Ocular and Adnexal Benign Reactive Lymphoid Hyperplasia

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9.1 Introduction

Oftentimes it is challenging even for the pathologist to distinguish an RLH lesion from various types of lymphoma, which, in this location, are most frequently of the small mature lymphocyte type. Indeed, the histologic architectural abnormalities and cytologic atypia of lymphoid proliferations, as indicators of potential neoplasia, are difficult to reliably identify morphologically. Before the advent of immunohistochemistry (IHC) and molecular methods, OAL were classified solely based on the histomorphologic characteristics into benign or RLH and malignant or lymphoma. An additional category of atypical lymphoid hyperplasia was introduced to accommodate cases with indeterminate histologic features and further complicated the already difficult distinction between benign and malignant lymphoid proliferations. It has now become clear that ancillary studies are essential in classifying the benign or malignant nature of lymphoid proliferations based on clonality and aberrant expression of surface and cytoplasmic antigens.

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9.2 Epidemiology

RLH accounts for 10–20 % of all ocular adnexal lymphoid proliferations in two large series of orbital lesions (Shields et al. 2004; Shinder et al. 2010). The age at presentation for RLH is widespread, varying between 7 and 80 years with a mean of 40–50 years depending on the study, and is not significantly different from the mean age of presentation for ocular lymphomas. RLH does not appear to have consistent gender predominance in various studies, with reported male to female ratios leaning either way (Shinder et al. 2010; Mannami et al. 2001; Stacy et al. 2010). Reports vary also regarding the predominant site of involvement, some describing RLH more frequently in the orbit, including the lacrimal gland and sac, and others in the conjunctiva (Fig. 9.1). Involvement of the eyelid has also been described but appears less common (Stacy et al. 2010; Coupland et al. 1998; Knowles et al. 1990). These differences may stem from different selection criteria for biopsy at various institutions and the resulting bias in tissue sent for examination. RLH is unilateral in the majority of cases, but bilateral orbital lesions or unilateral lesions associated with RLH in other body sites (salivary glands, axilla) are not uncommon, and are most frequently the manifestation of an autoimmune disease such as Sjögren's syndrome.

The clinical manifestations of RLH vary and depend on the site of involvement. Patients with conjunctival lesions often complain of foreign body sensation and show superficial

A.D. Singh (ed.), *Ocular and Adnexal Lymphoma*, Essentials in Ophthalmology,
DOI 10.1007/978-3-642-38499-8_9, © Springer-Verlag Berlin Heidelberg 2014

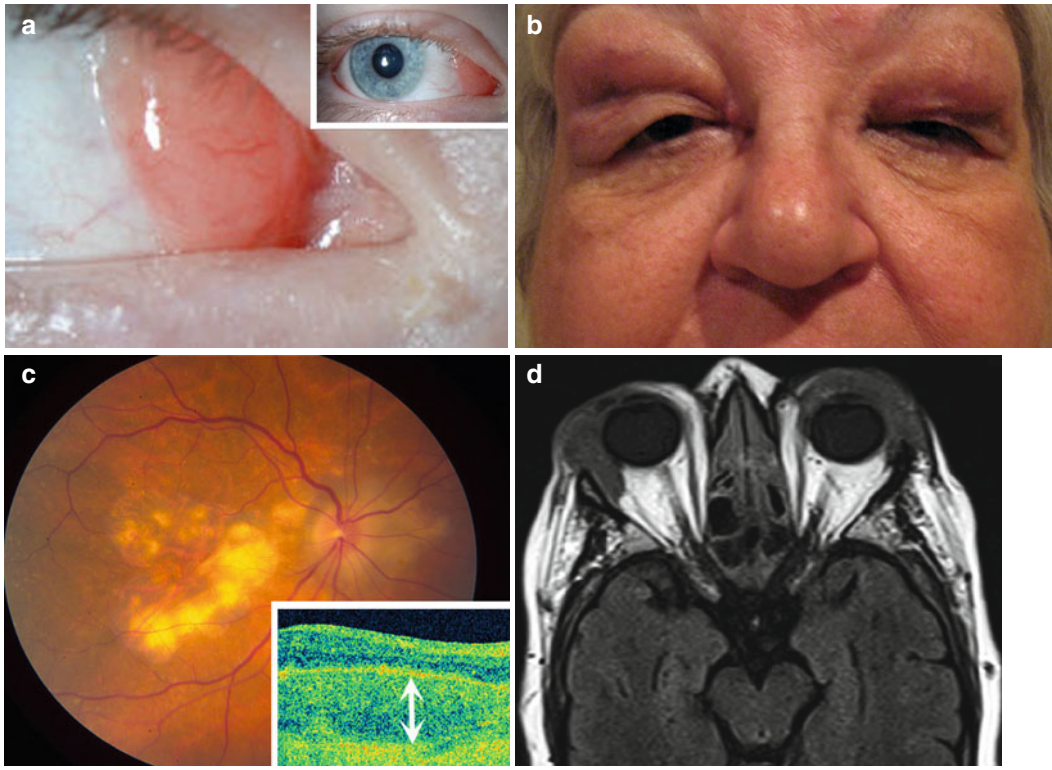

Fig. 9.1 Clinical presentations of reactive lymphoid hyperplasia. Salmon-patch lesion of the right eye which was biopsy proven RLH (**a**). Inset shows a lesion on the bulbar conjunctiva that was limited to the medial canthal region. Facial photograph of a patient with bilateral RLH of the lacrimal gland demonstrating fullness of both orbits and cheeks (**b**). Fundus photograph of the right eye of the same patient reveals creamy choroidal lesions consistent with uveal reactive hyperplasia (**c**). The inset demonstrates choroidal thickening observed on OCT (*arrow*). The left fundus and OCT revealed similar findings. MRI of same patient demonstrates bilateral lacrimal gland swelling (**d**). Reproduced with permission from: Stacy et al. (2010)

"salmon-patch" lesions. RLH involving the orbit or eyelid manifests with symptoms of swelling, fullness, exophthalmia, pain, and decreased visual acuity and may show palpable rubbery masses beneath the orbital rim on inspection. The size of the lesions is variable. CT imaging studies typically show one or multiple contrast-enhanced infiltrative masses in the eyelids or orbit, with molding to the ocular globe and other adjacent structures and extension along the rectus muscles. Features like mass heterogeneity and lack of bone destruction have been associated with RLH but lack sensitivity or specificity in distinguishing RLH from lymphoma (Westacott et al. 1991). On MRI, RLH lesions are enhanced with gadolinium, with T1-weighted signal that is hypo- or isointense and T2-weighted signal that is hyperintense to muscle. On ultrasound imaging, RLH appears as a variably shaped, regular acoustic structure with low to medium reflectivity.

The clinical and epidemiological characteristics of RLH described above are largely nonspecific and of little value for the differential diagnosis of lymphoma, which relies on histologic examination and molecular studies.

9.3 Etiology

The etiology of RLH is unclear. One hypothesis, based on knowledge from other organ sites, proposes that RLH represents a temporary benign precursor lesion with potential to progress to lymphoma. This theory postulates that RLH is initiated from a T-cell immunoregulatory imbalance that drives an exuberant proliferation of

B cells (Jakobiec 2008). The initially polyclonal B-cell proliferation, as hallmark for a benign lesion, may evolve in time to spawn multiple small B-cell clones (oligoclones), of which one may eventually come to predominate and form the basis for a neoplastic proliferation as in the case of marginal zone lymphoma. Whereas in stomach and small bowel chronic inflammatory stimulation produced by infections with *Helicobacter pylori* and *Campylobacter jejuni* has clearly been shown to carry a risk for progression to mucosa-associated lymphoid tissue (MALT) extranodal marginal zone B-cell lymphoma, no such association has been unequivocally proven for ocular and adnexal lymphoid proliferations. Some studies have reported a possible association between infection with *Chlamydia psittaci* and ocular lymphoid proliferations, in particular MALT lymphoma (Ferreri et al. 2005). However, several subsequent studies, including one from our institution, have failed to reproduce these results (Ruiz et al. 2007; Rosado et al. 2006; Vargas et al. 2006). Another infectious agent, proposed as causative in at least a group of RLH, is the Epstein-Barr virus, which in one case report was described as productive of a temporary and clonal B-cell proliferation in the conjunctiva that eventually disappeared without treatment. Such "reactive" EBV-induced B-cell clones complicate the initial histologic interpretation and act as a mimicker for lymphoma (Sharara et al. 2003).

A recent report described that an underlying multisystem inflammatory or autoimmune disease can be identified in approximately 50 % of RLH cases (Kubota and Moritani 2007). Of these underlying conditions, Sjögren's syndrome was the most frequent (4/7 cases), followed by Graves' disease, lupus erythematosus, and bullous pemphigoid (1/7 cases, each). Autoimmune diseases were identified also in patients with ocular MALT lymphoma but in a much lower proportion. The association between RLH and autoimmunity suggests again a possible role that chronic immune stimulation by autoimmune antigens may play into the development of polyclonal RLH which can potentially progress in a subset of cases to monoclonality and lymphoma. A recent case report attempted to illustrate such progression by describing a case of conjunctival MALT lymphoma in a patient with a contralateral lesion that was best classified histologically as RLH but revealed monoclonality on additional molecular studies (Fukuhara et al. 2012).

Other recent reports showed that in a number of RLH cases, subtle infiltration with plasma cells and focal fibrosis can be identified, as well as an increased serum IgG4:IgG ratio (Kubota and Moritani 2007; Matsuo et al. 2010). This group of patients had a different clinical history and diverse systemic associations than those with normal serum IgG4:IgG ratio, and the disease was shown to be occasionally associated with other IgG4-related conditions and even with B-cell clonality.

9.4 Histopathology

9.4.1 Light Microscopy

Reactive lymphoid hyperplasia (RLH) is regarded as a benign and reversible proliferation of lymphoid tissue, composed of an admixture of predominantly T cells and B cells with a polyclonal immunoglobulin profile. Most commonly, RLH presents as a dense infiltration of small, histologically bland lymphocytes with the formation of reactive lymphoid follicles of varying sizes, in an arrangement similar architecturally to that of a normal lymph node. Most follicles are round to oval but some may coalesce to form irregular-shaped structures. The germinal centers are expanded and composed of a mixture of centrocytes (small B cells with irregular or cleaved nuclei) and centroblasts (larger B cells with round to oval, non-cleaved nuclei and prominent nucleoli) (Fig. 9.2). The interfollicular areas are expanded, with prominent mantle zones. Other histologic features of RLH include prominent interstitial capillaries and the presence of admixed plasma cells, histiocytes, and rare eosinophils.

9.4.2 Immunohistochemistry (IHC)

Since the early 1980s IHC has emerged as an invaluable ancillary technique and is now commonplace in the standard diagnostic approach.

Relatively newer methods have been developed for detailed profiling of cell surface antigens like flow cytometry. The immunophenotypic profiling of lymphoid proliferations has greatly reduced the intra- and interobserver variability of morphologic interpretations and is essential for an accurate diagnosis.

Immunophenotypically (Fig. 9.2), the lymphocytes in RLH are a mixture of B cells (CD20-positive), mostly present in the follicles, and immunoregulatory T cells (CD3-positive, predominantly CD4-positive), primarily found in interfollicular areas and scattered in the follicular centers. Within the follicles, a meshwork of antigen-presenting follicular dendritic cells (CD21- and CD23-positive) is present, and tingible-body macrophages (CD68-positive) are also scattered in between B lymphocytes. Cell proliferation, as determined by the presence of mitoses or by IHC for the proliferation marker Ki67, is restricted to the germinal centers in a polarized manner. The reactive germinal centers are also positive for BCL6 (marker of B-cell activation) and CD10 (follicle center marker), and negative for BCL2 (antiapoptotic factor), which may only stain the rare T cells present in the follicles. BCL2 may also stain B cells in the mantle and marginal zone areas of the follicles' periphery. IHC for kappa and lambda immunoglobulin light chains usually shows a polytypic pattern of expression in the mantle zone B cells and the admixed plasma cells in the interfollicular areas.

Detecting the immunoglobulin light chain profile on B lymphocytes, while important diagnostically, is much more difficult by conventional IHC than on plasma cells in routine specimens. This is both because of the significantly lower expression of these proteins in B lymphocytes compared to plasma cells and due to antigen loss following formalin fixation resulting in high levels of background. An alternative and relatively newer method for detecting immunoglobulin light chain expression, chromogenic in situ hybridization (CISH), measures the intracellular levels of mRNA transcripts in formalin-fixed paraffin-embedded samples with significantly reduced background staining compared to IHC (Beck et al. 2003). Recent refinements of CISH methodology involving increased signal amplification boast a level of sensitivity approaching single molecule detection while maintaining a low background (Wang et al. 2012). On platforms like RNAscope (Advanced Cell Diagnostics), CISH for Ig-kappa/lambda mRNA expression is ideal for detecting light chain B-cell clonality patterns in lymphoid proliferations.

9.4.3 Flow Cytometry

When enough fresh material is available, flow cytometry analysis is an extremely useful method for analyzing the overall cellular composition (B, T, NK lymphocytes) and the detailed immunophenotype of the lymphoid proliferation, including the pattern of expression for kappa and lambda surface immunoglobulin light chains in B cells. With more recent improvements that allow the analysis of 6, 8, or more concomitant markers in a single tube, flow cytometry can identify very small abnormal cell populations comprising less than 1 % of the total events in the cell suspension, which could otherwise be missed on conventional IHC phenotyping. In one study, flow cytometry showed 94 % sensitivity and 96 % specificity for detecting clonal populations in ocular/orbital lymphoma lesions (Sharara et al. 2003).

Whereas polytypic B- and T-cell populations are the hallmark of benign lymphoid proliferations, caution is required when interpreting the data, as exceptions have been described. Apparent immunoglobulin light chain restriction was reported in a rare case of RLH that demonstrated positivity for EBV antigens, but was only temporary, resolving spontaneously with no therapeutic intervention (Sharara et al. 2003). Conversely, lymphoma is not automatically excluded by an apparent polytypic pattern of a lymphoid proliferation, which must be correlated with the histologic aspects and additional molecular studies (Sharara et al. 2003).

9.4.4 Polymerase Chain Reaction

Nucleic acid amplification by polymerase chain reaction (PCR) has replaced the lengthy Southern blotting methodology for detecting

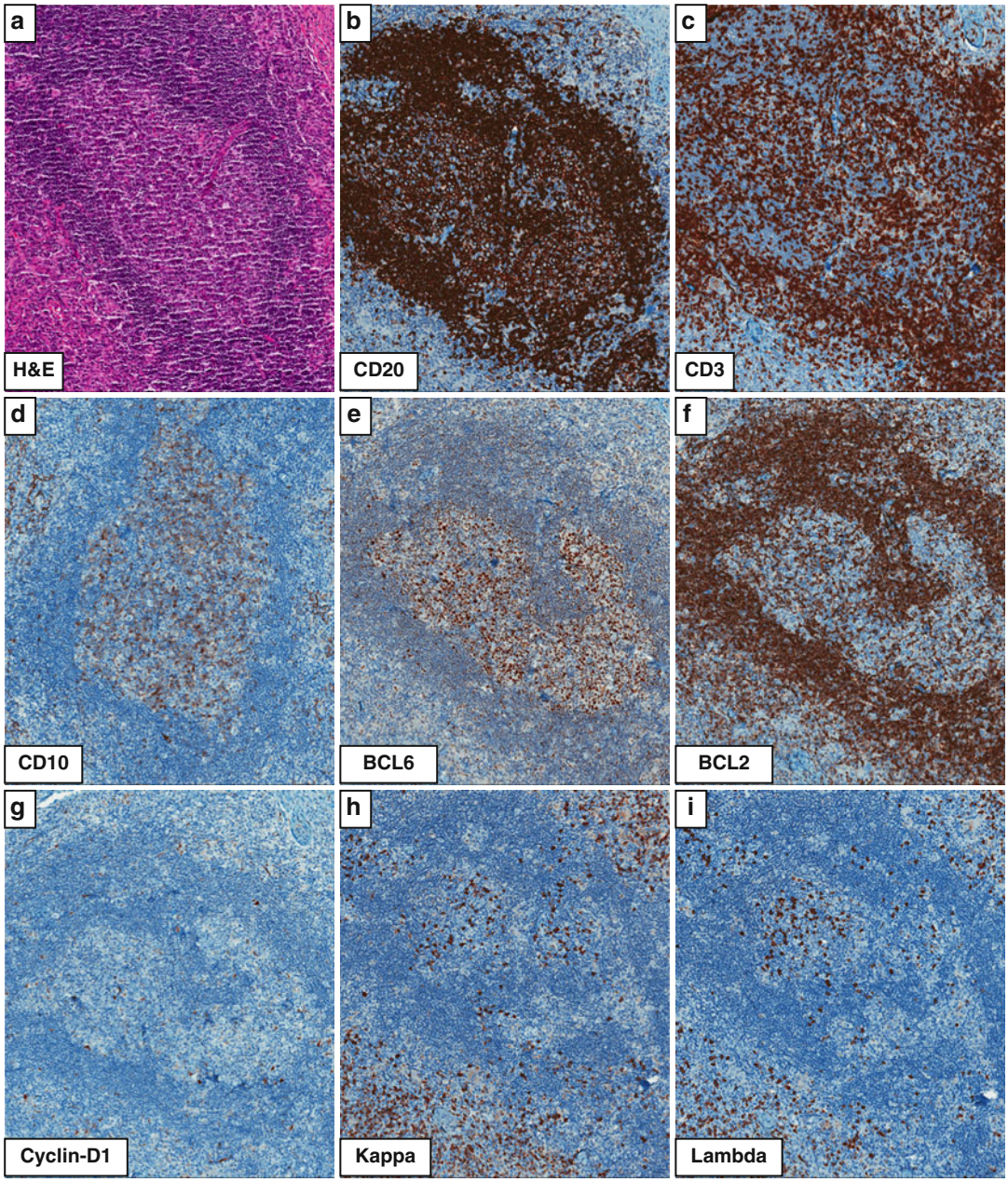

Fig. 9.2 Histologic and immunophenotypic features of reactive lymphoid hyperplasia. RLH is composed of reactive lymphoid follicles with prominent polarized germinal centers on H&E (**a**). The follicles contain mostly CD20-positive B cells (**b**). Scattered CD3-positive T cells are present in the interfollicular areas, mantle zone, and germinal center (**c**). The B cells in the germinal centers are CD10- and BCL2-positive (**d**, **e**). BCL2-positive B cells are present in the mantle zone but not in the germinal center (**f**). Cyclin-D1 is positive only in rare lymphocytes (**g**). Scattered plasma cells are polytypic for kappa and lambda immunoglobulin light chains (**h**, **i**)

clonal rearrangements of the immunoglobulin heavy chain locus (*IGH*), as well as *BCL2/IGH* rearrangements. Southern blots for T- and B-cell clonality require large quantities of DNA derived from frozen tissue, as the approach depends on predictable gel patterns produced via endonuclease digestion. Current clonality studies by PCR are performed on DNA extracted

from formalin-fixed paraffin-embedded tissue. Most studies have reported good to excellent sensitivities and specificities for this method for both systemic lymphoproliferative disorders and those involving the eye and orbit, including RLH (Mannami et al. 2001; Sharara et al. 2003; McKelvie 2010). However, correlation with histologic, IHC, and flow cytometry data is always required.

9.5 Differentiation Between RLH and Lymphoma

In the initial differential diagnosis of an OAL, several histologic features and patterns encountered in RLH lesions may mimic those of lymphoma and may complicate the interpretation and the subsequent ancillary work-up. Some of these features are summarized below.

Primary lymphoid follicles, devoid of germinal centers, and composed only of small monotonous-appearing naïve lymphocytes, with no intervening dendritic cells, may be present in RLH. Although these BCL2-positive follicles may appear malignant, they have reactive interfollicular areas and are negative for CD10 and BCL6, reflecting their lack of germinal center formation. They also lack large centroblasts as typically observed in certain types of lymphoma, follicular lymphoma in particular (see below).

Distinguishing RLH from certain types of lymphoma that can also display a follicular architecture is often difficult on morphology alone (Chap. 2). In follicular lymphoma, the follicles are more tightly packed, monotonous in size, often without a mantle zone, and are composed of monomorphic centrocytes. The follicle centers are characteristically positive for BCL2 and show a more diffuse cell proliferation. It has been described that rare BCL2-positive germinal centers in a background of seemingly RLH usually harbor monoclonal B-cell populations and constitute examples of early or "in situ" follicular lymphoma. In extranodal marginal zone lymphoma, the typical infiltrate consists of small lymphocytes with patchy clusters of plasma cells and monocytoid areas and scattered polykaryocytes (multinucleated cells, resembling follicular dendritic cells). Follicles, when present, can be intact or fragmented, with occasional "colonized" germinal centers best demonstrated by a CD21 or CD23 immunostain that highlights the follicular meshwork of antigen-presenting follicular dendritic cells. Infiltration of epithelial structures with resulting lymphoepithelial lesions is characteristic and permits distinction from other types of low-grade lymphoma. The neoplastic lymphocytes are negative for CD5, CD10, or cyclin-D1 in the majority of cases. Mantle cell lymphoma, a rare entity in the orbit, shows follicles with expanded mantle zones and diffuse infiltrates or colonization of normal follicles by small atypical lymphocytes that are characteristically positive for cyclin-D1.

9.6 Clinical and Pathologic Variants

9.6.1 Atypical Lymphoid Hyperplasia

The ambiguous category of atypical lymphoid hyperplasia (ALH) has been initially used to describe lymphoid proliferations with scattered large atypical cells, often with immunoblast morphology, increased interfollicular mitotic activity, or presence of small cells with irregular nuclear contours (Jakobiec et al. 1979). It has subsequently been used for lymphoid lesions with generally indeterminate histologic features such as diffuse proliferations of small mature lymphocytes without atypical features suggestive of neoplasia but also lacking germinal centers or mixed leukocyte composition indicative of a reactive process. The development of immunohistologic markers of molecular clonality has lessened the need for classifying lymphoid proliferations in the indefinite atypical category, as many lesions with "atypical" features can now be reliably classified directly as lymphoma on the basis of phenotypic or genotypic lymphocyte clonality. However, this category is still used by some authors to describe certain lymphoid lesions lacking B-cell clonality but with proliferating

behavior suggesting lymphoma. At our institution, this category is not used, and OAL with indeterminate histologic features are ultimately classified as RLH or lymphoma on the basis of Ig-kappa/lambda expression pattern and/or the presence or absence of clonal molecular rearrangements.

9.6.2 Progressive Transformation of Germinal Centers

A reactive process commonly associated with nodal follicular hyperplasia, progressive transformation of germinal centers (PTGC), is recently described also within the spectrum of ocular RLH (Amin and Ramsay 2012). It has been proposed that nodal PTGC is part of a progressive sequence starting with follicular hyperplasia, follicular lysis, and eventual PTGC caused by inward migration of T cells followed by mantle B cells. PTGC can be focal and limited to a small number of follicles or can be florid, involving numerous germinal centers. The inward migration of T cells and mantle B cells results in fragmentation of the germinal center into islands of centrocytes and centroblasts with obscuring of the mantle zone that gives the germinal center a "moth-eaten" edge. The pathogenesis of this process is unknown. PTGC has been associated with an increased incidence in nodular lymphocyte-predominant Hodgkin lymphoma (NLPHL). NLPHL is extremely rare in the orbit and is diagnosed by identifying the "lymphocyte-predominant" (LP) cells that are large, often surrounded by a collarette of CD3-, CD57-, and/or PD1-positive T cells, and are themselves positive for BCL6, occasionally positive for CD30 and negative for CD15 and CD20. PTGC must be differentiated from follicular colonization by small cell B-cell lymphomas, usually marginal zone lymphoma or rarely mantle cell lymphoma, leading to expansion of existing reactive germinal centers by small B cells. A helpful feature to distinguish between PTGC and B-cell lymphomas colonizing germinal centers is the clustering of T cells around the germinal center remnants in cases of PTGC. PTGC is usually associated with a background of RLH. Immunohistochemical staining for CD10 may help in distinguishing from follicular lymphoma, as only a few remnants of CD10 follicle center B cells are present in PTGC (Amin and Ramsay 2012).

9.6.3 Castleman's Disease

A benign inflammatory condition, Castleman's disease, has rarely been described affecting the orbit (Venizelos et al. 2010) and could in principle be considered a subtype of RLH. The disease is characterized by atrophied follicles with hyaline-vascular structures and expanded mantle zone in a characteristic "onion-skin" fashion. Mantle cell lymphoma, with prominent mantle zones, is in the differential diagnosis of this condition but is distinguished by the lack of hyaline-vascular lesions and cyclin-D1 positivity. Sclerotic follicles can be seen in follicular lymphoma, but in this neoplasm the mantle zones are not prominent, and the immunophenotype is characteristic with BCL2-positive germinal centers. The rare plasma cell variant of Castleman's disease has an increased association with several types of neoplasms including lymphoma.

9.6.4 Benign Inflammatory Conditions

Orbital "pseudotumor" is an inflammatory lesion of the orbit that, unlike RLH, is characterized by acute onset of ocular symptoms (pain, erythema, edema, loss of visual acuity) and a mixed inflammatory infiltrate composed of T and B cells, neutrophils, eosinophils, and prominent progressive vasculocentric fibrosis. The disorder is associated with systemic autoimmune diseases such as rheumatoid arthritis, inflammatory bowel disease, or Wegener granulomatosis and may be related to the IgG4-associated systemic disease (Origuchi et al. 2012).

Other systemic benign inflammatory conditions such as lupus erythematosus or Kikuchi-Fujimoto disease can also rarely affect the orbit, but the diagnosis should be prompted by the clinical presentation and the systemic involvement.

9.7 Treatment and Prognosis

The current treatment options for RLH lesions include a wait-and-watch approach or specific therapy. The latter option has no established definitive recommendations or guidelines for management but is most often adopted because of the location and symptomatology. An important aspect of management is monitoring for the risk of RLH to evolve to systemic lymphoma. Such risk has been estimated in older reports to be 27–29 % (Knowles et al. 1990; Knowles and Jakobiec 1980; Polito and Leccisotti 1996). Recent studies with more accurate diagnosis based on improved ancillary methods indicated the risk to be lower, less than 10 % (Mannami et al. 2001), and managed to more precisely distinguish RLH from neoplastic proliferations, showing a clear dichotomy in the clinical course of the two disease categories (Coupland et al. 1998; Sharara et al. 2003). Regardless of the treatment option and of the actual real chance of progression to lymphoma, careful clinical follow-up is still preferred and recommended in all cases of RLH. Specific therapy includes systemic corticosteroids, to which patients show an initial but often unsustained response. Surgical excision or cryotherapy may also be considered but carry the risk of scar formation and cosmetic alterations. Local radiotherapy, usually limited to 15–20 Gy, may also be effective for localized lesions. The recurrence rate for RLH after low-dose external beam radiotherapy has been reported at 5 % after 5 years follow-up in one study (Kennerdell et al. 1999). For lesions that are diffuse, refractory, or recurrent, the use of low-dose chemotherapy such as chlorambucil may be necessary for control.

Recent reports have described the successful use of biological response modifiers such as rituximab of bevacizumab in the treatment of RLH. Rituximab, a chimeric monoclonal antibody, targets the CD20 surface B-cell antigen. Rituximab is thought to promote the immune-mediated depletion of CD20-positive B cells and is approved for the treatment of several types of B-cell lymphomas, rheumatoid arthritis, and other autoimmune diseases. In the case of orbital RLH, rituximab therapy has been reported to result in 91 % responsiveness (Witzig et al. 2007), reduce the infiltrate size, and allow for consolidative radiotherapy (Talaulikar et al. 2010). Bevacizumab is an anti-vascular endothelial growth factor (VEGF)-A antibody approved for the treatment of metastatic colorectal cancer and studied as a treatment option for conditions that induce neovascularization of the ocular surface. Bevacizumab has been used successfully as an alternative therapy in a case of RLH with hypervascular infiltrates and medial limbal neovascularization that was not a candidate for surgical excision or radiation (Oh et al. 2011).

9.8 Summary

Representing the benign side of the OAL spectrum, RLH demonstrates clinical and radiologic features that are similar or indistinguishable from most lymphomas but require very different management and are associated with different clinical outcomes. The diagnosis of RLH and its imperative differentiation from lymphoma is ultimately accomplished by the pathologist based on histologic examination, supplemented with ancillary and invaluable immunophenotypic and molecular tools. Early detection, accurate diagnosis with improved methods, and new therapeutic options are promising factors for further improving the outcome of RLH and decreasing its risk of progression to lymphoma.

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