

86-Is pseudoexfoliation an immunological disease?

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Exactly 80 years ago today, a Finnish ophthalmologist by the name of Dr. Lindbergh first described the disease we know as pseudoexfoliation (PXF). Ever since the time of this initial description, it has been well known that the pseudoexfoliative material is distributed throughout the anterior segment of the eye, including the corneal endothelium, lens, ciliary body, and trabecular meshwork.

Only in recent years, however, have reports arisen that pseudoexfoliation can also involve the ocular adnexa, including the connective tissue of the orbital septum, and lids. Moreover, PXF material has been found systemically as well, including the heart, lungs, liver, kidney, and cerebral meninges.

In light of these and other recent findings, Ajay Auroroa, MD of New Delhi, raised the interesting question, "Is p an immunological disease?" in his talk at this year's AAO annual meeting. Co-authors of this work included Subhadha Pani, M.D., of Pondicherry, India, and Pran Nath Nagpal, M.D., of Ahmedabad, India.

Electron microscopy (EM) has demonstrated that the pseudoexfoliative material is composed of electron-dense fibers which are 25 - 35 nm in diameter, intermingled with smaller microfibrils ranging in size from 3 - 6 and 8 - 10 nm in diameter. Present knowledge states that PXF material is composed of either an altered basement membrane protein, amyloid, or elastin

Is it possible that unrelated cell types with the ability to secrete the extracellular matrix of basement membrane components, could have a common metabolic

lesion, which might explain the widespread distribution of PXF? This is the question posed by Dr. Aurora.

It is well known that in rheumatoid arthritis (RA), a connective tissue disorder, a specific antinuclear antibody (ANA) which has specific activity against joint fluid is expressed, and is found in high concentrations in the serum. The authors of the present study sought to examine the serum and aqueous levels of ANA in both PXF and control eyes to determine whether increased ANA levels might be associated with PXF.

43 eyes with PXF were examined histochemically with hematoxylin-eosin (H&E), Alcian blue, and Periodic Acid Schiff (PAS) stains. No EM studies were performed. Immunological studies were performed on 32 PXF eyes and on 23 control eyes, consisting of pre- and post-operative indirect immunofluorescent analysis of serum and aqueous ANA levels. Immunofluorescence was graded on a subjective scale ranging from 0 to 4.

Histochemical analysis revealed that lens epithelium is one of the sources of PXF material. Conjunctiva and trabecular meshwork, in comparison, did not demonstrate PXF material, a negative result which may have resulted from the lack of EM studies.

46.9% of eyes with PXF demonstrated ANA in the aqueous, compared to 8.7% of control eyes. This difference was significant ($p < 0.0001$). 34.4% of PXF eyes demonstrated ANA in the aqueous, but not in the preoperative serum. In contrast, none of the control eyes demonstrated ANA in the aqueous. This finding suggests that ANA may be abnormally produced and expressed in the anterior segment of eyes with PXF.

In Dr. Aurora's conclusion, he states that histochemical analysis shows that the lens epithelium is an important source of PXF material. More importantly, he

asserts that these early data suggest that a local immunologic process, possibly mediated or marked by ANA, may play a role in the development of PXF.

The discussion of this paper was by Gottfried O. Naumann, M.D., of Erlangen, Germany. Dr. Erlangen pointed out that while it is now generally accepted that PXF is a systemic disease, we still do not know what clinical significance the systemic deposition of PXF material has. Ocular effects of PXF, in contrast, are more well known.

For example, the breakdown of the blood-aqueous barrier has been demonstrated in PXF, and may contribute to the pseudoinflammatory signs seen in PXF. These pseudoinflammatory signs have lead Dr. Aurora and others to study whether PXF may be immunologically mediated.

The current study demonstrated a higher incidence of ANA in the aqueous of PXF compared to control eyes. Dr. Erlangen raised several important potential problems with the study. Demographic characteristics of the case vs. the control populations were not given, and may not be comparable between the two groups. In addition, neither PXF patients nor controls were either examined or stratified for the presence of glaucoma, which may be another confounding factor.

Most importantly, the authors of the current study fail to state why they selected ANA as the relevant marker for immunological activity in PXF. They also fail to offer a potential mechanism for how ANA can mediate the pathogenesis of PXF. These shortcomings are even more problematic because previous investigators have failed to demonstrate an immunologic basis for PXF.

For example, Dr. Ringwald in his active search for an immunologic basis for PXF, has instead come up with three compelling reasons why this is *not* be the case. These are: 1) PXF material is not immunologically active, 2) there are no

auto-antibodies directed at PXF material, and 3) abnormal amounts of immune complexes have not been found in sites known to be affected by PXF.

Therefore, the findings of the current study stand in contrast to the majority of the prior literature. While Dr. Ringwald thanked Dr. Aurora and colleagues for raising the need to further investigate the possibility of an immunologic basis for PXF, he cautions that the current findings will have to be replicated and better elucidated before any broad conclusions can be justified.