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Pathology of Vogt–Koyanagi–Harada disease

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Abstract Typical histopathologic features of Vogt–Koyanagi–Harada disease (VKH) include granulomatous panuveitis with preservation of the choriocapillaris and exudative retinal detachment. In the chronic stage of the disease, however, histologic changes consist of nongranulomatous uveitis followed, in the chronic recurrent stage, by granulomatous uveitis and involvement of the choriocapillaris. In chronic VKH the peripheral fundus scars are not Dalén–Fuchs nodules; they are, instead, indicative of focal chorioretinal atrophy with loss of retinal pigment epithelium.

Keywords Granulomatous uveitis · Vogt–Koyanagi–Harada disease · Sympathetic ophthalmia · Pathology · Choriocapillaris

Just as the clinical features of Vogt–Koyanagi–Harada disease (VKH) vary according to the stage of the disorder, the histopathologic features vary from a granulomatous panuveitis to a nongranulomatous choroiditis. The primary pathological feature of VKH is, however, diffuse thickening of the uveal tract caused by a nonnecrotizing granulomatous inflammation. This thickening is more prominent in the posterior part of uvea, the juxtapapillary choroid, gradually decreasing toward the equator and peripheral choroid. Inflammatory cell infiltration does not involve the choriocapillaris and the overlying retina. In the acute phase of VKH, retinal detachment with collection of subretinal fluid can be observed; such neurosensory detachment is not usually observed during the convalescent or chronic recurrent phases of the disease.

Histopathologic analysis of uveal granulomatous inflammations reveals infiltrations of mononuclear inflammatory cells, primarily lymphocytes, interrupted by focal aggregates of epithelioid histiocytes and multinucleated giant cells. The presence of epithelioid histiocytes marks the inflammatory process as a chronic granulomatous inflammation. Uveal granulomatous inflammations are usually divided into three distinct morphologic categories—first zonal, then sarcoidal, and finally diffuse.

Zonal granulomatous inflammation is characterized by three or more distinct zones of histologic change, typically including a central area of necrosis surrounded by epithelioid histiocytes or polymorphonuclear leukocytes. These latter cells, in turn, are surrounded by a zone of lymphocytes. The epithelioid cell zone may contain multinucleated giant cells. Zonal granulomatous inflammation is seen primarily in conjunction with infectious processes caused either by mycobacterium tuberculosis or by fungal elements, although immune processes such as rheumatoid arthritis and phakoanaphylactic endophthalmitis may also have a zonal pattern.

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In contrast, sarcoidal granulomatous inflammation consists of a discrete, well-delineated collection of epithelioid cells surrounded by lymphocytes. This granulomatous process is typically devoid of necrosis. Multinucleated giant cells can be observed at the site of epithelioid cell collections.

Diffuse granulomatous inflammation in indicative of lymphocytic infiltration throughout the uvea interrupted by focal collections of epithelioid histiocytes with or without multinucleated giant cells. This granulomatous process does not include necrosis and usually spares the overlying choriocapillaris. Typical examples of diffuse granulomatous uveitis include VKH and sympathetic ophthalmia (Fig. 1).

Inomata and Rao correlated the clinical features of VKH with histopathologic changes in five well-documented globes of patients in various stages of VKH [1]. They observed that the histopathologic changes that occur during the different stages of VKH include a granulomatous process in the acute phase and nongranulomatous inflammation during the chronic (convalescent) phase. The latter is typified by uveal infiltration of lymphocytes, few plasma cells, and an absence of epithelioid histiocytes [1]. During the chronic recurrent phase of the disease there is a granulomatous choroiditis with damage to the choriocapillaris.

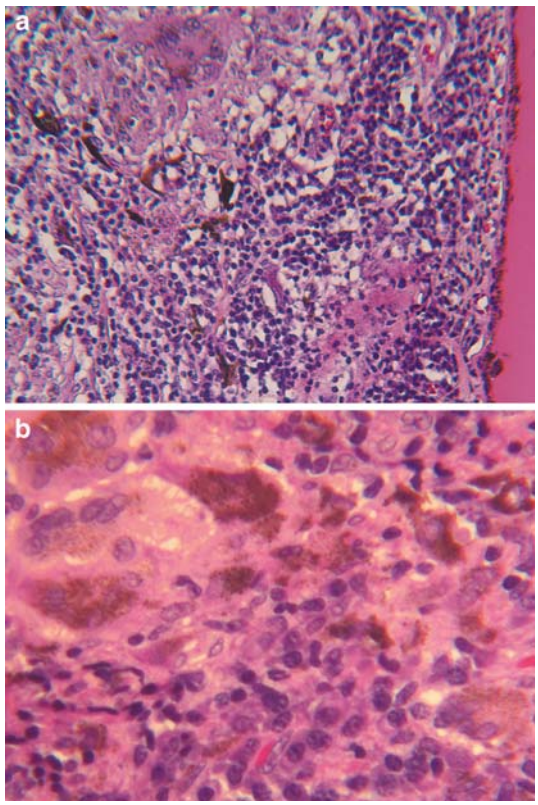

Fig. 1 Note diffuse non-necrotizing granulomatous inflammation with preservation of choriocapillaris (**A**). High magnification of the area adjacent to that depicted in (**A**) reveals multinucleated and epithelioid cells containing melanin pigment granules (**B**)

Acute uveitic stage

In the uveitic stage, the retina is detached from the retinal pigment epithelium (RPE). An eosinophilic exudate containing proteinaceous material is observed in the subretinal detached area. The choroid is diffusely infiltrated by lymphocytes, with focal aggregates of epithelioid histiocytes and multinucleated giant cells. Although there is no apparent uveal necrosis, the presence of intracytoplasmic uveal pigment granules is apparent in the macrophages, epithelioid cells, and giant cells. These histologic changes are virtually identical to those seen in sympathetic ophthalmia (Fig. 1). These melanin-containing cells have been studied extensively in eyes with sympathetic ophthalmia by using electron microscopic and immunohistochemical methods [2]. Ultrastructural analysis of these cells in sympathetic ophthalmia reveals mature individual melanin granules within the cytoplasm; immunohistochemical staining is positive for S-100 and muramidase and they bind to a lectin [2]. These observations indicate that the melanin-containing cells are histiocytic/macrophage in origin. The macrophages undergo morphologic changes and acquire a secretory function in the presence of activated T-cells and the cytokines of CD4+ T helper cells, for example γ-interferon, IL-1, IL-12 and others [2]. These altered macrophages are recognized histologically as epithelioid cells.

The exudative detachment typically seen during the uveitic stage of VKH indicates alterations in the RPE. Fluorescein angiography also reveals focal leakage at the RPE level in patients with acute stage VKH. Although at the level of light microscopy the RPE appears intact, during this acute phase lymphocytes can occasionally be seen under the RPE.

During this phase focal collections of mononuclear inflammatory cells noted under the elevated mounds of RPE represent formation of Dalén–Fuchs nodules [1]. These nodules consist of an mixture of lymphocytes, pigment-laden macrophages, epithelioid cells, and proliferated RPE cells, with altered histologic appearances, mimicking epithelioid histiocytes. These Dalén–Fuchs nodules are virtually identical to the Dalén–Fuchs nodules seen in sympathetic ophthalmia. Immunohistochemical studies reveal the presence of T suppressor/cytotoxic cells and macrophages in the Dalén–Fuchs nodules of sympathetic ophthalmia [3, 4]. Electron microscopic examination of such nodules shows altered RPE admixed with macrophages and lymphocytes [3].

In the acute stage of VKH, T-lymphocytes are seen in close proximity to uveal melanocytes. The melanocytes can express class II major histocompatibility complex, as noted in the convalescent stage of VKH disease [5, 6]. Such observations suggest that the melanocytes may play an active immunologic role in the development of uveitis and that they may potentially serve as antigen-presenting cells. Experimental studies by Yamaki et al. indicate tyrosinase peptides derived from the melanocytes could be the uveitogenic antigen in the induction of VKH disease [7].

Although extensive inflammatory cell infiltration occurs in the choroid during the acute phase of the disease, these inflammatory cells do not encroach on the choriocapillaris or retina. This feature is also virtually identical to that observed in sympathetic ophthalmia. The inflammatory cells in the vitreous vary in numbers. These cells seem to extend from the pars plana region, probably entering the vitreous through this site. The ciliary body is also infiltrated by a diffuse granulomatous process and both pigmented and nonpigmented ciliary epithelial layers are involved in the inflammatory process. As in the pars plana region, the inflammatory cells may gain access to the vitreous by passing through these epithelial cells. Either granulomatous inflammation or diffuse lymphocytic infiltration may be observed in the iris. Inflammatory infiltration is seen predominantly in the iris stroma. Although both the iris and the ciliary body are infiltrated by inflammatory cells, the infiltrate is less severe at these sites than the choroidal infiltration in the juxtapapillary region of the choroid.

Convalescent (chronic) stage

The convalescent stage is characterized by mild to moderate nongranulomatous inflammatory cell infiltration, usually with focal aggregates of lymphocytes containing occasional macrophages (Fig. 2). The choroid is depigmented at this stage, displaying spindle cells devoid of melanin granules [1]. Such findings indicate damage of the choroidal melanocytes with loss of melanin pigment. The RPE, however, seems to be intact with the normal complement of melanin granules. On clinical examination, the above changes appear as the characteristic ''sunset glow'' fundus of VKH. The other remarkable change during this chronic phase consists of numerous peripheral choroidal depigmented small atrophic lesions involving the overlying choriocapillaris, the RPE, and the outer retina [1]. In the past such depigmented lesions were erroneously thought to be Dalén–Fuchs nodules. Histopathologic analysis of the lesions reveals focal RPE loss with chorioretinal adhesions, however (Fig. 3). Such histologic changes explain the clinical observation of a window defect at the level of RPE as seen on fluorescein angiography.

According to Inomata and Rao, the depigmented atrophic lesions are smaller and more numerous than the occasional Dalén–Fuchs nodules seen during the acute uveitic stage or during the convalescent stage [1]. Although these researchers found no Dalén–Fuchs nodules at the periphery, this was the primary site for the atrophic lesions. On basis of such

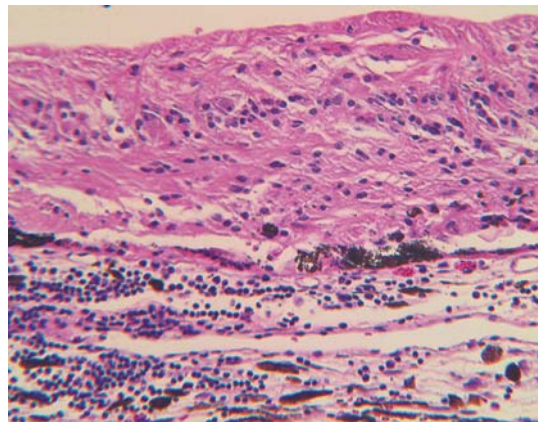

Fig. 2 Nongranulomatous inflammation reveals lymphocytic infiltration of the choroid

observations, Inomata and Rao concluded that the atrophic lesions seen in the peripheral fundi with a sunset glow appearance are not Dalén–Fuchs nodules [1] (Table 1).

Chronic recurrent stage

The chronic recurrent stage is characterized by a diffuse uveal infiltration consisting of a granulomatous process similar to that seen in the acute stage. The uveal thickening in the chronic recurrent stage is less prominent, however, and at this stage no retinal detachment is observed in enucleated eyes. Chorioretinal adhesions, with atrophy and/or proliferation of RPE, are common in the chronic recurrent stage [1]. The RPE proliferation tends to have a sessile papillary or tubular pattern preserving the morphologic features of epithelial cells, including apical microvilli and basal lamina, which are revealed by electron microscopy. Such proliferated RPE has the clinical appearance of hyperpigmented changes on opthalmoscopic examination. The RPE proliferation may be accompanied by the formation of subretinal neovascular channels and mound-like pigmented lesions that occasionally simulate pigmented neoplasia [8].

In other instances the hyperplastic RPE, devoid of pigmentation, may be clinically reorganized as subretinal fibrosis. The primary pathology of the subretinal fibrosis consists of metaplastic proliferated RPE, however [1]. In association with the RPE changes, photoreceptor degeneration and gliosis may be observed in the overlying neural retina. At this stage, the choriocapillaris is involved in the degenerative process, and chorioretinal adhesions are apparent at these sites [1].

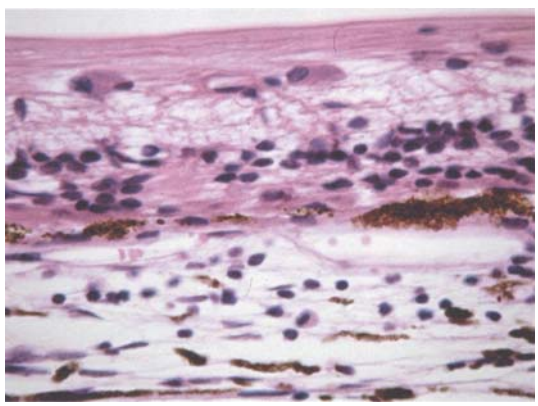

Fig. 3 Note the atrophic chorioretinal lesions in the peripheral fundus during the chronic stage of VKH

In the past researchers have emphasized that the choriocapillaris is absent in sympathetic ophthalmia but is involved in VKH [9]. This erroneous conclusion was based on examination of globes that were removed during the chronic recurrent stage of VKH as a result of complications such as cataract and glaucoma. In contrast, eyes with sympathetic ophthalmia were removed during the acute stage of the disease, not associated with complications. As reported by Inomata and Rao [1], examination of enucleated globes during the acute stage of VKH disease reveals preservation of choriocapillaris and granulomatous inflammation virtually identical to the findings seen in sympathetic ophthalmia other than the penetrating ocular injury (Table 2).

The classic histopathologic finding in VKH disease and sympathetic ophthalmia is the presence of Dalén–Fuchs nodules. These nodules are, however, relatively rare in enucleated globes with either VKH or sympathetic ophthalmia. Dalén–Fuchs-like nodules are, moreover, also seen in cases of sarcoidosis and other granulomatous choroiditis. Typical Dalén–Fuchs nodules have a hemispherical mound of proliferated RPE cells admixed with histiocytes and epithelioid mononuclear cells between the RPE and Bruch's membrane. This cellular composition of Dalén–Fuchs nodule depends on the stage of the disease; in the acute stage of VKH, the nodules contain mainly lymphocytes and macrophages, whereas in the convalescent stage, the nodules are made up of proliferated RPE with few inflammatory cells [1]. During the chronic recurrent stage, the nodules may be calcified, with homogenous basophilic staining in the section stained with hematoxylin–eosin [1].

Extraocular changes

Under the microscope the areas of cutaneous depigmentation that occur in VKH (vitiligo) contain focal aggregates of lymphocytes, mainly around the sweat glands, hair follicles, and small blood vessels of the dermis. The melanin-laden cells that are normally

Table 1 Dalén–Fuchs nodules differ from peripheral atrophic lesions noted in the convalescent phase of VKH

VKH	Dalén–Fuchs nodules	Peripheral atrophic lesions
Acute stage	Present	Absent
Distribution	Mainly in the posterior pole and equator	Present in the periphery
Number of lesions	Few	Numerous
In association with sunset glow fundus	No	Yes
Histology	Collections of lymphocytes, and histiocytes under proliferating RPE, forming Small nodules measuring 370 μm	Loss of RPE with chorioretinal adhesions, measuring 50–125 μm

Table 2 Comparison of histopathologic features of VKH and Sympathetic ophthalmia

Histopathology	VKH	SO
Diffuse granulomatous uveal inflammation	Yes	Yes
Absence of necrosis	Yes	Yes
Sparing of choriocapillaris in acute phase	Yes	Yes
Dalén–Fuchs nodules	Yes	Yes
Chorioretinal scars/adhesions in chronic recurrent phase	Yes	Yes
Loss of melanocytes in chronic phase	Yes	Yes
Penetrating injury	No	Yes

distributed along the basal layer of the epidermis are disrupted; at the site of vitiligo they are absent. Also at the site of vitiligo dermal inflammatory infiltrate may contain melanin-containing macrophages. The inflammation is made up of macrophages and T-cells, similar to the changes noted in the uvea. Most T cells express CD4 molecules; some express CD8. Histologically the alopecia reveals mononuclear cell infiltration with a release of melanin pigment from the matrix into the dermal papillae and surrounding perifollicular sheaths of hair follicles. The lymphocytic infiltration around the hair follicle is primarily made up of T-cells.

In summary, the histopathologic features of VKH include granulomatous, diffuse, and non-necrotizing infiltration of the uvea, The choriocapillaris is preserved in the acute uveitic stage but this vascular component becomes involved during the chronic recurrent stage of the disease. The choroidal melanocytes are damaged by the inflammatory process, and loss of these melanocytes clinically manifests as a sunset glow fundus. Histopathologic observations and immunohistochemical findings suggest that VKH is a T-cell altered immune process that is directed at the melanocytes. With the exception of the inciting penetrating injury characteristic of sympathetic ophthalmia, the pathologic features of VKH and sympathetic ophthalmia are virtually identical.

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