Amyloid and the cornea

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Disclosure of interest(s) P. van der Valk

None
The patient

• The patient was a woman, born in 1965.

• She underwent her first perforating keratoplasty (PKP) in 1995 (no information about this)
• In 1999 another PKP was performed (left)
• In 2005 again a left PKP was done and a few months later a corneal biopsy was suggestive of rejection.
• In 2009 a right PKP was performed
• After that she was lost to follow-up

• The slide scanned and submitted was from the 1999 specimen
• The pictures from the 1999 and 2005 specimens
The patient

- In 1999 clinical data on the pathology request form were:

- Corneal dystrophy, clinically suspicious of Reis-Buckler dystrophy. However split-lamp examination also revealed deeper depositions reminiscent of a macular dystrophy

- Query: Macular dystrophy? Reis-Buckler dystrophy? Lattice dystrophy?
Congo red staining
Amyloid in the cornea -1-

- Amyloid in the cornea can be part of a systemic disease (e.g. Familial Amyloidosis Finnish or Meretoja syndrome with a mutation in the *gelsolin* protein)

- It can also reflect an “exclusively” corneal disease

- Amyloid depositions are a hallmark of a group of diseases linked to a chromosomal locus on chromosome 5q31

- The gene involved is BIGH3, the protein kerato-epithelin of Transforming Growth Factor-β Induced
Amyloid in the cornea

• The involved dystrophies are:
  - Reis-Bucklers CD: (R124L) (*)
  - Thiel-Behnke CD: (R555G)
  - Lattice CD type 1: (R124C) *
  - Granular CD type 1: (R555W)
  - Granular CD type 2/Avellino: (R124H) *

• Additional mutations exist causing variants of these dystrophies, clinically and histologically

• Histologically, these disease are characterized by either or both amyloid * and “granular” deposits
The aforementioned dystrophies are clinical and ophthalmological entities.

They have a typical slitlamp picture, that often translates to a certain histology.

However, it has become clear that all are related to mutations in the aforementioned, single protein, i.e. Transforming growth factor-β induced (TGFBI) or kerato-epithelin.
GCD 1
Reis-Buckler
Transforming Growth Factor Beta-induced or Kerato-epithelin
The protein is induced by TGF-β; it contains RGD domains, suggesting a function in cell-ECM interactions. The protein seems to inhibit such interactions. It has a role in enchondral bone formation.

From: Carcia-Castellanos et al., Structure 25: 1740-1750, 2017
Amyloid in the cornea

- Curiously, in some conditions and sometimes in the same localization within the cornea, either granular deposits (crystalization) occur

  - OR (and)

- Protein misfolding leads to amyloid deposition

Masson Trichrome

H&E
Amyloid in the cornea

• **Why is this?** *(to be honest. We don’t know! Could it be...?...)*

• 1) The structural consequences of the mutation?

• 2) The consequences for 1 or more of the functions of TGFBI (loss of function)?

• 3) The localization (superficial protein with loss of mitochondrial functioning: $O_2$ impact?)?

• 4) Combinations thereof?
Amyloid in the cornea

- The mutation influences the degradation of the TGFBI protein, with the generation of a number of different size proteins.
- Some of these are more amyloidogenic than others, some apparently tend to crystalize.
Amyloid in the cornea

- The long and the short is that the mutation influences the site and the appearance of the depositions in the cornea and the age of onset, in a reproduceable way

- Many mutations seem to correlate to a clinical entity (e.g. H527R to Lattice dystrophy), but some can be found in several entities (e.g. A546D in GCD and LCD)

- In some cases additional mutations are present; this influences the correlation
Epithelium

Bowman's membrane

Stroma

Descemet's membrane

Endothelium

**Bowman's layer mutation**
- R124L
- R555Q
- R555W
- L509R
- H626R
- R124H
- H626P
- A546D
- V631D
- A546T
- H626R
- T538P
- R124C
- A620D
- I522N

**Stromal mutation**
- G594V
- H626R
- P501T

**Increasing age**
Amyloid in the cornea -2-

• Apart from these genetic conditions amyloid depositions can be found in conditions that are not linked to a specific protein

• This can be seen in a variety of unrelated disorders, i.e. keratoconus, fish eye disease, other non-amyloid-linked corneal dystrophies

• This suggests a more “general” mechanism of dealing with tissue damage in the cornea
Fish eye disease

Congo red stain

Apple green birefringence under polarized light!
Amyloid in the cornea
- Conclusions -

• Various causes, both hereditary/genetic or secondary

• The hereditary cases are Transforming growth facto-beta Induced-/kerato-epithelin- related

• The mutation causes crystalline and/or amyloid depositions AND decides the site of the depositions AND predicts the age of onset, in a reproducible way

• A new classification for these corneal dystrophies is worked on