environment.[11] HLA-DQB1*0301 has been found to be associated with all subtypes of MMP and a similar association was found between HLA-DR4 and ocular cicatricial pemphigoid (OCP).[12] These associations may be related to HLA's influence on T-cell function in recognizing BMZ antigens with subsequent anti-basement autoantibody production.[13] However, these specific HLAs could also influence the gut microbiota and intestinal inflammation.

Although we cannot entirely exclude the possibility that the MMP and UC in our patient was coincidental, the complete resolution of pemphigoid activity after proctocolectomy suggests a causative relation between colonic inflammation and the MMP. The role of the gut microbiome in MMP has never been investigated. Recognizing an association between UC and MMP opens the possibility for further studies on the precise pathogenesis of cicatricial conjunctival disease by investigating the role of gut microbiota and its disturbance in such conditions. Additionally, further study may help our understanding of how MMP can be potentially managed by modulating the gut microbiota. Greater understanding the nature of gut microbiota and its manipulation will revolutionize our approach to ocular surface inflammatory diseases and facilitate in the development of novel treatments.

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