Anterior segment involvement in vitreoretinal lymphoma: clinical manifestations, molecular findings and in vivo confocal microscopy

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ABSTRACT

Background Intermediate and posterior manifestations of vitreoretinal lymphoma (VRL) are well characterised. However, there is limited information on anterior segment involvement in VRL. This study aimed to describe the anterior manifestations of VRL, and their association with molecular testing.

Methods Retrospective analysis of patients with biopsy-proven VRL. Study variables included anterior segment manifestations, findings from slit-lamp photos and in vivo confocal microscopy (IVCM) when available. MYD88 L265P mutation and cytology in the aqueous humour, retinal and systemic findings were also analysed.

Results The analysis included 108 eyes of 55 VRL patients. Anterior segment involvement was present in at least one visit in 55 eyes (51%) of 33 patients (60%); it included keratic precipitates (dendritiform with branching and irregular margins in 33 eyes, dust-like in 16 eyes and large granulomatous in 12 eyes), cells in the anterior chamber (51 eyes) and posterior synechiae (2 eyes). IVCM was available for 41 eyes and showed different morphologies of keratic precipitates, including floral, spikes and mulberry patterns (66%, 56% and 20%, respectively). MYD88 L265P mutation in the aqueous humour was detected in 10/21 (48%) eyes with no anterior segment involvement and 24/37 (65%) eyes with anterior segment involvement.

Conclusions Anterior segment manifestations are often present in VRL and include dendritiform and dust-like keratic precipitates. IVCM in VRL can identify different patterns associated with keratic precipitates. MYD88 L265P mutation in the aqueous humour of VRL patients can also be found in eyes without significant anterior segment involvement.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Vitreoretinal lymphoma is a malignant neoplasia that can masquerade as uveitis. While posterior segment manifestations of vitreoretinal lymphoma have been widely investigated, there is more limited information on the anterior segment features of the disease.

WHAT THIS STUDY ADDS

⇒ This study provides a comprehensive review of the anterior segment features of vitreoretinal lymphoma in a large cohort of patients, including a detailed analysis of keratic precipitates and changes seen on in vivo confocal microscopy. It also analysed the correlation between anterior segment findings and molecular testing.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ This study helps to identify the anterior segment changes associated with vitreoretinal lymphoma. It provides guidance for practitioners in the differential diagnosis of uveitis and use of molecular tests when suspecting masquerade syndromes.

INTRODUCTION

Vitreoretinal lymphoma (VRL) is a life-threatening neoplasia with protean ophthalmic manifestations, challenging diagnosis and complex treatment. Its management is multidisciplinary and includes ophthalmology, oncology and radiology subspecialties.[1] Early diagnosis of VRL is critical and can be achieved by promptly recognising the ocular findings associated with this disease.

VRL belongs to the uveitic masquerade syndromes. It usually presents as intermediate and posterior uveitis; anterior segment involvement ranges from 25% to 75% of cases.[2 3]

While the intermediate and posterior segment manifestations are well recognised and have been extensively studied on clinical examination and multimodal imaging, there is limited information regarding the anterior segment involvement in VRL.[1 4–9] Previous studies reported cases with cellular hypopyon, keratic precipitates (KPs) and manifestations on in vivo confocal microscopy (IVCM), but their prevalence, clinical presentation and association with molecular findings are poorly defined.[10–13]

The aim of this study was to report the anterior segment manifestations, molecular findings and IVCM changes in VRL. These data can contribute to the diagnosis of VRL and help to expand the clinical spectrum of this disease.

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MATERIALS AND METHODS

This study was an observational, retrospective analysis of patients with biopsy-proven VRL seen at two tertiary referral centres for uveitis, the Department of Ophthalmology of San Raffaele Scientific Institute, Vita-Salute San Raffaele University, Milan, Italy, and the Department of Ophthalmology at Feinberg School of Medicine, Northwestern University, Chicago, Illinois from 2015 to 2022.

All patients with either primary VRL, primary central nervous system (CNS) and/or systemic lymphoma associated with vitreoretinal involvement were included. Other inclusion criteria were: age ≥18 years old and biopsy-proven lymphoma either on ocular samples, CNS or systemic specimens. Exclusion criteria were: presence of other uveitis etiologies, such as sarcoid, tuberculosis, syphilis or ocular toxoplasmosis, and incomplete electronic medical charts.

Data from all the visits available within the study period were reviewed. Variables analysed were anterior segment findings, including the presence and features of KPs, anterior chamber inflammation graded according to the standardisation of uveitis nomenclature (SUN) criteria, intraocular pressure (IOP), iris and lens features.[14] KPs were categorised according to the description present in the chart and anterior segment photos into three categories (large granulomatous, dendritiform with branching and irregular margins, and dust-like) and two colours (whitish and brown). Variable analysed were attributed to VRL treatment if appearing within 2 weeks after therapy initiation or during treatment cycles; instead, they were considered part of VRL manifestations if seen before treatment initiation or during remission. Available results of anterior chamber tap for presence of the MYD88 L265P mutation were analysed in patients seen in Milan as previously described.[15] Results of cytopathology on anterior chamber tap were reviewed in a case seen in Chicago. When available, images obtained by slit-lamp photography, and IVCM (Heidelberg Engineering, Heidelberg, Germany) were also reviewed.

IVCM was performed under topical anaesthesia with 0.4% oxybuprocaine hydrochloride (Novesina; Laboratoires Thea, Francia) in a subset of patients seen in Milan. Confocal microscopic images of the epithelium, subepithelial nervous plexus, stroma and endothelium of each eye were taken. Each frame was saved and evaluated by two independent graders (CDB and GF). Poor-quality images not allowing lesions description were excluded. The KP morphology and appearance on IVCM were graded as dots, flowers, mulberries or spikes. The floral pattern appeared as a hyperreflective centre with a surrounding petaloid configuration as previously reported.[11] The spike pattern was characterised by the presence of spindle-like deposits on corneal endothelium. The mulberry pattern was defined by a cluster of cells adherent to corneal endothelium and expanding towards the anterior chamber.

Descriptive statistical analyses were performed with GraphPad (GraphPad Software, San Diego, California, USA) and included mean and SDs.

RESULTS

One hundred and eight eyes of 55 VRL patients (mean age at diagnosis 67±12 years; 34 females, 62%) were included. Anterior segment involvement was present in at least one visit in 55 eyes (51%) of 33 patients (60%). Table 1 illustrates the features associated with anterior segment involvement. Associated CNS lymphoma was present in 32/55 (58%) of eyes with anterior involvement and 36/53 (68%) of those without anterior involvement.

Table 1 Features associated with anterior segment involvement in vitreoretinal lymphoma

	Anterior involvement	No anterior involvement
No of eyes (%)	55/108 (51)	53/108 (49)
No of patients (%)	33/55 (60)	22/55 (40)
Age (mean±SD)	68±12	66±12
Follow-up—months (mean±SD)	19±19	13±19
Pseudophakic eyes (%)	28/55 (51)	16/53 (30)
Associated CNS lymphoma—eyes (%)	32/55 (58)	36/53 (68)
Positive acqueous MYD88—eyes (%)	24/37 (65)	10/21 (48)
Positive vitreous MYD88—eyes (%)	16/23 (70)	4/8 (50)

CNS, central nervous system.

Slit-lamp findings

Anterior segment manifestations included KPs (50/55 eyes with anterior involvement—91%) and cells in the anterior chamber (51/55 eyes; 93%). Twenty-two out of the 33 patients with anterior involvement (67%) had bilateral manifestations.

KPs were classified in at least one visit as dendritiform, with branching and irregular margins, in 33/55 eyes (60%), dust-like in 16/55 eyes (29%) and large granulomatous in 12/55 eyes (22%) (figure 1). KPs had a whitish-creamy colour in 38/44 eyes (86%) and brown pigment in 6/44 eyes (14%); in the remaining eyes, the colour of KPs was not reported. KPs were diffusely distributed in 36/44 eyes (82%), and limited to the inferior cornea in 8/44 eyes (18%); in the remaining eyes the distribution of KPs was not described. None of the patients presented with hypopyon. KPs changed shape in 12/50 eyes (24%) compared with the previous presentation in case of recurrence of anterior segment involvement or after treatment. Posterior synechiae were present in 2/55 eyes of 2 different patients (4%).

Anterior segment findings seen after the start of VRL treatment included the development of anterior chamber cells, large granulomatous KPs, and IOP increase after intravitreal rituximab (10 eyes of 6 patients). Only two eyes developed granulomatous KP independently of intravitreal rituximab. Corneal epithelial toxicity was seen after intravitreal methotrexate (two eyes of two patients).

In vivo confocal microscopy

IVCM was available for 41 eyes of 22 patients. On IVCM, we observed different KPs morphologies: hyper-reflective dots, floral, spike or mulberry patterns (figure 2). Hyper-reflective dots on the corneal endothelium were present in 31 eyes (76%), floral KPs in 27 eyes (66%), spikes KPs in 23 eyes (56%) and mulberry KPs in 8 eyes (20%). Among eyes with floral KPs, an incomplete floral pattern was observed in 27 eyes, and a complete type in 18 eyes. Different eyes showed more than one pattern in the same set of IVCM images.

Endothelial guttae were noted in four eyes. The corneal nerves' morphology was preserved in all examined eyes. In the retrospective review of IVCM images, no large cells with pleomorphic nuclei, scant cytoplasm and multiple prominent nucleoli consistent with VRL cytopathology were definitively observed.

Laboratory findings

The results of MYD88 analyses are shown in table 1. MYD88 L265P mutation in the aqueous humour was found in 10/21 (48%) eyes with no anterior segment involvement and 24/37 (65%) eyes with anterior segment involvement.

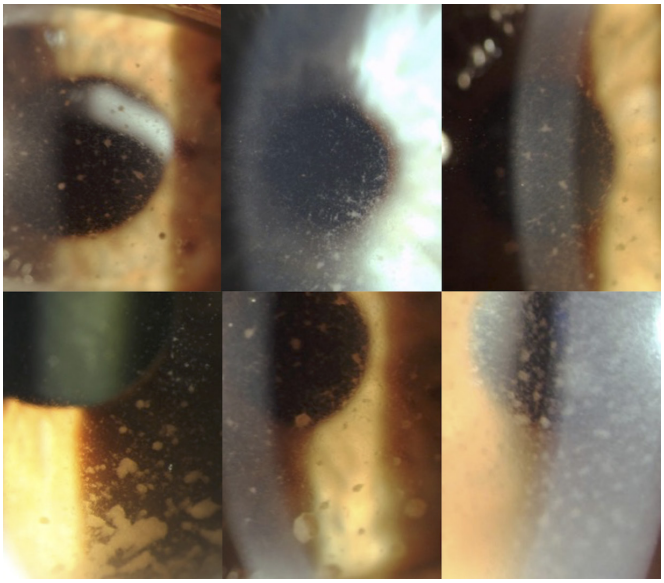

Figure 1 Examples of keratic precipitates in vitreoretinal lymphoma. Upper row dendritiform keratic precipitates with branching and irregular margins. Bottom row large granulomatous keratic precipitates.

Additional findings

Intraocular pressure was higher than 24 mm Hg in at least one visit in 12 eyes. In five eyes, IOP was higher than 40 mm Hg after treatment with intravitreal rituximab. Cytology on anterior chamber taps was performed in one eye with large granulomatous KPs (shown in the bottom left panel of figure 1) and showed enlarged atypical lymphoid cells with condensed chromatin and scant cytoplasm consistent with VRL.

DISCUSSION

In this paper, we analysed the anterior segment manifestations in a large cohort of patients with VRL, focusing on their clinical appearance and associations with imaging and molecular findings.

On clinical examination, VRL can be associated with anterior segment inflammation in a considerable number of eyes. Cassoux *et al* reported anterior segment inflammation in approximately 25% of eyes with VRL at presentation.[16] Among these, tiny KPs were observed in the majority, while mutton fat KPs were present in only two eyes. They also observed cellular hypopyon in one eye and posterior synechiae in two eyes. Other reports observed the presence of pseudohypopyon in patients with VRL, either of B or T-cell origin.[12]

In our series, dendritiform KPs were the most common type of KPs; in some cases, the dendritiform KPs were pigmented, but in the majority of cases they appeared whitish or transparent. Dendritiform KPs in VRL appeared more interconnected than stellate KPs seen in Fuchs uveitis and were often associated with or started off as endothelial dusting. Large granulomatous KPs were mostly observed after intravitreal chemotherapy with rituximab and were associated with transient IOP elevation.[17] This reaction is consistent with previous observations that found temporary IOP increase in up to 60% of patients receiving intravitreal rituximab for VRL and mutton-fat KPs in 35% of them.[18] Dust-like endothelial reaction was seen in 30% of eyes with anterior manifestations. Anterior chamber cells were common in VRL and, in some cases, they were described in the charts as atypical because of their large size compared with inflammatory cells observed in anterior uveitis.

Molecular analysis of anterior chamber taps for MYD88 L265P mutation was available for a subset of eyes in our cohort.[15] Positive MYD88 L265P mutation was found not only in VRL with anterior manifestations but also in eyes with no significant anterior segment involvement. The presence of intermediate or posterior VRL manifestations probably played a critical role in the molecular sensitivity of this technique. In our series, all the patients had a cytopathological diagnosis of large B-cell lymphoma, either on CNS, systemic or ocular specimens. The presence of MYD88 L265P mutation in the aqueous humour was used to confirm ocular involvement in patients with biopsy-proven CNS lymphoma, or to prompt more invasive investigations, such as vitreous or retinal

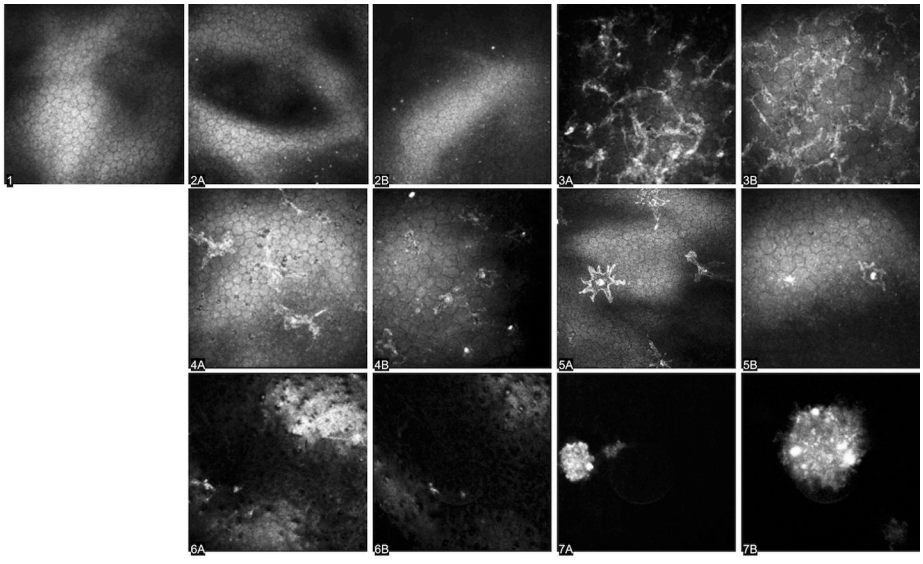

Figure 2 Representative findings at in vivo confocal microscopy in our study. (1) Normal endothelium of a healthy patient. (2A, 2B) Hyperreflective dots among regular endothelium. (3A, 3B) Spicules of spindle-like deposits. (4A, 4B) Incomplete flowers and (5A, 5B) complete flowers: two distinct floral patterns associated with KPs. (6A, 6B) Guttae. (7A, 7B) Mulberry cluster of KPs expanding towards the anterior chamber. KPs, keratic precipitates.

biopsies, to confirm the diagnosis of VRL when the manifestations were limited to the eye.[19] In addition, some authors have used serial detection of MYD88 L265P mutation from the aqueous humour to assess the response after intravitreal chemotherapy.[20 21]

IVCM contributed to the morphological characterisation of anterior segment features of VRL eyes. Irregular lymphocytes with pleomorphic nuclei, condensed chromatin, scant cytoplasm and multiple prominent nucleoli consistent with VRL cytopathology have been previously described in IVCM images of VRL.[22–24] However, we did not observe cells definitively consistent with this description in our study, probably because of the retrospective nature of our analysis and because IVCM scans were directed towards areas of KPs. Previous studies using IVCM showed the features of KPs in different conditions, including ocular syphilis, herpetic uveitis, sympathetic ophthalmia and Vogt-Koyanagi-Harada.[25 26] In VRL, Mahendradas *et al* showed the presence of KPs appearing with a floral pattern on IVCM in three patients.[11] We observed a floral pattern in two-thirds of our sample, and spikes and mulberry KPs patterns less frequently. Hyper-reflective dots were also observed, but these have been described as non-specific deposition of material on corneal endothelium largely seen in pseudoexfoliation syndrome.[27] Future studies should explore the specificity of floral, spikes and mulberry patterns in VRL.

There are multiple limitations to this study. The retrospective nature of the analyses did not allow for a complete evaluation of all the subjects and for a diagnostic assessment of the anterior segment features. The subjective description of the clinical findings might vary from different clinicians, especially when describing the morphological features of KPs and cells, and this might have affected our results. IVCM images were limited to a small portion of the cornea and did not allow a comprehensive evaluation of all the possible findings described in VRL; also, previous treatments of anterior segment manifestations might have affected our results.

In conclusion, VRL is often associated with anterior segment involvement. These manifestations include dendritiform and dust-like KPs, and different features observed on IVCM. In addition, eyes with no significant anterior segment involvement can have positive results for molecular testing of MYD88 L265P mutation. These results can help diagnose, follow-up and treat patients with VRL, expanding the clinical spectrum of this disease.

Correction notice This article has been updated since it was first published. The affiliations for Dr Giulio Ferrari have been changed.

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