Chapter

OCT Applications in Conjunctival Disease

Raffaele Piscopo, Michele Lanza, Luigi Mele and Mario Bifani Sconocchia

Abstract

Today the of anterior segment optical coherence tomography (ASOCT) has become an irreplaceable tool in the management of various pathologies and also in many surgical techniques. The cornea has been widely studied in many pathologies with ASOCT, but now also the conjunctival study with ASOCT allows to obtain a detailed imaging of the normal and pathological conjunctiva, so that in many conjunctival diseases the ASOCT is a useful tool to help the clinicians. In this chapter we will briefly discuss the results of the imaging of the oct appearance of the normal conjunctiva with ASOCT and its present and potential use in the conjunctival pathologies.

Keywords: anterior segment OCT, conjunctival diseases, conjunctiva, conjunctival tumors, optical coherence tomography

1. Introduction

The clinical application of ocular coherence tomography (OCT) and angio-OCT is today increasing and their use is not only focused on the retina so that, since the introduction of anterior OCT in the late 1990s, many other ocular pathologies of the eye have also been studied.

Today anterior segment OCT (ASOCT) is mainly used in corneal pathology since several years and its use is necessary in the management of the clinical and surgical activities [1–4].

Today there are different models of ASOCT and they can be mainly classified on the basis of the type of technology used to perform the scan: the time-domain technology, the spectral-domain technology, the swept source and, lately, also the angio-OCT study of the conjunctival and scleral vessel has been studied.

The aim and the ideal use of ASOCT in the anterior segment, especially in the conjunctiva, is to give an "optical biopsy" which can help the clinician in several ways: to distinguish among the various conjunctival tumors, to assess if a certain surgical technique has been effective or, in the future, to distinguish in the early stage between a neoplastic and inflammatory conjunctival disease.

The studies which discuss the use of such technologies have been focused on three main areas of interest: the characterization of the normal human conjunctiva with its possible variations, the use in the glaucoma filtering surgery and the study of the conjunctival pathologies.

2. Normal conjunctiva

The conjunctiva is composed of two layers: the epithelium and stroma. The epithelium consists of well-organized cell layers in both stratified squamous and columnar types. The stroma is a connective tissue of fibrous and vascular elements in a less organized disposition.

All these anatomy concepts have found a great correspondence in the OCT imaging, so that the aspect of the conjunctiva in the OCT image presents typical features as shown in several reports [5–10]. The use of ASOCT on the normal conjunctiva is a complete and useful tool since the OCT imaging already provides a detailed representation of healthy limbus, sclera and conjunctiva. These studies were mainly focused on evaluating the qualitative (the complete visualization of the anatomy) and quantitative (the thickness of the different stratus) aspects of this layer. The normal OCT appearance is shown in **Figure 1**, where it is possible to recognize a small hyporeflective zone (epithelium) on the top resting on a greater hyperreflective area (stroma and Tenon capsule). Differentiating among the various layers is easy thanks to the different brightness OCT features. The epithelium, consisting of well-aligned cell layers, results as hyporeflective part, because of the less scattering of the incident light from OCT.

The OCT image of the stroma is characterized by an higher brightness signal because of its different composition up above described: so this part of the tissue highly scatters the OCT incident light, thus it appears hyperreflective and clearly visible beneath the conjunctival epithelium.

The conjunctival stromal OCT characteristic is quite different from the corneal stroma, as reported in previous studies [9]: the superficial and deeper layers of the stroma are composed by an adenoid layer containing lymphocytes and mast cells laying on a fibrous layer which produces an increase in reflectivity.

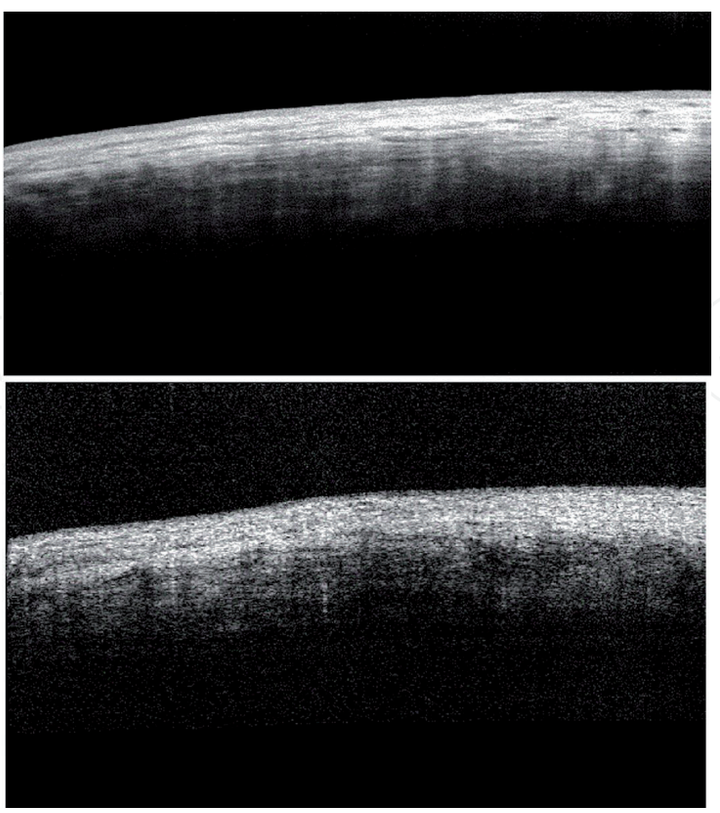

Figure 1.
Conjunctival OCT in a normal subject: the multistratified cylinder epithelium appears as a hyporeflective area, laid on a dense, hyperreflective connective layer. The lower reflective Tenon capsule is separated by a visible demarcation.

The underlying Tenon capsule has a high reflectivity similar to the conjunctival stroma in the OCT image. The distinction of these two layers is not always recognizable, possibly depending on the relationship between the stroma and the tenon: a clingy apposition near the limbus, for instance, makes the differentiation hard [7]. Thickness has been the most quantitative feature which has been studied: a detection of its variation could be an important sign of conjunctival health (edematous or thinning pathologies).

In their study, [7] Feng and Simpson reported the mean bulbar conjunctiva epithelial thickness was 44.9 ± 3.4 μm in 13 healthy subjects.

Another study reported the epithelial thickness being 42.0 ± 7.5 with a slight reduction in the group with a higher age [11], while also the stroma was measured to be about 240 (ranging from 140 to 304) in a report of 2013 [12].

A key concept is that significant variations in thickness may be found, mainly depending on the measurement locations (nasal, inferior, temporal or superior conjunctiva). These findings are consistent with the conjunctiva's anatomical characteristics: it is known that the stroma thickens in the fornix and thins at the limbus, but also differences in the different meridian have been shown in one report published by Read et al. [9].

The author demonstrated some interesting features:

- On average, the conjunctiva was significantly thicker in the nasal meridian (270 ± 90 μm) compared to the temporal meridian (mean thickness 249 ± 59 μm) ($p < 0.001$).

- The conjunctiva exhibited its minimum thickness at the scleral spur location (0 mm) for both the temporal (mean 218 ± 55 μm) and nasal meridians (mean 223 ± 40 μm); however, the pattern of change in thickness away from the scleral spur differed between the two meridians. For the temporal meridian, the conjunctiva increased to its maximum thickness at the 1 mm location (mean 267 ± 59 μm), whereas the nasal meridian exhibited its maximum thickness (mean 364 ± 122 μm) at the 4 mm location.

- The conjunctival thickness measures also showed some significant changes with age, reducing in thickness from childhood into early adulthood. These changes are reasonable if we consider histological studies demonstrating that the mucous layer (goblet cell density) reduces in early adulthood.

3. The use of oct in glaucoma

The evaluation of the postoperative effectiveness of glaucoma surgery is a well validated use of the anterior OCT [6, 8, 13].

The anterior OCT allows a detailed representation of the bleb architecture, giving information of the shape and functionality of a postsurgical bleb. Moreover, with ASOCT it is possible to observe if a bleb is functioning well and to know details about the wall and the internal architecture of the bleb.

Reports in literature show that there are a lot of aspects of the OCT conjunctival appearance which can be used to assess the functionality of the blebs: the internal aspect (diffuse or flat) [14], the internal bleb reflectivity (low reflectivity or high) or the wall thickness [15, 16].

There is also another interesting use described in literature, described by Mastropasqua et al.: the authors stated that the application of ASOCT for studying bleb modifications before and after bulbar massage is useful as it is possible to observe an increase of the bleb-wall thickness, intraepithelial microcysts, and the

fluid-filled cavity area [13]. The study by Guthoff et al. [17], instead, analyzes the effect of the needling on the bleb ASOCT appearance.

4. The use of oct in Conjunctival pathologies

4.1 Conjunctival tumors

One of the most studied and validated applications of ASOCT regards conjunctival tumors.

Many reports [18–24] demonstrate that the OCT study of conjunctival tumors can help the clinician to: make the diagnosis, help to distinguish among different types of neoplasm or between benign and malign neoplasms, help to assess the follow up after the surgical excision of the tumor.

The classification of the conjunctival tumors may be summarised in the congenital and acquired lesions.

The acquired lesions can be distinguished in: pigmented and non-pigmented or, depending on the origin of the mass, in surface-epithelial, melanocytic, fibrous-vascular, myogenic, neural, lipomatous, lymphoid, histiocytic, leukemic or metastatic.

Essentially the most studied conjunctival lesions are the pigmented-melanocytic. This family of lesions includes nevus, racial melanosis, PAM (primary acquired melanosis) and melanoma. Among the non-melanocytic neoplastic lesions, the most frequently studied are squamous cell carcinoma and lymphoma.

4.1.1 Nevus

Nevus is the most common melanocytic tumor of the conjunctiva. It shows up as a discrete variably pigmented, slightly elevated sessile which usually remains quite stable during life with <1% risk of transformation into malignant melanoma. Histopathologically, a conjunctival nevus is composed of nests of benign melanocytes in the stroma near the basal layers of the epithelium.

A periodical follow-up, together with photographic comparison, is the best way to verify whether it is growing: sometimes you may need the mass excision if any growth is documented.

4.1.1.1 OCT appearance

The study of Shields et al. on 22 conjunctival nevi demonstrated that all margins of conjunctival nevi can be observed through ASOCT (high resolution in 100% of anterior borders and 82% of posterior borders). The sensitivity of AS-OCT for the detection of intrinsic cysts in a conjunctival nevus is 80%, its specificity is 100%, its positive predictive value is 100%, and its negative predictive value is 60% [22].

Regarding conjunctival nevi we can conclude that ASOCT seems to be more accurate in assessing the extent of these tumors as long as the nevus is not very thick and not heavily pigmented.

AS-OCT can also be used for differentiating a nevus from melanoma: unlike melanomas, the nevi usually contain intralesional cystic space (their presence usually confirms a chronic pathology) [21].

(Note that it is still debated whether the presence of cysts does not definitively rule out malignancy.)

4.1.2 Primary acquired melanosis (PAM)

Primary acquired melanosis, a frequent benign conjunctival pigmented lesion, can evolve into conjunctival melanoma. It is usually observed in middle-aged or elderly patients and, in contrast with conjunctival nevus, it is patchy, flat, and non-cystic and it is usually not well circumscribed. This lesion may arise with or without atypia, and the presence of the atypia leads to a 50% chance of melanoma [25].

4.1.2.1 OCT appearance

Histopathologically, PAM is characterized by the presence of abnormal melanocytes near the basal layer of the epithelium so the PAM ASOCT images is characterized by normal thickness but moderately hyperreflective basal epithelium with no invasion of the subepithelial space [21].

4.1.3 Squamous cell neoplasia

Squamous cell neoplasia may be classified in CIN or squamous cell carcinoma, depending on whether it presents as a localized lesion confined to the surface epithelium (conjunctival intraepithelial neoplasia or dysplasia) or as a more invasive pathology which has broken through the basement membrane and invaded the underlying stroma. (squamous cell carcinoma).

4.1.3.1 Conjunctival intraepithelial neoplasia (CIN)

CIN (others prefer the terms mild, moderate, or severe dysplasia) appears as a fleshy, sessile or minimally elevated lesion usually arising at the limbus in the interpalpebral fissure and less commonly in the forniceal or palpebral conjunctiva A white plaque (leukoplakia) may be present.

Histopathologically, it is characterized by the presence of immature abnormal cells. The several types of displasia depend on the presence of these abnormal epithelial cells which may partially (mild dysplasia), nearly fully (moderate dysplasia) or fully replace (severe dysplasia) the normal cells. Carcinoma-in-situ represents full thickness replacement by abnormal epithelial cells.

4.1.3.2 OCT appearance

Due to its epithelial onset, distinctive criteria of ASOCT are a thickened, hyper-reflective epithelial layer with an abrupt transition from normal to abnormal epithelium [23].

Shousha et al. [26] demonstrated that the use of UHR-OCT (ultra-high resolution OCT) in the diagnosis and follow-up of conjunctival and corneal intraepithelial neoplasia (CCIN) is possible.

In the different types of CIN the authors found thickened hyperreflective epithelium and abrupt transition from normal to hyperreflective epithelium. Their results demonstrated that macroscopically resolved residual tumor nodules can be visualized by UHR-OCT [26]. A disadvantage of UHR-OCT is that it is not high enough to assess intracellular characteristics.

4.1.4 Squamous cell carcinoma

As above mentioned, the SCC develops when the abnormal cells have invaded the stroma. Histopathologically, invasive squamous cell carcinoma is characterized

by malignant squamous cells that have violated the basement membrane and have grown in sheets or cords into the stromal tissue.

4.1.4.1 OCT appearance

In the OCT imaging a squamous cell carcinoma is recognizable since the epithelium appears hyperreflective and thickened [27]. Several reports demonstrated that the ASOCT may be useful in the differentiation between SCC and similar lesions like amelanotic melanoma and corneal fibrosis or from pterygia with a very good correlation with histopathology [23, 26, 27]. HR-OCT can also be used for the monitoring of the resolution of SCC during therapy. In this way, HR-OCT can detect subtle residual epithelial thickening which is not visible on clinical examination [20].

4.1.5 Malignant melanoma

A Conjunctival is characterized by a high clinical variability. It may be pigmented and tan or, more generally, elevated conjunctival lesion, located in possible several parts of conjunctiva.

Histopathologically, conjunctival melanoma is composed of variably pigmented malignant melanocytes within the conjunctival stroma. Patients are typically 60–70 years old and present with a nodular mass arising either de novo, from a nevus, or from PAM with atypia [25]. Often prominent feeder vessels and surrounding flat PAM are present. Melanoma-related death rates are 5–17% at 5 years and 9–35% at 10 years, depending on the precursor lesion. Non-limbal locations portend a poorer prognosis. De novo melanomas tend to have the worst prognosis. Local recurrence is common and it can be 45% at 5 years and 59% at 10 years [25].

4.1.5.1 OCT appearance

AS-OCT images show a hyperreflective subepithelial lesion. The epithelium is a normal to slightly thick layer of epithelium with variable hyperreflectivity of the basal epithelium, which suggests some involvement of the epithelium with atypical melanocytes [21].

4.1.6 Conjunctival lymphoma

Conjunctiva lymphoma may appear as a diffuse, slightly elevated pink mass, termed "salmon patch." The usual localization is at the fornix, usually hidden by the eyelid in the superior and inferior quadrants and not in the horizontal exposed parts of the bulbar conjunctiva or the limbus. Sometimes they arise from caruncle or plica semilunaris, but almost never in the palpebral conjunctiva.

The Oct appeareance: a recent published study [21] showed the AS-OCT appearance of the lesion, characterized by a normal layer of epithelium overlying homogeneous, dark, hyporeflective subepithelial lesions with smooth borders (**Figures 2** and **3**). The lesions can often contain monomorphic, stippled, dot-like infiltrates that correspond to the infiltration of monoclonal lymphocytes.

The author states that for both melanomas and lymphomas, ASOCT images do not always help the clinician obtain a definitive diagnosis as they do for OSSN, but can help guide the differential diagnosis. Nevertheless, the histopathologic analysis of tissue is needed for final confirmation.

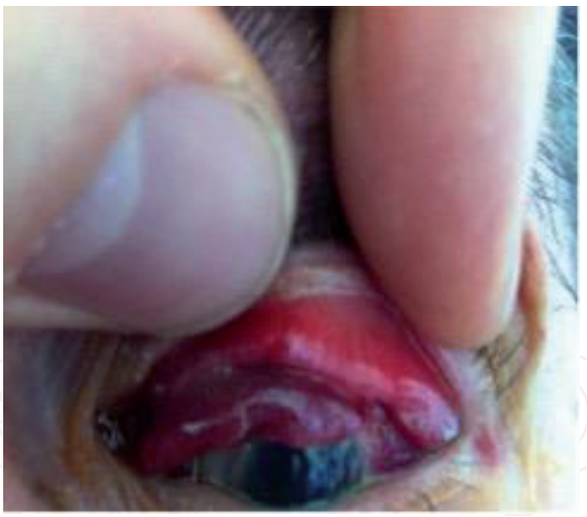

Figure 2.
Clinical appearance of conjunctival lymphoma.

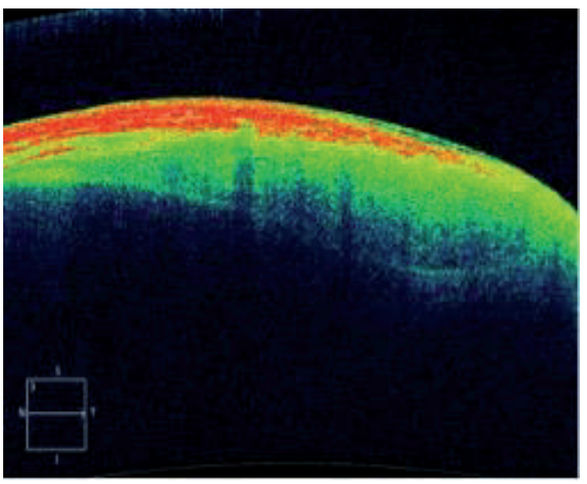

Figure 3.
OCT image: note the hyporeflective lesion with smooth posterior border.

4.2 Conjunctival diseases

4.2.1 Pterygium

In the pterygium the ASOCT can represent a useful tool if the corneal stromal invasion needs to be evaluated and also in the postoperative management.

ASOCT images of pterygia demonstrate a thin or normal layer of epithelium with varying levels of hyperreflectivity overlying a dense, hyperreflective, fibrillary subepithelial lesion that is between the corneal epithelium and Bowman's layer [21].

One of the aspects possibly involved in its recurrence is the pterygium length. Welch et al. studied the difference between the measurements of a pterygium using a slit-lamp or the ASOCT imaging. They demonstrated that ASOCT allows to accurately determine the extension of a pterygium on the cornea [28]. Moreover, ASOCT can help to distinguish pterygia from OSSN: various reports [18, 26–28] demonstrated statistically significant differences in epithelial thickness and location between these two lessons (thicker and epithelial for OSSN thinner and subepithelial for pterygia). Kieval et al. showed [27] that the average epithelial thickness in

the 17 epithelial squamous cell carcinomas (SCC) was 346 μm, compared to 101 μm in the 17 pterygia. Using a cut-off value of 142 μm results in a sensitivity of 94% and a specificity of 100% in differentiating SCC from pterygia.

However, this imaging technique was less useful in evaluating pigmented lesions [20].

4.2.2 Graft-versus-host disease (GVHD)

Graft-versus-host disease (GVHD) is a major complication following allogeneic hematopoietic. It usually involves several organs, and the ocular involvement occurs in ~60% of GVHD patients [1, 3, 4], particularly affecting cornea, conjunctiva, lids and lacrimal gland, resulting in a wide spectrum of ocular complications [29–31] (**Figure 4**).

A report of Peng Li et al. [32] investigates the role of the device in GVHD with a surprising result: the conjunctival image of GVHD shows a characteristic imaging with a much higher OCT signal on the surface in GVHD patients compared to those in normal subjects (**Figure 5**), most likely due to the conjunctival keratinization and to the conjunctival lymphatic vessels dilated.

4.2.3 Ocular cicatricial pemphigoid

Mucous membrane pemphigoid (MMP) is an autoimmune, sub-epithelial blistering, potentially blinding disease characterized by scarring and shrinkage of mucosal membranes, including the conjunctival mucosa, oral cavity, esophagus, trachea and genitals [34]. When clinical signs are detected firstly in the conjunctiva, the disease is named "ocular cicatricial pemphigoid" (OCP) [33, 34] (**Figure 6**).

The diagnosis of ocular cicatricial pemphigoid (OCP) is challenging, especially when the pathology is in its early stages, due to the OCP a specific ocular signs which are not easy to recognize through slit lamp examination [35].

The ethiopathogenic mechanism by which the OCP produces its typical conjunctival lesions is a subepithelial inflammation mediated by autoimmunity against a multiplicities of possible antigens located in membrane basement of the deeper layers of the conjunctiva: this process leads t to a subconjunctival fibrosis and cicatricial conjunctivitis. Therefore, the ASOCT could potentially be a useful device to detect and study initial modifications of the conjunctival areas where OCP starts its damages, possibly when it is not recognizable by using the slit lamp alone. In our cohort of patients (unpublished data), we noticed in a great percentage some abnormalities in the OCT image: (**Figure 7**) a diffuse increase of optical reflectivity

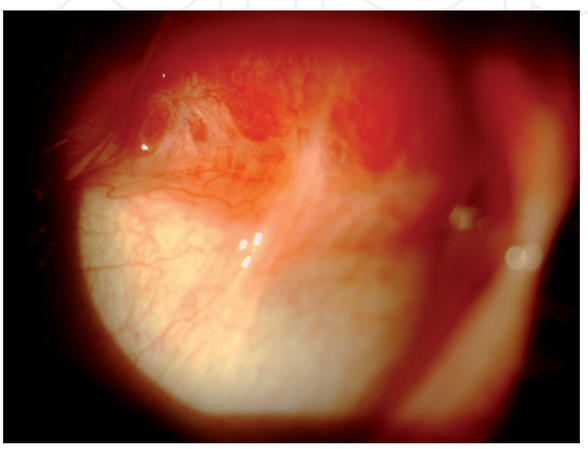

Figure 4.
Image of conjunctiva from a patient suffering from GVHD: a symblephara with the surrounding subepithelial fibrosis.

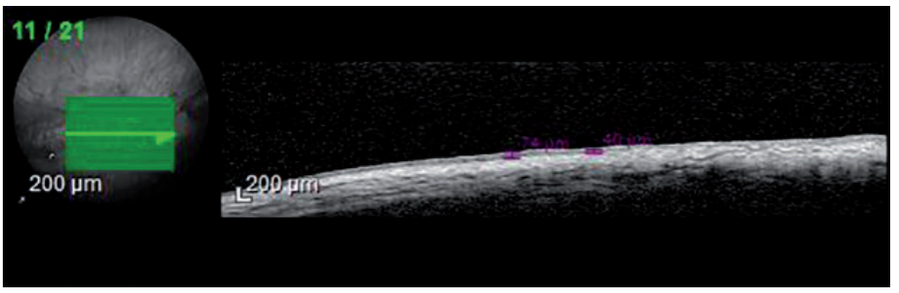

Figure 5.
OCT appearance of GVHD: diffuse hyperreflectivity of both epithelial and stromal area.

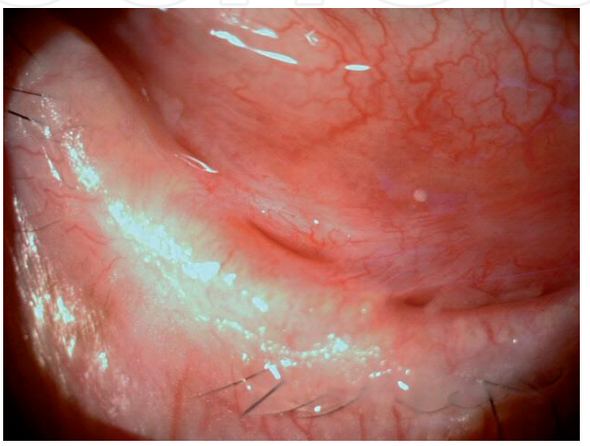

Figure 6.
Ocular cicatricial pemphigoid: note the fornix foreshortening and symblephara.

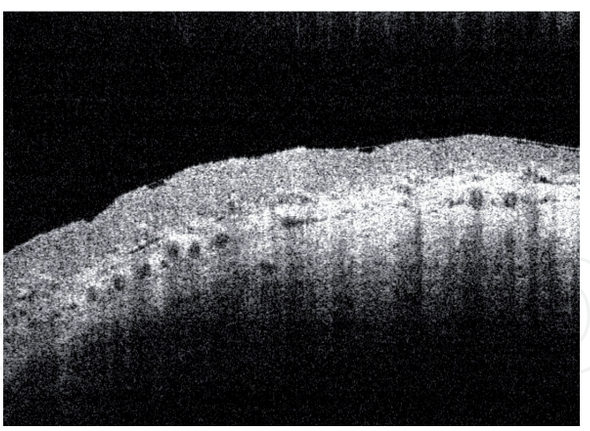

Figure 7.
OCT appearance of the patient in ***Figure 6****.*

located in the sub-epithelial conjunctival space and the presence of some folds located at different depths in the conjunctival substantia propria thickness, appearing in different shapes. These signs are usually located in the subepithelial space (distance 25 ± 8 µm from epithelium).

Conflict of interest

None of the authors have conflict of interest.

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