Lessons From Localized Chronic Rhinosinusitis With Nasal Polyps

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Tissue remodeling is a hallmark of chronic rhinosinusitis with nasal polyps (CRSwNP). In CRSwNP, the important features of remodeling include increased tissue edema and fibrin deposition associated with abnormalities in the coagulation cascade. Barrier dysfunction results in the leakage of fibrinogen from the vasculature into the sinus mucosa in CRSwNP. It is then converted enzymatically by thrombin to fibrin which further cross links and forms the matrix. Under physiologic conditions, tissue plasminogen activator (t-PA), a serine protease, coverts plasminogen to plasmin which in turn further induces degradation of the fibrin matrix into dimers and prevents from fibrin deposition. In nasal polyps, expression of t-PA is known to be significantly decreased compared to uncinate tissues from control subjects or patients with CRS.

The expression of t-PA was first known to be regulated by type 2 inflammation as this is the dominant endotype in most of the Western countries. As about half of the CRSwNP patients in Asia demonstrate non-type 2 inflammation, a question remains as to whether similar findings are present in cases with polyp with non-type 2 inflammation. The first comparative study was published in 2013. Although both eosinophilic and non-eosinophilic CRSwNP demonstrated higher fibrin deposition compared to the control tissue, the fibrin deposition was significantly higher and the levels of d-dimer and t-PA were lower in eosinophilic CRSwNP compared to non-eosinophilic one. Therefore, it can be concluded that tissue remodeling regarding fibrin deposition due to coagulation pathway abnormalities is more prominent in eosinophilic CRSwNP.

The following study was published in 2020 by the same authors. Their study demonstrated that non-type 2 cytokines such as interferon (IFN)-γ, and type 2 cytokines significantly downregulated the expression of t-PA in the nasal epithelial cells. On the contrary, when IL-17, a typical type 3 cytokine, was applied to nasal epithelial cells, the expression of t-PA was upregulated. Among non-eosinophilic CRSwNP, type 3-alone endotype had lower t-PA. Taken together, their study concluded that both eosinophilic and non-eosinophilic CRSwNP lead to excess fibrin deposition, which may be responsible for polypogenesis. However, it seems likely that non-eosinophilic CRSwNP with different endotypes act differently; type 1 (IFN-γ) leads to...
fibrin deposition by reduced expression of t-PA, while type 3 (IL-17) leads to fibrin degradation by increased t-PA. Therefore, due to the heterogeneity of endotypes in non-type 2 CRSwNP, it may have less prominent fibrin deposition overall, compared to type 2 CRSwNP.

In the current issue, Chen et al. demonstrated similar findings in continuation with their previous reports. They categorized CRSwNP into 3 different pathologies: eosinophilic CRSwNP, non-eosinophilic CRSwNP, and antrochoanal polyp (ACP). They revealed the underlying endotypes of the 3 categories: eosinophilic CRSwNP as type 2, non-eosinophilic CRSwNP and ACP as a mixture of types 1 and 3. Unlike the other categories, ACP had no single type 3 endotype. Compared to non-eosinophilic CRSwNP, ACP had higher levels of neutrophil infiltration and expressions of myeloperoxidase (MPO), IL-8, and IFN-γ. The polyps in all 3 categories demonstrated increased fibrin deposition as well as decreased t-PA and d-dimer levels compared to the control tissue, with more prominent changes in ACP. The level of t-PA was negatively associated with type 1 cytokine (IFN-γ), IL-8, and MPO in all types of the disease. However, type 2 inflammatory markers, IL-13 and eosinophil cationic protein (ECP), showed negative correlations with the level of t-PA only in eosinophilic CRSwNP, suggesting that interactions between the coagulation cascade and tissue inflammatory profile may differ. Fibrin deposition and associated tissue edema were originally known to be elevated in type 2 inflammation. However, this study made it clear that fibrin deposition is also increased and even higher in non-eosinophilic CRSwNP compared to eosinophilic CRSwNP.

The pathogenesis of ACP is still unknown, but histological analyses reveal increased neutrophil infiltration with marked edema. One of the hypotheses that explain the pathogenesis of ACP is that increased intrasinus pressure after blockage of natural ostium leads to prolapse of the polyp tissue into the nasal cavity through the accessory ostium. Mostafa et al. demonstrated increased lymphatic vessels in the transition zone between the normal mucosa and the polyp pedicle, suggesting the possibility of lymphatic obstruction as an initial pathogenesis. Factors associated with ACP, such as increased maxillary volume and high prevalence of anatomical variation around the natural ostium further suggest that anatomical or mechanical abnormalities are the primary etiology in the disease pathogenesis. However, consistent results regarding the treatment outcome of ACP are that complete resection of polyp attachment reduces disease recurrence. This implies that the pathogenesis of the disease might be somewhat simplified.

In this current issue, Chen et al. demonstrated that none of the patients with ACP revealed type 3-alone endotype, unlike eosinophilic and non-eosinophilic CRSwNPs. Analysis of inflammatory cells showed that CD138⁺ plasma cells and CD3⁺ T cells were significantly increased in eosinophilic and non-eosinophilic CRSwNPs, whereas they were not in ACP compared to control tissues. This suggests that the role of acquired immunity mediated by T and B cells might be less significant in cases of ACP. Chronic inflammation constituted by the innate immunity with type 1-dominant endotype appears to be a consequence secondary to the primary anatomical or mechanical etiology. This characteristic can be differentiated from non-eosinophilic CRSwNP, which is thought to be a somewhat heterogenous disease.

Current guidelines distinguish between localized and diffuse CRSwNPs. Unlike diffuse CRSwNP, localized CRSwNP has unique clinical characteristics. With the exception of allergic fungal rhinosinusitis, which often occurs bilaterally and frequently recurs, the treatment outcome of localized CRSwNP is generally good. Thus, localized CRSwNP may entail less heterogeneity. Currently, most studies on CRSwNP focus on diffuse CRSwNP, whereas studies on localized CRSwNP are not as popular as those on diffuse one. However, the
research on localized CRSwNP could be important as it may provide some helpful clues for understanding the pathophysiology of CRSwNP.

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