

## Atypical Granular Corneal Dystrophy: A Case Report

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### ABSTRACT

Three cases of atypical granular corneal dystrophy (GCD) in the same family were reported. The patients had a history of progressively decreased visual acuity and foreign body sensation. The pathological findings showed hyaline deposits beneath the corneal epithelium and stroma. The patients had an unusual and atypical clinical presentation of GCD characterized by a rapid progression of clinical manifestation and early deterioration of visual acuity.

**Key words:** atypical granular corneal dystrophy (GCD), pedigree, *BIG-H 3* gene, penetrating keratoplasty.

### INTRODUCTION

Granular corneal dystrophy (GCD) is predominantly an inherited condition manifested by opacities located centrally in the cornea in the first decade of life or in puberty. The clinical picture is bilateral discrete, grayish-white opacities that involve the superficial stromal layers of the cornea (Haddad et al.,1977). The patients present with a different appearance and slit lamp examination. Histopathologic studies with a light microscope show that the opacities are hyaline deposits in the stroma, within and beneath the epithelium staining with Masson trichrome, periodic acid-Schiff (PAS) and sometimes with Congo red (Jones and Zimmerman,1961; Folbrg et al.,1988). The rod-shaped bodies (electron-dense deposits) may be seen by electron microscope (Akiya and Brown,1970).

The lesions tend to aggregate, enlarge, and increase in number, spreading both peripherally and more deeply. A clear-zone around the corneoscleral limbus remains characteristically present. Central disk-shaped opacities are formed after the third or fourth decade of life. Patients usually experience only gradual decrease in visual acuity and may maintain useful vision for a long time (Haddad et al.,1977). The objective of this study was to examine three cases of atypical GCD who presented with a rapid progression of clinical manifestation and early visual deterioration.

### MATERIALS AND METHODS

A retrospective chart review of 3 patients seen between 1997 and 2001 at the cornea clinic, Maharaj Nakorn Chiang Mai Hospital, Chiang Mai University and given a diagnosis of atypical granular corneal dystrophy was performed. Informed consent was obtained from all patients.

Each case, the following preoperative data were collected: age, sex, complete ocular and family history, uncorrected visual acuity, slit-lamp biomicroscopy, and pathological results (case 1).

## RESULTS

### Case 1

A 40 year old Thai man was seen at the cornea clinic of Maharaj Nakorn Chiang Mai Hospital, with history of progressively decreasing visual acuity six years ago and mild foreign body sensation in both eyes for about three years ago. The patient's medical history was unremarkable.

Slit lamp examination showed corneal opacities with subepithelial haziness involving corneal stroma. A clear-zone around the corneoscleral limbus was observed in both eyes. An irregularity of the epithelium was not stained with fluorescein. Bowman's membrane appeared to be glossy and thickened with dense white opacities in a honeycomb-like arrangement. The Descemet's membrane and endothelium appeared normal (Figure 1). The visual acuity was finger count at one foot in the right eye and hand motion in the left eye. His mother had no known ocular disease. He did recall that his father had periodic episodes of blurring of his vision involving both eyes, a problem that had dated back to his childhood.

In September 1998, an eight-mm penetrating keratoplasty procedure (PKP), cataract extraction, and intraocular lens implantation were performed on the left eye, and in July 1999, the same procedure was performed on the right eye. The post-operative course was uneventful with uncorrected visual acuity at 6/12 in each eye. In May 2000, the patient developed graft rejection in the left eye. However, the graft gradually became clear with intensive corticosteroid therapy and uncorrected visual acuity was 6/24 by August 2000.

In February 2000, the patient presented with small bilateral white materials at the epithelium of the central corneal graft. The lesions tended to develop crumb-like opacities, and evidence was found of recurrent dystrophy in both eyes (Figure 2). Then he developed post-keratoplasty corticosteroid-induced glaucoma. Trabeculoplasty was performed when medical therapy failed in January 2001.

Some members of his family, who underwent ocular examination, reported similar corneal findings the onset of signs and symptoms increased in severity with age. The youngest member was 13 years old; the oldest was 73 years old. There was a strong family history of corneal dystrophy which was shown in the family pedigree (Figure 3).

### Case 2

A 40 year old Thai woman was first examined at the cornea clinic in March 1999. She complained of decreased visual acuity. Family history showed a dominant mode of inheritance with strong penetrance for this disorder (Figure 3). Her grandfather and her brother have had the same signs and symptoms. The visual acuity was count finger at one foot in both eyes.

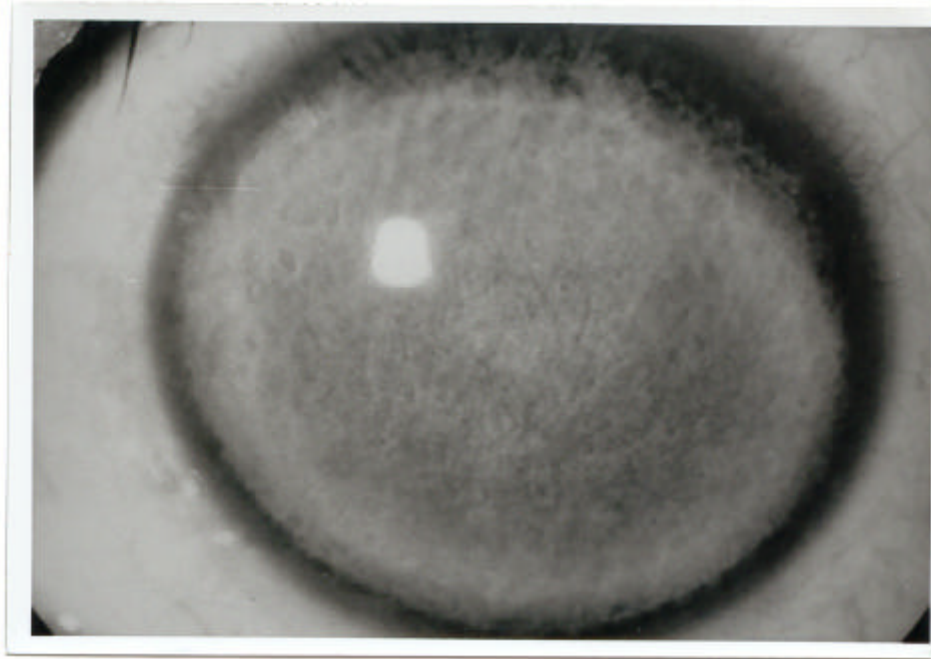


Figure 1. Case 1: The subepithelial haziness involved corneal stroma in atypical granular corneal dystrophy. A clear-zone around the corneoscleral limbus was observed.

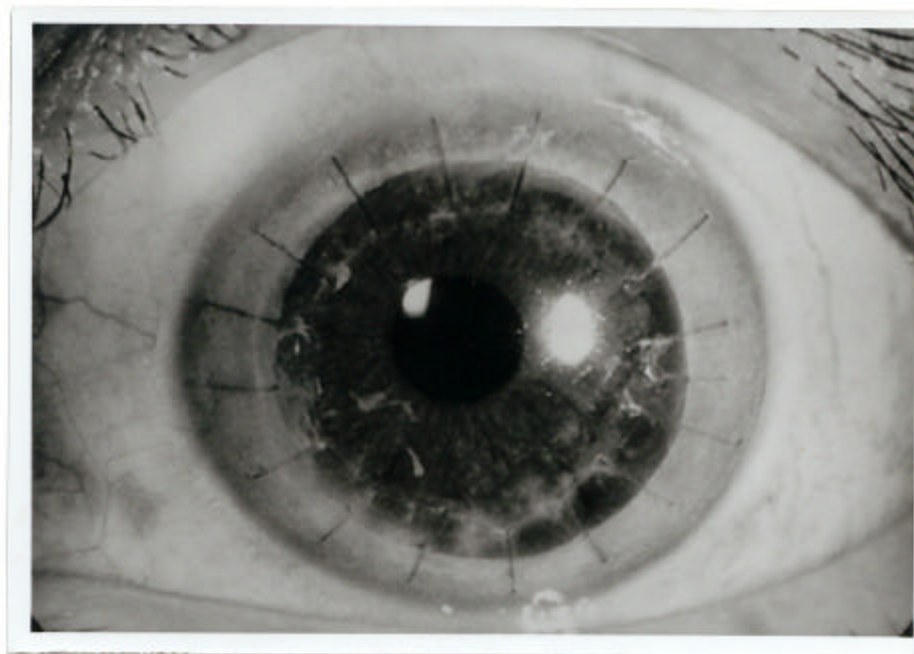


Figure 2. Case 1: After penetrating keratoplasty at 17 months, small white materials at the epithelium of central corneal graft were noted which was the evidence of recurrent dystrophy.



Slit lamp examination showed the abnormal patchy opacities limited to the central cornea with clear zones in corneoscleral limbus in both eyes. There are opacities at the level of Bowman's membrane which seemed to project into the epithelium and stroma with epithelial irregularity.

### **Case 3**

A 16 year old young Thai man had an eye examined three years ago after reporting decreasing vision that dated back to his childhood. The visual acuity was 6/60 in both eyes.

Slit lamp examination showed corneal opacities with subepithelium haziness, irregular corneal epithelium with spared limbus in both eyes. The corneal stroma was involved with diffuse patchy opacities and thickening in the area of Bowman's membrane. The endothelium was normal. He has a strong family history of this disease with high penetrance (Figure 3). He had been given artificial tears.

### **PATHOLOGY**

The corneal specimens from case 1 were reviewed in routine H&E stained sections (Figure 4): The epithelium was thick with irregularities of the basement membrane. The histologic finding was that the eosinophilic deposit located beneath the epithelium involved Bowman's membrane and corneal stroma. There were widespread deposits in the subepithelium and corneal stroma. It looked like a "granule" corneal epithelium with a variable degree of thickening. The subepithelium and stroma contained pink eosinophilic amorphous materials stained negatively with Congo red. The entire thickness of the stroma, predominately at anterior stroma area, was stained red with Masson trichome (Figure 5) but stained negatively with PAS (Figure 6).

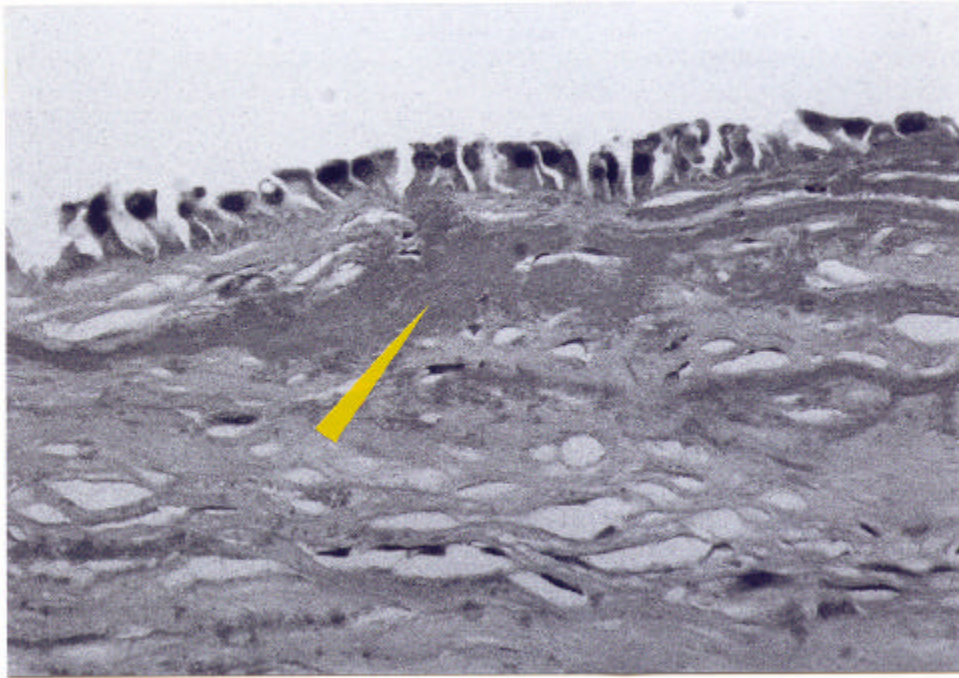


Figure 4. Case 1: Light microscopy of corneal specimen reveals prominent subepithelial and stromal deposits (arrow) (Hematoxylin-eosin, X80).

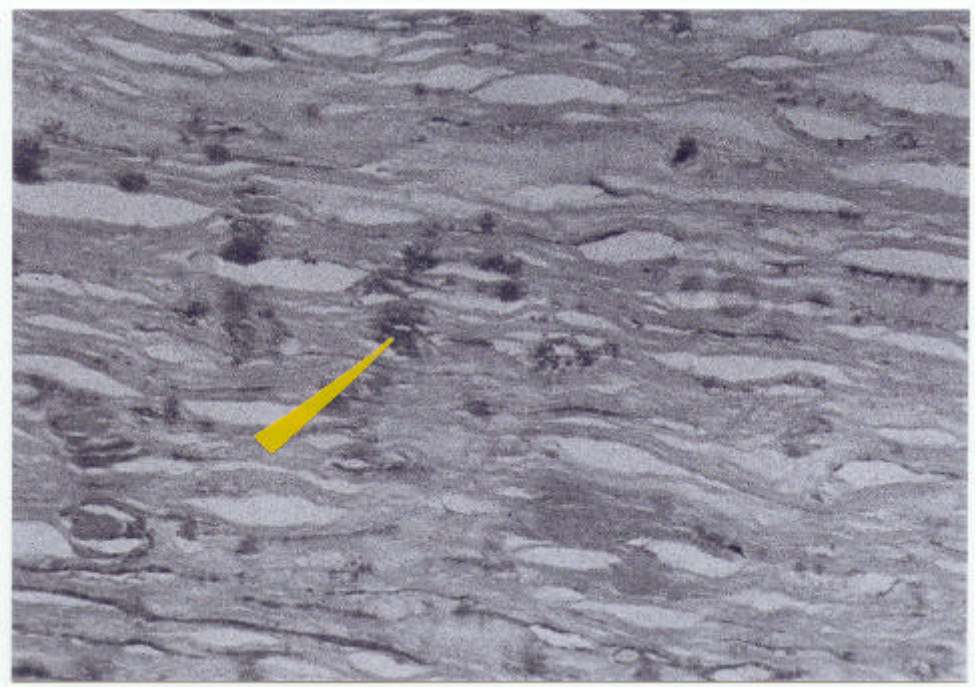


Figure 5. Case 1: Light microscopy of morphologic features of corneal stroma hyaline deposits (arrow) is stained with Masson trichrome (X300).

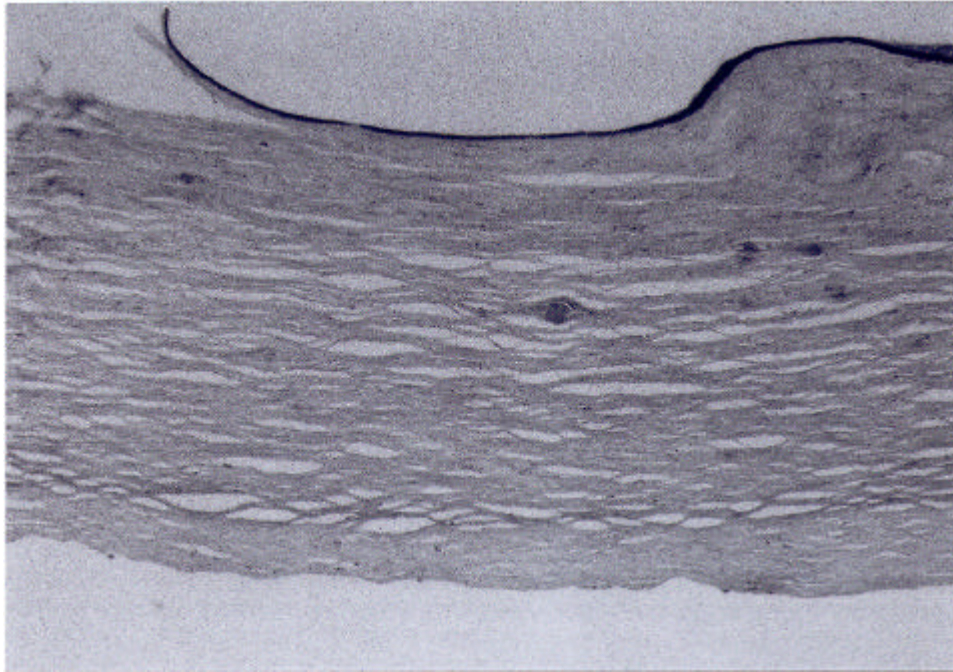


Figure 6. Case 1: Light microscopy of morphologic features of corneal stroma deposits is stained negatively with periodic acid-Schiff (X80).

## DISCUSSION

GCD is transmitted as an autosomal trait. The corneal opacities usually are apparent in the first decade of life as small, discrete, sharply demarcated, grayish white opacities in the anterior axial stroma (Haddad et al.,1977). GCD can be divided into at least three types based on clinical appearance: 1) the classic form of GCD, 2) Aveillino corneal dystrophy 3) a superficial variant of GCD. These dystrophies share identical corneal deposits that stain red after the application of Masson trichrome stain and that appear as rod-shaped bodies in transmission electron microscopy (Dighiero et al.,2000). We suspected the patients in this study were a superficial type which had widespread hyaline deposits in the subepithelium and corneal stroma.

In contrast to classic GCD, these three cases are unusual for GCD because of an atypical clinical presentation characterized by an earlier age of visual impairment, a rapid progression of clinical manifestation, early visual deterioration of visual acuity and the rapid need for surgical treatment and the earlier recurrences after PKP.

The main reasons for the first consultation were decreased visual acuity and foreign body sensation. The first symptom occurred during the fourth decade of life for classic GCD, but bilateral corneal opacities occurred rapidly after six years. The rapid progression of the clinical manifestations leading to PKP was probably caused by diffuse spreading along the Bowman's layer and stroma that led to early secondary epithelium changes. In this study, GCD was diagnosed by clinicopathology report.

Genetic linkage studies have shown that the mutations responsible for stromal corneal dystrophies are located within chromosome 5q. The mutations in the *BIG-H 3* gene associated with each of the corneal dystrophies (granular, lattice, Avellino, and Reis-Bucklers) were reported (Dighiero et al.,2000; Mashima et al.,1999; Steeten et al.,1999).

This report has not yet been defined at the molecular level. The study presents clinical and histological records of three members in three generations who were affected with atypical clinical manifestation of GCD with a strong family history of this disorder. This indicates that molecular studies are needed for an adequate classification of corneal dystrophies. The molecular genetics of this family, in addition to the clinical and histologic pictures, may provide a better definition of these so-called atypical cases.

PKP and lamellar keratoplasty procedure (LKP) have a good visual outcome in granular corneal dystrophy. Visual acuities after both procedures were not statistically different. Recurrence of the dystrophy within the graft material was almost universal within four years. It first appeared centrally and superficially. The recurrence-free interval was independent of size and type of graft performed (Lyons et al.,1994) and multiple grafts may be necessary.

Phototherapeutic keratectomy (PTK) can be useful to treat anterior corneal dystrophies both before and after PKP. PTK has favorable effects on the ocular surface health because of concurrent improvements in corneal sensitivity, tear function, and conjunctival squamous metaplasia grade with visual improvement (Dinh et al.,1999; Dogru et al.,2001).

PTK can restore and preserve useful visual function for a significant period of time in patients with anterior corneal dystrophies (Dinh et al.,1999). Even though corneal dystrophies are likely to recur eventually after PTK, twenty-three percent of eyes with GCD were found to have a significant recurrence a mean 40.3 months after PTK (Dinh et al.,1999; Dogru et al.,2001). The lesions of this reported spread involved the deep stroma. Therefore, the patient was managed with PKP rather than LKP or PTK. Dogru et al., (2001) have suggested that the recurrence of the corneal dystrophy was associated with a decline of the ocular surface health parameters and stromal keratocytes may play an important role in recurrence.

## CONCLUSIONS

Granular corneal dystrophy (GCD) is a predominately inherited condition that has many different in clinical presentations. The ocular and family history, slit lamp and routine histologic examination support the diagnosis of atypical GCD.

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