

# A case of conjunctival intraepithelial neoplasia with spheroidal degeneration: a clinicopathological study

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## Dear Editor,

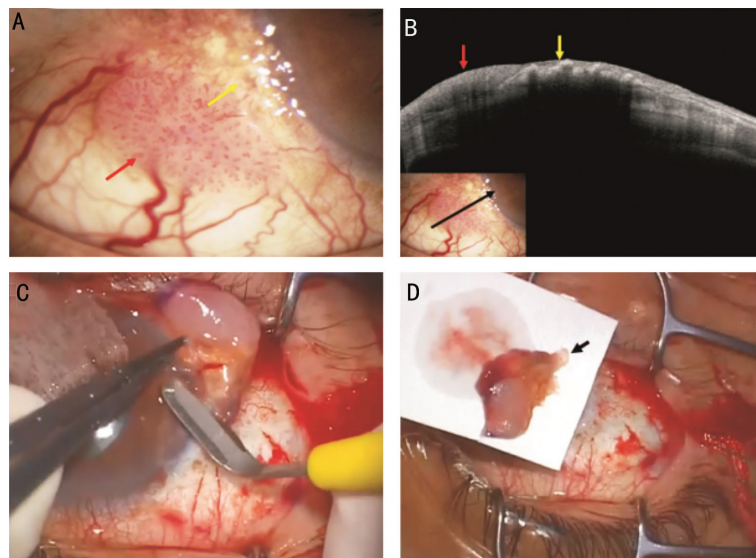
I am Shoichiro Ota from Hokkaido University hospital, Japan. Conjunctival intraepithelial neoplasia (CIN) is a disease concept that includes dysplasia and carcinoma *in situ*. Pathologically, CIN is characterized by tumor cell proliferation located within the epithelium with preservation of the basement membrane<sup>[1]</sup>. In addition to histological diagnosis, anterior segment optical coherence tomography (ASOCT) plays an important role in clinical diagnosis, showing diffuse epithelial thickening with homogeneous high-intensity reflection in case of CIN<sup>[2-3]</sup>.

Spheroidal degeneration is a collection of golden spheres deposited in the keratoconjunctival tissue, first reported by Fraunfelder *et al*<sup>[4]</sup> in 1972. It is usually found in the pinguecula, and identified as cell-free amorphous deposits in histopathology<sup>[5]</sup>; however, the origin and OCT findings of spheroidal degeneration have yet been elucidated. The aim of this study is to report a case of CIN with spheroidal degeneration, and to analyze the correlation between ASOCT findings and histopathology. Written informed consent was obtained about the use of medical record for the case report from this patient. This case study adhered to tenets of Declaration of Helsinki. Institutional review board waived approval of this study as a clinical study application because this is a single case report.

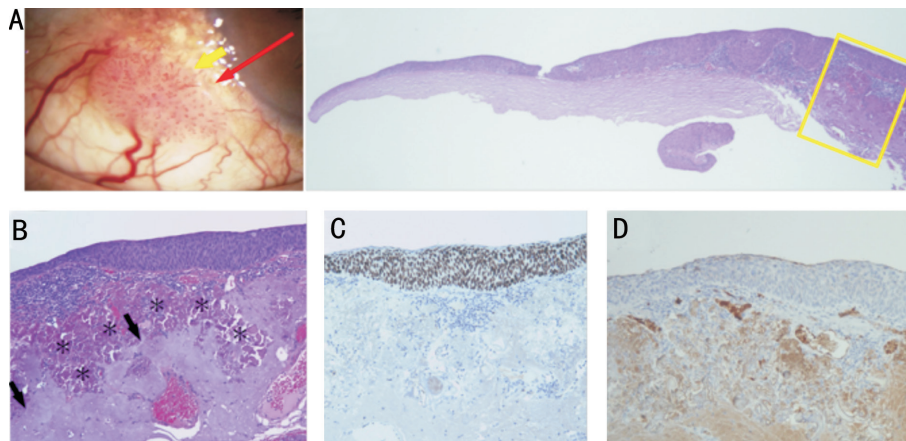
**Case Report** A 76-year-old man was aware of right

conjunctival hyperemia and visited a nearby doctor. He has been observed for normal tension glaucoma. The patient was followed up for 2mo as a clinical diagnosis of an inflammatory lesion, but the symptom did not improve. Since the conjunctival tumor was then suspected, he was referred to our department. The best-corrected visual acuity at the first visit was 1.2 and 0.1 in his right eye (OD) and left eye (OS), respectively. The intraocular pressure is 12 mm Hg OD and 13 mm Hg OS. Slit-lamp examination showed a sessile elevated papillary mass lesion at the inferotemporal conjunctiva OD. In that area, fireworks-like blood vessels on the tumor surface together with dilated blood vessels flowing into the tumor were found. In addition, there were yellow granular lesions on the corneal limbus continuous with the papillary tumor (Figure 1A). The OCT findings of the tumor lesion displayed diffuse homogenous high-intensity reflection (Figure 1B, red arrow), as well as a heterogenous band-shaped hyper-intensive reflection corresponding to the yellow granular lesion (Figure 1B, yellow arrow). From clinical findings, CIN and squamous cell carcinoma were listed as differential diagnoses, and total tumor resection with 3 mm surgical margins and cryopexy were performed (Figure 1C). The resected tumor tissue was placed on a disinfected filter paper to clarify the location of the yellow granular lesion in the corneal limbus, and pathological sections were made accordingly, looking at the cross section of the granular lesion (Figure 1D, arrow). The patient was eventually diagnosed with CIN based on the pathological findings, where the surgical margins were free of tumor cells, and no additional treatment was performed. The patient was well without local recurrence or systemic metastasis 2mo after the surgery.

The pathological findings of this case demonstrated the atypical epithelium toward the conjunctival side (Figure 2A), while normal corneal epithelium was found in the corneal margin. Abnormal squamous epithelial cells were found in the central papillomatous tumor without sub-basement membrane invasion, which allowed us to diagnose CIN. Pathological findings at the yellow granular lesion depicted by slit-lamp examination showed basophilic, spherical uniform non-structured configurations beneath the tumor epithelium, which is consistent with spheroid degeneration (Figure 2B, asterisks).



**Figure 1** Slit-lamp examination (A), OCT findings (B) and intraoperative findings (C, D) in a patient with CIN A: Slit-lamp examination of the conjunctival tumor; B: OCT findings showing cross section of the conjunctival tumor, yellow arrows reveal heterogenous hyper-reflective foci; C: The tumor was resected with a safety margin of 3 mm including the yellow granular lesions; D: Black arrow indicates the corneal margin.



**Figure 2** Histological findings in a patient with CIN and spheroidal degeneration A: Pathological findings of the cross section in the slit-lamp examination corresponding to the red arrow. Normal corneal epithelium was found in the corneal stump, together with the atypical epithelium toward the conjunctival side. B: Pathological findings of the cross section (yellow square of A) corresponding to the yellow arrow. Basophilic and spherical uniform non-structured configurations under the atypical subepithelial membranes were observed (asterisks), which are considered spheroidal degeneration. A collection of degenerated elastic fibers was found around the spheroidal degeneration (black arrows). C: Immunostaining for Ki67. Atypical epithelial cells were Ki67 positive. D: Immunostaining for IgG. IgG was positive in the sub-conjunctival epithelium, including the spheroidal degeneration site.

A collection of degenerated elastic fibers consistent with solar elastosis was found around the spheroidal degeneration (Figure 2B, arrows). Immunostaining for Ki67, a proliferation marker, was positive for atypical epithelial cells, consistent with findings of CIN (Figure 2C). Spheroidal degeneration and solar elastosis were positive for IgG (Figure 2D). The margin of excision was free of tumor cells.

#### DISCUSSION

This study for the first time demonstrated the clear clinicopathological correlation in CIN containing spheroidal degeneration. Although the origin of spheroidal degeneration has not been elucidated yet, Johnson and Overall<sup>[6]</sup> suggested

that fibrinoid degeneration is correlated with the degeneration, where IgG plasma protein deposition may also be contained. CIN commonly shows diffuse thickening of the epithelium and high-intensity reflections by ASOCT<sup>[2-3]</sup>; however, OCT findings of spheroidal degeneration have not been reported. In this study, ASOCT demonstrated heterogeneous granular hyper-intensity reflection in spheroidal degeneration. Immunohistochemistry revealed IgG accumulation in the degenerated spheroidal region, as reported in corneal spheroidal degeneration<sup>[6]</sup>. Solar elastosis is usually found in pinguecula tissues, where ASOCT showed a subepithelial diffuse mass beneath the thinner epithelium with mild reflection<sup>[3]</sup>. Almost

half of conjunctival squamous cell neoplasia contains solar elastosis<sup>[7-8]</sup>, and the ASOCT findings of the CIN display diffuse homogenous high-intensity reflection<sup>[3]</sup>. However, the origin of spheroidal degeneration or its correlation with solar elastosis has not been determined. Taken together, heterogenous hyper-reflective lesions observed by OCT in this study feature conjunctival spheroidal degeneration, which might result from the microscopical properties and/or accumulation of high molecules such as IgG. The authors here propose that the ASOCT findings in spheroidal degeneration be “hyper-reflective foci”.

There is no previous report of CIN with spheroidal degeneration like this case, that could be considered extremely rare. As described above, spheroidal degeneration is often found in pinguecula and is histologically seen as acellular deposits<sup>[5]</sup>. In this case, there are 2 possibilities of the pathologies underlying CIN containing spheroidal degeneration: CIN was originated from the epithelium of the pinguecula, or CIN arising around the pinguecula infiltrated the pinguecula. In this case, the main tumor is an elevated pinkish papillary tumor, and posed the fireworks-like neovascularization typical of CIN. In addition, the papillary tumor was continuous with the yellow granular lesion due to spheroidal degeneration on the corneal side, where the Ki67-positive tumor epithelium became flattened. Taken together, CIN together with spheroidal degeneration might come from bulbar conjunctival tumor cell invasion to the pinguecula.

Surgical treatment options for CIN are commonly local tumor excision including partial lamellar scleroconjunctivectomy technique or enucleation. In the former excision, limbus-based pentagonal or circular conjunctival incision with 3-4 mm outside the tumor margins revealed favorable outcomes with low recurrence rates<sup>[9-10]</sup>. However, in this case, although the question was whether the safety margin should include yellow lesions observed by slit-lamp examination, the safety margins of 3 mm were set including the yellow lesions in this case. Histopathology subsequently proved intraepithelial tumor invasion upon the spheroidal degeneration, while there was free of tumor cells in all the surgical margins. Therefore,

in case of CIN combined with spheroidal degeneration, the preoperative safety margin should be carefully considered.

In conclusion, this is the first case with CIN containing spheroidal degeneration. ASOCT is critical to identify the spheroidal degeneration, depicting heterogenous band-shaped hyper-reflective foci.

#### ACKNOWLEDGEMENTS

**Conflicts of Interest:** Ota S, None; Kase S, None; Tanaka T, None; Ishida S, None.

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