
Retinal and Choroidal Manifestations in Bartonellosis, Lyme Disease, and Syphilis

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Abstract

Infections with bartonellosis, lyme, and syphilis are not uncommon, especially in selected populations of patients who are at risk. Ocular manifestations, which include retinal and choroidal diseases, are protean and may be initial presentations of the infections or may represent extension of the systemic infectious processes. The diagnosis is often established clinically, with serologic evaluations performed for confirmation. Therapy is targeted with specific anti-infectious agents aiming directly at the underlying infectious organisms. Systemic corticosteroid may be used subsequently to provide complementary control of the inflammation. Ocular involvements, similar to central nervous system disease, mandate intravenous administration of therapeutic agents over sufficient treatment duration.

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Keywords

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Introduction

The human eye can offer critical clues to the presence of systemic diseases, which may be manifested initially as ocular morbidity. In such cases, information obtained from careful ocular examination may aid in the diagnosis. On the other hand, the diagnosis of selected systemic diseases warrants detailed ocular examination, as the eye is often involved. The index chapter will discuss the diverse retinal and choroidal manifestations in ocular Bartonellosis, Lyme disease, and syphilis.

Bartonellosis

The first manifestations of ocular bartonellosis were first described by Henry Parinaud in 1889. Parinaud reported three patients presenting with follicular conjunctivitis, regional lymphadenopathy, and chronic fever, in addition to a prior history of contact with pets [1]. The newly reported manifestations were named Parinaud's oculoglandular syndrome (POGS). Over the following years, the association of POGS and exposure to pets was confirmed in several reports [2, 3]. Several decades later, an association was established between the POGS and cat scratch disease (CSD) [3], an infectious disease that was first described by Debré et al. in 1950 and characterized by tender and swollen regional lymph nodes [4]. An association between CSD and neuroretinitis was first suggested by Sweeney and Dance in 1970 [5] and confirmed 7 years later by Donald Gass [6].

For nearly a century, the etiologic agent of POGS and CSD was not identified; it was not

until the evolution of biomolecular technology in the mid-1990s of the past century that allowed the identification of *Bartonella henselae* as the causative agent of CSD [7, 8]. In 1994, Golnik and associates were the first to report a serologic evidence of systemic Bartonella infection in patients with neuroretinitis [9]. Since the early 1990s, *B. henselae* has been incriminated in an increasing list of medical conditions including POGS, CSD, neuroretinitis, focal retinochoroiditis, and bacillary angiomatosis [10, 11].

B. henselae is one of 21, so far identified, Bartonella species. Of these 21, eight species have been found to cause human diseases, four of which (*B. henselae*, *B. quintana*, *B. grahamii*, and *B. elizabethae*) have been linked to ocular complications [12]. In immunocompetent individuals, Bartonella species are capable of causing Oroya fever, Trench fever, endocarditis, myocarditis, bacteremia, cat scratch disease, and neuroretinitis. The list of diseases grows even longer in immunocompromised patients to include chronic fevers, bacteremia, peliosis hepatitis, and bacillary angiomatosis [12].

Epidemiology

The prevalence of CSD has been estimated to be 9.3 per 100,000 population with an annual incidence rate of about 22,000 cases and approximately 2,000 annual hospitalizations and with an annual cost of health care, estimated in 1993, of 12 million US dollars [13].

Over 90% of patients report a history of having been scratched by a cat, often a kitten. Children younger than 10 years of age are particularly susceptible to Bartonellosis, constituting nearly 80% of cases [10].

Cat-to-cat transmission of *B. henselae* is mediated by the cat flea (*Ctenocephalides felis*). The role of fleas, however, in transmission of infection to humans, is unknown, although flea feces remain infectious for long periods and could transmit *B. henselae* through direct inoculation of open wounds or mucous membranes, such as the conjunctiva [14]. Cat-to-human transmission may occur from trauma (scratch), inhaling materials infected by cats, being licked by infected animals, or rubbing one's eye after contact. Human-to-human transmission has not been reported.

It is estimated that the total population of cats in United States is around 60 million with nearly one-third of all homes having a cat. It is also estimated that 10–40% of domestic cats have asymptomatic bacteremia [15]. Kittens in particular are susceptible to infection with *B. henselae* and may have asymptomatic bacteremia for several weeks, whereas some adult cats have been shown to be chronic carriers. Multiple infections within the same family have been reported [16]. However, removal of the cat from the house is considered unnecessary as the overall rate of human transmission is generally low [17].

Typical manifestations of CSD include conjunctival injection, watery discharge, and foreign body sensation. A granulomatous nodule, usually unilateral, develops in the palpebral conjunctiva, surrounded by follicles, intense chemosis, and injection. The nodule may be single, flat, and large, or multiple and raised. The fornices and bulbar conjunctiva may also be involved. Corneal involvement usually consists of superficial punctate keratitis but rarely causes significant keratitis [18]. The outcome of CSD is usually benign with recurrences uncommon possibly because of lasting immunity [19].

POGS is classified as an atypical manifestation of CSD and occurs in approximately 3–7% of all CSD infections with clinical manifestations occurring, typically, 1–2 weeks post infection [20]. A primary inoculation lesion in the conjunctiva, skin, or mucous membrane has been identified in about 76% of patients [21].

Microbiology

Bartonella, formerly known as *Rochalimaea*, are a genus of Gram-negative facultative intracellular bacteria. *Bartonella* belong to the phylum Proteobacteria, to the order Rhizobiales, which makes *Bartonella* a close relative to the *Brucella* species [22–24]. *Bartonella* carried its name after the Peruvian microbiologist Alberto Barton who, in 1905, discovered the etiologic agent of Oroya fever: the *Bartonella bacilliformis*.

Bartonella are fastidious and highly resilient rods requiring long incubation of up to 4 weeks in enriched media. Within their host, *Bartonella* reside inside erythrocytes or endothelial cells, which can lead to bacteremia, hemolytic anemia, endocarditis, or even an angioproliferative response [25, 26]. *Bartonella* cannot oxidize glucose; however, they use glutamate and succinate as their sources of carbon. Whereas *B. henselae* colonies tend to be rough and produce pitting of the agar, *B. quintana* colonies are usually smooth, with little or no pitting [27].

Bartonella can cause a necrotizing or focally suppurative response, such as that observed in CSD, in immunocompetent patients. In immunocompromised patients, however, the response typically will be vasoproliferative as seen in bacillary angiomatosis [28]. Analysis of primary skin lesions and affected lymph nodes shows a granulomatous inflammation with a center of necrotic material surrounded by concentric layers of inflammatory cells, most commonly histiocytes, lymphocytes, and nucleated giant cells [29].

The ability of *Bartonella* to induce a vasoproliferative response (bacillary angiomatosis) in immunocompromised hosts could be partially explained by their ability to parasitize endothelial cells [30, 31]. At the same time, the ability of some *Bartonella* species, such as the flagellated *B. bacilliformis*, to cause hemolysis and sometimes life-threatening anemia (as in acute infections of Oroya fever) could be explained by their ability to invade the red blood cells. *B. henselae* has also been observed to penetrate human red blood cells in a fashion similar, yet slower, to that observed in cats [32].

Clinical Findings in Cat Scratch Disease

Systemic Manifestations

Cat scratch disease follows, in most cases, a benign course and usually resolute without complications. A lesion at the primary inoculation site, in the form of macule, papule, or pustule, is usually the first manifestation of CSD. The primary lesion is sometimes accompanied by mild to moderately severe flu-like symptoms including headache, anorexia, nausea, vomiting, and sore throat. The flu-like symptoms are usually associated with regional lymphadenopathy, which slowly resolves over the ensuing weeks or months. The affected nodes are frequently tender and may even be suppurative. The lesion at the primary inoculation site occurs in 25–60% of patients, usually 3–10 days following the injury and 1–2 weeks before the onset of constitutional symptoms. Ocular involvement has been estimated to occur in 5–10% of patients with CSD [33].

Other less common systemic manifestations of CSD include encephalitis (1–2%), osteomyelitis (less than 1%), and hepatosplenic disease (less than 1%) [27].

Ocular Manifestations

The eye is the most commonly affected non-lymphatic organ in CSD [33]; however, not all patients experience obvious systemic manifestations, and some patients with systemic *B. henselae* infection fail to provide a history of recent cat or flea exposure. In this sense, recognition of suggestive ocular findings often leads to specific serologic testing and the correct diagnosis (Table 7.1) [27].

Parinaud's Oculoglandular Syndrome (POGS)

In his overview of 1,200 patients with CSD, Carithers, in 1985, found that approximately 4% of patients (n=48) with symptomatic cat scratch disease suffered from the oculoglandular syndrome of Parinaud (POGS), making it the most commonly encountered ocular complication of cat scratch disease [33]. The typical presentation of POGS includes conjunctival irritation, eye redness, and foreign body sensation. Discharge is

Table 7.1 Ocular manifestations of bartonellosis, Lyme, and syphilis

Fundusoscopic findings	Bartonellosis	Lyme	Syphilis
Retinal vasculitis	+	+	+
Vascular occlusion	+	+	+
Macular edema	+	+	+
Macular pucker	–	+	+
Multifocal retinitis	+	–	–
Diffuse or focal retinochoroiditis	+	+	+
Serous retinal detachment	+	+	–
Retinal pigment epithelial detachment	–	+	–
Ciliochoroidal detachment	–	+	–
Cotton-wool spots only	–	+	–
Retinal bacillary angiomatosis	+	–	–
Optic neuritis	+	+	+
Neuroretinitis	+	–	–
Macular star	+	–	–
Optic atrophy	–	–	+
Choroidal neovascular membrane	–	+	+
Retinal tear	–	+	–
Pseudoretinitis pigmentosa	–	+	+
Mimicking white dot syndrome	+	+	–

usually serous; nevertheless, purulent conjunctivitis with abscess formation may occur. On examination, POGS typically presents with granulomatous conjunctivitis associated with regional lymphadenitis. Lesions may involve the palpebral conjunctiva in the form of either a single flat nodule or multiple raised vegetations with surrounding erythema; necrosis of the overlying conjunctival epithelium and ulceration may ensue. Regional lymphadenitis typically involves preauricular lymph nodes; submandibular and cervical lymph nodes may also be affected [18, 34, 35]. The granuloma disappears over period of weeks, leaving no scar. Lymphadenopathy regresses over weeks or months, depending on the severity of the infection; however, in many cases, the lymphadenopathy progresses to suppuration [33].

The differential diagnosis of unilateral granulomatous conjunctivitis includes, in addition to cat scratch disease, other infections like tularemia, tuberculosis, syphilis, sporotrichosis, and acute *Chlamydia trachomatis* [36]. At the same time, not all cases of POGS seem to be caused by *B. henselae*; positive serology for *B. quintana* was detected in one patient with POGS, and herpes simplex virus type 1 was detected by culture and PCR testing in another patient [37, 38].

Retinal and Choroidal Manifestations and Complications

Retinal and choroidal manifestations and complications of CSD include neuroretinitis, focal retinitis, focal choroiditis, multifocal retinitis, multifocal choroiditis, intermediate uveitis, vasculitis, vascular occlusions, and bacillary angiomatosis [9, 36, 39–46]. Panuveitis, acute unilateral maculopathy, macular hole, secondary unilateral glaucoma, and serous retinal detachments have also been reported [47–52].

Neuroretinitis (Leber's Neuroretinitis)

Neuroretinitis is a unique form of optic neuropathy characterized by optic disk swelling in the presence of a partial or complete macular star [53]. Leber first described neuroretinitis in 1916 as acute unilateral visual loss associated with optic disk swelling and a macular star [54]. Gass later observed that neuroretinitis was simply a unique form of exudative optic neuropathy with transudation into the macula [6]. Despite being originally described as a unilateral disease, neuroretinitis has been reported to manifest as bilateral optic disk swelling with macular star formation [55, 56].

Among 14 patients with neuroretinitis, Suhler et al., in 2000, found nine patients (64%) to have elevated IgM or IgG for *B. henselae* [44], making CSD the most common cause of neuroretinitis [12]. Despite this high percentage of *B. henselae* seropositivity in patients with neuroretinitis, the true prevalence of neuroretinitis in patients with systemic *B. henselae* infection is unknown. It was proposed, nevertheless, to occur in 1–2% of patients [12]. *B. elizabethae*, *B. grahamii*, and *B.*

quintana have also been reported by serology and PCR testing to be associated with neuroretinitis [57–59].

Although uncommon, simultaneous or consecutive retinitis or neuroretinitis in patients with POGS or CSD has been reported [55]. Some cases of neuroretinitis have been accompanied by localized serous retinal detachment [60]. Macular star typically develops 2–4 weeks later; some patients, however, never develop macular star [61]. It has been proposed that the combination of neuroretinitis and serous retinal detachment can be an early indicator of systemic *B. henselae* infection [61].

The optic nerve swelling usually resolves spontaneously in 2–8 weeks, either leaving a normal disk appearance or a mild residual pallor. Macular exudates remain stable for several weeks, after which a gradual regression begins; the most extensive macular exudates may take up to 12 months to resolve [10]. Patients regain most of their visual function; however, some patients sustain functional damage in the form of decreased contrast sensitivity, dyschromatopsia, and reduced optic nerve functions [42].

Other patients developed massive angiomatous inflammatory disk mass associated with subretinal and intraretinal exudates [39, 62]. Cases of neuroretinitis of similar or more severe picture have been reported in HIV patients with CSD [45, 63, 64].

The differential diagnosis of neuroretinitis includes, in addition to cat scratch disease, Lyme disease, syphilis, leptospirosis, sarcoidosis, malignant hypertension, diabetic retinopathy, pseudotumor cerebri, toxoplasmosis, and toxocara [53].

Multifocal Retinitis and Choroiditis

Several forms of choroiditis and retinitis have been reported in CSD, some of which may mimic other retino-choroidal conditions [40, 65–67]. Diffuse choroiditis associated with CSD has been reported to cause multiple pinpoint leaks on fluorescein angiography (FA) mimicking Vogt-Koyanagi-Harada disease [67]. A case of multifocal choroiditis, associated with positive serology for *B. henselae* in a 12-year-old boy,

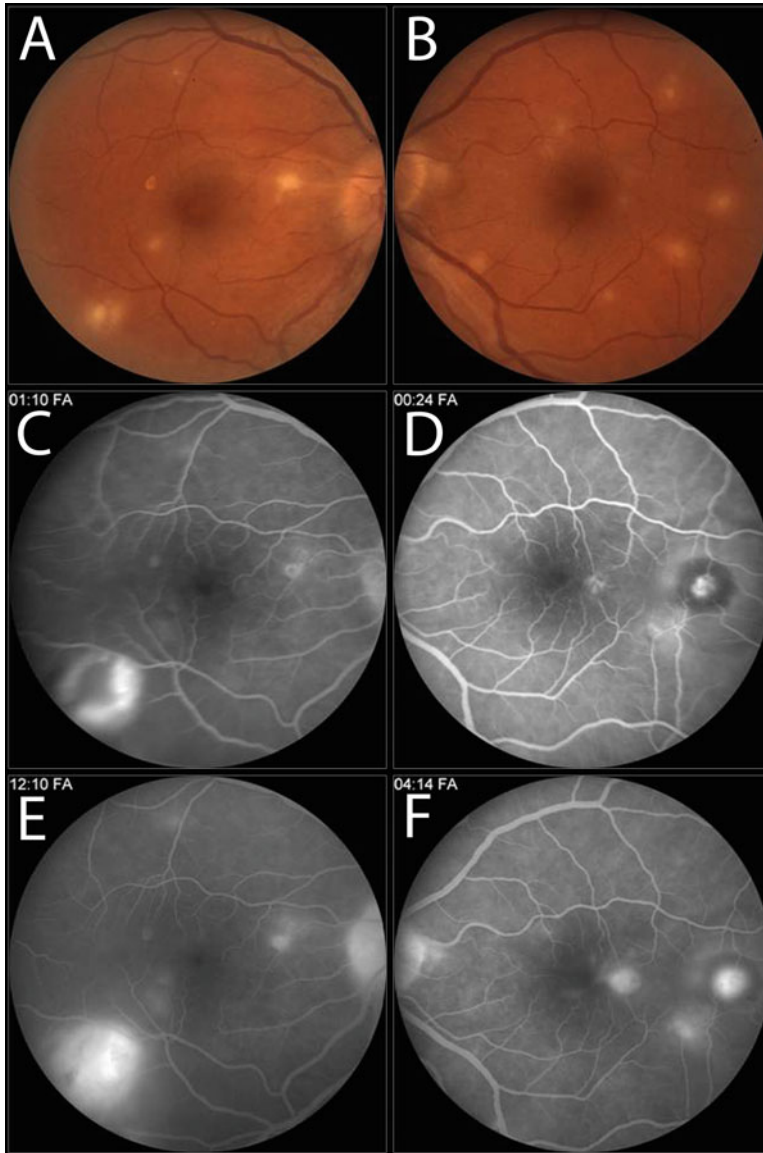


Fig. 7.1 A case of bilateral chorioretinitis mimicking birdshot chorioretinopathy in an immunocompromised patient with *Bartonella henselae* infection. Color fundus photographs from the right (a) and left (b) eyes showing multiple *creamy yellow* chorioretinal lesions in

the macular region. Mid-frames of FA of the right (c) showing hyperfluorescent ring inferotemporal to the macula with diffuse leakage in the late frames (e). Early frames of FA from the left eye (d) showing abnormal hypofluorescent ring with late leakage (f)

has been reported mimicking the picture of multiple choroidal metastases [66].

Multifocal retinitis in cat scratch disease may also present as bilateral, multiple, intraretinal white infiltrates, 100–300 μm in size, resembling one of the white dot syndromes, typically

multiple evanescent white dot syndrome or acute posterior multifocal placoid pigment epitheliopathy [9, 40, 65]. It may also represent mimicking birdshot choroidopathy (Fig. 7.1) [68]. The white dots usually clear after 2–3 weeks without a trace. CSD-associated

multifocal retinitis/choroiditis should be included in the differential diagnosis of white dot syndrome [40].

Foci of retinochoroiditis have also been observed in the absence of neuroretinitis or macular exudates [40–43, 60]. The presence of multifocal retinitis and/or choroiditis can be a clue to the diagnosis of *B. henselae* infection in cases of optic disk edema when associated with peripapillary serous retinal detachment, especially when subretinal or intraretinal exudates are absent [61].

Vasculitis and Vascular Occlusion

Ocular complications associated with retinochoroiditis in CSD may include vasculitis [46] with arterial [40, 43, 65] and/or venous [10, 65] occlusions causing severe visual loss.

Peripapillary Bacillary Angiomatosis

Bacillary angiomatosis is a dermatological disorder that had been observed in severely immunocompromised AIDS patients and characterized cutaneous vascular proliferations that clinically and pathologically resemble Kaposi's sarcoma [69]. LeBoit and associates have suggested a similarity between the organisms found in CSD and those found in bacillary angiomatosis [70]. That association has been confirmed in subsequent studies [11, 71]. *Afpia felis*, once thought to be the causative agent for CSD, was initially suspected to be the etiologic agent for bacillary angiomatosis [72, 73]. However, several subsequent studies [7, 74–76] have identified *B. henselae* as the more likely causative agent of both cat scratch disease and bacillary angiomatosis.

In 1998, Warren et al. reported a case of an HIV-positive patient presenting with a focal area of hemorrhagic retinal necrosis in one eye and multiple midperipheral intraretinal hemorrhages and several cotton-wool spots in the other eye. Retinal biopsy from the retinal lesion revealed findings similar to those seen in bacillary angiomatosis, with multiple tufts of proliferating vascular endothelial cells with fibroblasts and fusiform-appearing cells. Steiner variation

of the Warthin-Starry stain revealed clusters of *B. henselae*. The diagnosis was confirmed using PCR amplification of 16S rRNA of *B. henselae* [64]. Matsuo and colleagues characterized the FA findings in cat scratch disease presenting in four patients with granuloma and abnormal vascular network. In three patients, the granuloma and vascular network arose from the optic disk. They considered this finding a hallmark of fundus manifestation of cat scratch disease [77]. Curi et al. have reported in 2006 similar retinal finding in three HIV-positive patients with peripapillary abnormal vascular networks (tufts). All three patients were seropositive for *B. henselae* [78].

Uveitis

Both intermediate uveitis and panuveitis have been reported in several cases with CSD [79–81]. It has also been presumed that most patients with focal retinochoroiditis or neuroretinitis associated with CSD have a mild to moderate vitritis and sometimes significant non-granulomatous anterior uveitis [10, 62, 82, 83].

In their study on 19 patients with unexplained unilateral uveitis and high positive IgG and/or IgM titers, Kerkhoff and Rothova found six patients to be positive for HLA-B27 (32%). Of these six patients, five patients had severe posterior segment involvement with papillitis, macular edema, and vitritis, with duration of active intraocular inflammation of 6 months or more. Their observation led them to suggest that *B. henselae* infection may be either a trigger or risk factor for anterior uveitis in HLA-B27-positive patients as evidenced by the higher seroprevalence rate for *B. henselae* and by the more severe and chronic course of the posterior segment complications in those patients [84]. In 2004, a vitreous biopsy acquired from a patient with HLA-B27 bilateral panuveitis tested positive for *B. henselae* using enzyme-linked immunosorbent assay and PCR-based testing [85]. Bilateral anterior uveitis has also been reported in HLA-B27-negative 9-year-old girl that was serologically positive for *B. henselae* [86].

Diagnosis

Historically, a skin test for cat scratch disease, Hanger-Rose test, was one of the original diagnostic criteria for CSD. The antigen was obtained from a suppurative lymph node and used as a skin-test antigen. A dose of 0.1 ml of the antigen is inoculated intradermally with a positive reaction creating a central papule or erythema measuring 0.5–1 cm in diameter after 48–72 h. The size of the skin reaction, however, did not correlate with the severity of the illness.

Currently, with the advent of other serological and PCR tests, the risk of using foreign human lymphoid tissue outweighed its benefits [87]. The new diagnostic criteria for cat scratch disease include the following:

1. History of contact with a cat or kitten with presence of a scratch.
2. Primary inoculation site either cutaneous or ocular.
3. Serological tests – Two serologic tests are available for the confirmation of *B. henselae* exposure: indirect immunofluorescence test (IFA) and enzyme-linked immunoassays (ELISA). The sensitivity and specificity of both tests are variable, depending on the laboratory performing the tests; however, the CDC-processed tests yield above 90% for both [88].
 - (a) IFA is developed by the Centers for Disease Control and Prevention. In 1992, Regnery et al. described the IFA test for detection of the anti *B. henselae* IgG. The test was reported to have a sensitivity between 88% and a specificity of 97% [75, 88, 89], with titers greater than 1:64 being considered positive.
 - (b) ELISA test for *B. henselae* is commercially available from several laboratories. Sensitivity and specificity are variable, depending on the laboratory, which results in greater false-negative results [89].

Both IFA and ELISA tests depend on the robust immune response from the host. Because of that, the accuracy of both tests in immunocompromised patients is significantly lower [27]; the sensitivity and specificity of IFA test may drop

below 70% in patients infected with HIV [27, 90]. A single positive IFA or ELISA titer for IgG or IgM antibodies is generally sufficient to confirm CSD. IgG levels rise during the first 2 months after disease onset, followed by a gradual decline [88]. IgM titers provide greater predictability than IgG with the ELISA method; however, in order to achieve high specificity and sensitivity, the results need to be combined with other diagnostic criteria. Moreover, cross-reactivity with other Bartonella species, especially *B. quintana*, is possible and may result in false-positive results [89, 91, 92].

Biopsy and Testing

The specimen can be obtained from the granulomatous conjunctival lesion or the inflamed lymph node. Testing of the specimen may include:

1. Staining

Direct detection of bacteria in tissue specimens by Warthin-Starry silver stain has traditionally been used [93, 94]; however, this stain is unreliable and lacks species specificity.
2. PCR testing

PCR amplification of 16S rRNA has been developed by Relman and associates using the *B. henselae* 16S ribosomal RNA gene [95]. PCR testing for *B. henselae* was successfully used to identify *B. henselae* infection in specimens from conjunctiva and from lymph node biopsies and aspirates [96–99]. PCR amplification of 16S rRNA is highly sensitive and specific in detecting Bartonella species; however, PCR-based tests are not yet commercially available [12].
3. Culture

Bartonella species can be cultured from biopsy specimen by using enriched agar at 35–37°C with 5% CO₂. Different Bartonella species tend, however, to grow better on different culture media; for example, *B. henselae* is cultured more effectively on heart infusion agar with 5% defibrinated rabbit blood [100, 101]. Tissue or blood specimens can take up to 4 weeks before growth is detected on the culture media. Specimens from blood yield better results when

a lysis centrifugation system, in which the blood specimen is lysed before it is inoculated onto the enriched media, is used [22].

With the advent of new biomolecular laboratory techniques over the past few decades, the diagnosis of cat scratch disease now relies heavily on serologic testing and, to a lesser extent, on culture or PCR-based analysis of tissue and/or fluid samples [12].

The diagnosis of CSD can be made when the clinical manifestations of the disease are combined with a serologic or a pathologic confirmation. However, other serious infections such as Lyme disease, syphilis, leptospirosis, toxoplasmosis, and toxocara should be considered and excluded in addition to the noninfectious causes such as sarcoidosis, malignant hypertension, diabetic retinopathy, pseudotumor cerebri, and malignancies, especially lymphoma and tumor metastasis. If diagnosis could not be made using the above mentioned guidelines, a biopsy may be warranted to confirm the diagnosis.

Therapy

With only few publications reporting permanent ocular damage, the overall prognosis of cat scratch disease in immunocompetent patients is generally good. Immunocompetent patients with cat scratch disease tend to have self-limited disease that resolves completely within 2–4 months in majority of cases, even without treatment. The benign nature of CSD makes the necessity of antibiotic treatment doubtful, and because of that, definitive treatment recommendations for CSD and its ocular complications have not yet been established.

In 1992, before *B. henselae* was recognized as the causative agent in CSD, Margileth presented the therapeutic outcomes of 18 different therapeutic agents in 268 patients with cat scratch disease. Margileth concluded that rifampin, ciprofloxacin, gentamicin, and trimethoprim/sulfamethoxazole have the most reasonable probability of efficacy, with rifampin 10–20 mg/kg/day every 12–24 h being the most effective in the group [21].

In 1998, however, Bass et al. reported, based on the results of a prospective, randomized study of therapy of CSD, that a single 500-mg dose of azithromycin followed by four daily doses of 250 mg resulted in faster resolution of lymphadenopathy when compared to placebo at 1 month [102].

Due to the risks associated with CSD in HIV-positive patients, antibiotics are often required to control the infection [90]. In 1999, Koehler and Relman reported a dramatic response to treatment either with doxycycline or erythromycin in immunocompromised patients with CSD [90]. Such dramatic success of erythromycin and doxycycline in treating CSD in patients with HIV encouraged the use of antibiotics in treatment of immunocompetent patients with severe ocular or systemic complications of *B. henselae* infection.

Doxycycline is usually given in an oral dose of 100 mg twice daily. Doxycycline has better intraocular and central nervous system penetration than erythromycin and is often preferred to erythromycin in treatment of ocular complications of CSD. Erythromycin, on the other hand, is preferred in children younger than 12 in order to avoid the possibility of tooth discoloration that often occurs with doxycycline treatment. An intravenous combination of doxycycline and erythromycin can be helpful in severe infections [90]. Rifampin, in an oral dose of 300 mg twice daily, can also be added to the combination.

Immunocompromised individuals with CSD can also be treated using azithromycin in a single dose of 500 mg, followed by four daily doses of 250 mg or by doxycycline in a dose of 100 mg three times daily [27, 102].

Antibiotic treatment and observation should continue for several months because of the possibility of recurrence. The duration of treatment is usually 2–4 weeks in immunocompetent patients and up to 4 months for immunocompromised patients [90]. Recurrences in HIV-positive patients have been reported even after prolonged treatment [100]. Long-term use of doxycycline or erythromycin may be useful for preventing recurrences in HIV-positive patients [101].

Oral corticosteroids have been effective in reducing the inflammation and improving the visual function in cases with systemic and posterior ocular manifestations. However, the necessity of corticosteroids therapy in isolated POGS has not been established [103, 104].

Management of pain caused by suppurative lymphadenopathy may include NSAIDs. Although aspiration of the lymph node can be done, it is not recommended because a fistulous tract may develop, and discharge may persist for several months resulting in permanent scarring. Children with CSD should be managed in association with a pediatrician specializing in infectious disease.

Controversies and Perspectives

The method of transmission of Bartonella infection to humans is still unknown. It is controversial whether the cat flea or flea feces is responsible for some cases of cat-to-human transmission. It is controversial whether *B. henselae* is the only causative agent of CSD or some other Bartonella species, as well as other bacteria, are responsible for some cases. Both the safety and the value of the use of foreign human lymphoid tissue to diagnose CSD, through the Hanger-Rose skin test remains controversial, especially after the advent of other serological and PCR tests that make the risk of its use outweigh its benefits. The necessity of treatment with antibiotics in immunocompetent patients with ocular involvement is also controversial given the benign nature of the disease.

Clinical Pearls

- *B. henselae* seropositivity has been associated with nearly two-thirds of all cases of neuroretinitis.
- The infection is transmitted to humans from infected domestic cats, especially kittens.
- Children and adolescents make up 80% of cases of CSD.

- Ocular involvement occurs in only 5–10% of all cases of CSD.
- Ocular involvement in CSD is usually in the form of unilateral granulomatous conjunctivitis with watery discharge and foreign body sensation. The presence of a single, large, and flat nodule in the bulbar or palpebral conjunctiva associated with regional lymphadenopathy helps with the diagnosis of CSD, especially when the primary inoculation site can be identified.
- Retinal and choroidal manifestations of CSD include neuroretinitis, multifocal retinitis and choroiditis, vasculitis and vascular occlusion, intermediate and diffuse uveitis, and retinal bacillary angiomatosis.
- Neuroretinitis may be associated with optic disk swelling, focal serous retinal detachment, and macular star.
- The outcome of the disease is generally benign; however, in some cases, a residual damage, in the form of optic disk pallor, decreased contrast sensitivity, dyschromatopsia, and abnormal visually evoked potentials, may happen.
- The diagnosis of CSD can be made when the clinical manifestations of the disease are combined with a serologic or a pathologic confirmation.
- Biopsy is only required when the clinical manifestations and laboratory confirmations are inconclusive.
- Antibiotic treatment ideally should be reserved for immunocompromised patients and for immunocompetent patients with severe sight-threatening ocular involvement.
- Recurrence of disease is not uncommon in immunocompromised patients due to the lack of long-lasting immunity. Longer courses of antibiotics treatment may be required in such patients.

Lyme Disease

Lyme disease, or borreliosis, first described by Steere in 1977 as an epidemic of oligoarticular arthritis in several Connecticut communities, is a multisystem disease that also involves the eye and its adnexa [105]. Lyme disease is caused by a spirochete belonging to the genus *Borrelia* and is transmitted to humans by the bite of certain infected *Ixodes* ticks in temperate climate zones [106]. Three *Borrelia* species frequently cause Lyme disease in humans: *Borrelia burgdorferi sensu stricto*, *Borrelia garinii*, and *Borrelia afzelii* [107, 108]. *B. burgdorferi sensu stricto* is found primarily in North America and Europe, while *B. garinii* and *B. afzelii* are found throughout Eurasia [107–110].

Lyme disease presents in three stages: localized early, disseminated early, and persistent late. In the first stage (3–30 days following the tick bite, which includes the incubation period), clinical findings include erythema chronicum migrans rash (classic annular skin lesion, target rash) and flu-like symptoms. Clinical findings in the second stage (weeks to months) include signs and symptoms of serious organ involvement, including neurological and cardiac systems and joints. In the third stage (months to years), the skin, joints, heart, and nervous systems are involved; however, the most common disorder is chronic severe relapsing Lyme arthritis, which in some patients may lead to permanent joint disability. The symptoms in all stages can overlap, and many patients do not manifest all stages [111].

Diagnosis

There are two ways to diagnose Lyme disease: one is considered a clinical diagnosis and the other is made as a definitive diagnosis. Clinical diagnosis is based on finding the pathognomonic skin rash (erythema chronicum migrans) in a patient with either a history of tick bite or who has recently been in regions in which Lyme disease is common. In patients who are unaware of

tick bite or in a non-endemic area, presence of erythema chronicum migrans and the involvement of two organ systems are enough for diagnosis. For a definitive diagnosis, cultures from the plasma, skin lesions, synovial fluid, and cerebrospinal fluid in Barbour-Stoenner-Kelly medium must be conducted. The probability of diagnosis is high in the early stages of the disease [112].

In the chronic stages, polymerase chain reaction can be used [113]. The enzyme-linked immunosorbent assay (ELISA) and an indirect immunofluorescence antibody test (which is less accurate but may be used when ELISA is not available) are used to detect the presence of specific antibodies to *B. burgdorferi*. The disadvantages of these tests are limited sensitivity and long latency to become positive, decreased response after antibiotic treatment, and cross-reactivity with other spirochetes [114, 115]. Because of these issues, serological testing must be reserved for patients who have uveitis of unknown cause and at least one other manifestation of the disease; if any of these tests are positive or uncertain, they should be followed by the Western immunoblot, which is more accurate and very helpful in confirming the diagnosis.

Other diagnostic tests include antibody capture enzyme immunoassay, lymphocyte antigen stimulation, and detection of antibodies in urine. Studies are underway to create more accurate serological tests for Lyme disease.

The Centers for Disease Control and Prevention made Lyme a reportable disease in 1982, and the current definition of a case of Lyme disease includes any one of the following [116]:

1. Development of erythema chronicum migrans within 30 days of exposure in an endemic area; size of lesion should be ≥ 5 cm
2. Without erythema chronicum migrans, history of exposure to endemic area, with signs involving one organ system, and a positive laboratory test
3. No history of exposure to endemic area but presence of erythema chronicum migrans as well as involvement of two organ systems
4. No history of exposure to endemic area but with erythema chronicum migrans and a positive serology

Ocular Manifestations

Because many ophthalmologists and general practitioners may not be aware of the clinical ocular features of Lyme disease, ocular Lyme borreliosis is often underdiagnosed. Ocular manifestations can involve any of the ocular structures, and, while generally occurring in stage 2, they can occur at any stage either in the presence or absence of other organ involvement (Table 7.1). Ocular involvement, including conjunctivitis, periorbital edema, and mild photophobia, may be noted in as many as 11% of patients during the first stage of the disease [111]. Severe ophthalmic manifestations and intraocular inflammation first occur during stage 2. A number of conditions have been observed in later periods of stages 2 and 3, including stromal keratitis, granulomatous iridocyclitis with or without uveitis, intermediate uveitis, vitritis, panuveitis, retinitis, retinal vasculitis, choroiditis with or without serous retinal detachment, optic disk edema, optic neuritis, ischemic optic neuropathy, optic atrophy, ocular motor cranial neuropathies, Bell's palsy, Argyll Robertson pupil, Horner's syndrome, temporal arteritis, orbital myositis, and cortical blindness. In this chapter, we will evaluate retinal and choroidal changes in Lyme disease under the following headings:

1. Intermediate uveitis
2. Retinal vasculitis, branch retinal artery occlusion, and cotton-wool spots
3. Neuroretinitis
4. Choroiditis, chorioretinitis with or without serous retinal detachment
5. Miscellaneous: Cystoid macular edema and macular pucker, retinal pigment epithelial detachment, retinitis pigmentosa-like clinical presentation, choroidal neovascular membrane, acute posterior multifocal placoid pigment epitheliopathy (APMPPE)-like clinical presentation, retinal tear, and ciliochoroidal detachment

Intermediate Uveitis

Intermediate uveitis refers to inflammation localized to the anterior vitreous, pars plana, and peripheral retina. Infectious causes of intermedi-

ate uveitis are Epstein-Barr virus (EBV) infection, human T cell lymphotropic virus type 1 (HTLV-1) infection, cat scratch disease, hepatitis C, tuberculosis, and Lyme disease [117]. Lyme disease is a causative factor in 0.6% of all intermediate uveitis cases. Patients with intermediate uveitis due to Lyme disease typically present with complaints of floaters, blurred vision, or a vague, ill-defined disturbance of vision [118]. Involvement is usually bilateral, although asymmetric [117, 119]. Symptoms may often wax and wane over many months. The clinical picture most frequently seen is that of a syndrome resembling pars planitis complicated by posterior and granulomatous anterior chamber inflammation, which is inconsistent with classic intermediate uveitis, in which anterior chamber symptoms are not regularly encountered [120]. However, in some cases, the patient may present with mild anterior chamber reactions [121]. The hallmark of the disease is vitritis, which consists of vitreous cells that form aggregates, commonly referred to as snowballs, which are quite common and, although often noted in the inferior vitreous peripherally, may be found throughout the vitreous cavity. Inflammation of the pars plana may progress to form organized exudates called snowbanks. Inflammation-induced fibrovascular proliferation within the vitreous, vitreous base, and pars plana may result in retinal tears and rhegmatogenous retinal detachment [120]. However, intermediate uveitis in Lyme borreliosis can be seen even in the absence of severe ocular complaints [122].

Retinal Vasculitis, Branch Retinal Artery, Retinal Vein Occlusion, and Cotton-Wool Spots

Retinal vasculitis is a sight-threatening inflammatory disease that involves the retinal vessels. Retinal vasculitis may be either symptomatic or asymptomatic. If the retinal vascular changes occur in the periphery of the fundus without vitreous involvement, patients may have minimal or no symptoms. The condition results in sheathing and angiospasm, as well as arterial and/or venous occlusion. Inflammation of macular blood vessels can cause macular edema.

Retinal vasculitis due to Lyme disease was first presented in 1990 by Dr. U. Schonherr and associates at the International Conference on Borreliosis in Stockholm, Sweden, based on observing two individuals with this condition in a case series of ten patients. In 1991, Smith et al. published three cases of retinal vasculitis that were found to be seroreactive for Lyme borreliosis [123]. In the same year, Lang et al. reported a 43-year-old man admitted because of recurrent vitreous hemorrhage, who was diagnosed as bilateral occlusive retinal vasculitis with proliferative retinopathy due to Lyme disease with positive IgM and IgG serology for *Borrelia burgdorferi* [124]. In 1995, Leys et al. reported seven patients with retinal vasculitis due to Lyme disease with clinical and serologic evidence of *Borrelia burgdorferi* infection [125]. Three patients presented with abrupt loss of vision due to acute retinal vasculitis, and all demonstrated engorged veins, hemorrhages, perivenous infiltrates, and retinal white spots. Arterial occlusions were observed in two patients, and leakage was present from the veins, white spots, and the optic disk on fluorescein angiography. Four patients had signs of chronic uveitis with vitritis, cystoid macular edema, and retinal vasculitis, which were associated with neovascularization and vitreous hemorrhage in one patient and with optic neuritis in another patient [125]. Karma et al. reported a case series of ten ocular Lyme borreliosis patients in 1995 [126]. In this study, six of seven patients with uveitis had retinal vasculitis [126]. They extended this series to include an additional ten ocular Lyme borreliosis patients and published the series in 2000 [127]. Among the new patients in this extended series, two patients had evidence of retinal vascular involvement: one had peripheral multifocal chorioretinitis with panuveitis and the other had a branch retinal vein occlusion, possibly caused by a vasculitic mechanism as well [127]. Based on these results, they concluded that retinal vascular involvement in ocular Lyme borreliosis may be more common than previously thought [127].

Lightman et al. reported a branch retinal artery occlusion due to Lyme disease in a 37-year-old Caucasian woman [128]. The patient

presented with a scotoma above fixation in her left eye upon awakening. There was no known history of a tick bite or skin rash. The anterior segments were normal, and there was mild bilateral vitritis. The right optic nerve was slightly swollen, the retinal arterioles were irregular in caliber, and a cotton-wool spot was present above the disk. The left posterior segment had an inferotemporal branch retinal artery occlusion, ischemic whitening of the inferior macula, multiple cotton-wool spots, mild disk edema, and focal irregularity of some arterioles. FA demonstrated a branch retinal artery occlusion in the left eye and bilateral disk edema. Positive serological tests and clinical response to antibiotics made the diagnosis of ocular borreliosis [128]. The author proposed that an immunologic response to *Borrelia burgdorferi* causes vasculitis and obliteration of small vessels, as seen in connective tissue diseases, which are known to cause retinal arterial obstruction [128].

The pathogenesis of CWS is an occlusion of a feeder arteriole and capillaries, leading to vacuoles of various sizes and representing accumulated axoplasm in the nerve fiber layer due to ischemia. CWS in uveitis is often found not only in HIV infection but also in cytomegalovirus, tuberculosis, cryptococcal infection, Behcet's disease, leptospirosis, and human T-lymphotropic virus type I. Klaeger et al. observed a 54-year-old woman who presented with recurrent iritis in her right eye and was diagnosed with ocular borreliosis and treated with doxycycline 100 mg bid for 3 weeks. After multiple recurrences of uveitis in her right eye, she presented with CWS in her left fundus (Fig. 7.2) and was treated with pentoxifylline 400 mg three times a day and salicylic acid 100 mg a day. The CWS gradually resolved but without proof that the resolution had been influenced by the therapy [129]. The patient Klaeger et al. presented differs from the Lightman et al. case in the absence of retinal whitening and focal irregularity of arterioles. Therefore, the only fundus finding of the Klaeger et al. case was CWS [129]. As a conclusion, Klaeger et al. advised ruling out ocular borreliosis in patients presenting with otherwise unexplained CWS [129].



Fig. 7.2 Fundus photograph from a patient with positive serology for Lyme disease showing multiple cotton-wool spots (CWS) in the left eye. All CWS are nearly equidistant from the optic disk, some are confluent, while some overlie major vessels (Reprinted with permission from Klaeger AJ, Herbert CP. Cotton wool spots as possible indicators of retinal vascular pathology in ocular Lyme borreliosis. *Int Ophthalmol.* 2010 Oct;30(5):599–602. Epub 2008 Oct 15)

Neuroretinitis

Neuroretinitis typically presents in the form of white retinal lesions that may vary in size and topography. An associated mild or moderate vitreous inflammation is commonly observed. FA shows early hypofluorescence and late staining of large acute white retinal lesions and isofluorescence or moderate hypofluorescence of small active retinal lesions.

The first case of neuroretinitis due to Lyme disease was reported in a 13-year-old girl by Lesser and colleagues in 1990 [130]. Winterkorn et al. published another case of neuroretinitis due to Lyme in a 21-year-old girl in the same year [131]. Schönherr et al. reported a 22-year-old white female with bilateral Leber's stellate neuroretinitis after a viral-like illness [132]. Seroconversion for *Borrelia burgdorferi* and resolution of symptoms and signs during therapy with 200 mg doxycycline resulted in a diagnosis of Lyme disease [132]. In a case series including ten patients, Karma et al. reported

four cases of neuroretinitis, three of which were bilateral and all accompanied by retinal vasculitis [126]. One year later, the same author reported a long-term follow-up of a chronic Lyme neuroretinitis that was unresponsive to systemic antibiotic therapy [133]. In 2001, Lochhead et al. reported a case of neuroretinitis due to Lyme disease in a 7-year-old girl that developed after bilateral papilledema and diagnosed by a positive Lyme IgG/M serology and cerebrospinal fluid PCR [134].

Choroiditis and Chorioretinitis with or Without Serous Retinal Detachment

Choroiditis is the inflammation of the choroid. Inflammation may be diffuse, called multifocal choroiditis, or in patches, known as focal choroiditis. If the inflammation involves both the choroid and retina, it is named chorioretinitis. Typically, the only symptom is blurred vision.

The first case of bilateral multifocal choroiditis due to Lyme disease with exudative retinal detachment was reported by Bialasiewicz et al. in 1988 [135]. This case was a 32-year-old woman who was diagnosed with Vogt-Koyanagi-Harada disease and treated with oral corticosteroids by the referring ophthalmologist. At the presentation, bilateral inflammatory cells in the anterior chamber and vitreous, diffuse choroidal infiltration with exudative retinal detachment that extended peripherally between 4 o'clock and 8 o'clock, cystoid maculopathy, and choroidal thickening on B-scan ultrasonography were noted. However, diagnosis of bilateral diffuse choroiditis with exudative retinal detachment due to Lyme disease was made via demonstration of Lyme IgM antibodies in sera [135]. Wilk et al. also reported two cases of bilateral disseminated choroiditis with exudative retinal detachments in *Borrelia burgdorferi* infection [136]. In a survey of 84 Lyme arthritis patients, Huppertz et al. reported ocular inflammation in three of them [137]. One of the patients, a 13-year-old girl, presented with bilateral intermediate uveitis and right retinal detachment. A diagnosis of Lyme borreliosis was made when antibodies to *Borrelia burgdorferi* were detected in the patient's serum; she was then treated with systemic tetracyclines.

Since arthritis recurred and vision deteriorated further, she was also treated with ceftriaxone and underwent bilateral pars plana vitrectomy. Arthritis disappeared and uveitis abated with permanently reduced visual acuity [137].

In 1993, Niuotta et al. reported a unilateral multifocal chorioretinitis due to Lyme disease in a 22-year-old myopic man [138]. Although both anterior segments were normal, multiple foci of chorioretinitis confined to the posterior pole were observed in his right retina while the left fundus was normal. The diagnosis of unilateral multifocal chorioretinitis due to Lyme disease was confirmed via demonstration of Lyme IgM antibodies in sera [138]. A case series reported by Karma et al. in 1995 included a 70-year-old female patient with chorioretinitis in both eyes [126].

Other Ocular Manifestations

Cystoid Macular Edema and Macular Pucker

Cystoid macular edema (CME) associated with Lyme disease is occasionally reported. Breeveld et al. reported a 29-year-old man with bilateral intermediate uveitis with mild anterior chamber reaction without posterior synechiae [121]. The patient had bilateral CME confirmed by FA that responded subsequently to antibiotic therapy [121]. A patient with retinitis pigmentosa-like clinical presentation reported by Karma et al. in 1993 also had CME [139]. Preac-Mursic et al. reported a 24-year-old panuveitis-iridocyclitis patient whose first isolation of *Borrelia burgdorferi* was accomplished with an iris biopsy [140]. In that patient, they reported CME, macular pucker, and an exudative inferior retinal detachment [140]. Guex-Crosier et al. presented a case with CME due to recurrent pars planitis with two episodes of acute pericarditis [141]. Karma et al. reported a 5.5-year follow-up of a Lyme neuroretinitis patient in 1996 [133]. The 29-year-old woman had intense hyperfluorescence of cystoid pattern at the juxtapapillary area in both eyes, which extended to the foveola in the left eye at presentation [133]. The patient received oral prednisone, which has no effect either on vision or fundus changes with the diagnosis of idiopathic uveitis. Two years later, the patient was admitted

with retinal edema of the same magnitude, but cystoid degeneration was also noted in both maculae. Additionally, a lamellar hole with macular pucker developed in the left macula [133]. Reibaldi et al. treated a case of CME due to Lyme disease that did not respond to antibiotic therapy with intravitreal triamcinolone acetate injection. One month following the injection, visual acuity was 1.0 and the CME had completely resolved [142].

Retinal Pigment Epithelial Detachment

Koch et al. reported a 41-year-old man who, 6 months following a tick bite, was admitted with the complaint of headache and blurred vision in both eyes due to clover-shaped parapapillary retinal pigment epithelial detachment (PED) in both eyes, which involved the macula in the left eye [143]. Although there was only moderately increased immunoglobulin in the aqueous humor and serum, they initiated 4 g/day ceftriaxone disodium for 14 days; the PEDs disappeared within a few days and visual acuity returned to normal. Although the immunoglobulin values remained unchanged, diagnosis of neuroborreliosis with retinal PEDs was made after considering the history of a tick bite and response to treatment. The author assumed that the tissue around the optic nerve head, which does not have an effective blood-brain barrier, allowed the spirochetes to spread from the central nervous system into the sub-pigment epithelial space, thus causing the observed peripapillary pattern of PED [143]. Wu et al. reported a 7-year-old child who developed bilateral pigment epithelial mottling at the fovea 1 year after resolution of papilledema due to Lyme disease [144].

Retinitis Pigmentosa-Like Retinopathy

Zierhut et al. reported an extensive depigmented choroidal atrophy in the entire anterior retina, accompanied by pigment clumping similar to retinitis pigmentosa, in a patient who had positive serological tests for syphilis and Lyme disease [145]. In 1993, Karma et al. reported a 15-year-old girl who presented with atrophic RPE, attenuated arterioles, equatorial corpuscular pigmentation in the left fundus, and bilateral pale disks [139].



Fig. 7.3 A fundus photograph from the right eye of a patient with presumed ocular Lyme borreliosis marked optic disk swelling with a *gray-yellow* lesion in the center of the macula surrounded by hard exudates. Similar exudation is also seen around the optic disk (Reprinted with permission from Amer R, Brannan S, Forrester JV. Inflammatory choroidal neovascular membrane in presumed ocular Lyme borreliosis. *Acta Ophthalmol.* 2009;87:346–348)

Biomicroscopy revealed opacity of the posterior capsule and posterior vitritis in the left eye. A fluorescein angiogram of the left fundus revealed exaggerated choroidal fluorescence in the initial phases, delayed retinal circulation, incomplete filling of the venules, and cystoid macular edema in the late phases. A diagnosis of Lyme disease was made with the aid of CSF and vitreous fluid specimens PCR [139].

Choroidal Neovascular Membrane

Amer et al. described the occurrence of inflammatory choroidal neovascular membrane (CNVM) in two patients with Lyme disease [146]. Both cases had a history of tick bite and responded to IV ceftriaxone treatment; however, because both were seronegative, their diagnosis was clinically based [146]. The first patient, a 16-year-old male, had an elevated gray-yellow lesion in the center of the macula surrounded by subretinal fluid and fine retinal hemorrhages on its surface as well as temporal to it (Fig. 7.3). There were circinate hard exudates surrounding it and similar exudates nasal, superior, and inferior to the optic disk. In the second patient, a



Fig. 7.4 Fundus photograph from a patient with negative serology for Lyme disease showing a *yellow* subfoveal lesion with marked fibrosis of the overlying retina and retinal striae radiating between the lesion and the optic disk. Flat subretinal hemorrhage is noted at the inferotemporal margin of the lesion (Reprinted with permission from Amer R, Brannan S, Forrester JV. Inflammatory choroidal neovascular membrane in presumed ocular Lyme borreliosis. *Acta Ophthalmol.* 2009;87:346–348)

38-year-old healthy female, fundus examination revealed a subretinal yellow macular lesion with marked overlying retinal fibrosis and retinal striae extending nasally (Fig. 7.4). Small deep retinal hemorrhages were noted on its inferotemporal edge [146].

Acute Posterior Multifocal Placoid Pigment Epitheliopathy-Like Picture

Bodine et al. reported a 32-year-old man who had multifocal choroiditis without vitreous involvement [147]. At presentation, the patient had multiple white lesions at the level of the choroid in both eyes. In FA, patches of hyperfluorescence and hypofluorescence in the macula, with staining in the late transit of the left eye, and patches of hypofluorescence in the inferior retina of the right eye were detected. The other lesions had a central area of staining surrounded by a hypofluorescence halo. During the follow-up, additional white choroidal lesions were noticed in the midperipheral fundus in both eyes, and older lesions had begun to atrophy and become lightly pigmented. Using the serial ELISA of the patient's serum and cerebrospinal fluid specimen, the author suggested the diagnosis of Lyme disease and treated the patient with

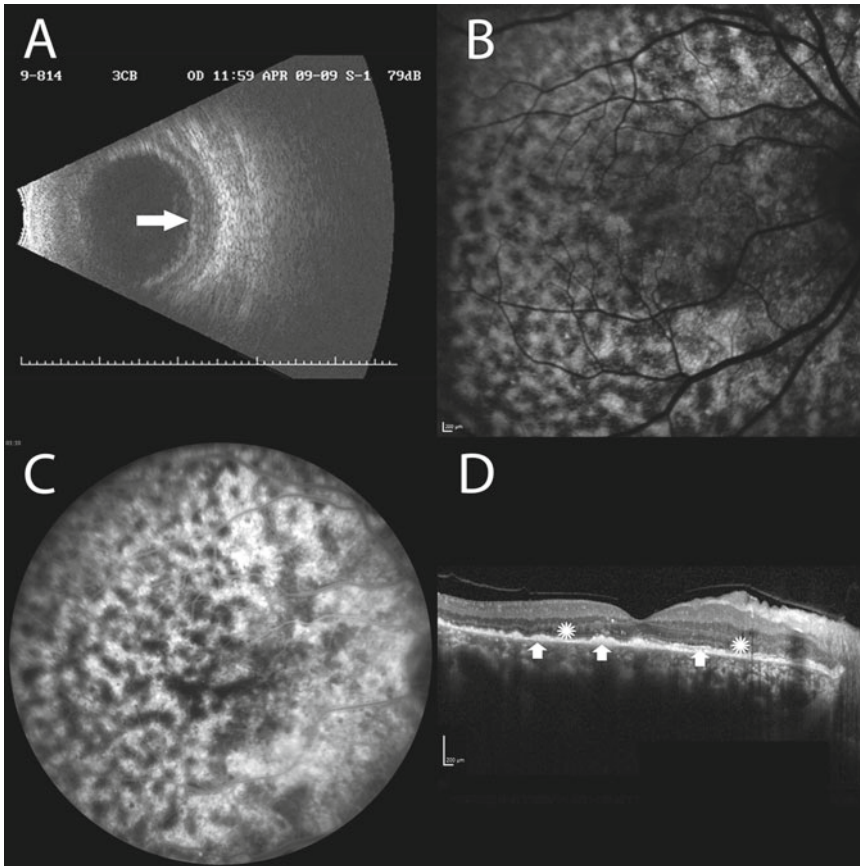


Fig. 7.5 Case of recurrent ciliochoroidal detachment in a patient with positive serology to *Borrelia burgdorferi*. Transverse B-scan ultrasonography (a) directed toward the ciliary body nasally in the right eye, showing extensive, shallow elevation of the ciliary body (arrow). Autofluorescence (b) and mid-phase FA (c) images from the same eye showing leopard skin pattern of alternating

hypo- and hyperfluorescence, indicating the recurrent and long-standing nature of the detachment. Horizontal section of spectral domain optical coherence tomography across the fovea of the same eye (d) showing damage to the retinal pigment epithelium and photoreceptor layers (arrows) with attenuation of the outer nuclear and outer plexiform layers of the retina (asterisks)

intravenous ceftriaxone. Following that treatment and during the follow-up, no new choroidal lesions appeared and the old lesions became moderately pigmented; the retinal lesions were unchanged. Bodine et al. concluded that some of the cases of APMPE may actually have been Lyme disease [147]. Wolf et al. screened the sera of 18 patients who possessed all of the characteristic fundus and fluorescein angiographic appearances of APMPE for *burgdorferi*-specific antibodies. They could not demonstrate any serologic immune response to *burgdorferi* to support an association between these two disorders [148].

Retinal Tear

In 1991, Smith et al. published three cases of retinal vasculitis who were found to be seroreactive for Lyme borreliosis [123]. In one of the cases, a 25-year-old patient presented with a whitish deposit in the preretinal space and a retinal tear in the left eye at 1:30 with whitish exudative material on an attached flap and vitritis [123].

Ciliochoroidal Detachment

We have recently evaluated a 74-year-old man (Fig. 7.5) who presented with bilateral ciliochoroidal detachments and macular edema in the right eye. Slit-lamp examination revealed

no cells or flare in the anterior chambers. Funduscopy revealed multiple, bilateral, and symmetrical hypo- and hyperpigmentations resembling a leopard-spot pattern. FA showed patchy areas of hyperfluorescence corresponding to the areas of RPE hypopigmentation, with no leakage or staining. B-scan showed diffuse choroidal thickening and mild vitreous opacities in both eyes, with ciliochoroidal detachment in the right eye. Optical coherence tomography showed macular edema in the right eye and epiretinal membrane in the left. Lyme disease serology was positive for IgG and negative for IgM. Subsequently, the patient was started on IV ceftriaxone (2 g/day) for 28 days. The improvement continued over the following months with complete resolution of the ciliochoroidal detachments in 2 months.

Therapy

In case of acute disease in adults, treatment involves oral 100 mg doxycycline twice daily or 500 mg amoxicillin three times for 14–21 days. In case of doxycycline and amoxicillin allergy, oral cefuroxime 500 mg twice daily or erythromycin 250 mg four times daily for 14–21 days is recommended. In children, treatment of acute disease involves oral amoxicillin 50 mg/kg/day in three divided doses for 14–21 days. In case of penicillin allergy, oral cefuroxime 30 mg/kg/day in two divided doses for 14–21 days is recommended [149, 150].

In case of neurological and/or ocular involvement in adults, treatment involves intravenous (IV) ceftriaxone 2 g once a day or cefotaxime 2 g every 8 h for 14–28 days. In case of ceftriaxone or penicillin allergy, doxycycline 100 mg orally three times a day for 30 days is recommended. In children, treatment involves IV ceftriaxone 75–100 mg/kg/day (maximum 2 g) once a day for 14–28 days or IV cefotaxime 150 mg/kg/day (maximum 6 g) in 3–4 divided doses for 14–28 days [149, 150].

In a case of tick bite, a single dose of 200 mg doxycycline should be given within 72 h for prophylaxis [150, 151].

Controversies and Perspectives

The diagnosis of Lyme disease can be controversial and difficult. The presence of positive titer to *Borrelia burgdorferi* does not necessarily establish a diagnosis of Lyme disease. Appropriate clinical findings and symptoms should also exist at presentation. Most clinicians would agree that once the infection is treated completely (e.g., ocular Lyme disease should be treated with intravenous antibiotics), the infection is eradicated. Unless the patient is re-infected, repeated anti-microbial therapy is not required after initial treatment.

Clinical Pearls

- Lyme disease is a clinical diagnosis. Ancillary tests are performed to confirm the diagnosis.
- Erythema chronicum migrans rash might not always be annular and may occur as a more homogenous pink or red lesion.
- Serological tests are not needed for diagnosis of early Lyme disease. Four or six weeks are needed to develop antibody response.
- During the diagnostic workup, IgM and IgG tests must be ordered first. Western blot testing is ordered as a follow-up test when the initial tests are positive or indeterminate. Do not skip IgM and IgG tests.

Syphilis

Syphilis is an infectious disease caused by the bacterium, *Treponema pallidum* [152]. Treponemas are motile, spiral-shaped bacteria belonging to the Spirochaeta family. Many *Treponema* species are harmless members of the normal flora in humans. However, pallidum, endemicum, and pertenu are some of the pathogenic subspecies causing venereal syphilis, endemic syphilis, and yaws, respectively [153]. Syphilis is a sexually

transmitted disease, most commonly acquired via direct contact with a syphilitic sore [154–156]. It is conventionally divided into three stages: primary, secondary, and tertiary. A chancre is considered definitive for primary syphilis. A rash, with or without constitutional symptoms, indicates secondary syphilis. Cardiovascular disease, gummatous lesions, or neurologic manifestations such as tabes dorsalis, general paresis, seizures, or hemiparesis indicate tertiary syphilis [155].

Ocular Manifestations

Ocular manifestations usually occur in the secondary and tertiary stages of the disease [156] but can potentially occur at any stage (Table 7.1) [157, 158]. A review by Aldave and colleagues categorized ocular manifestations according to the stage of syphilis [156]. Retinal vasculitis and pigmentary mottling in “salt-and-pepper” pattern were seen in congenital syphilis cases. In cases of secondary syphilis, eyes were usually involved after other systemic manifestations had resolved. Retinal manifestations were similar in secondary and tertiary syphilis with necrotizing retinitis, neuroretinitis, retinochoroiditis, and serous retinal detachment, with cystoid macular edema being seen in both [156]. Optic nerve findings were slightly different between the two stages: disk edema was seen in both and optic atrophy and gumma were mainly seen in tertiary syphilis.

After a period of low incidence, there has been a resurgence of syphilis reported across the world [159–165]. In the United States, a decline in syphilis cases was reported between the years 1990 and 2000 [166–168]. However, between 2001 and 2007, the number of cases of primary and secondary syphilis increased from 3.0 to 6.6 per 100,000 of the population. In San Francisco, the number of syphilis cases increased from 44 in the year 1999 to 522 in the year 2003, while in the UK, a 15-fold increase in incidence was noted during the same period. Ocular syphilis is seen most commonly among African-American men [157], with high incidence among men who have

sex with men (MSM) and are co-infected with HIV [165, 167–169].

Ocular syphilis can affect any layer of the eye, with uveitis being the most common overall clinical manifestation [170]. Uveitis at times can also be the sole manifestation of the disease and may be seen within 6 weeks of the primary syphilis infection [171]. Chorioretinitis, vitritis, and vascular sheathing have been reported as common posterior segment manifestations of ocular syphilis, with chorioretinitis usually being the most common [156, 157, 172].

There are no pathognomonic ocular clinical presentations of syphilis; therefore, it is important to have a high index of suspicion among the high-risk populations described above, including African-American MSMs who are HIV-positive, and to be vigilant for the presence of systemic signs and symptoms of the disease.

Retina and Choroid

Retinal and choroidal involvement in syphilis usually occurs together. If the neurosensory retina is involved first and choroid and RPE are involved later, the finding is described as retinochoroiditis; if the choroid and RPE are involved first and the neurosensory retina later, it is known as chorioretinitis [172].

Chorioretinitis has been described as large areas of atrophic scarring bordered by proliferation of the RPE. Choroidal vessels, RPE, and outer retinal layers may be absent within the scarred areas [173, 174]. Two patterns of chorioretinitis have been described in literature: diffuse and localized. The diffuse form usually occurs in secondary syphilis and is characterized by multiple grayish-yellow chorioretinal lesions that may or may not be associated with vitritis, vasculitis, retinal edema, and retinal detachment. The lesions may fuse to give the appearance of general retinal whitening similar to that seen in herpetic retinitis [159]. A localized form usually occurs in the later stages and is characterized by focal pale yellow subretinal lesions at the level of the RPE that typically occur around the optic disk and macula and may be associated with vitritis, shallow retinal detachment, papillitis, or retinal vasculitis [175, 176]. Such presentation

was initially described by Gass as syphilitic lesions mainly involving the RPE and given the name acute syphilitic posterior placoid chorioretinitis (ASPPC) [176]. Gass et al. described six patients who had large, placoid, yellowish lesions with pale centers at the level of the pigment epithelium in the macula and juxtapapillary areas. All eyes had associated vitritis, and FA showed a leopard skin pattern with early hypofluorescence and late staining [176]. The pathogenesis of this clinical lesion is believed to be due to the spread of spirochetes into the RPE. Another hypothesis is that immune complex deposition in the retina leads to this clinical picture [177]. Multiple similar cases have been reported in the literature since then [167, 178–186]. This lesion is thought to be more common among patients with decreased immunity, for example, HIV-positive patients with syphilis and following steroid treatment [179, 181, 182]. However, it has recently been reported in immunocompetent patients as well [178, 183–185]. Menon and colleagues reported “Ganzfeld” electroretinogram (ERG) and multifocal ERG findings in their patient with ASPPC [185]. The readings were markedly reduced and undetectable, respectively; treatment with penicillin led to complete resolution of these functional defects, suggesting reversible loss of function in their patient with ASPPC. Bellamann and colleagues reported increased fundus autofluorescence in the area corresponding to the lesions of posterior placoid chorioretinopathy [186]. Although characteristic of syphilis in the appropriate clinical setting, these placoid lesions are not unique to syphilis; they may also be seen in serpiginous choroiditis, viral retinitis, and acute posterior placoid pigment epitheliopathy.

Morgan and colleagues described two cases of acute syphilitic chorioretinitis [175]. The first patient was a young woman with a history of positive serology for syphilis, who presented with decreased vision in one eye. Examination revealed active inflammation in the anterior chamber and scattered foci of chorioretinal involvement throughout the posterior pole. The second patient also presented with acute unilateral loss of vision. In this case, there were no

obvious signs of inflammation in the anterior chamber. Funduscopy examination revealed venous sheathing, shallow macular detachment, and infiltrates in the macula at the level of the RPE. This patient’s FA showed staining and leakage of the affected retinal veins and chorioiditis localized to the macula. Both patients showed prompt response to IV penicillin with resolution of the lesions and improvement of vision. These cases described two different forms of syphilitic chorioretinitis: one had a diffuse chorioretinitis associated with anterior chamber inflammation, while the other had a more localized chorioretinal involvement with evidence of vasculitis.

Blodi and colleagues studied the histological appearance of four eyes with syphilitic chorioretinitis [173]. In two eyes, there was proliferation of the RPE cells into the choroid through a break in the Bruch’s membrane, while in the other two there was proliferation of glial tissue through similar breaks in the Bruch’s membrane. The fundus examination of one eye with glial proliferation showed multiple atrophic partly hyperpigmented patches and attenuated and sheathed vessels, while the other case showed macular scarring. Of the two eyes with RPE proliferation, one was a case of congenital syphilis and had inactive chorioretinitis with extensive scarring, while the other eye showed chorioretinal adhesions.

Focal or multifocal chorioretinitis can occur in the secondary or tertiary stages of syphilis. Features more specific to secondary syphilis include isolated vitritis and vascularized iris nodules; gummas are seen in tertiary syphilis [156].

Browning and colleagues described a patient who developed a lesion morphologically and angiographically very similar to that seen in birdshot chorioretinopathy [157]. They reported it as a broad band of pale inflammatory change in the choroid and retina in the absence of vasculitis; vitritis was concomitantly present; FA showed delayed venous return from the site of the lesion. After treatment with penicillin, the inflamed area of choroid became depigmented and FA findings remained the same at 1-month follow-up. Villaneuva and colleagues reviewed the clinical findings of 20 patients diagnosed

with posterior uveitis secondary to syphilis [172]. They categorized the patients as having acute or chronic disease based on whether it had been less than or more than 3 months since disease onset. Diffuse chorioretinitis was found to be the most common manifestation in 11 of the 12 patients with chronic disease; one patient had chronic retinal vasculitis. Among the eight patients with acute disease, multifocal chorioretinitis was seen in four, and one patient had acute retinal vasculitis. Chorioretinitis may be associated with retinal vasculitis, edema of the optic disk, serous retinal detachment [171], or tractional retinal detachment [169]. Lesions are most commonly located in the posterior pole and mid-periphery and may increase in size with time [175].

Ocular syphilis can occur with isolated involvement of the retina in the form of focal retinal edema, vasculitis, or papillitis with minimal to absent involvement of the anterior chamber [155, 171].

Jumper and colleagues described three cases of exudative retinal detachment occurring in association with uveitis and periphlebitis; although vision did not normalize, the detachments resolved completely following antibiotic treatment [187]. The authors suggest that earlier treatment may lead to a better visual outcome. In another case of retinal detachment secondary to syphilis, *Treponemas* were identified in the subretinal fluid; however, despite aggressive treatment that included penicillin, the patient had a poor visual outcome with recurrence of detachment [188].

In 2003, Anand and colleagues reported a case of multifocal central serous retinopathy occurring bilaterally in a patient with neurosyphilis in the absence of any other signs of ocular inflammation [189]. The RPE detachment resolved slowly over the course of 2 years, and the patient maintained good vision. However, it could not be established with certainty whether these detachments were secondary to syphilis.

Necrotizing retinitis can be caused by a number of etiological agents such as toxoplasma, HSV, and CMV, including *Treponema pallidum*. In HIV-positive MSMs, any of these agents,

including *Treponema pallidum*, might be the causative agent, and it may be impossible to distinguish them from each other clinically. However, accurate identification of the etiological agent is important to ensure correct treatment, which in the case of syphilis is associated with an excellent visual outcome. Mendelsohn and colleagues discuss the case of a 32-year-old man who presented with blurred vision, redness, and pain in his right eye [190]. The patient did not fit into the “typical” demographic pattern of a syphilitic patient; the patient revealed a monogamous sexual relationship only with his wife. On examination, there was evidence of anterior uveitis; funduscopy showed a pale optic disk with ill-defined borders, and yellowish-white patches of retinitis were scattered over the posterior pole with evidence of vascular sheathing and some vascular occlusion. There was no evidence of any skin lesions. The presentation was typical of acute retinal necrosis; only a positive VDRL and FTA-ABS directed the authors towards a diagnosis of syphilis. The patient later admitted to homosexual contact and was subsequently treated with penicillin. Apart from a transient worsening of symptoms due to the Jarisch-Herxheimer reaction, the patient had an uneventful clinical course and vision was restored to normal over the course of several weeks. The authors discuss that it may not always be possible to distinguish syphilitic retinitis from CMV retinitis, herpes retinitis, or ARN. In another case series of 20 eyes with ocular syphilis, four patients presented with panuveitis and necrotizing retinitis. These were mistakenly treated initially with acyclovir, which was later switched to penicillin when laboratory testing identified syphilis infection [167].

We recently published a diagnostic challenge that discussed the case of an HIV-positive patient with unknown immune status who presented with a severe anterior uveitis with hypopyon (Fig. 7.6), vitritis, vasculitis, and optic disk edema [191]. The consultants discussed the possible etiologies: agents, acute retinal necrosis, syphilis, as well as noninfectious causes such as sarcoid and malignancy were possible differentials. However, iritis and hypopyon in a patient with retinitis are less likely to be present in a case of acute retinal

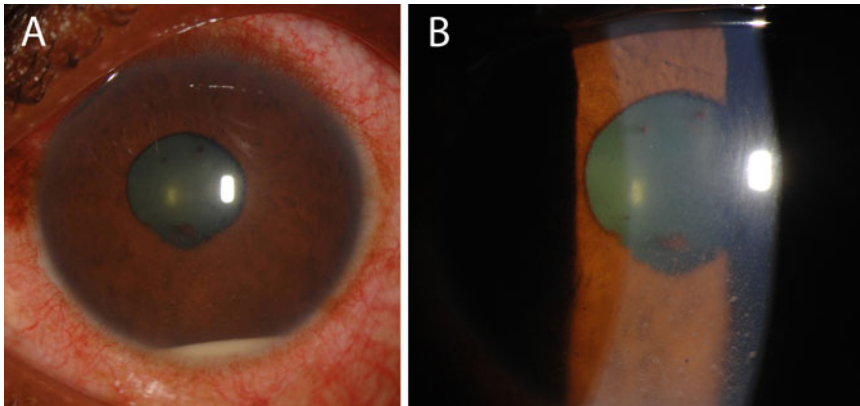


Fig. 7.6 Slit-lamp photograph of the anterior segment of the left eye, illustrating conjunctival injection, posterior synechiae, and hypopyon (a) and mutton fat keratic precipitates (b)

necrosis versus a case of syphilis. In cases when a patient's CD4 cell count is known, the differential can be narrowed down further. For example, CMV retinitis occurs in patients with very low CD4 counts, while ocular syphilis occurs in patients with comparatively higher CD4 counts. None of the cases of ocular syphilis reported by Shalaby and colleagues had CD4 cell counts less than 70 cells/mm³; in the case series by Balba, CD4 counts ranged between 388 and 594 cells/mm³ [169, 192].

There are a few cases reported where morphology may help over serology for the diagnosis of ocular syphilis [159]. Wickremasinghe and colleagues reported a case series of five patients with ocular syphilis who had very similar patterns of involvement; each had areas of inner retinitis with several preretinal/inner retinal dots and retinal arteriolitis. They treated two of their patients empirically with penicillin based on the above described fundus appearance despite negative serology. One of the patients treated empirically was later found to have a positive serology for syphilis.

Retinal involvement may rarely present with a picture very similar in appearance to retinitis pigmentosa (RP). Morgan and colleagues describe a case in which a patient was initially given the diagnosis of RP before being identified as having syphilitic retinopathy [175]. Villanueva described this finding in a case of chronic chorioretinitis

causing significant RPE damage [172]. Skalka and colleagues discuss that presence of vitritis, areas of chorioretinal atrophy, and perivasculitis are more likely to be seen in patients with syphilis than in those with RP [193]. The blood vessels in syphilis are less stenosed, and the disease is more likely to be unilateral. In both RP and syphilis, electroretinogram shows reduction in amplitude of the waves depending on the extent of retinal damage. However, in syphilis, A and B wave latencies remain normal, while in RP they are prolonged.

Retinal Vasculature

Retinal arterioles and venules may both be involved, or there may be isolated involvement of either one [175, 194, 195]. Vascular involvement may be limited to staining of vessels only visible on FA, or it may be seen as tortuous vessels with extensive exudation [159]. Vascular involvement may be followed by neovascularization or stenosis of the retinal vessels [159, 175].

Yokoi and colleagues report a case of irreversible damage of retinal vessels due to syphilitic vasculitis occurring in the secondary stage of the disease [196]. They describe a patient who presented with severe loss of vision in his left eye for 3 weeks before presentation. Examination showed minimal presence of uveitis or vitritis. Funduscopy examination showed hemorrhages, white exudates,

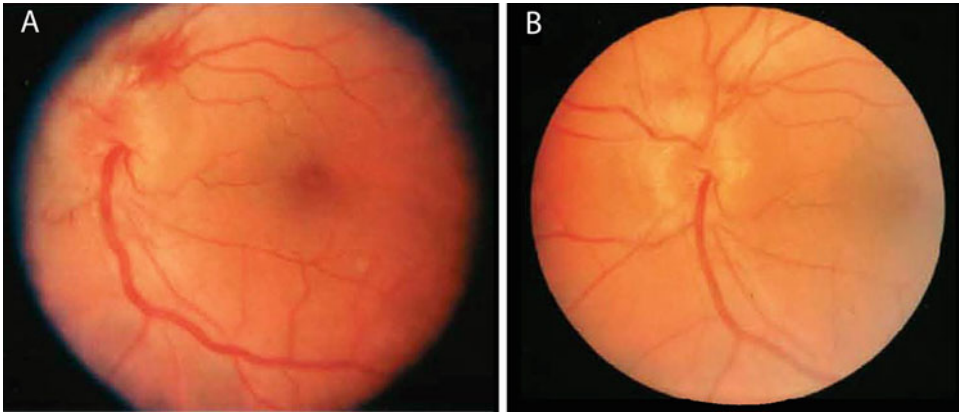


Fig. 7.7 Fundus photograph of the left eye showing optic disk swelling, peripapillary flame hemorrhage, and venous distension; the patient did not have vitritis at presentation (a). Twenty-four days after initiation of treatment with intravenous penicillin, there is remarkable resolution of the fundus abnormalities (b) (Adapted

with permission from Browning D. Posterior segment manifestations of active ocular syphilis, their response to a neurosyphilis regimen of penicillin therapy, and the influence of human immunodeficiency virus status on response. *Ophthalmology*. 2000;107:2015–2023)

and severe edema in the posterior pole with vascular sheathing at the mid-periphery. FA showed delay in filling and hyperpermeability of the vessels; some vessels were completely occluded and showed no filling with dye. Six-month follow-up after treatment demonstrated resolution of the edema, hemorrhages, and exudates. However, the peripheral capillary non-perfusion and occlusion of the sheathed vessels persisted.

Morgan and colleagues described a patient who presented to them with complaint of a scotoma, the presence of which was verified on Amsler grid [175]. Funduscopy revealed multiple cotton-wool spots and one particularly large cotton-wool spot corresponding to the scotoma in his visual field. FA revealed the presence of capillary non-perfusion at that point. No other evidence of inflammation was described in their case. The patient was treated with IV penicillin for 10 days, but no further follow-up was available regarding the resolution of the scotoma.

Optic Disk

The optic nerve may be affected unilaterally or bilaterally, and involvement can occur as perineuritis, optic neuritis, retrobulbar neuritis, or papilledema (Fig. 7.7) [197]. Involvement of the optic

disk may manifest as field defects or rapid vision loss, while morphologically it does not appear to be different from any other disease entity involving the optic nerve. Inflammation of the optic nerve may occur in isolation, or there may be concomitant inflammation of the vitreous and aqueous humor [197]. Other syphilitic manifestations include a well-demarcated opacified area of RPE around the disk [157] and a bilateral presence of optic disk edema with surrounding splinter hemorrhages [157, 197] that may even be present at the macula, leading to very poor vision [197].

Prokosch and colleagues compared the visual outcomes of 60 cases of syphilitic optic neuritis reported in literature [197]. They reported better outcomes in HIV-negative patients and in patients who received treatment with corticosteroids in addition to penicillin and probenecid. The benefit of additional steroid treatment did not seem to apply to the HIV-positive population.

Corticosteroids, however, should be used with caution in patients with syphilis. Zamani and colleagues cite a case of a 38-year-old Caucasian male who presented with decreased vision and color sensitivity [179]. Three weeks after treatment with oral prednisone only, his vision worsened and yellow placoid lesions developed around his macula. Discontinuation of steroid treatment

was followed by resolution of the lesions and improvement of vision by the next follow-up visit 5 days later. At this time, the patient was found to be positive for RPR and VDRL and was treated successfully with ampicillin. This case highlights the importance of correctly identifying syphilis at the outset as steroid treatment alone, without antibiotics, can lead to adverse outcomes.

Indocyanine Green Angiography in Ocular Syphilis

Mora and colleagues described the indocyanine green (ICG) findings in 16 eyes with ocular syphilis. Their review of late frames in 11 eyes showed multiple scattered hyperfluorescent areas in the mid-periphery [198], which were later confirmed in another case report [183]; late hyperfluorescence around retinal vessels was identified in one patient in their series [198]; and two eyes in their series showed ICG abnormalities in the absence of findings on clinical examination and FA. These findings suggest the possibility of using ICG as a diagnostic tool when suspicion is high, but funduscopy and FA do not reveal any abnormalities.

Association Between HIV and Syphilis

Before the advent of penicillin, syphilis was identified as one of the most common causes of eye infection [172]. In recent years, there has been a resurgence of ocular syphilis among HIV-infected individuals, with syphilis being identified as the most common bacterial cause of uveitis [169]. HIV co-infection leads to a rapid progression of ocular syphilis [199] with more severe manifestations [168, 200], which are frequently bilateral and involve the posterior segment [169, 176, 197, 201, 202]. In a review of literature of syphilitic optic nerve manifestations, Prokosch and colleagues reported a lower rate of improvement in the HIV-positive versus the HIV-negative population [197]. Historically, CMV retinitis has been the most commonly reported ocular infection associated with HIV [203]; however, ocular

syphilis is becoming increasingly common among HIV patients and must be kept in mind as a differential when considering etiological agents of retinitis in this population [192]. Ocular syphilis does not seem to occur only in the immunocompromised state of HIV infection; clinical manifestations have been reported in literature irrespective of CD4 cell count and whether or not the individuals are receiving antiretroviral treatment [167, 169, 192]. Shalaby and colleagues reported that HIV-positive patients who were not receiving antiretroviral treatment experienced severe involvement of the eye with syphilis. Over a 12-year period, ocular syphilis was identified in 0.6% of 2,085 HIV-positive patients [169]. Most of their patients had a CD4 count less than 200 cells/mm³, but none had a CD4 count lower than 70 cells/mm³. Later, in 2006, Balba and colleagues compared the occurrence of ocular syphilis before and after the era of HAART [192]. In a retrospective chart review of 453 patients screened for syphilis between 1997 and 2001, 16 cases were identified to have syphilis, but none had ocular manifestations; however, between 2001 and 2002, they identified three cases of ocular syphilis. All three cases were MSMs, and their CD4 counts ranged between 388 and 594 cells/mm³. They discussed that restoration of the immune system did not protect HIV-positive individuals from ocular involvement with syphilis but instead made it more likely to experience the inflammatory manifestations of the disease [192]. They reported blurred vision to be the most common presenting complaint; bilateral posterior uveitis was observed in all three patients, while one patient also had retinal detachment [192]. Ocular syphilis, in patients who are HIV-positive, has been reported to cause papillitis, optic neuritis, branch retinal vein occlusion, necrotizing retinitis, periphlebitis, and serous and exudative retinal detachment among other manifestations [168, 201, 202, 204].

Clinical Importance of Ocular Syphilis

Ocular syphilis can be the first manifestation of syphilis and HIV status of a patient. In the case

series published by Browning and colleagues, ocular syphilis was the first manifestation of HIV status in three of the five patients who were HIV positive [157]. In another case series of 12 patients (20 eyes), ocular manifestations of syphilis were the first signs of a positive HIV status in three patients [167]. In the retrospective case series reported by Shalaby and colleagues, ocular complaints were the first manifestations of syphilis in half of their patients, some of whom were later identified to have a concomitant rash [169].

Ocular syphilis may go unrecognized, especially in the private practice setting. According to a retrospective chart review of 14 patients by Browning and colleagues, six patients were seen by ophthalmologists prior to presenting to them; syphilis was not identified as the etiological agent in any of the six patients, who were instead treated with different formulations of steroids [157].

Therapy

Ocular manifestations of syphilis are usually associated with neurological involvement and therefore should be treated according to the recommendations for neurosyphilis. The Centers for Disease Control (CDC) recommends aqueous crystalline penicillin G 18–24 million units administered as 3–4 million units IV every 4 h or as a continuous infusion for a total of 10–14 days. If patient compliance is certain, an alternative regimen is procaine penicillin 2.4 million units intramuscular (IM) once daily, plus probenecid 500 mg orally four times a day, both taken for a total of 10–14 days [205].

For penicillin-allergic patients, ceftriaxone 2 g daily IM or IV for 10–14 days can be used. However, there is a possibility of cross-reactivity between cephalosporins and penicillins. In such cases, one may consider skin testing to confirm allergy; if positive, follow with desensitization [205].

Also, if ocular syphilis is suspected or diagnosed, one needs to perform a cerebrospinal fluid (CSF) examination to complete the evaluation. If pleocytosis is detected, one needs to repeat CSF

examination every 6 months until the cell count becomes normal. If the cell counts do not decrease after 6 months or remain abnormal after 2 years, consider re-treatment and closely follow the patient [205].

Corticosteroids play an important role in the treatment of ocular syphilis. However, steroid treatment should be initiated at the appropriate time. If continued for long without appropriate antibiotics, it can lead to worsening of the disease with increased treponemal load and development of new lesions. However, initiating steroid treatment in association with antibiotics plays an additive role in combating the infection and also helps to avoid the Jarisch-Herxheimer reaction [156, 178, 179].

Jarisch-Herxheimer reaction is a febrile reaction usually occurring within the first 24 h of initiating treatment for syphilis. It has been reported to cause transient worsening of symptoms [190], but some cases may experience a very severe reaction [206, 207]. Pournaras and colleagues report a case of bilateral giant tears and retinal detachment developing in an emmetropic 45-year-old man 2 weeks after starting penicillin treatment for syphilitic uveitis [207]. The inflammation associated with severe vitritis may have been exacerbated by the inflammatory changes associated with the Jarisch-Herxheimer reaction, leading to giant retinal tears in this patient. Danesh-Meyer and colleagues recommend pretreatment with corticosteroids a few hours before commencing penicillin treatment to avoid having a severe Jarisch-Herxheimer reaction [208].

The Center for Disease Control (CDC) guidelines state that antibody titers of the non-treponemal tests, for example, VDRL or RPR, are reflective of disease activity [152]. However, cases have been reported in the literature that have severe eye disease despite having low titers [209]. Manifestation of ocular symptoms occurring after previous treatment for syphilis may account for the low antibody titers in some patients with ocular involvement of the disease [172]. Also, VDRL and FTA-ABS should both be performed for accurate diagnosis as VDRL alone without an FTA-ABS test may cause one to miss many cases of ocular syphilis [209].

Controversies and Perspectives

The incidence of ocular syphilis is increasing and the disease can present in many different ways. Morphology of the lesions is generally not believed to be helpful in the diagnosis of the disease; however, as mentioned in the text, cases where morphology rather than serology pointed to the diagnosis have been reported in literature. We have discussed most of the retinal and choroidal manifestations reported in the literature. However, there may be newer ways in which syphilis may present. As co-infection with HIV continues to modify the progression of this disease, it is important to be vigilant for the presence of syphilis when patients from high-risk populations present with ocular inflammation. However, in some cases, patients simply may not give history of high-risk behavior. Therefore, demographics, history, examination, laboratory tests, including treponemal and non-treponemal antibody tests, imaging modalities, and in some cases retinal function tests should all be used effectively to allow one to make the correct diagnosis. Posterior segment involvement should not be looked at in isolation as a concomitant anterior chamber inflammation as well as systemic signs and symptoms may direct one toward the diagnosis. Prompt identification and treatment can lead to rapid and full recovery in most cases.

There are debates regarding the significance and the correct timing of performing the CSF examination in patients with syphilis. The CSF-VDRL test is not very sensitive for detection of antibodies, and in HIV-positive patients, CSF protein levels and cell counts are usually abnormal without actual invasion of the CNS by the *Treponemas*. Also, CSF pleocytosis persists for long periods of time in patients who are co-infected with HIV. Therefore, the presence of cells on follow-up CSF examination is not necessarily an evidence of treatment failure. Close clinical correlation is required. CSF examination is recommended for cases of ocular syphilis. However, for infection limited to the anterior

chamber, its significance is debatable. Although the CDC does not recommend a different treatment regimen for HIV-positive versus HIV-negative patients with syphilis, it is likely that HIV-positive patients may have higher rates of treatment failure and complications, and in some cases, a more aggressive treatment approach may be needed.

Clinical Pearls

- Ocular syphilis is frequently associated with neurosyphilis; CDC recommends CSF examination in these patients.
- For diagnosis of ocular syphilis, both the non-treponemal (i.e., VDRL, RPR) and treponemal tests (i.e., FTA-ABS) should be performed to avoid missing the diagnosis.
- CDC recommends testing for HIV infection in patients diagnosed with neurosyphilis; strongly consider HIV testing in any patient presenting with ocular syphilis.
- Ocular infection with *Treponema pallidum* is considered tertiary syphilis and requires complete therapeutic course of 10–14 days with intravenous therapy; treatment with intramuscular antibiotics is often not sufficient.
- Syphilis has no pathognomonic manifestations; one needs to consider the diagnosis in patients who have risk factors for acquiring the infection.
- One needs to rule out infectious causes of inflammation before initiating treatment with steroids; appropriate treatment of ocular syphilis with intravenous penicillin often yields excellent visual outcome.

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