• Letter to the Editor •

A new pathological perspective on juvenile open angle glaucoma with chromatin decondensation and trabecular meshwork damage: a case report

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Dear Editor,

We are writing this letter to present a case of juvenile open angle glaucoma (JOAG) and the unique pathological changes observed in its trabecular meshwork (TM).

JOAG constitutes a distinct subclassification of primary open angle glaucoma (POAG) defined by onset prior to age 40. Clinically, this condition manifests as elevated intraocular pressure (IOP), anatomically open anterior chamber angles, and characteristic glaucomatous optic neuropathy. Management frequently necessitates surgical intervention due to refractory responses to medical therapy[1]. Epidemiologically, JOAG demonstrates marked interpopulation variability; within the United States, prevalence estimates approach 1 in 50 000 individuals, imposing significant socioeconomic burdens[2]. Genetic investigations consistently identify mutations in the *MYOC* gene as the predominant genetic association, although pathogenic variants in *CYP1B1* and *LTBP2* also constitute established risk factors[3]. This underlying genetic heterogeneity contributes to diverse phenotypic expressions, including differential IOP severity, anomalous angle development patterns, and varying modes of inheritance.

While multiple treatment exists for JOAG, its precise pathogenesis remains incompletely elucidated. Histopathological research has been impeded by challenges in specimen acquisition. Analyses demonstrate that developmental immaturity of TM results in thickened compact tissue comprising disorganized cells and abnormal extracellular matrix deposits anterior to Schlemm's canal, obstructing aqueous outflow[4]. Ultrastructurally, extensive fingerprint-like basement membrane material deposition within the inner cribriform and outer corneoscleral TM, which resemble steroid-induced glaucoma pathology, contributes to cribriform layer thickening and outflow obstruction[5]. Nonetheless, nuclear-level structural abnormalities specific to JOAG remain undocumented. Surgical TM tissue from a medically refractory 7-year-old JOAG patient uncovered pathological alterations including TM architectural disruption and chromatin decondensation within TM cells, thereby contributing novel insights into JOAG pathogenesis.

Ethical Approval This report was approved by the ethics committee of Peking University People's Hospital (2024PHB090) and followed the tenets of the Declaration of Helsinki. Written informed consent was obtained from the adult subject and the minor's legal guardian. The subjects did not receive any stipend.

CASE PRESENTATION

Following comprehensive ophthalmic assessment, a 7-year-old male was diagnosed with JOAG. IOP measurements (Goldmann applanation tonometry) peaked at 51 mm Hg in the right eye and 38 mm Hg in the left eye. Cup-to-disk ratios measured 0.8 and 0.6, respectively. Slit-lamp biomicroscopy and gonioscopy demonstrated moderately deep anterior chambers with open angles. Supplementary diagnostic outcomes are detailed in Figure 1. Retinal nerve fiber layer analysis (Figure 1A, Spectralis OCT, Heidelberg Engineering, Inc., Heidelberg, Germany) exhibited pronounced structural

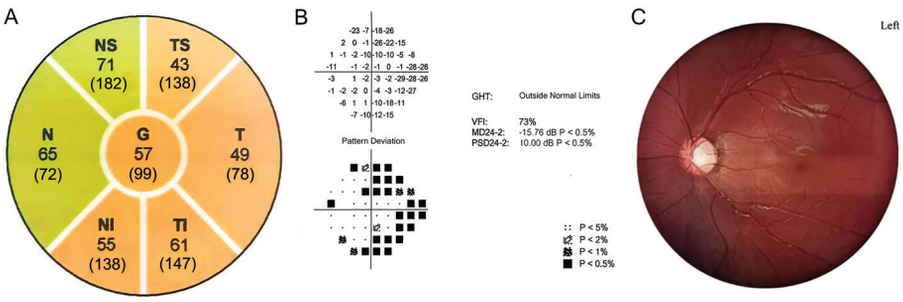


Figure 1 The preoperative examination results of the left eye A, B: Thinning of the retinal nerve fiber layer and visual field defect in the corresponding area can be observed; C: Enlarged cup-to-disc ratio is shown in the fundus photography. G: Global; N: Nasal; NS: Nasal-superior; NI: Nasal-inferior; T: Temporal; TS: Temporal-superior; TI: Temporal-inferior; GHT: Glaucoma Hemifield test; VFI: Visual field index; MD: Mean deviation; PSD: Pattern standard deviation.

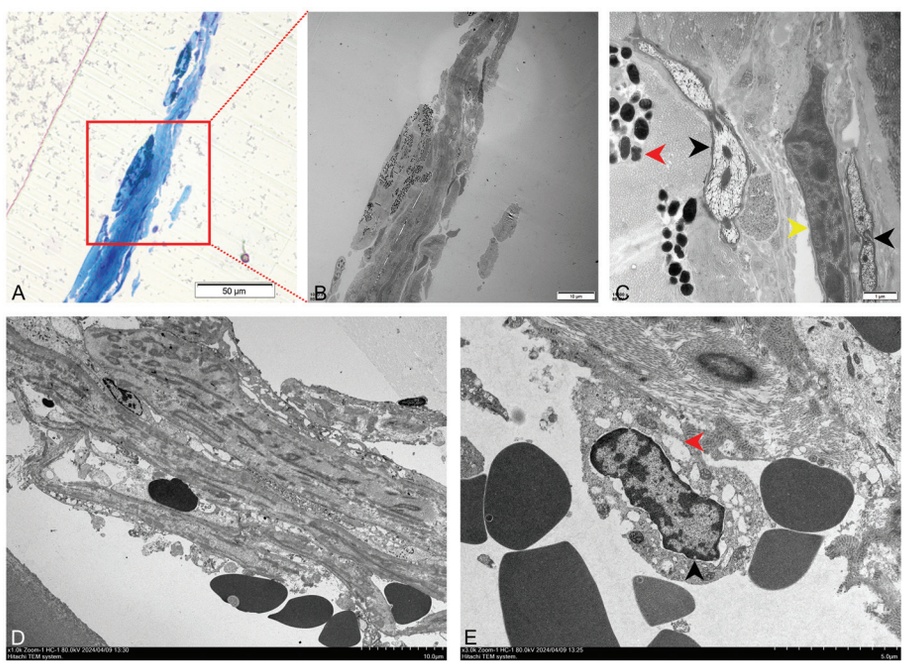


Figure 2 Histopathologic image of TM from the patient with JOAG (A–C) and POAG (D–E) A: Toluidine blue staining shows local enrichment of nucleic acids (original magnification ×400); B: A large number of nuclei are observed (×1050, 80 kV); C: Local image (×11 500, 80 kV) shows nuclei with remarkable chromatin decondensation (black arrowhead) and without chromatin decondensation (yellow arrowhead) in JOAG. Pigment particles can also be observed (red arrowhead); D: Numerous TM fibers with a reticular distribution were observed in the TM of POAG eyes (×1000, 80 kV); E: In POAG eyes (×3000, 80 kV), vacuolated endoplasmic reticulum (red arrowhead) was observed within the TM cells, while no significant chromatin decondensation was observed in the cell nuclei (black arrowhead). TM: Trabecular meshwork; JOAG: Juvenile open angle glaucoma; POAG: Primary open angle glaucoma.

deficits, while visual field testing [Figure 1B, Swedish Interactive Threshold Algorithm (SITA) fast 24-2 test of the Humphrey visual field analyzer 750i, Carl Zeiss Meditec, Dublin, CA, USA] revealed significant functional impairment. These collective findings indicate severe glaucomatous optic neuropathy necessitating urgent IOP reduction. Fundus photography (Figure 1C, CLARUS 500 Fundus camera, Carl Zeiss Meditec, Dublin, CA, USA) confirmed enlarged cup-to-disk metrics without additional fundus pathology. Comprehensive genetic screening encompassing the proband and immediate family members identified no pathogenic variants. Despite maximal medical therapy comprising Brinzolamide, Brimonidine, Timolol, and Tafluprost eyedrops supplemented by intravenous mannitol, IOP persisted at 20–22 mm Hg bilaterally. Consequently, bilateral gonioscopy-assisted transluminal trabeculotomy was performed, including excisional TM biopsy from the left eye for histopathological assessment. Postoperative IOP reduction was sustained with stabilization confirmed at 6-month follow-up.

Histopathological analysis of TM specimens from JOAG (Figure 2A–2C) patients revealed characteristic alterations. JOAG specimens exhibited substantial fusion of trabecular beams with diminished intertrabecular spaces, increased collagen deposition, and pigment accumulation (Figure 2A–2B),

collectively contributing to elevated outflow resistance. Additionally, these specimens demonstrated reduced TM cellularity accompanied by diminished cytoplasmic content, indicating functional impairment within the TM. JOAG further presented considerable nuclear heterogeneity featuring filamentous chromatin patterns suggestive of partial decondensation (Figure 2C).

For comparison with JOAG manifestations, the histopathological features of the TM from a POAG patient were demonstrated in Figure 2D and 2E. The TM specimens presented in this study were obtained from a 65-year-old woman with a five-year POAG history. Her IOP was stabilized at approximately 14 mm Hg under sustained dual therapy with carteolol and latanoprost. Owing to progressive cataract development, she underwent combined phacoemulsification, intraocular lens implantation, and Kahook Dual Blade goniotomy. The TM excised during surgery subsequently underwent histopathological analysis. In POAG specimens, TM architecture displayed a reticular organization with electron-dense fiber deposition (Figure 2D). At the cellular level, the principal pathological alteration involved prominent endoplasmic reticulum dilatation within TM cells (Figure 2E), while nuclear morphology remained essentially unaffected.

DISCUSSION

Histopathological examination of TM tissue from a JOAG patient revealed structural disorganization, collagen fiber replacement of TM cells, pigment particle accumulation, and chromatin decondensation within TM cells. These morphological alterations could increase aqueous humor outflow resistance, suggesting a potential role in JOAG pathogenesis. Previous investigations identified significant accumulations of extracellular material organized in a fingerprint-like pattern within trabeculectomy specimens from JOAG patients, leading to thickening of the juxtacanalicular connective tissue. This finding closely resembled alterations observed in corticosteroid-induced glaucoma[5]. However, changes in nuclear chromatin morphology associated with JOAG have not been previously described.

In this case, chromatin decondensation was observed, potentially contributing to TM cell dysfunction. Chromatin organization critically regulates genomic accessibility to maintain cellular homeostasis by modulating gene expression patterns[6]. The detected chromatin decondensation may disrupt TM cell transcriptomic profiles, impairing mechanosensitive signaling and phagocytic functions. Specifically, diminished chromatin compaction could expose epigenetically silenced genomic regions, thereby activating aberrant expression of extracellular matrix remodeling enzymes. These epigenetic alterations potentially initiate a pathological feedforward loop, wherein elevated oxidative stress (OS) perpetuates chromatin instability, sustaining a self-amplifying pathogenic microenvironment within the TM. OS and chronic inflammation significantly elevate aqueous humor outflow resistance in JOAG. Chronically inflamed microenvironments necessitate chromatin decondensation to facilitate inflammatory gene transcription. Concurrently, OS triggers neutrophil extracellular trap (NET) formation, a process fundamentally reliant on chromatin decondensation[7]. NET perpetuate OS and sterile inflammation through tissue damage and sustained inflammatory cascades. Although NET production is neutrophil-specific, TM cells in this case exhibit analogous chromatin decondensation patterns despite their phagocytic function, suggesting chronic inflammatory reprogramming in non-immune cells.

Another possible explanation posits that exogenous mechanical forces induce chromatin decondensation and softening[8]. However, comparable alterations were not significantly observed in POAG. Chromatin decondensation also occurs during processes requiring active DNA transcription, such as organ development. Given that anterior angle dysgenesis constitutes a critical pathogenic mechanism in JOAG[1], chromatin decondensation may involve an aberrant or arrested developmental process. Further investigations into JOAG pathogenesis are required to elucidate the precise mechanism underlying this chromatin reorganization.

As JOAG represents a distinct subtype of POAG, a comparative histological analysis of the TM from a POAG patient was conducted. Findings revealed significantly more extensive TM structural disruption in the POAG case than observed in the JOAG specimen. Increased outflow resistance may arise from the characteristic densely packed, net-like distributed TM fibers exhibiting high electron density, as documented in prior studies[9-10]. However, notwithstanding less severe TM disruption than the POAG subject, the JOAG patient presented profoundly elevated, pharmacologically unresponsive IOP and severe visual impairment. This discrepancy implies potential alternative mechanisms of outflow pathway impairment specific to JOAG pathogenesis. Notably, a distinctive finding exclusively observed in the JOAG patient was pronounced chromatin decondensation within TM cells. This phenomenon likely signifies TM cellular dysfunction, thereby suggesting a pivotal pathological mechanism underlying JOAG distinct from POAG.

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