3 Histopathology of Choroidal Neovascularization

Evangelina Esposito, Julio A. Urrets-Zavalia, and Pablo Zoroquiain

3.1 General Histopathology of CNV

The globe is composed of three layers: fibrous sheet, vascular sheet, and nervous sheet. The first is composed of the cornea and the sclera, and provides the structure of the eye. The second, called the uveal tract, is composed of the iris, ciliary body, and the choroid. The third is composed of the retina. The choroid is a pigmented and highly vascularized component of the uveal tract in the eye, allowing for light absorption and providing oxygen and nutrients to the outer retina. Anatomically, the choroid extends from the ora serrata to the optic nerve head and is located at the posterior two-thirds of the eye between the sclera and retina. Anteriorly, it is followed by the ciliary body and the iris. Its thickness varies in humans from 0.1 mm anteriorly and 0.22 mm posteriorly (Fig. 3.1); however, it decreases by age 90 to about 80 μm [1]. The choroid is composed of vessels that are derived from the anastomosis of branches of the ophthalmic artery. These are the posterior ciliary arteries, and penetrate the sclera posteriorly, approximately 6 mm far from the optic nerve. The arteries then branch into terminal arterioles that feed the choriocapillaris. These subsequently drain into venules that merge to form the 4–5 vortex veins at the equator of the sclera [2].

The choroid and the retina are anatomically and functionally related, the retinal pigmentary epithelium (RPE), photoreceptors and the choriocapillaris are described as a functional unit [3]. Choroidal neovascularization is controlled by a dynamic balance between membrane-bound and diffusible substances with properties that either promote or inhibit blood vessel development [4].

Choroidal neovascularization is a major cause of blindness, and is characterized by the three patterns of growth of newly formed vessels from the choriocapillaris through Bruch's membrane, infiltrating sub-RPE space (type 1) (Fig. 3.2), between retina and RPE (type 2) or combined (type 3) [5]. The mechanism of this neovascularization is not well elucidated.

Any damage in the Bruch's membrane or RPE may lead to CNV, which represents an altered healing process secondary to a chorioretinal injury. In this scenario, no single cause for CNV

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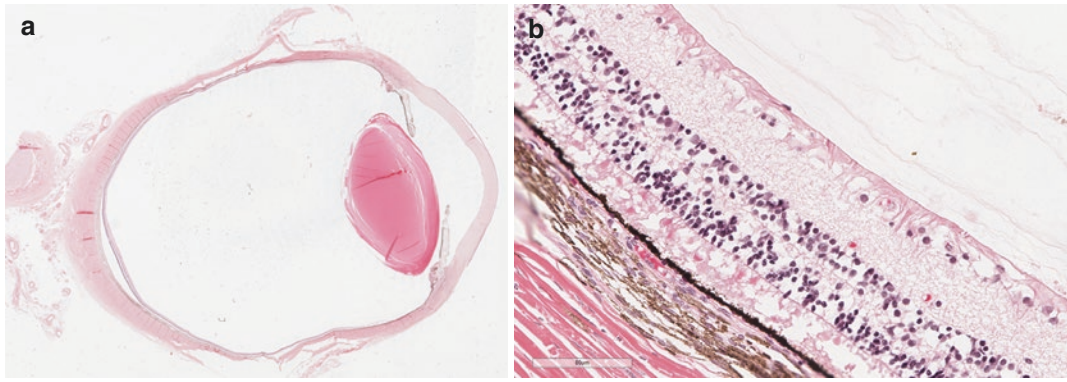

Fig. 3.1 Histology of the choroid. (**a**) The choroid is the posterior aspect of the uveal tract, located between the retina and the sclera (7×). (**b**) The sclera, choroid, and retina (400×)

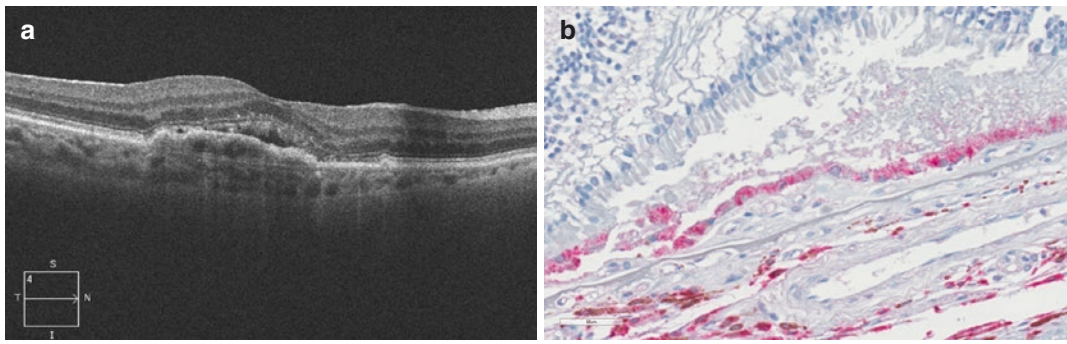

Fig. 3.2 Choroidal neovascularization. (**a**) SD-OCT image showing sub-RPE proliferation. (**b**) The histopathology of CNV, note the fibrovascular membrane located between Bruch's membrane and RPE. Bruch's membrane in this image is thickened and showed some external excrescences (400×)

is identifiable. Rather, it represents a broad spectrum of conditions arising from different etiologies. On light microscopy, different amounts and types of blood vessels, inflammatory exudate or infiltrate, fibrosis and scaring process are seen. A spectrum of findings can be found, with more "active" lesions, similar to any other granulation tissue or more "scarring" lesions on the other side. On electron microscopy, the most common cellular components are RPE, macrophages, erythrocytes, fibrocytes, and vascular endothelium. The most common extracellular components are 24-nm collagen and fibrin [6]. Clinically, this altered healing process is called CNV membranes. If this repair process is composed only by fibrous tissue without the proliferation of vessels above Bruch's membrane (or the blood vessels are fully regressed) the term scar is used.

In each disease, CNV may be accompanied by findings associated with the primary injury. In children and young adults, the development of CNV usually is secondary to choroidal osteoma, pathologic myopia, punctate inner choroidopathy, hereditary macular dystrophy, and angioid streaks but may also be idiopathic [7].

3.2 Inflammatory Associated CNV

Both infectious and noninfectious uveitic entities can lead to CNV [8]. Of the clinically evident inflammatory CNV, the vast majority are classic CNV on fluorescein angiography and type 2 CNV on optic coherence tomography imaging (OCT) [9, 10]. Inflammatory associations of

CNV are usually related to breaks in RPE or Bruch's membrane. Moreover, they are usually associated with granulomas, scars, or choroidal granulomas [11].

3.2.1 Non-granulomatous Inflammation

On histopathology, non-granulomatous processes can be defined as a predominantly exudative and distortive process. Contrary to this, proliferative changes are subtle (i.e., granulomas, lymphoid aggregates, exuberant granulation tissue). As a sequela of uveitis, the choroid may show focal or diffuse areas of atrophy or scarring. Retinochoroiditis or chorioretinitis may destroy Bruch's membrane and the retinal pigment epithelium. Due to the fact that the regenerative capabilities of these tissues are poor, most cases will develop CNV with the possibility of fibrosis and chorioretinal fusion [9].

3.2.1.1 Presumed Ocular Histoplasmosis Syndrome (POHS)

In focal disease processes, such as POHS, antigen deposition in the area of the Bruch's membrane leads to a focal inflammatory response, a break in the Bruch's membrane, and granulation tissue proliferation (CNV) into the subretinal space [5]. CNV may appear peripapillary (Fig. 3.3) or juxtafoveal, and is known to be a prominent feature in POHS [12, 13].

3.2.1.2 Punctate Inner Choroidopathy (PIC)

PIC is a multifocal choroiditis that affects young myopic women. It presents with blurred vision, photopsias, or paracentral scotomas. Multiple small, round, subretinal yellow-white lesions are observed in the posterior pole that heal and subsequently form small atrophic scars. Sometimes, a shallow neurosensory detachment may overlay the lesions. CNV may complicate PIC in more

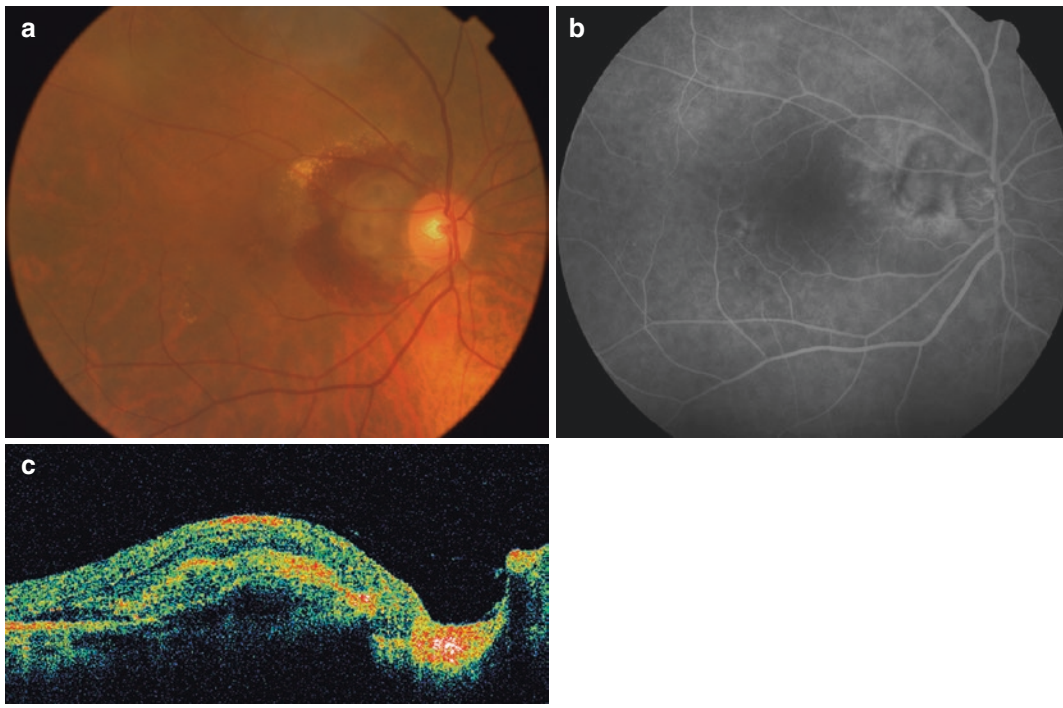

Fig. 3.3 Peripapillary CNV (**a**) Funduscopic image (**b**) Fluorescein angiography (**c**) OCT image

than 50% of cases, and they develop within 1 year of initial disease [9].

3.2.1.3 Serpiginous Choroiditis (SC)

Serpiginous choroiditis is a rare chronic, progressive, recurrent, bilateral asymmetric, posterior uveitis of unknown etiology. It is very important to differentiate between classic SC and serpiginous-like choroiditis before initiating aggressive immunomodulatory therapy, knowing the relationship of the latter with tuberculosis [14].

The disease extends centrifugally from the peripapillary region toward the posterior pole. Visual acuity may be severely compromised when the disease progresses through the macula, or when a submacular CNV membrane develops. CNV complicates serpiginous choroiditis in up to 35% of cases. As it occurs within an area of chorioretinal disturbance, it is sometimes difficult to detect clinically, and is more readily detected by fluorescein angiography and OCT.

3.2.1.4 Acute Posterior Multifocal Placoid Pigment Epitheliopathy (APMPPE)

APMPPE is a rare inflammatory bilateral intraocular disease that affects generally healthy young adults, characterized by sudden onset of paracentral scotomas, photopsia, and blurred vision, and the appearance of multifocal yellowish-white placoid lesions of different sizes in the posterior pole and mid-periphery. Visual symptoms recover after a course of a few weeks, and healing of fundus lesions leaves a mottled RPE or an irregularly pigmented and atrophic chorioretinal scar [15]. In the acute phase, on fluorescein angiography lesions show early hypofluorescence followed by late hyperfluorescence (Fig. 3.4). Very rarely, a CNV membrane may develop within an area of a healed lesion [16].

3.2.1.5 Behçet's Disease

Behçet's disease (syndrome) is characterized by retinal vasculitis, recurrent bilateral iridocyclitis with hypopyon, aphthous ulcers of the mouth and genitalia, dermatitis, arthralgia, thrombophlebitis, and neurologic disturbances. The disease is most common in men, especially between the ages of 20 and 30 years.

Pathological examination of the eyes diagnosed as Behçet's disease show a serohemorrhagic exudate containing polymorphonuclear leukocytes in the vitreous and in the anterior and posterior chambers. There are extensive areas of retinal necrosis. Depending on the stage of the disease, mononuclear and polymorphonuclear leukocytes can be found in the choroid. The choroidal infiltrate is predominantly composed of CD4 T lymphocytes, with some B lymphocytes and plasma cells (Fig. 3.5). If retinal necrosis affects Bruch's membrane it may develop CNV.

3.2.1.6 Pars Planitis

This disease usually affects children or young adults. The histopathologic features include detachment and collapse of the vitreous body with fibrous organization of the vitreous base, chronic inflammatory cells in the vitreous, edema of the optic nerve head and macula, retinal phlebitis and periphlebitis, preretinal membranes associated with breaks in the internal limiting membrane, anterior traction of the peripheral retina, and no significant choroiditis, cyclitis, or peripheral chorioretinal atrophy (Fig. 3.6) [17]. Choroidal neovascularization is a rare complication of intermediate uveitis, and pathophysiologic consideration suggests that chronic disc edema may be a risk factor for this condition [18].

3.2.2 Granulomatous Inflammation

Granulomatous inflammation is a type of chronic inflammation characterized by a cellular infiltrate of histiocytes. In addition, lymphocytes, plasma cells, and polymorphonuclear cells, such as eosinophils and neutrophils may be also observed [19, 20].

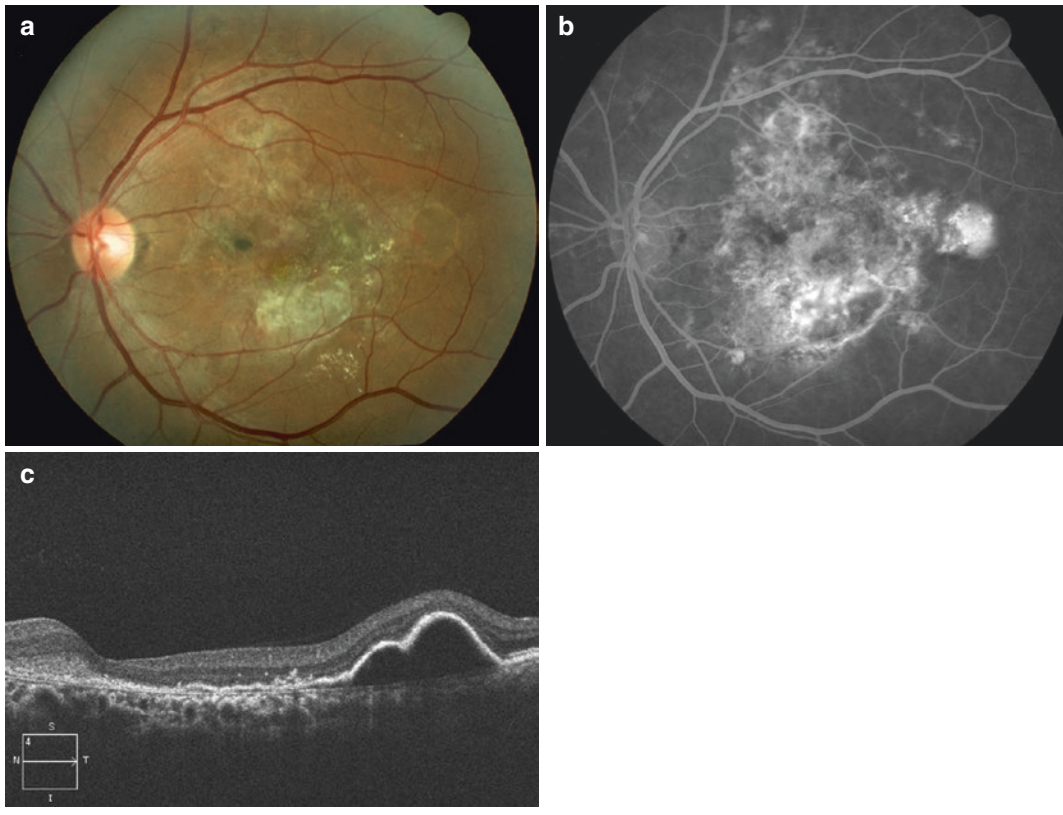

Fig. 3.4 Acute posterior multifocal placoid pigment epitheliopathy (**a**) Funduscopic image (**b**) Fluorescein angiography (**c**) SD-OCT image

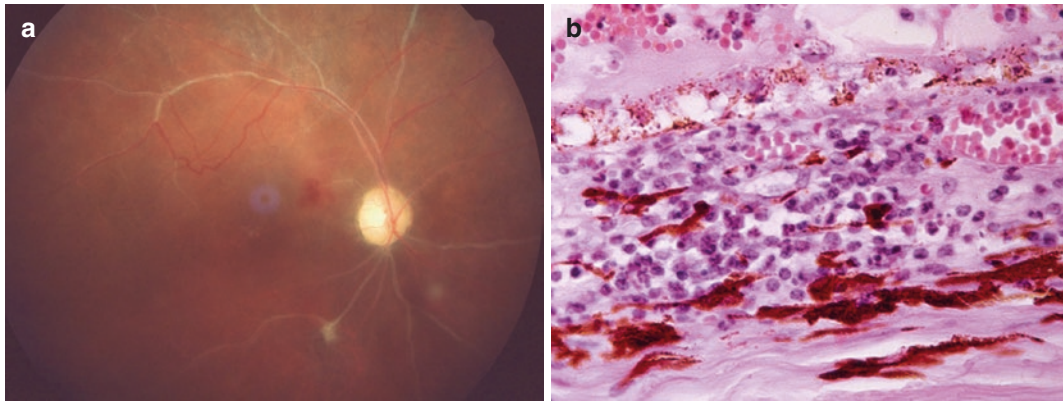

Fig. 3.5 Behçet's disease (**a**) Funduscopic image (**b**) Full thickness choroidal inflammatory infiltrate composed of lymphocytes, neutrophils, and plasma cells are seen. No vasculitis is present. Reprinted from Choroidal Disorders, 1st edition, Esposito, et al, Choroidal Histopathology, Pages No. 21-48, Copyright 2017, with permission from Elsevier

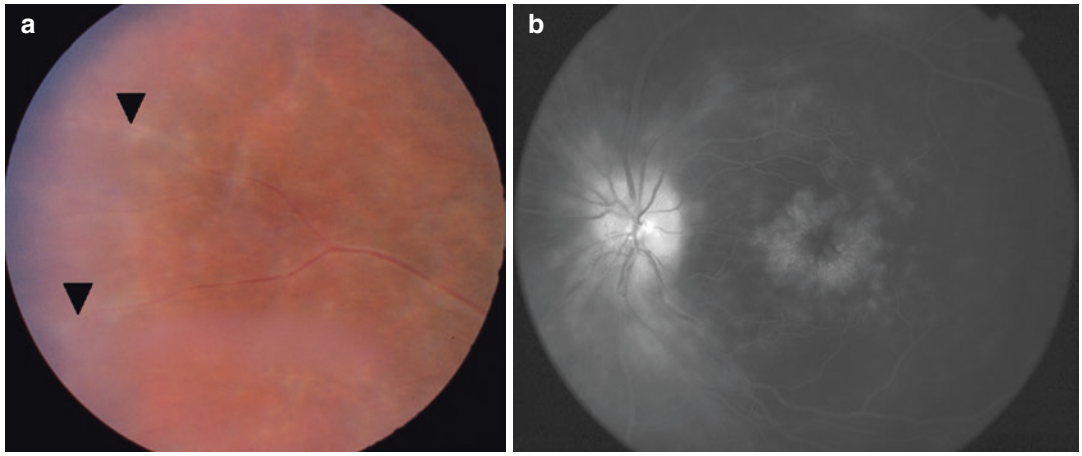

Fig. 3.6 Pars planitis (**a**) Funduscopic image showing peripheral vasculitis (arrowheads) (**b**) Fluorescein angiography showing macular edema

3.2.2.1 Toxoplasmosis

Ocular toxoplasmosis is a parasitic infection of the eye caused by the protozoan *Toxoplasma gondii*. Infections may be congenital or acquired through the ingestion of uncooked and infected meat, contaminated vegetables or water [21].

This disease typically affects the posterior pole of the eye and the lesions can be solitary or multiple and can further be subclassified as active or scaring. Active lesions are gray-white and accompanied by exudation, vasculitis, and choroiditis (Fig. 3.7).

The normally clear vitreous is compromised and becomes hazy due to the infiltration of inflammatory cells. The patient will generally not complain of pain, but rather of an increase in floaters and a possible decrease in vision in the affected eye [22]. The scarring begins from the periphery of the lesion, and progresses toward the center with variable pigmentation changes [23].

T. gondii primarily affects the retina and secondarily the choroid, although choroidal lesions do not occur in the absence of retinal infection.

Histopathological confirmation may be obtained by chorioretinal biopsies, and more rarely, enucleation. The toxoplasma cysts, bradyzoites, and tachyzoites can be identified with hematoxylin and eosin (H&E), immunohistochemistry, or by PCR [24]. However, the majority of the cases are diagnosed clinically and CNV complication is uncommon [25]. Although the parasite is confined to the retina, breaks in Bruch's membrane will permit the contact of the choroid with the infectious antigen, thereby causing an inflammatory response. This may lead to CNV that appears at the border of the scar and the healthy retina [25].

Ocular toxoplasmosis often presents as extensive granulomatous inflammatory infiltration of the choroid and areas of necrosis in Bruch's membrane. In immunocompromised patients, the inflammatory infiltrate may be minimal or absent. Therefore, the focal areas of necrosis are important clues to make the correct diagnosis of toxoplasmosis [24].

3.2.3 Tuberculosis

Tuberculosis is an infectious disease caused by the acid-fast bacilli *Mycobacterium tuberculosis* and is characterized pathologically by the formation of granulomas with a central area of caseous necrosis. The most frequent route that the bacilli reaches the eye is through the bloodstream [19].

In posterior uveitis caused by tuberculosis, the ocular changes can be divided into four groups: choroidal tubercles, choroidal tuberculoma, subretinal abscess, and serpiginous-like

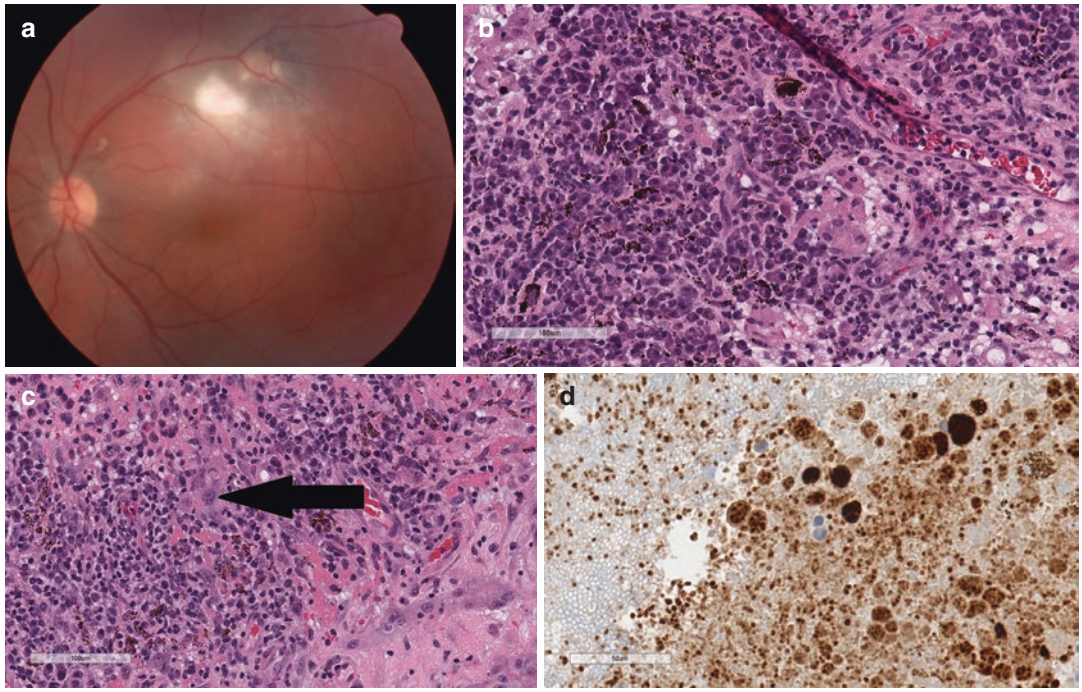

Fig. 3.7 Toxoplasmosis (**a**) Funduscopic image (**b**) The inflammation extends to the inner part of the choriocapillaris. Note the dense lymphocytic and plasmocytic reaction of the choroid and the multinucleated giant cell (arrow) H&E 200×. (**c**) Bradyzoites cyst (arrow) H&E 200×. (**d**) The microorganisms are highlighted with anti-toxoplasmosis immunohistochemistry (DAB 200×)

choroiditis (SLC) [26]. The exact mechanism of SLC in tuberculosis remains unknown. It may represent an immune-mediated hypersensitivity reaction (type IV) without the presence of acid-fast bacteria in the choroid or retinal pigment epithelium [26]. The lesions are usually multifocal, bilateral, noncontiguous to optic disc, and are commonly associated with mild vitreous inflammation. There are two distinct clinical patterns: discrete, multifocal choroiditis lesions that are initially noncontiguous but later progress to form diffuse lesions with an active edge, resembling serpiginous choroiditis; and less commonly, a solitary, plaque-like lesion. Neovascularization, when present, has been reported as Type 1 (sub-RPE) [27].

The disease is characterized pathologically by the formation of one or multiple granulomas [28]. The histology of the granuloma reveals central necrosis surrounded by histiocytes/epithelioid cells mixed with multinucleated giant cells, Langhans type, and a rim of small lymphocytes (Fig. 3.8).

These inflammatory phagocytes in turn are surrounded by lymphocytes. The necrotic area usually contains few bacteria, which can be visualized on Ziehl–Neelsen acid-fast stain as red rod-shaped organisms. However, several organisms can also be seen in the necrotic macrophages that line caseous necrosis. In some granulomas, the organisms can be seen in multinucleated giant cells (Fig. 3.3) or more frequently, they may not be detected by the histologic staining techniques [26]. Currently PCR-based diagnostic tools are highly sensitive and specific [29].

In the choroid, these tubercles/tuberculomas may involve all layers of the choroid. In the early stages, the overlying RPE remains normal but is disrupted during later stages as the tubercles increase in size. The surrounding choroid is essentially normal except for some lymphocytic infiltration [26, 30–33].

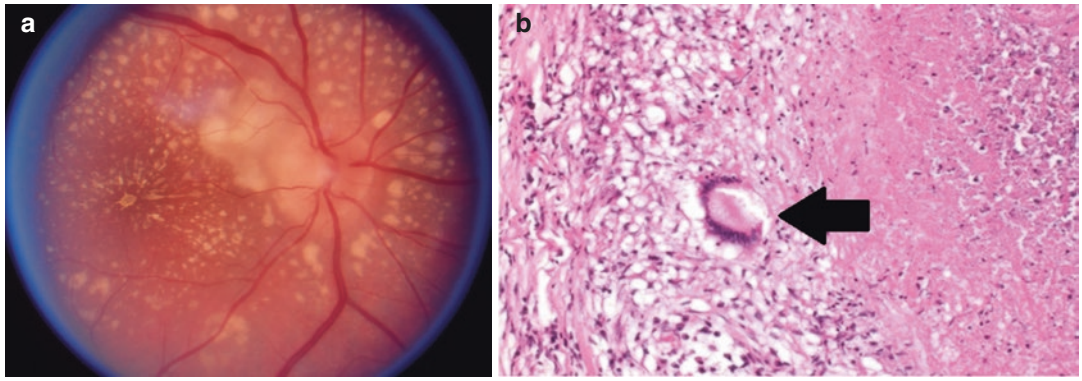

Fig. 3.8 (**a**) Fundus image of the left eye of a patient with tuberculosis (**b**) Chronic choroidal granulomatous inflammation with caseous necrosis and Langhans multinucleated giant cells (arrows). A rim of lymphocytes surrounding the granuloma is seen

3.2.4 Vogt–Koyanagi–Harada (VKH) Syndrome

Vogt–Koyanagi–Harada (VKH) syndrome is a bilateral granulomatous uveitis that is associated with integumentary, auditory, and central nervous manifestations [34].

The pathogenesis underlying VKH is thought to be autoimmune, with T cells mounting a response against melanocytes. There are acute and chronic stages of the disease, with the former responding well to corticosteroid treatment; chronic disease may have recurrent bouts of acute activity [35]. In the eye, VKH presents with posterior uveitis or diffuse granulomatous panuveitis, in association with serous exudative detachment and disc hyperemia, secondary to increased permeability and leakage of the choroidal vessels [34, 36]. Anterior segment inflammation can also occur concomitantly with subclinical posterior uveitis [37]. Chronic VKH can lead to the pathognomonic sunset glow fundus, corresponding to the degeneration of the retinal pigment epithelium [38].

Chronic VKH can also result in peripapillary atrophy [36] and subretinal fibrosis leading to neovascularization, which are poor prognostic factors [39]. Submacular choroidal neovascularization may be another cause of significant vision loss in VKH syndrome and may occur in up to 9% of cases [9, 40]. Type 2 accounts for all cases of CNV complicating these cases [9] and the macular and peripapillary areas seem to be the most frequently affected areas by this complication [41].

The histopathology of the choroid depends on the stage of the disease. In acute VKH, there is generalized granulomatous inflammation of the choroid with uveal thickening [42]. This is due to the infiltration with lymphocytes, macrophages, epithelioid cells [36], and plasma cells. The sensory retina may be detached from the pigment epithelium by a protein exudate with eosinophils [43]. Dalen-Fuchs nodules, which are clusters of macrophages and RPE cells located over Bruch's membrane, may also be observed (Fig. 3.9) [35]. In the early stages, the choriocapillaris is usually spared.

In contrast, the choroidal inflammation in chronic VKH is non-granulomatous [38]. Infiltrates are still primarily lymphocytic, and there is marked thinning of the uvea. There may be obliteration of the choriocapillaris. Dalen-Fuchs nodules are absent; instead, there is loss of the melanin granules in the retinal pigment epithelium. Nearby these are focal areas of hyperpigmentation, which are compensatory hyperproliferations of RPE; these tend to be arranged in papillary or tubular patterns [35]. Chronic recurrent VKH resembles acute VKH on histopathology, characterized by granulo-

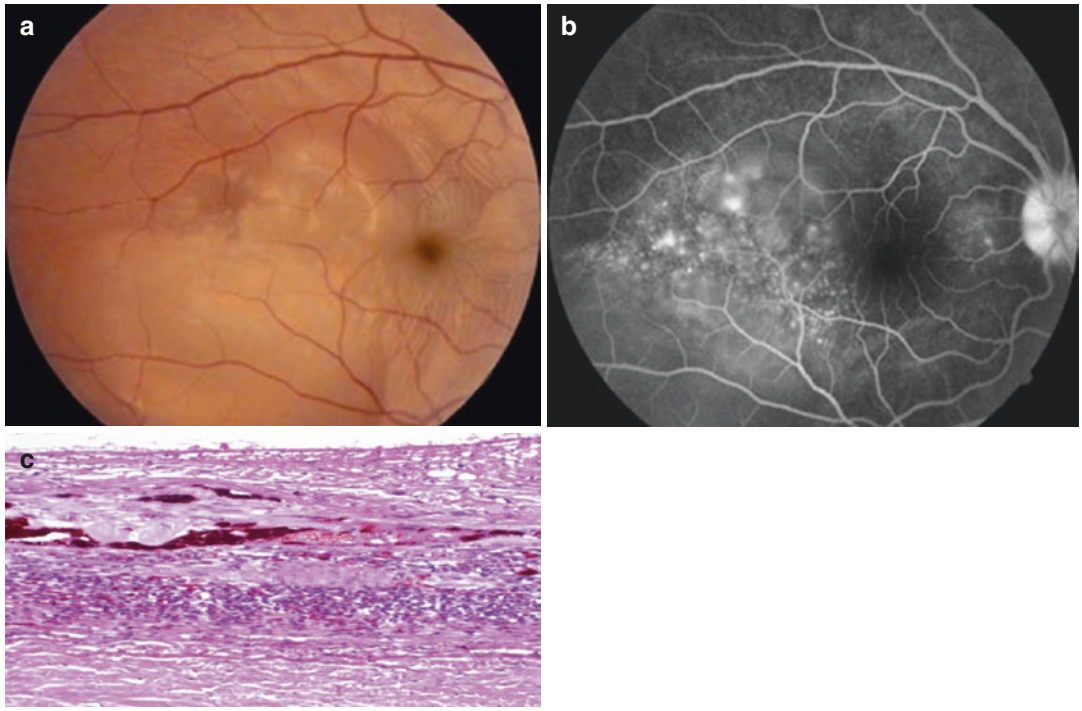

Fig. 3.9 Vogt–Koyanagi–Harada syndrome. (**a**) Funduscopic image (**b**) Fluorescein angiography (**c**) Dalen-Fuchs nodules are clusters of macrophages and RPE cells overlying Bruch's membrane. These are characteristic of acute VKH and chronic recurrent VKH. Note the dense choroidal lymphocytic infiltrate

matous inflammation and Dalen-Fuchs nodules but with less uveal thickening and loss of choroidal melanocytes [43].

3.2.5 Sarcoidosis

Sarcoidosis is a noninfectious inflammatory granulomatous disease that may involve a single or multiple systems. The lungs, lymph nodes, skin, the central nervous system, and the eye can be involved.

Posterior segment involvement is reported in 14–28% of patients [44], and these can present as posterior uveitis and sarcoid nodules of the optic nerve, retina, and choroid [45]; vitritis with or without inflammatory snowballs [46], retinal vasculitis, chorioretinitis, vascular occlusions, macular edema, papilledema [44] and retinal detachment [47]. The development of a CNV complex is not common, though when present, has been reported as type 2 CNV [10].

Sarcoid nodules or tubercles are pathognomonic of this disease. On histology, these are circumscribed noncaseating granulomas composed of primarily lymphocytes in association with Langerhans giant cells and macrophages [48]. Tubercles of the same size are usually seen in isolation, although these may sometimes coalesce. Clusters of the epithelioid and Langerhans cells are usually surrounded by lymphocytes or plasma cells and may either be separated by connective tissue or form conglomerates (Fig. 3.10) [49].

Also observed are perivascular exudates that correlate with "candle-wax drippings" on indirect ophthalmoscopy, perivascular lymphocytic and neutrophilic infiltration, and vascular sheathing [50]. Acid fast and Gomori methenamine silver stains for fungi and bacteria, respectively,

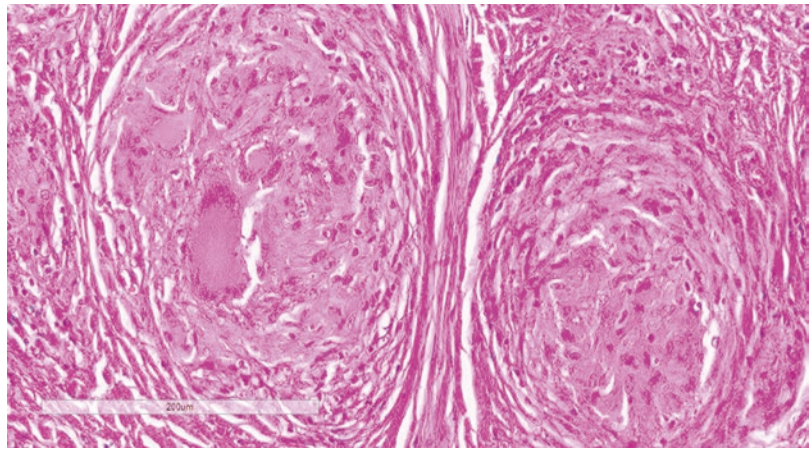

Fig. 3.10 Sarcoid nodules. Note the discrete, compact granulomas consisting of histiocytes, lymphocytes, and giant cells. The granulomas are separated by connective tissue. No necrosis is seen

should be negative, and there should be no signs of a foreign body inciting the reaction [51].

Sarcoidosis resembles other granulomatous diseases on histology, such as histoplasmosis, leprosy, and tuberculosis based on the discrete pattern in which cellular infiltration is arranged [49]; the infrequency of necrosis and the occasional distinctive asteroid and Schaumann bodies that can be seen on sarcoid nodules [52].

3.3 Degeneration Associated CNV

3.3.1 Neovascular Age-Related Macular Degeneration (AMD)

AMD classically presents in a person over 50 years old with sudden blurred central vision, metamorphopsia, and/or a central or paracentral relative scotoma.

Neovascular AMD, also known as wet or exudative AMD, affects 10–20% of all AMD patients, and is a leading cause of severe visual impairment among the elderly population living in high- or middle-income countries [53]. Inflammation can play a key role in the treatment and pathophysiology of this condition. It is considered that the primary event is the deposition of extracellular material (drusen). This material seems to be highly pro-inflammatory leading to the inflammatory state [54].

Almost always, choroidal submacular neovascularization occurs in the context of preexisting clinical manifestations of dry or non-exudative AMD, such as macular retinal pigment epithelium (RPE) irregularities, drusen, and/or patchy or geographic atrophy [55].

Biomicroscopy of the fundus shows a localized area of a shallow neurosensory detachment that may be exudative, hemorrhagic, or mixed. Also, an RPE detachment may be the initial clinical sign or accompany the neurosensory detachment, and is clinically observed as grayish or dark, well-delineated dome-shaped subretinal elevation.

CNV development among patients with AMD can be characterized as type 1 (subretinal), type 2 (outer retinal), or mixed based on clinical and examination (including imaging) findings Fig. 3.11 [56]. A majority of CNV are type 2 lesions with abnormal growth of vasculature into the outer retinal space. CNV seen in AMD are usually subfoveal and are associated with the presence of drusen and retinal pigment epithelial abnormalities due to the accumulation of lipofuscin material. On the other hand, the retinal pigment epithelium is often intact in individuals with CNV [57]. The proposed mechanism of development of CNV is the focal breach of the retinal pigment epithelium due to infection/inflammation leading to growth and entry.

Most of AMD CNV are type 2 (external sensory retinal) and are accompanied by drusen and

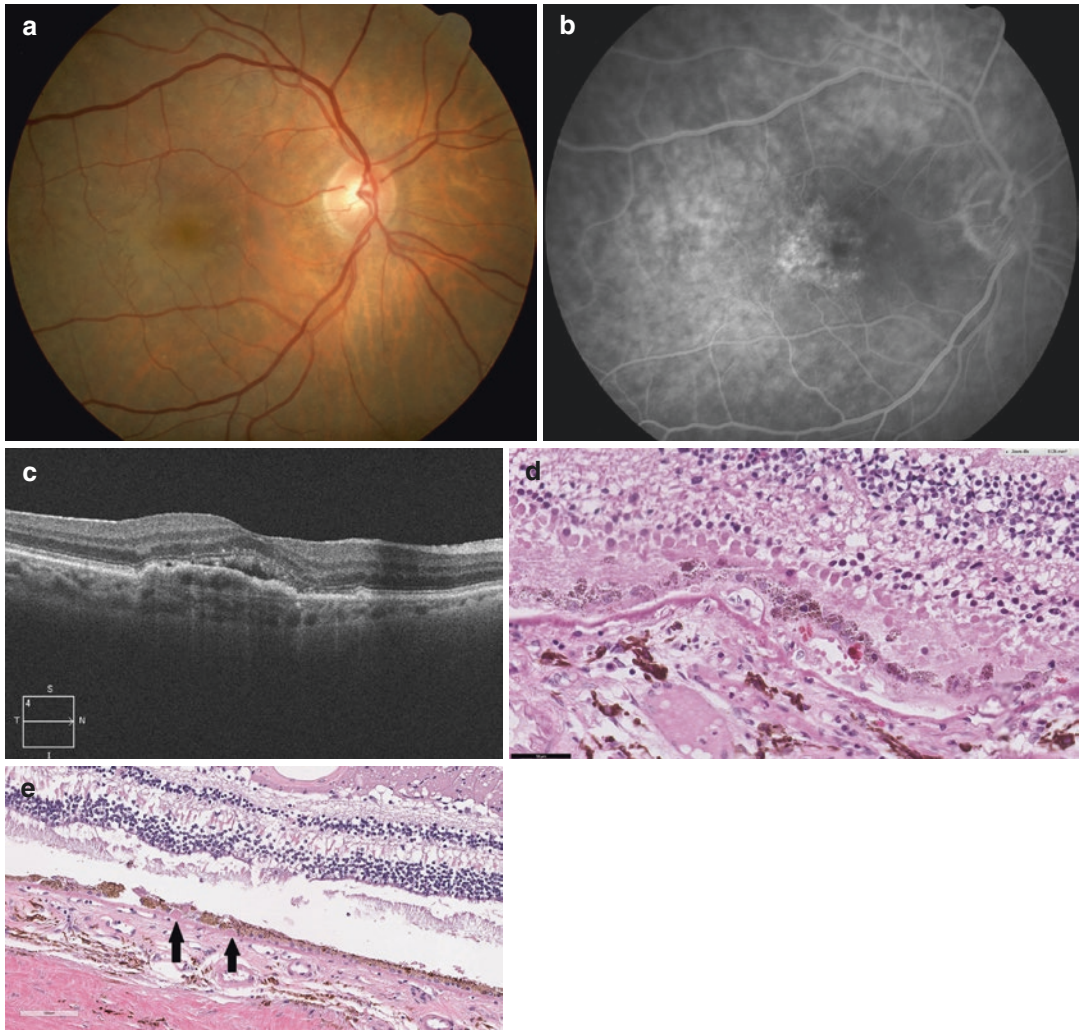

Fig. 3.11 Neovascular age-related macular degeneration type 1 (**a**) Funduscopic image (**b**) Fluorescein angiography (**c**) SD-OCT image (**d**) A thickened Bruch's membrane with diffuse drusen formation is seen. Note on the right two ghost vessels with red blood cells. (**e**) Dry AMD with drusen (arrows) and no CNV H&E (200×)

RPE abnormalities similar to those of Dry AMD such lipofuscin deposition [56] and is nicely delineated by fluorescein angiography [58].

Type 1 CNV can also be seen under the RPE, and presents clinically as an RPE detachment. Later, CNV membranes disrupt the RPE and invade the subretinal space (type 3). Type 2 gets through RPE directly into the sub-neurosensory space.

With optical coherence tomography (OCT), type 1 is observed as a well-delineated RPE detachment, or as an irregular elevation and later disruption of the submacular RPE, accompanied by subretinal hemorrhage or fluid, disruption of the outer neurosensory retina, and neurosensory cystoid edema. Type 2 CNV is easily identified between RPE and neurosensory retina, and also neurosensory detachment and edema are generally observed.

Progressively, in untreated or unresponsive-to-treatment cases, a disciform fibrotic scarring of the macula forms, surrounded by an area of chorioretinal atrophy [58].

3.3.2 Myopic Neovascular Maculopathy

Progressive elongation of the globe observed in high myopia produces a biomechanical stretching of the retina, RPE, and choroid [59] accompanied by a straightening and thinning of retinal vessels with reduction of retinal vascular flow, and a diminished density of the retinal capillary network and choriocapillaris [60–62]. These events appear to induce several degenerative processes of the macular region [63, 64]. In one study evaluating patients with unilateral myopia complicated with neovascular maculopathy by means of color Doppler imaging, higher resistivity index in posterior ciliary arteries were found when compared with the non-myopic fellow eye [65].

Myopic neovascular maculopathy is one of the most frequent and severe vision-threatening complications in highly myopic patients and is the most frequent cause of submacular choroidal neovascularization in persons under the age of 50 years [66]. It may be observed in up to 10% of patients with high myopia, being more frequent in women [67].

Although its pathogenesis is not well established, some predisposing risk factors have been found, such as degenerative changes in Bruch's membrane, thinning of choriocapillaris, and slowing of the choroidal circulation [68, 69].

Biomicroscopically, the subretinal choroidal neovascularization is generally observed as a round, flat, or minimally elevated brown or grayish spot, sometimes accompanied by a small hemorrhage in the surroundings. Although it may be observed in a highly myopic eye without evident myopic fundus changes at the posterior pole [66], it presents generally in an eye with diffuse macular atrophy, patchy atrophy in the macular area, and lacquer cracks [70]. Frequently, the subretinal neovascular membrane develops at the edges of a lacquer crack, atrophy plaque, or steep staphylomatous area [70].

About 35% of bilateral highly myopic patients with neovascular maculopathy in one eye may develop neovascular maculopathy in the contralateral eye within 8 years [70].

Choroidal neovascularization in high myopia is less aggressive and expansive than AMD and tends to regress and cicatrize spontaneously, leaving a subretinal scar area of irregular cicatricial hyperplasia of the RPE named Fuchs spot, surrounded by progressive chorioretinal atrophy [71].

Fluorescein angiography delineates quite well the generally small neovascular membrane. However, in cases with advanced macular patchy chorioretinal atrophy the lesion may become hardly identifiable.

In OCT, the acute neovascular membrane appears as a well-circumscribed non-homogenously hyper-reflective lesion in the subretinal space, with a subtle amount of subretinal exudation and intraretinal cystoid edema, not always present in the initial phase.

Long-term visual prognosis is poor for untreated or unresponsive-to-treatment lesions. At 10 years after onset 96% of cases will have a visual acuity of less than 20/200 [72].

3.3.3 Pachychoroid Related CNV

In normal subjects, submacular choroidal thickness measured by means of OCT ranges between 250 and 330 μm, and is thinner temporally and nasally. It may decrease with aging, in high axial length, and in certain diseases such as glaucoma, pseudoxanthoma elasticum, and birdshot chorioretinopathy [73]. A diffuse choroidal thickening may also be observed in normal eyes without any pathologic consequence.

Pachychoroid is a term to describe focal or diffuse choroidal thickening, dilated vessels in Haller's layer (pachyvessels) that may represent the full extent of choroidal thickness, and thinning of Sattler's layer and choriocapillaris [74, 75].

Another important feature of pachychoroid is choroidal vascular hyperpermeability, evidenced by indocyanine green (ICG) angiography [76].

Pachychoroid constitutes a clinical entity comprising a spectrum of diseases that includes central serous chorioretinopathy, pachychoroid pigment epitheliopathy, polypoidal choroidal

vasculopathy, and pachychoroid neovasculopathy [74].

The latter consists in a choroidal neovascular complex that develops overlying the RPE (type 1 neovascularization) in a localized area of dilated choroidal vessels and choroidal thickening, diagnosed by means of OCT, and may progress to polypoidal choroidal vasculopathy [77].

Clinically, besides some focal RPE abnormalities, choroidal neovascularization occurs in the absence of age-related degenerative changes such as drusen and atrophy, or other types of degenerative disease [77]. Irregular and shallow RPE detachments are very characteristic of this entity. Under this area, a complex choroidal vein network may be visualized by OCT angiography [77, 78].

A variant of this syndrome is peripapillary pachychoroid, described recently by Phasukkijwatana et al., and is characterized by pachychoroid around the optic disc, choroidal folds, hyperopia, short axial length, nasal macular edema and/or detachment, and occasional optic disc edema [79].

The pathogenesis of pachychoroid and its associations remains unknown.

3.3.4 Polypoidal Choroidal Vasculopathy (PCV)

Polypoidal choroidal vasculopathy (PCV) is a variant of type 1 choroidal neovascularization, characterized by abnormal focal vascular branching network and terminal saccular dilatation resembling polyps that may bleed and exudate profusely under the neurosensory retina of the posterior pole in longstanding lesions. Polypoidal lesions may sometimes be identified as a subretinal orange bulging lesion principally located around the optic disc and the macular area, are frequently bilateral, and are less frequently observed with drusen than in AMD [80]. Risk factors include male gender, smoking, hyperlipidemia, obesity, and hypertension. ICGA is the gold standard for their diagnosis, but they can also be observed with fluorescein angiography as long as the anomalous network is not covered by a dense hemorrhage plaque [81].

3.3.5 Macular Telangiectasia

Macular telangiectasia comprises a variety of clinical pictures characterized by altered juxta- or parafoveolar retinal capillaries. It may be classified into two major forms. Type 1 is the congenital form, also known as mac tel type 1, and is usually unilateral. Type 2, also known as mac tel type 2, is presumably acquired, affecting both eyes of middle-aged and older individuals [82].

Intraretinal neovascularization is a frequent complication of mac tel type 2, and is more often observed temporal to the fovea, and may extend to the subretinal space and choriocapillaris. Intraretinal and subretinal lipid deposits, subretinal or retinal hemorrhage, and macular edema, and a right-angle retinal venule are reaching the center of the lesion are key clinical findings [83].

3.3.6 CNV Secondary to Angioid Streaks

Histopathology has shown that angioid streaks are caused by breaks within an abnormally thickened and often calcified Bruch's membrane [84]. The overlying RPE is atrophic but not necessarily discontinuous and the blood–retinal barrier is intact. CNV is represented by blood vessels that invade the break, breach the epithelium, and proliferate in the subretinal space [85].

3.3.7 Best Associated CNV

Usually the ganglion cell layer and inner and outer plexiform layers of the central retina are edematous, and the outer segments showed focal atrophy, lipofuscin-like material under the macular RPE. Bruch's membrane changes such as disruption or thickening were also observed along with CNV [86].

3.4 Traumatic Associated CNV

3.4.1 Post-trauma CNV

Ocular blunt trauma is a major cause of preventable visual loss secondary to posterior segment complications, such as vitreous hemorrhage, retinal detachment, macular hole, traumatic optic neuropathy, choroidal rupture, and CNV [87]. Choroidal rupture is a break in the choroid, Bruch's membrane, and RPE, and 5–10% of those eyes may develop a late CNV [88]. Choroidal ruptures located closer to the fovea, as well as longer ruptures, were at higher risk for developing CNV, 82% occurring within the first-year post trauma [88]. Clinically they present as a relatively small, flat, or slightly elevated hemorrhagic or grayish plaques that typically develop within or at the border of a chorioretinal traumatic scar.

3.4.2 LASER Induced CNV

Classically, immediately after laser treatment histopathology shows coagulative necrosis involving all retinal layers that in 3 weeks evolve to a marked retinal attenuation and chorioretinal scarring [89]. The irradiated cells show vacuolation damage to the inner retinal layers and some of them vacuolation in their inner segments, pyknotic nuclei, or degeneration in the fiber layer of Henle. Increase in output energy results in increasing trauma at damaged sites. According to the LASER power, a breakdown of the pigment epithelium and Bruch's membrane may be seen [90]. Neovascularization shares the common histopathological characteristics at the margin of the LASER scar.

3.5 Tumoral Associated CNV

3.5.1 Choroidal Osteoma

Choroidal osteoma is a benign ossifying tumor affecting more frequently young women that presents ophthalmoscopically as a white or pale well-defined flat or slightly elevated mass, found around the optic disc or in the macula. The high tissue density lesion is also evidenced by ultrasonography and CT of the orbit [91]. Vision may decrease slowly as the result of degenerative changes at the choriocapillaris and RPE over the years. However, sudden visual loss may occur as the consequence of serous or hemorrhagic macular detachment from choroidal neovascularization (CNV) [92].

The histopathological description of choroidal osteoma in the literature is limited. On histopathology, choroidal osteomas appear as mature bone with marrow spaces connected to each other and filled with connective tissue [93, 94]. The bony trabeculae contain osteoblasts, osteocytes, and occasionally osteoclasts [94]. Superficially, some of the marrow spaces will have feeder vessels that connect to choriocapillaris beneath Bruch's membrane. The lumen of the choriocapillaris can be obliterated by the tumor in most areas [94]. An atrophied and depigmented RPE layer is usually seen overlying the tumor [93, 94]. In addition, subretinal exudates and a degenerated photoreceptor layer above the tumor, with loss of nuclei, can be observed [93, 94].

3.5.2 Choroidal Nevus

Choroidal nevi are benign tumors, generally ophthalmoscopically observed as a dark-gray flat or minimally elevated lesion, and most frequently observed posterior to the equator and extrafoveolar. Patients with subfoveolar nevi are at certain risk of visual loss because of choriocapillaris disruption and subsequent disruption of photoreceptor outer segments. Also, a CNV complex may develop at the margins or over the choroidal nevus generating a serous neurosensory detachment [95]. In longstanding cases lipid deposition may precipitate in the subretinal space contouring the CNV lesion (Fig. 3.12).

Choroidal nevi arise from melanocytic cells derived from the neural crest [96, 97]. In general, the cells of a nevus cell are "plumper" than the normal melanocytes of the choroid and ciliary body. Morphologically, nevi are classified into

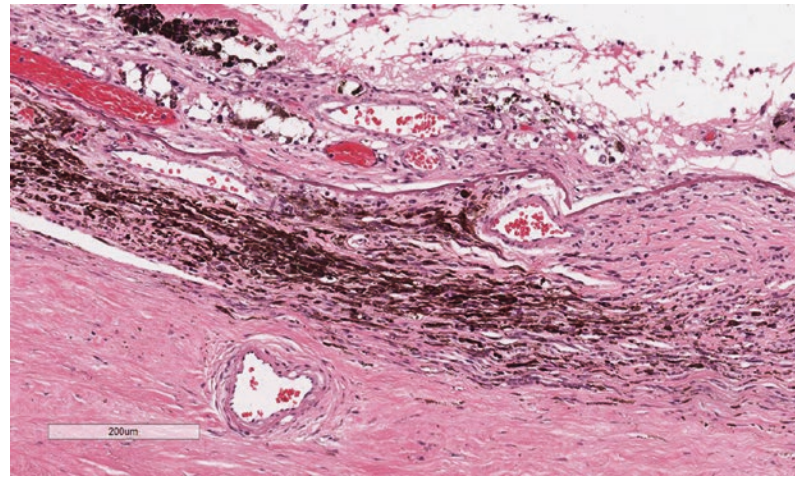

Fig. 3.12 Choroidal nevus. Note the CNV characterized by a vascularized fibrous membrane over Bruch's membrane. RPE and outer retinal segments are disrupted, H&E (100×)

four types: polyhedral, fusiform, spindle, and balloon cells [97].

1. Polyhedral nevus cells: This is the most common cell type found in nevi of the ciliary body and choroid. Its voluminous cytoplasm is densely packed with melanin, obscuring nuclear details. When sections are thoroughly bleached, a rather small, round, uniformly basophilic nucleus without a prominent nucleolus is seen. This cell accounts for over two-thirds of the mass in the majority of these nevi. It is indistinguishable from those cells that compose the melanocytomas of the optic disc and from those that diffusely thicken the choroid in congenital ocular melanocytosis.
2. Spindle nevus cells: This is considered the second most frequent cell type in benign pigmented tumors of the choroid. It is a small, spindle-shaped cell with a slender, intensely basophilic nucleus. Unlike polyhedral cells, these cells consistently contain little or no pigment and are often distributed in a striking manner in the outer portions of a nevus. Only rarely does this cell type make up the bulk of a nevus, which is then characteristically only lightly pigmented.
3. Fusiform and dendritic nevus cells: These cells are less intensely pigmented than the polyhedral cells and display a larger nucleus with a slightly loose chromatin pattern and occasionally even a small nucleolus. Furthermore, the cytoplasm is more abundant than in the spindle melanocytes.
4. Balloon cells: This subtype of cells is similar to cells found in cutaneous nevi. These are large cells with abundant foamy cytoplasm.

Histopathological alterations in the structures surrounding choroidal nevi include narrowing or dilatation of the choriocapillaris, atrophy and clumping of the retinal pigment epithelial (RPE), drusen formation, serous detachment of the neurosensory retina, subretinal neovascularization, and lipofuscin deposition [97–99].

3.6 Development Alterations or Malformations Associated CNV

3.6.1 Coloboma

Choroidal coloboma is a congenital malformation characterized by a failure during embryogenesis of the inner and outer layers to fuse along the optic fissure [100].

The simultaneous closure of the fissure and retinal differentiation, together with subsequent retinal growth, are vital with respect to the pathophysiology of the fissure in that only the inner neuroblastic layer of the retina, with its Müller cells, fuses across the fissure. The outer neuro-

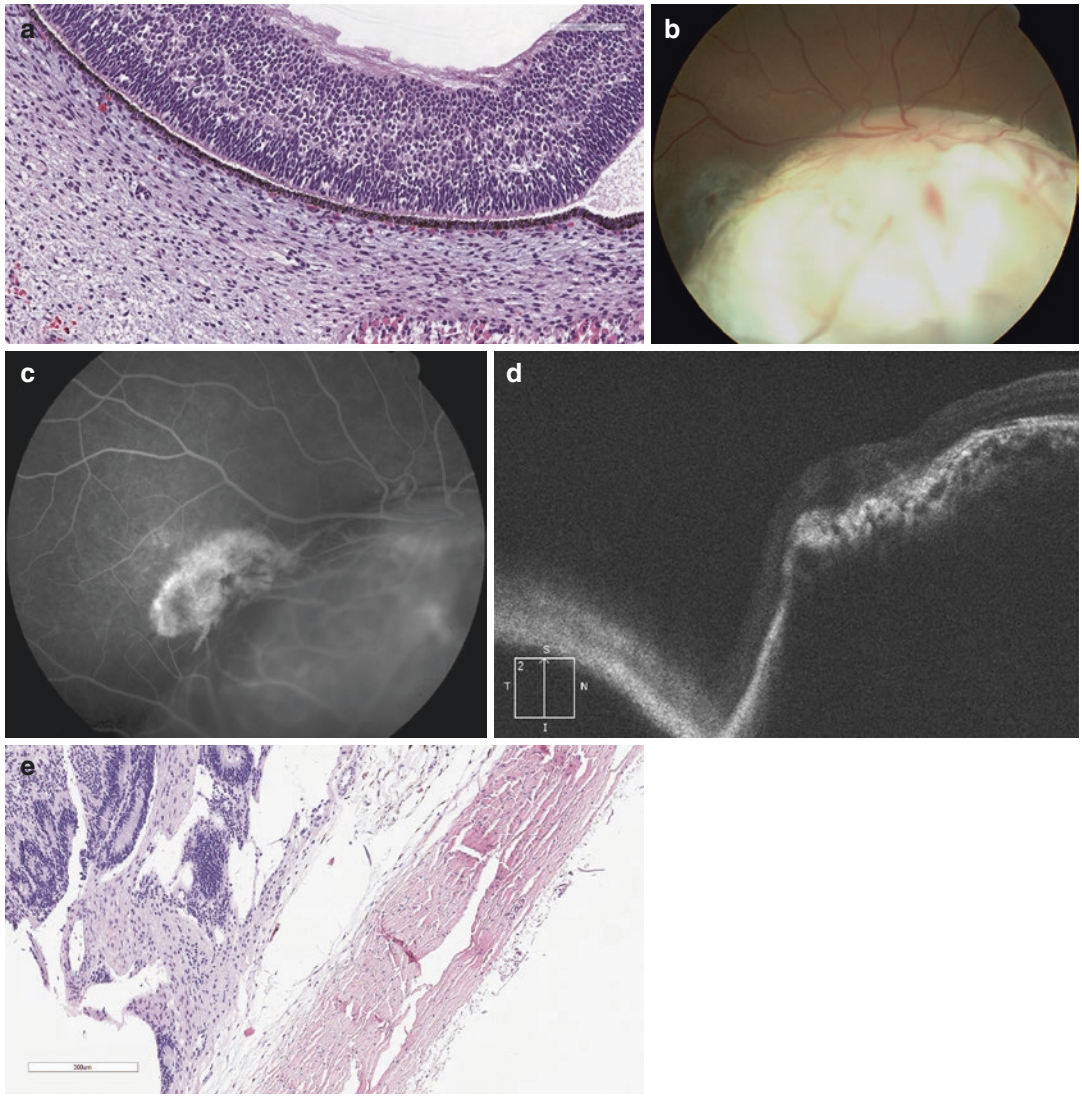

Fig. 3.13 Coloboma. (**a**) Histology of a normal developing eye in the 8th gestational week. Note the primitive two layers of the retina, immature choroid and sclera H&E 200× (**b**) Funduscopic image (**c**) Fluorescein angiography (**d**) SD-OCT image Histology of coloboma. The choroid is replaced only by a loose connective tissue. The retina in this image is dysplastic with rosette formation

blastic layer reverts and connects to the RPE (Fig. 3.13) [101].

As described by Schubert (2005), common histologic findings are [101]:

Pediatric coloboma is characterized by an intercalary membrane in direct contact with the sclera, central glial triangle, point of reversal and duplication of the photoreceptor layer, locus minoris resistentiae, and lateral displacement of the RPE. Also variable degrees of vascularization at the junction between the external limiting membrane and the RPE, the choroid ends together with the RPE and may be thickened and the sclera is thinned. Intrascleral rosettes may be present.

In adult coloboma marginal retinal vessels, marginal choroidal thickening and hyperplasia of the RPE are encountered together with vessels with intimal hyperplasia and absence of the glial

triangle, point of reversal, duplication, and locus minoris resistentiae. The choroid is absent at the center and the sclera is thinned.

Choroidal neovascularization favors the margin of colobomas, with vessels tending to grow toward the intercalary membrane [102–104].

3.7 Unknown: Idiopathic CNV

The pathophysiological processes in idiopathic CNV remain unclear. Histopathology of this lesion may correspond to the general description of CNV [6].

Key Learning Points

CNV is a repair response during the healing process after injury due to the poor regenerative properties of the retina, Bruch's membrane, and choriocapillaris.

Choroidal neovascularization represents a nonspecific response to different etiologies.

In each disease, CNV may be accompanied by findings associated with the primary etiologic condition.

CNV may be localized in any part of the retina, but macular involvement is common.

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