

# Clinicopathologic report of anterior subcapsular cataracts after combined administration of corticosteroids and cyclosporine following renal transplantation

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We report a 20-year-old man who was referred for bilateral anterior subcapsular cataracts. He had a history of renal transplantation and had been treated with prednisolone, mycophenolate mofetil, and cyclosporine for the previous 3 years. He presented with gradual bilateral visual loss starting 6 months earlier. On slitlamp examination, bilateral anterior subcapsular cataracts were detected in both eyes. Appropriate surgery was performed and histopathological examination done for the anterior capsule specimen. Hematoxylin–eosin staining of the anterior capsule revealed significant subcapsular scar formation in the context of fibroblast proliferation.

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Cataracts are classified by location of opacity within the lens structure as cortical (anterior and posterior), nuclear, subcapsular (anterior and posterior), and mixed.<sup>1</sup> Several factors can lead to cataract formation including age, congenital condition, secondary (drug-induced, secondary to disease), and trauma.

Cataract is also a major vision-limiting factor following organ transplantation, usually in the context of steroid intake. New cataract formation after transplantation developed in 11% to 38% of patients without cataract at the time of transplantation and can occur as early as 6 months after transplantation.<sup>2</sup> The main ocular complication associated with renal transplantation and its therapeutic regimen is posterior subcapsular cataracts.<sup>3</sup> Several assumptions about corticosteroid effect on lens cells have been described,

but the exact mechanisms are not well understood. Transparency of the lens is the result of highly ordered lens cell architecture and arrangement of protein molecules within the lens fibers. Any insult to this integrity results in cataract formation, which is related to type, duration, and site of insult that occurs to different parts of the lens. The ocular disturbance following renal transplantation is mostly due to immunosuppressive drugs, especially corticosteroids.<sup>4–10</sup>

We discuss a clinicopathologic report of an atypical form of anterior subcapsular cataracts. Based on our previous studies of the basement membrane of the lens anterior capsule,<sup>11,12</sup> we presume that this form of cataract might be due to alterations in the lens barriers, leading to disturbed lens nutrition after prolonged intake of combined administration of corticosteroids and cyclosporine following renal transplantation.

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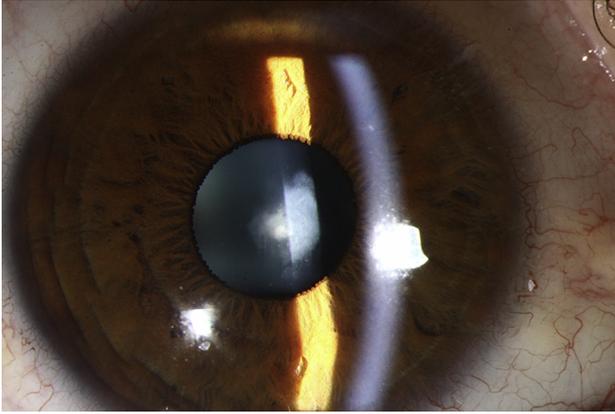
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## CASE REPORT

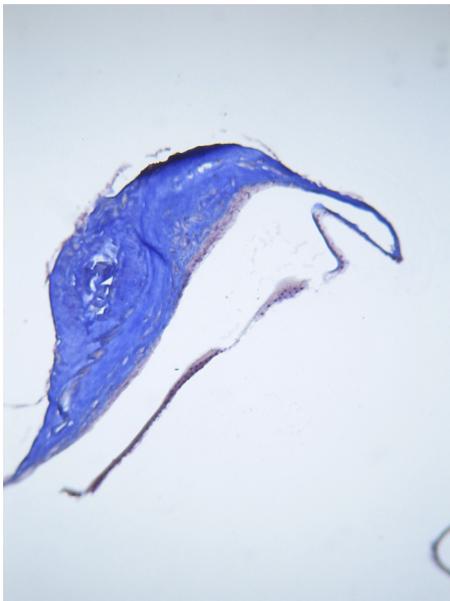
A 25-year-old man with a history of kidney transplantation was referred to our hospital with a complaint of gradual bilateral loss of vision for 6 months. He had a history of kidney transplantation 3 years previously, which was rejected, and a second kidney transplantation 6 months earlier. He had been on a regimen of prednisolone (1 mg/kg/day, tapering to 15 mg/day) accompanied by mycophenolate mofetil 2 gr/day and cyclosporine 250 mg/day for 3 years.



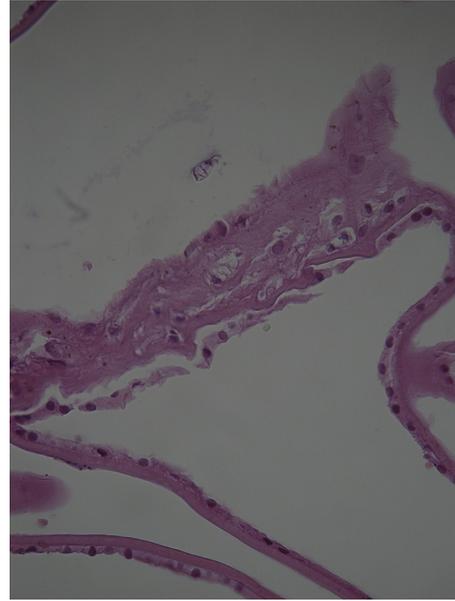
**Figure 1.** Dense anterior subcapsular opacity on slitlamp examination of the left eye.

On ophthalmologic examination, decrease of visual acuity in both eyes was detected. The uncorrected distance visual acuity (UDVA) was 7/10 in the right eye and 5/10 in the left eye and did not improve with spectacle correction. The slitlamp examination showed bilateral anterior subcapsular opacities (Figure 1).

Because the UDVA was more limited in the left eye, the first surgical intervention was done in that eye. Cataract extraction by sutureless clear corneal phacoemulsification and intraocular lens implantation under topical anesthesia



**Figure 3.** Trichrome-Masson staining showing dense hyaloids and fibrin formation under basement membrane of central part of the anterior capsule.



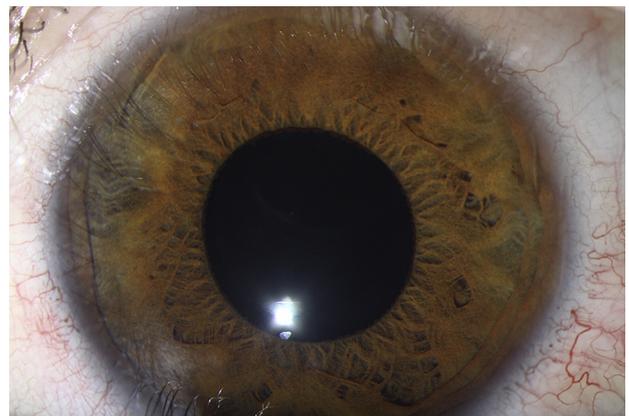
**Figure 2.** Hematoxylin-eosin staining of the anterior capsule shows significant subcapsular scar formation in the context of fibroblast proliferation.

was performed. The anterior subcapsule of the lens was sent for histopathological examination. Hematoxylin-eosin staining of the left anterior capsule of the lens revealed focally thickening fibrotic scar tissue with significant subcapsular scar formation in the context of fibroblast proliferation (Figures 2 and 3).

One week following cataract surgery, the eye was quiescent and the UDVA was 20/20 (Figure 4).

## DISCUSSION

Cataract is a main cause of visual disturbance following transplantation and is common in transplantation patients. The most common ocular complication following renal transplantation is posterior subcapsular cataract.



**Figure 4.** Postoperative slitlamp examination of the left eye.

Cataracts induced by systemic steroid therapy are usually detected as a posterior subcapsular cataract. However, the exact mechanism of cataract formation due to steroid therapy is unclear.<sup>5</sup> The pathogenic mechanism of steroid-induced cataract remains unclear. Several hypotheses suggest that glucocorticoids exert their effect on normal lens cellular functions by dysregulation of proliferation, differentiation, migration, or apoptosis.<sup>2</sup>

It is not known whether glucocorticoids exert their effect through binding to specific glucocorticoid receptors, nonspecific glucocorticoids binding in the lens, binding to a membrane receptor, or through a metabolic effect as a result of glucocorticoids binding to a glucocorticoid receptor at another site.<sup>2,10</sup> Glucocorticoid-receptor complex binding DNA may result in modulating the expression of target genes, affecting transcription, and modulating the expression of another gene.<sup>2</sup>

Another hypothesis is that glucocorticoid exposure may disturb protective antioxidative systems in the lens by glutathione depletion levels, making the lens prone to oxidative stress, which destabilizes protein conformation, leading to cataract formation.<sup>2,10</sup>

Some studies have suggested that another mechanism of steroids is changes in growth factor production in the eye, such as fibroblast growth factor and transforming growth factor  $\beta$ , which are necessary for lens fiber development and growth. The effect of corticosteroids on these growth factors leads to impairment in the differentiation process, which can result in loss of lens transparency and cataract development. In the study by Petersen et al.,<sup>10</sup> ion imbalance in the lens, which was caused by glucocorticoids, was detected.

Corticosteroids are an essential component of most immunosuppressive regimens currently used in renal transplantation, and cyclosporine (cyclosporin A) is commonly administered in addition to immunosuppressive drugs to reduce the side effects of the steroidal components. The rate of steroid-induced cataracts increased with the combined use of cyclosporine and steroids, despite the reduction in total dose of systemic steroids. Some studies show that using cyclosporine may accelerate the development of steroid-induced cataracts. The pattern of cataracts with the use of cyclosporine is different with more atypical cataract types.<sup>6,8,9</sup> On the other hand, transplantation itself increases all types of cataract.<sup>6</sup> No notable direct relationship between the development of posterior subcapsular cataract and renal disease, duration, and type of dialysis has been found.<sup>3</sup>

In the classical corticosteroid-induced posterior subcapsular cataract, the anterior capsules of steroid-affected lenses have revealed abnormalities of

epithelial structures, and in some cases a specific reticulated pattern was seen.<sup>6</sup>

Long-term glucocorticoid treatment leads to changes in gene expression, which result in prolonged modulation of important signaling pathways leading to dysregulation of cell function in different regions of the lens.<sup>2</sup> As glucocorticoids act through binding to specific glucocorticoid receptors, there may be an individual susceptibility of the lens to corticosteroids related to interindividual receptor heterogeneity.<sup>3</sup>

The lens epithelium is surrounded by the aqueous humor with a gradient of growth factors and effectors present, which the specific regions of epithelial cells respond to differently because of the concentration gradient.<sup>2</sup>

It is well-documented that long-term corticosteroid therapy leads to posterior subcapsular cataract formation.<sup>13,14</sup> To our knowledge, no report has proved an anterior subcapsular cataract may be associated with corticosteroid therapy.

In most cases, the type of cataract following renal transplantation is posterior subcapsular cataract, but in our case the patient presented with anterior subcapsular cataract after transplantation, proved by pathological documentation. He had no history of cataract at the time of transplantation and no history of ocular trauma, retinoblastoma, inflammation, or dermatological disease, which may cause anterior subcapsular cataract.<sup>15</sup>

The mechanism of cataract formation induced by glucocorticoid is not known<sup>12</sup> and several hypotheses have demonstrated actions of glucocorticoid, as discussed above. Different combinations of insults to the lens may be present in different regions of the lens, which then leads to lens cell dysfunction. In our case, bilateral anterior subcapsular cataracts and fibrosis of the anterior capsule were linked to renal transplantation and its immunosuppressive regimen.

We presumed that the atypical form of cataract in this young man might be due to structural changes in the basement membrane of the anterior capsule and its subsequent effect on lens nutrition in the context of prolonged intake of combined systemic steroid and cyclosporine and solid organ transplantation. The histopathological examination of the anterior capsule supported our hypothesis.

In conclusion, renal transplantation and its related therapeutic regimen may be associated with the development of atypical forms of cataracts, such as anterior subcapsular lens opacities. Systemic intake of cyclosporine may have a modulatory role in changing the pattern of cataract formation from posterior subcapsular to anterior subcapsular by altering the lens barriers, leading to disturbed lens

nutrition and, eventually, vision-limiting lens opacities. Regular screening of visual acuity and ophthalmic examinations are recommended in renal transplant patients.

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