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Local chemotherapy with conjunctival bevacizumab injections in case of lymphoma tumor

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Lymphoma is the most common type of blood cancer. It affects white blood cells, lymphocytes, when at least one condition is present: faster replication of abnormal cells, longer life than normal lymphocytes. Non-Hodgkin lymphoma (NHL) is the most common type among three significant categories of lymphoma. Approximately eight percent of all NHL constitutes marginal zone lymphoma (MZL). They are three types of MZL: extranodal, nodal, and splenic. Extranodal MZL, or mucosa associated lymphoid tissue (MALT), is the most common form of MZL. It occurs more commonly in women at the average age of 60 years.

Isolated conjunctival lymphoma accounts for approximately 5–25% [1–3] of ocular adnexal lymphomas (OAL), the average age of onset is 60-65 years old. Bilateral involvement occurs in 10–15% of cases, there is a slight predilection of males (54% men *vs*. 46% women), and the average age of diagnosis is approximately 35 years [4]. The risk of spreading is about 37%, during five years 10–15%, and for ten years 28% [2, 3].

There are different therapeutic approaches, with no consensus for the gold standard. This report is the first case report of treatment of the recurrence after surgical excision with multiple Bevacizumab injections (Avastin, Roche 2,5 mg/0,1 mL) directly into the tumor area.

A 50-year-old healthy woman presented to our clinic with a giant red mass of bulbar conjunctiva between 11:30 and 8 o'clock; the main complaint was cosmetics and decreased vision secondary to excessive tearing. Best corrected visual acuity (BCVA) was 0.63, and intraocular pressure was normal (17 mm Hg). She noticed the onset of changes approximately two years before our examination. A prominent red lesion started growing from the bulbar conjunctiva's inferior side near the fornix. After surgical excision, the histopathological description could be consistent with MALT type B cell lymphoma with infiltration of the small lymphocytes T (CD3+, CD5+), focal cluster of lymphocytes B (CD20+, CD3–, CD23–, cyclin D1–, CD21–, bcl2+, bcl6–, CD1–, IgM+/–, IgD+) and scattered sarcoid like granulomas. The lesion regrew seventeen months later and spread from 12 to 8 on the bulbar conjunctiva of her right eye. The treatment options were secondary excision or radiotherapy, which the patient did not accept.

We decided to make local chemotherapy with conjunctival bevacizumab injections directly into the tumor mass. After the initial three-monthly injections of 0.1 mL/2.5 mg (Fig. 2), we gave seven more injections (6, 9, 11, 13, 15, and 17 months). The lesion disappeared ultimately (Fig. 3). No systemic or local adverse events occurred during

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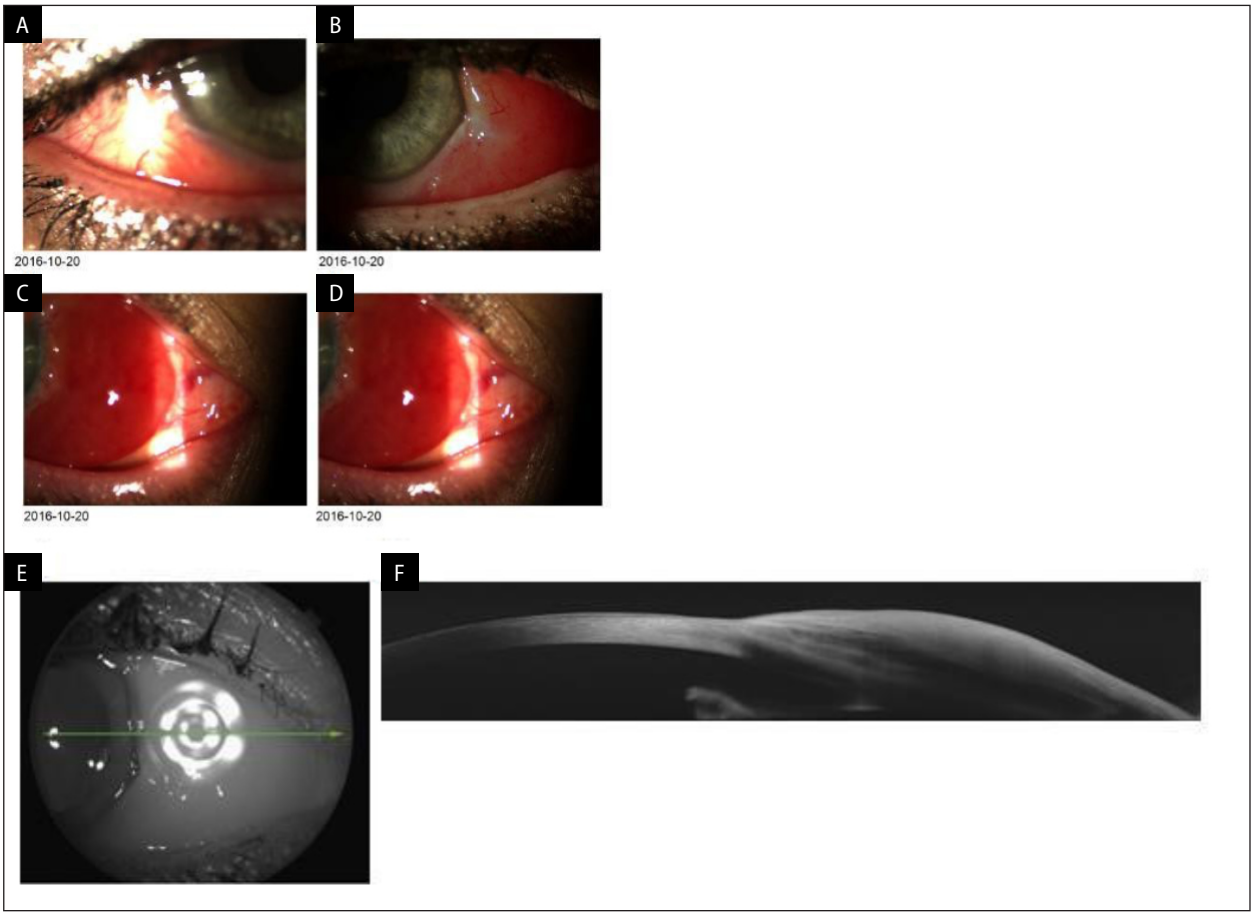

Figure 1. A–D. The patient's right eye shows a subconjunctival, red, prominent mass extending from 11:30 to 8 o'clock. Vessels are dilated, with severe tortuosity. Bulbar Conjunctiva is oedematose; **E, F.** Optical coherence tomography (OCT) scan of this lesion shows intact conjunctival epithelium, with homogeneous, hyperreflective mass extending up to the Tenon capsule

and after treatment. Five years after the ending of therapy, there is no evidence of local or systemic involvement.

In high-resolution anterior swept-source optical coherence tomography (SS-OCT) scans (Topcon Swept Source DRI OCT Triton) of the tumor, we observed a distinct, homogeneous, low-reflective mass of the lymphoma covered by the intact, healthy conjunctival epithelium. After three monthly injections, we followed the hyperreflectivity in the upper subepithelial assembly of the lymphoma, which could be a sign of the healing process-fibrosis. Seventeen months later, there was no sign of the tumor, neither clinically nor in OCT imaging. In all OCT scan images, there were no signs of the involvement of the substantia propria.

Conjunctival lymphoma accounts for approximately 25% of OAL. Oncologists should do systemic examinations repeatedly to exclude spreading to other organs [1, 5]. The current approaches to the treatment of local, unilateral conjunctival lymphoma are excision [4, 6], external beam radiation therapy (EBRT) [2], or intralesional immunotherapy with rituximab or interferon-alpha [1, 2]. Alternative treatments include observation (elderly/fragile), antibiotic therapy with clarithromycin or doxycycline [6–8], local bleomycin [9], or bevacizumab injections [10].

Ferreri and al. [1] reported treatment of MALT lymphoma of the conjunctiva with intralesional rituximab injections, four weekly followed by six monthly injections. The authors achieved the complete resolution of the lesion in 12 of 20 patients (60%).

In our case, surgical excision or cryotherapy was impossible because of the size of the lesion and lifelong troubles with scaring dry eye syndrome and cosmetics. The patient did not accept local ra-

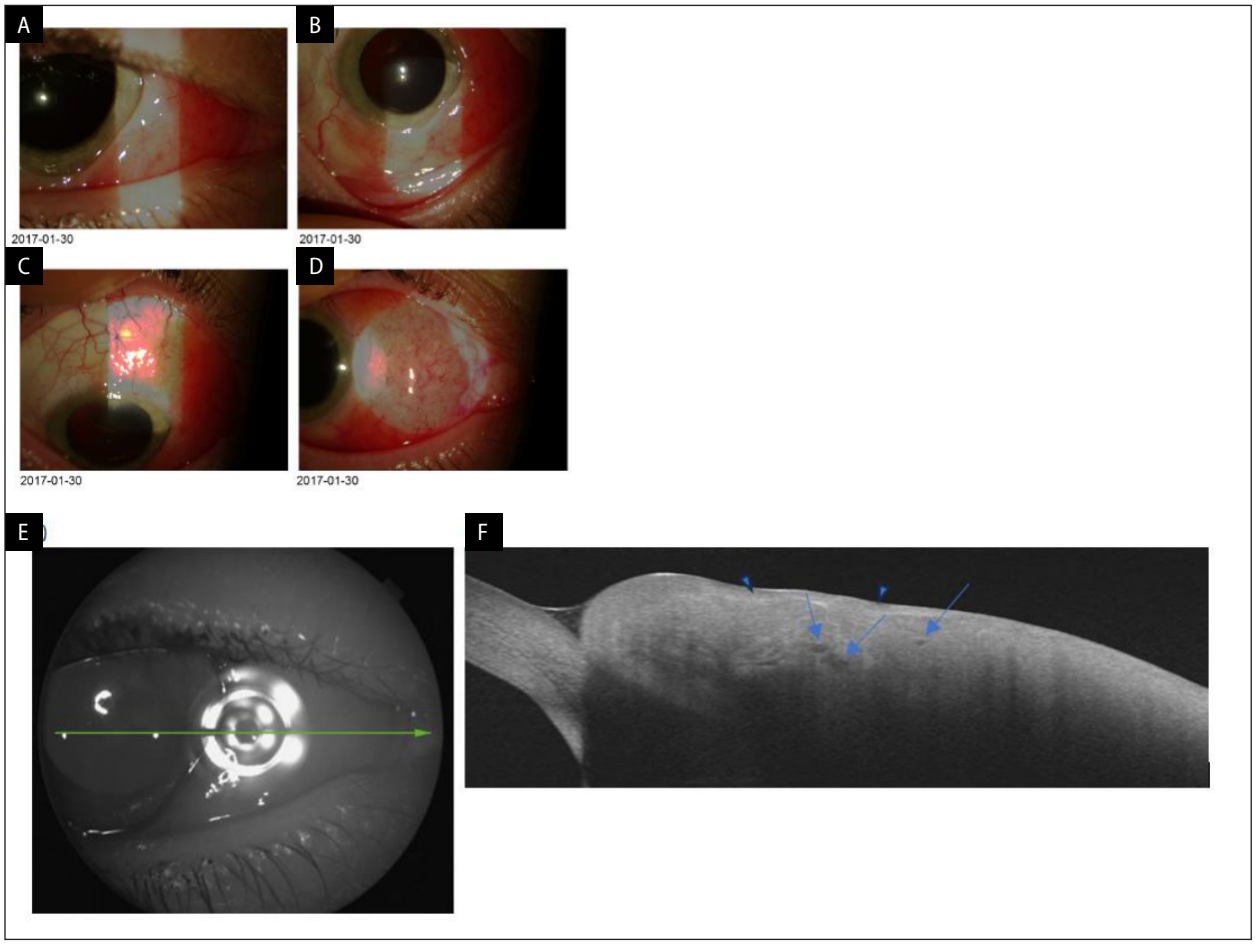

Figure 2. A–D. Right eye after three injections of bevacizumab subconjunctival. The color of the lesion is much paler and the lesion tends to be smaller. It is possible to o see cross-sections of small vessels (arrows) in the optical coherence tomography (OCT) scan of this lesion (**E, F**). The mass is less homogenous, and the subepithelial lesion is concave and much more hyperreflective (arrowheads), which could indicate fibrosis

diotherapy because of the risk of developing cataracts, lacrimal gland dysfunction, dry eye, ocular pain, conjunctival irritation, and epiphora [2]. We decided to use bevacizumab, widely used in ophthalmology to treat wet age-related macular degeneration (AMD) and diabetic macular edema, due to the pronounced vascular appearance of the lesson. Bevacizumab is a humanized monoclonal antibody (MAb) inhibiting the action of vascular endothelial growth factor (VEGF). (https://www.clinicaltrialsarena.com/projects/avastin/).

Oh et al. [10] reported treatment of benign lymphoid hyperplasia with bevacizumab injection. The difference was that we treated the recurrency of lymphoma not with a single injection but multiple injections for 20 months.

VEGF is a specific angiogenesis growth factor that binds to receptors on blood vessels and stimulates the formation of new blood vessels. Bevacizumab blocks VEGF receptors, mainly type 1 and 2, by tying them [11].

Although the primary growth factors promoting lymphangiogenesis are VEGFC and D, they both target VEGFR-2, -3 and VEGFR-3, respectively. Bevacizumab is a potent VEGFR-1 and -2 blocker, and it can influence the expression of VEGF-C and acts as an inhibitor of lymphangiogenesis and angiogenesis [5].

The possible explanation of the successful outcome in this recurrent case is that the tumor's growth mechanism combined both angiogenesis and lymphangiogenesis, and bevacizumab addressed both.

Bevacizumab injections should be considered a safe and effective treatment option in cases of lymphangiomas with evidence of prominent vas-

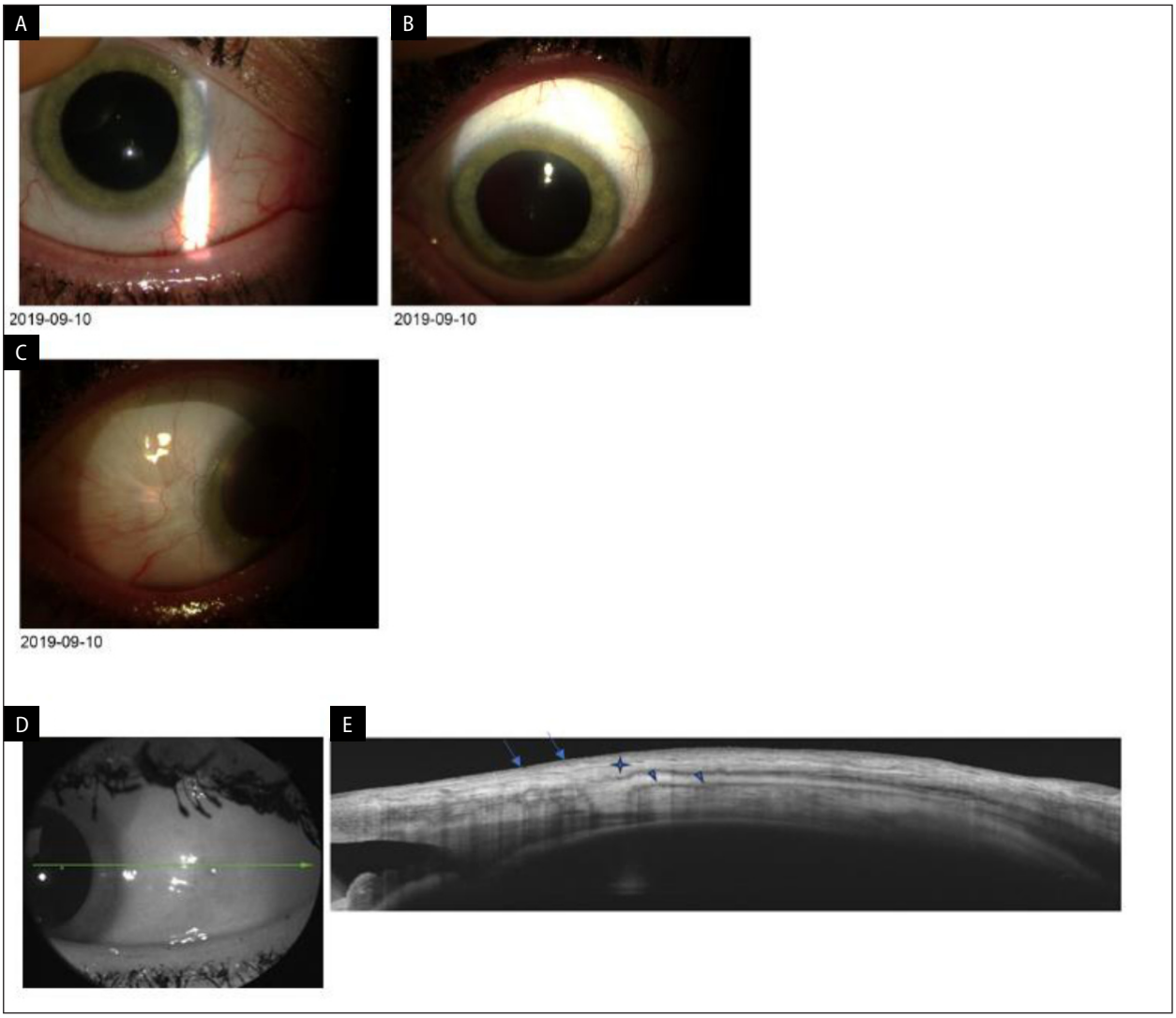

Figure 3. A–C. Right eye after ten injections, seventeenth months later. Slight dilatation of the conjunctival vessels, especially from the nasal side; **D, E.** Optical coherence tomography (OCT) of the anterior segment shows the disappearance of the lesion and standard cross-section of the conjunctiva. The homogenous mass's disappearance and the normal stroma reappearance (asterisk), covered with hyperreflective epithelium (arrows). Tenons capsule (arrowhead), dashed arrow sclera

cular components. We didn't find any systemic or local activities in five years of observation.

It is also worth mentioning that anterior OCT is a potent tool for non-invasive diagnosing and follow-up. In this case, there is an excellent correlation between clinical and OCT findings.

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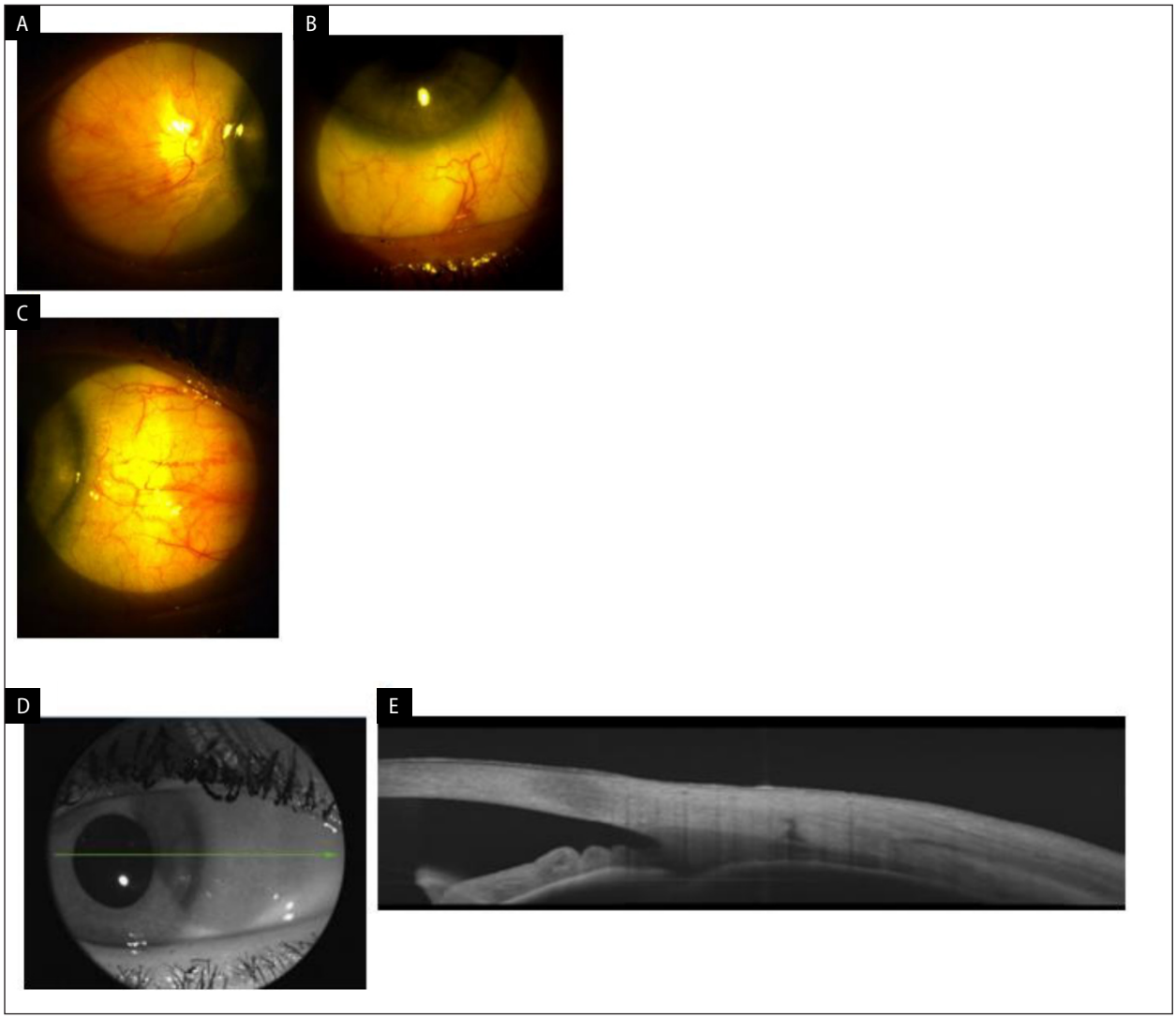

Figure 4. A–D. Right eye after seven years from the onset of lymphoma. The standard appearance of the conjunctiva, both in clinical and optical coherence tomography (OCT) examinations

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