Benign Reactive Lymphoid Hyperplasia of the Conjunctiva in Childhood.

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**SUBTITLE**

This investigation of benign reactive lymphoid hyperplasia of the conjunctiva in children indicated the clinical course was benign, rarely recurrent and not associated with a malignant transformation in our cohort.

**ABSTRACT**

**BACKGROUND/AIMS:** Our aim is to the report the clinical and histopathological features of benign reactive lymphoid hyperplasia (BRLH) of the conjunctiva in children and the outcomes of treatment.

**METHODS:** A retrospective chart review was performed of children aged 0-18 years, diagnosed with conjunctival BRLH from January 2000 to December 2013 at 2 large ophthalmology hospitals in the Middle East. Data were collected on patient demographics, features of the lesions, the site of the lesion, location, adnexal involvement, lymph nodes involvement, local spread, histopathology and molecular genetic studies of the cases (if available), outcomes of treatment and recurrence.

**RESULTS:** There were 24 patients with lymphoid lesions classified as conjunctival BRLH during the 12-year period evaluated in this study. The mean age at diagnosis was 11.6 years. Twenty-three patients were males (96%). Systemic medical history included 3 patients with bronchial asthma, one patient with Down’s syndrome, one patient with generalised skeletal malformation, and one patient with gastritis. The initial uncorrected visual acuity was 20/30 or better in 93.5% of the eyes. At presentation, the tumour was unilateral in 12 cases (50%). The conjunctival mass was located on the bulbar conjunctiva in all cases. The mass was present nasally in 96% of lesions. No cases (that were tested) had an infectious aetiology. Polymerase chain reaction demonstrated monoclonality suggestive of lymphoma in two cases; however this did not alter the final diagnosis as BRLH per histopathological criteria and clinical course,

**CONCLUSIONS:** All investigated cases of paediatric conjunctival BRLH had a benign clinical course with no local or systemic dissemination and a male predominance. Recurrence was rare, and in our cohort, not associated with malignant transformation.

**INTRODUCTION**

Benign reactive lymphoid hyperplasia (BRLH) of the conjunctiva is a rare, polyclonal proliferation of lymphoid tissue that typically occurs in older children and young adults. (1,2) There is a higher predilection for males. (3,4) The medially-located conjunctiva is most commonly affected. (3-6). The largest study of conjunctival masses in children reported BRLH representing 85% of lymphoid tumours and only 2% of all masses. There has been no associated systemic lymphoma. (7,8)

Conjunctival BRLH is least likely to transform to lymphoma when compared to BRLH involving other ocular structures: (20% followed by orbit and eyelid in 35% and 67%, respectively). (1,2) Despite this, a biopsy of the lesion and systemic evaluation are essential for diagnosis. Classification of these lesions requires histopathological evaluation, immunophenotyping using either flow cytometry or immunohistochemistry (IHC) and molecular studies, such as immunoglobulin heavy chain polymerase chain reaction (IgH-PCR).

Histopathologically, BRLH includes diffuse infiltrate of mature lymphocytes within the substantia propria, multiple deep and superficial lymphoid follicles with germinal centres and plasma cell infiltrate. IHC studies indicate the tumour is polyclonal, containing a mixture of B cells with different immunoglobulin and T cells with various surface antigens receptors located in the inter-follicular zones.(2) The secondary lymphoid follicles express reactivity to BCL-6 and CD10 but their centres fail to express BCL-2, which an is an anti-apoptotic protein. The follicular dendritic cells within the germinal centres express CD23. (1) DNA rearrangement studies using IgH-PCR significantly reduce the number of histopathologically indeterminate lymphoid tumours, by helping to distinguish BRLH from true lymphomas.

The pathogenesis and aetiology of conjunctival BRLH remains unknown. A history of conjunctivitis causing chronic antigen stimulating mechanism may play a role in the oncogenesis (9) *Chlamydia psittaci* infection was found to be present in 80% of Italian patients with ocular adnexal lymphoma, and can be detected in tumour tissue and peripheral blood mononuclear cells. (10) *Chlamydia pneumoniae, Chlamydia trachomatis, Helicobacter pylori*, Epstein-Barr virus (EBV), human T-cell lymphotropic virus have been also described as potential causes. (11-14) In one study, *C. psittaci* DNA was present in 12% of conjunctival BRLH cases. (10) Another study of 6 cases of conjunctival BRLH in patients < 31 years old, reported no cases with Chlamydia species or Epstein-Barr virus. (6) Most of these aforementioned studies (6, 10-14) enrolled adults and may not be representative of conjunctival BRLH in children.

Conjunctival BRLH is generally surgical excised with postoperative topical steroids. Treatment of the conjunctival lesion should include low-dose external beam irradiation (2000-4000 cGy) if the lesion is localised to the conjunctiva and causing significant visual problems. Other options include excisional biopsy and cryotherapy, local interferon injections or observation. These lesions typically have a favourable outcome with follow-up periods reaching up to 3 years (1,9) In cases associated with infectious etiologies, antimicrobial therapy appears to be beneficial. (14) One study reported successful treatment with subconjunctival injection of bevacizumab. (15) Recurrence of BRLH is rare and does not necessarily imply a malignant disease.(16)

The pathogenesis, pathological, IHC features and clinical course of the condition have not been extensively studied. (17,5) In this study, we present a cohort of 24 cases with detailed clinical information, histomorphological and immunohistochemical examination, with additional molecular testing, giving us the opportunity to better understand the clinical and histopathological features of BRLH in children and study the clinical outcomes of this disease.

**METHODS**

A retrospective chart review was performed of children aged 0-18 years, diagnosed with conjunctival BRLH from January 2000 to December 2013 at King Khaled Eye Specialist Hospital and King Saud University Medical City in Riyadh, Saudi Arabia.

The clinical information from all patients was reviewed and the following data were collected: age, gender, onset, duration, visual acuity, photos, presence/absence of systemic disease, family history of ocular surgery or tonsil/adenoidectomy, and the main signs and symptoms. Data included the features of the lesions, the site of the lesion, laterality, size, location, adnexal involvement, lymph nodes involvement, local spread and type of laboratory investigations. Histopathology and molecular genetic studies of the cases and the treatment plan and recurrences were recorded.

All patients underwent physical examination by paediatricians with follow up, which included complete blood count (CBC), kidney and liver functions tests and chest radiographs. Computerized topography (CT) scans of the brain and orbits were performed in one case. These tests helped to rule out regional or systemic disease while the patient was waiting for a biopsy, and because the initial differential diagnosis included a lymphoma. According to the surgical reports, all the conjunctival masses were completely excised and sent for histopathological examination. For histopathology, the specimens were embedded in paraffin and underwent routine staining with hematoxylin and eosin. At the time of diagnosis IHC of the tissue specimens was based on the pathologist’s preference in 12 out of 24 cases. In specimens from 12 cases where adequate tissue was available and the initial evaluation for testing was deemed appropriate to rule out lymphoma, additional IHC was performed using a standard IHC staining protocol using the following antibodies: CD3, CD20, BCL2, BCL6, CD10, CD5, CD23, CD43, IgD, and Cyclin D1. Other cases were deemed as BRLH, and no further testing was requested. Two pathologists (DPE and HA) reviewed all slides. The excised tissue of one case in which clinical recurrence was noted was sent to King Faisal Specialist Hospital and Research Center, a referral centre for selected IHC testing.

IGH gene rearrangement studies were performed at the Department of Cellular Pathology in the Royal Liverpool University Hospital, UK using a standard protocol. This protocol involved DNA extraction with proteinase K digestion and published PCR Biomed-2 primers using a semi-nested technique. The products were analyzed in 2% agarose gel, electrophoresed then visualized with an ultraviolet light illuminator, as previously described.

Selected cases where remaining tissue was available in the blocks (n=5 cases) underwent IHC staining to detect infectious agents for EBV (EBV-LVM1) and Epstein-Barr nuclear antigen 2 (EBNA2), cytomegalovirus and *Helicobacter pylori*. One specimen underwent PCR testing for Epstein-Barr virus.

**RESULTS**There were 24 patients with lymphoid lesions classified as conjunctival BRLH during the 12-year period evaluated in this study. The mean age at diagnosis was 11.6 years (median, 11 years; range, 7–17 years). Twenty-three patients were males (96%). On average these children presented to the King Khaled Eye Specialist Hospital 3.75 months (median, 3 months; range 1 week- 2 years) after they first noticed the lesion. Systemic history included 3 patients with bronchial asthma, one patient with Down’s syndrome, one patient with generalized skeletal malformation and one patient with gastritis. Surgical history included 5 patients (22%) who had undergone tonsillectomy/adenoidectomy. Two patients reported a history of ocular trauma prior to presentation (10%).

The initial uncorrected visual acuity was 20/30 or better in 93.5% of the eyes. The remaining eyes had uncorrected vision of 20/80 or 20/40. At presentation, the tumour was unilateral in 12 cases (50%) and bilateral in 10 cases (40%). The right eye was involved in 7 cases (29%), left eye in 5 cases (21%), and both eyes in 10 cases (45%).

The conjunctival mass was located on the bulbar conjunctiva in all cases. The mass was present medially in 96% of lesions, and laterally in 8%. The caruncle was involved in 7 patients (29%). The mean tumour size base X base was 6.5x4.6 mm (range, 3x3 mm to15x8 mm). All patients underwent excisional biopsy. Six patients (25%) were initially treated medically with no noticeable improvement before excision as follows: 4 received topical steroid, 2 received anti-allergy drops (8%) and 1 received antibiotic ointment (4%). The demographic data and clinical presentation are summarized in Table 1.

Table 1. Demographic, clinical data and outcome in all cases of benign reactive lymphoid hyperplasia.

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|  | **Age (Y)** | **Sex** | **VA** | **Duration (M)** | **Side** | **Location** | **Base width in cm** | **Base length in cm**  | **Adnexal involv.** | **L. N. involvment** | **Local disease** | **Medical Illness**  | **Tonsil/adn-tomy** | **Treatment trial** | **total f/u** | **Recurrence** |
| Case 1 | 10 | m | 20/20 20.20 | 1 | ou | Medial conj | 1.2 | 0.5 | curuncle | - | - | - | - | - | 69 | - |
| Case 2 | 11 | m | 20/25 20/20  | 4 | od | Medial conj | 0.6 | 0.7 | - | - | EKC | - | - | erythromycine | 57 | - |
| Case 3 | 13 | m | 20/20OU | 6 | od | Medial conj | 1.5 | 0.2 | - | - | - | Asthma | - | - | 48 | - |
| Case 4 | 10 | m | 20/20 OU | 24 | ou | Medial conj | 1 | 0.5 | curuncle | - | EKC | Asthma | - | topical steroid | 63 | - |
| Case 5 | 17 | m | 20/25 & 20/15 | 2 | od | Medial conj | 1.2 | 0.8 | - | - | - | - | - | - | 75 | - |
| Case 6 | 7 | m | 2025 &20/25 | 0.75 | ou | Medial conj | 0.5 | 0.5 | - | + submental | - | - | + | - | 63 | - |
| Case 7 | 9 | m | 20/20 OU | 2 | os | Medial conj | 0.6 | 0.6 | - | - | - | - | - | - | 61 | - |
| Case 8 | 10 | m | 20/20 OU | 3 | os | Medial conj | 0.4 | 0.5 | curuncle | - | old trauma | scletal malform. | - | - | 94 | - |
| Case 9 | 15 | m | 20/50& 20/25 | 6 | os | Medial conj | 1.5 | 0.8 | - | - | conjuctivitis | gastritis | - | - | 98 | - |
| Case 10 | 12 | m | 20/20& 20/20 | 1 | os | Medial conj | 0.4 | 0.3 | - | - | VKC | - | + | anti-histamine  | 90 | - |
| Case 11 | 9 | m | 20/20OU | 1 | od | Medial conj | 0.55 | 0.4 | - | - | - | Asthma | - | topical steroid | 39 | - |
| Case 12 | 10 | m | 20/20OU | 4 | od | Medial conj | 0.6 | 0.5 | curuncle | - | VKC | - | - | topical steroid+anti-histamine | 14 | - |
| Case 13 | 10 | m | 20/20 OU | 3 | ou | Medial conj | 0.4 | 0.3 | - | - | - | - | + | topical steroid | 22 | - |
| Case 14 | 13 | m | 20/25 20/28.5 | 4 | ou | Medial conj | 0.5 | 0.5 | - | + submental | VKC | adenoid | + | - | 28 | - |
| Case 15 | 15 | m | 20/20 OU | 0.25 | ou | Medial conj | 0.5 | 0.2 | - | - | Conjunctivis | - | - | - | 57 | - |
| Case 16 | 14 | m | 20/20 OU | 6 | od | Medial conj | 0.6 | 0.4 | - | - | - | - | + | - | 46 | - |
| Case 17 | 10 | m | 20/20ou | 1 | os | Medial conj | 0.8 | 0.7 | curuncle | - | trauma | - | - | - | 31 | - |
| Case 18 | 10 | m | 20/20 OU | 0.25 | ou | Medial conj | 0.7 | 0.3 | curuncle | - | - | - | - | - | 48 | + after 1 year |
| Case 19 | 12 | m | 20/25 OU | 5 | ou | Medial conj | 1 | 0.6 | curuncle | - | - | Down syndrome | - | - | 33 | - |
| Case 20 | 12 | m | 20/20 20/25 | 1.5 | OS | Medial conj | 0.4 | 0.4 | - | - | - | - | - | topical steroid | 28 | - |
| Case 21 | 11 | m | 20/28.5 20/20 | 1 | OS | Medial conj | 0.5 | 0.5 | - | - | - | - | - | - | 50 | - |
| Case 22 | 17 | m | 20/20 OU | 2 | ou | Medial conj | 1 | 1 | - | - | - | - | - | - | 12 | - |
| Case 23 | 8 | f | 20/20ou | 1 | os | Medial conj | 4 | 2 | - | - | - | - | - | - | 16 | - |
| Case 24 | 16 | m | 20/20 ou | 1 | os | Lateral | 1.5 | 1 | - | - | - | Diabetes | - | - | 30 | - |

Histopathological examination of hematoxylin and eosin stains showed secondary lymphoid follicles separated by wide areas with well-defined mantle and marginal zones. The follicles’ germinal centres were composed of different population of lymphocytes, dendritic cells, and macrophages with visible mitotic figures (Figure 1).

A complete lymphoma IHC panel was performed in 10 cases (43%) while in 9 cases (37.5%) selected IHC staining were performed to confirm the diagnosis of BRLH and to exclude lymphoma. For the remaining 7 cases (29%), light microscopy was sufficient to confirm the diagnosis of BRLH. IHC features that confirmed BRLH in most cases, included the B cells in the germinal centres staining positively with CD20, CD10, BCL-6 and negatively with BCL-2. Differentiated T cells stained positively with CD3, CD5 and CD43. The CD23 stain highlighted the follicular dendritic cell meshwork, and stained a subset of mantel zone lymphocytes, BCL-2 and IgD. All 10 complete panel cases showed negative staining with Cyclin D1 while the eleventh case cyclin D1 was not used. Table 2 shows the 10 cases with complete IHC panel of stains and 4 additional cases were at least CD3 and CD20 stains were performed either alone or with additional stains.

Table 2: Results of IHC tests for 14 cases of benign reactive lymphoid hyperplasia of the conjunctiva with complete panel in 10 cases and incomplete panel in 4 cases.

|  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | **CD3** | **CD20** | **BCL-2** | **BCL-6** | **CD10** | **CD5** | **CD23** | **CD43** | **IgD** | **cyclin D1** |
| Case 1 | + | + | - | + | NAD | + | NAD | + | NAD | NAD |
| Case 2 | + | + | - | + | + | - | - | - | + | - |
| Case 3 | + | + | - | + | + | - | - | - | - | - |
| Case 4 | + | + | - | + | + | + | + | + | + | - |
| Case 5 | + | + | - | + | + | + | + | + | + | - |
| Case 6 | + | + | - | + | + | + | + | + | + | - |
| Case 7 | + | + | - | + | + | + | + | + | + | - |
| Case 8 | + | + | - | + | + | + | + | + | + | - |
| Case 9 | + | + | - | + | + | + | + | + | + | - |
| Case 10 | + | + | NAD | NAD | NAD | NAD | NAD | NAD | NAD | NAD |
| Case 11 | + | + | - | + | + | + | + | - | + | NAD |
| Case 12 | + | + | \_ | + | + | + | + | + | + | - |
| Case 14 | + | + | - | + | + | NAD | NAD | NAD | NAD | NAD |

*NAD=No available data*

Gene rearrangement studies were performed in 12 cases (50%). (Table 3) IgH-PCR studies demonstrated polyclonal lymphoid populations in 7 patients, but 2 cases were positive for monoclonal B-cell population, suggestive (but not conclusive) of a lymphoma (Figure 2). These two cases were were re-evaluated carefully and discussed with the treating physician and the pathologists. One case had a full panel consistent with features of BRLH staining positively for CD3, CD20, BCL-2, BCL-6, CD10, CD5, CD23, CD43, IgD, cyclin D1. This confirmed the benign nature of the lesion in that case. The second case only CD3 and CD20 were positive;, however the morphologic appearance histopathologically and the clinical course of the lesion in that case were in favour of BRLH.

Table 3: Outcomes of gene rearrangement analysis performed on 12 available samples using polymerase chain reaction of benign reactive lymphoid hyperplasia of the conjunctiva in children.

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| --- | --- |
| Case 1 | Negative for monoclonal B-cell population |
| Case 2 | Failed |
| Case 3 | Negative for monoclonal B-cell population |
| Case 4 | Negative for monoclonal B-cell population |
| Case 5 | Negative for monoclonal B-cell population |
| Case 6 | Negative for monoclonal B-cell population |
| Case 7 | Positive for monoclonal B-cell population |
| Case 8 | Failed |
| Case 9 | Negative for monoclonal B-cell population |
| Case 10 | Positive for monoclonal B-cell population |
| Case 11 | Negative for monoclonal B-cell population |
| Case 12 | Failed |

IHC staining for infectious agents was negative in all cases that the tests were performed. Testing was negative for herpes simplex virus type 1 (n=3), type 2 (n=3), cytomegalovirus (n=3) and *Helicobacter pylori* (n=3). For EBV 2 testing, there were negative stain results for EBNA2 and EBV-LMP1 and a 3rd case had negative results for Epstein-Barr encoding region (EBER) in situ hybridization to detect EBV. IHC staining for infectious agents was not performed in all cases due to limited tissue availability.

Mean duration of follow-up was 49 months (range, 12 to 98 months). BRLH recurred in 2 patients at 1 year and 2 years postoperatively. Recurrence in both cases was clinically similar to the primary lesion. One recurrent case underwent excisional biopsy, and histopathological examination demonstrated that this was benign. We elected to observe the other case and there have been no changes in the size of lesion at the time of writing this study. None of the patients developed regional or systemic disease based on follow up systemic clinical evaluation and work up by a specialized paediatrician in addition to our routine ophthalmological examination. (Table 1)

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**DISCUSSION**

Conjunctival lymphoid lesions are rare in children with only scattered case reports (1,6,17). Some have postulated that in children, BRLH represents an aberrant immune response as opposed to a neoplastic process. (18,19) This is in contrast to numerous patients reported with adult conjunctival lymphomas. Furthermore, conjunctival lymphoid lesions are rarely associated with systemic lymphoma. (20) The current study reports a comprehensive evaluation of lymphoid conjunctival lesions in children that includes clinical features and follow-up as well as histopathological and molecular analysis. We have identified 24 patients with lymphoid lesions classified as conjunctival reactive lymphoid hyperplasia over a 12-year period. The mean patient age at diagnosis was 11.6 years (median, 11 years). Twenty-three patients were males (96%). These outcomes are consistent with previous reports in children and adults where older males were more susceptible to develop atypical lymphoid lesions and lymphoma. (1,2)

Some patients in our study had a history of other systemic infections and diseases: three patients had a history of bronchial asthma, and 5 children had a history of tonsillectomy, adeno-tonsillectomy, or adenoidectomy, which is 10 times higher than the normal population. (21) To our knowledge, there are no reports of systemic association with BRLH. Since enlarged tonsils are also a form of BRLH, one can speculate that the conjunctival lesion might represent a further site of extranodal lymphoid hyperplasia. Although there have been suggestions of infectious aetiologies for BRLH and lymphomas all our tested cases were negative for infectious agents.However, this was performed in total of 5 cases only, which might not be conclusive. On the other hand, chronic or acute inflammation from allergic causes was present in 26% of patients in our study.

The majority (94%) of the tumours in our report involved the medial bulbar conjunctiva, which concurs with reports in the literature. (5, 17,18) Clinically, the medial bulbar conjunctiva is the most commonly affected site with occasional caruncular involvement. (5, 6,20) The rate of caruncular involvement (29%) in our study was comparable to the literature. (5,17) Notably, in many mammals, regularly occurring conjunctival follicles, which usually form solitary nodules have bright germinal centres indicating lymphoid cell proliferation after antigen contact (22).This likely occurs in the bulbar region, with conjunctival follicles occurring at a younger age then regressing later in life. (22,23) Hence the tumour may present in different locations based on age. (23,24)

Childhood BRLH patients are usually healthy boys with no history of systemic lymphoma (5,,6,17,20). In our series, almost all the patients (23/24) were healthy boys. Six patients (27%) underwent initial medical therapy such as topical steroids, anti-allergy or antibiotic with no noticeable improvement before excision. However a clinical response has been reported with steroid and radiotherapy. (25)

Children with conjunctival BRLH have no association with systemic lymphoma and the tumours are localised to the ocular adnexa. However, in select cases the best approach is more specific studies and/or systemic examination with special attention to lymph node and basic blood work to detect primary tumours in the body or any spread from the presenting lesion. (6,17) The conjunctiva is the least frequently reported ocular site associated with systemic lymphoma. (2) This observation concurs with the majority of studies of conjunctival tumours in children that report lymphoid tumours represent approximately 2% only of all tumours, while all cases but one were BRLH. (7, 9)

Histopathologically, the BRLH lesion is a single, localised lesion with no invasion of the periocular structures. The lesion appears as dense infiltrate of mature lymphocytes within the conjunctival substantia propria with multiple nests of lymphocytes forming follicles with germinal centres. (17) These features were present in all our cases. The features included positive staining of germinal centres with CD20, CD10, BCL-6 and failure to express BCL-2 while differentiated T cells stain positively with CD3, CD5 and CD43. (26,27) This was consistent in all our cases that underwent full IHC panel staining including the case that was monoclonal by gene rearrangement analysis.

**Gene rearrangement studies**

PCR-IGH and IGK gene rearrangement studies can detect B-cell lymphoma in up to 90% and false negatives are attributed to hypermutations and the use of consensus primers, which are not complimentary to their target regions. (24)
Sharara et al (17) reported a child presenting with bilateral nasally-located bulbar conjunctival tumour histopathologically and immunophenotypically consistent with BRLH. However, molecular analysis was suggestive of follicular lymphoma, and the lymphocytic infiltrate resolved with no recurrence.(17) We observed similar findings in two cases where B-cell monoclonality was demonstrated by PCR. These particular cases emphasize the importance of performing PCR gene rearrangement studies prior to confirming the working diagnosis of BRLH. Notably, it has been reported that in children, BRLH can show conflicting results between the PCR findings and the histopathological/IHC characteristics where lesions present clinicopathologically as polyclonal BRLH while expressing monoclonality in PCR yet maintaining a benign course clinically and with sufficient periods of follow up.(18) These unusual and rare cases challenge the importance of molecular testing in changing the clinical management of these patients and have been observed in 2 of our cases

Malignant transformation of BRLH has not been reported to date, and recurrence, though rare, usually presents at the edge of the excised lesion. (5,6,17) However in a more recent review on lymphoid hyperplasia of the orbit and adnexae, authors have suggested a minimum follow up of five years in spite of the relative favourable prognosis. (28) In our series with the longest follow up of 98 months, recurrence was recorded for only 2 cases. The recurrent lesion was similar to the first tumour, which was excised in one case and without evidence of a malignant transformation. The other case was observed and to date, there have been no changes in the size of lesion.

The pathogenesis of BRLH has been studied in relation to infectious aetiology, however the relationship between an infectious aetiology and BRLH is not well established. It has been suggested that these conjunctival lymphoid lesions that are associated with EBV may represent spectrum of reactive infiltrates. (13,29) IHC staining for EBV by EBER and EBV-LMP, which are markers for active and latent EBV infections are commonly used in adeno-tonsillar tumours in addition to PCR techniques, which are also used to detect infections in cases of conjunctival lymphoma. (17,29) Others have tried animal models to establish a similar association with EBV infection with lymphoid lesion. (30) Positive immunostaining for EBV in conjunctival BRLH has been shown in two separate reports of conjunctival BRLH.(17,29) In our study only five patients underwent evaluation for an association to infectious aetiology none has positive staining. As only a limited number of specimens were tested, judicious interpretation of this result is warranted.

In summary, we report a large case series of conjunctival lymphoid lesions in children that were confirmed to be BRLH. All case followed a benign clinical course with no local or systemic dissemination with a male predominance. The mean age at the time of diagnosis of was 11 years. The majority of tumours involved the nasal bulbar conjunctiva appeared as a salmon-pink lesion. On histological examination and IHC, most cases showed typical features consistent with reactive lymphoid hyperplasia. However, PCR demonstrated monoclonality suggestive of lymphoma in two cases. The clinical course was benign without recurrence in these cases. Recurrence was rare and not associated with malignant transformation of the tumour.

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**FIGURE LEGENDS**

Figure 1. (A) Image of the right eye with benign reactive lymphoid hyperplasia of the conjunctiva. (B): Reactive lymphoid follicles with germinal centres (X50 magnification; hematoxylin and eosin stain). (C): The B-lymphocytes with follicular pattern (X100 magnification) CD20. (D): IGH gene analysis with polymerase chain reaction (PCR) indicating the presence of monoclonal B-cell population for case 10.

Figure 2. (A): Initial presentation of benign reactive lymphoid hyperplasia of the conjunctiva in the right eye and (B): Recurrence in the right eye with features of BRLH.