Tuberculosis-related Uveitis

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1 Review of Tuberculosis Related Uveitis

Tuberculosis (TB) infection is considered common worldwide affecting one-third of the world's population especially in developing economies, immigrant populations, and immunocompromised patients in developed nations (Bloom & Murray, 1992). According to the World Health Organization, the highest prevalence has been reported in Southeast Asia (Department of Health of the Philippines, National Tuberculosis Control Programme). The incidence of tuberculosis has reported to increase with the increase in the HIV infected population (Tollefson et al., 2013). TB is a chronic infection caused by Mycobacterium tuberculosis (M. Tuberculosis) which is a particularly aggressive microorganism. The host's defense is based on the induction of cellular immunity, in which the creation of a granulomatous structure is considered to have an important role (Bloom & Murray, 1992). M. tuberculosis is regarded the most insidious microbial human pathogen known. This bacillus is able to induce an infection in the human body, the so-called latent tuberculosis infection (LTBI), which is considered persist for a long period of time, even, for the whole life (Bloom & Murray, 1992). It is currently reported that around a third of the world’s population (2.5 billion people) has an LTBI (Guimaraes et al., 2012). 10% of people with LTBI are disclosed to develop active TB, contributing to 9 million new cases and 2 million deaths every year (Guimaraes et al., 2012). This is considered as a catastrophic process with no apparent end in sight as all these TB infections constantly generate new LTBI cases (approximately 100 million a year) (Rivest et al., 2013). The incidence of tuberculosis-related uveitis (TRU) is also shown to have a rising trend (Campos et al., 2008; Mathur & Biswas, 2012). In a Western urban multi-ethnic population, patients from Asia, TB history or contact in the past are considered at higher risk of TRU (Rodriquez et al., 1996). The purpose of this chapter is to review the pathogenesis of tuberculosis, ocular manifestations, diagnosis and differential diagnosis of TRU. Furthermore, this chapter addresses the new diagnostic criteria for intraocular tuberculosis specifically, IFN-gamma Release Assays (IGRAs) and polymerase chain reactions.

2 Pathogenesis of Tuberculosis-related Uveitis

The natural history of LTBI is considered to start with inhalation of an infected aerosol, which allows the bacilli to reach the alveolar spaces and subsequently to be phagocytosed by the alveolar macrophages (Cordero-Coma et al., 2010). The bacilli avoid the phagolysosome union, and reported to grow until they destroy the macrophage, which in most cases results in necrosis if the macrophage has not previously induced its own apoptosis (Cordero-Coma et al., 2010). This rupture of the infected macrophage temporarily stops bacillary growth by releasing them into the stressful extracellular milieu, where it is thought that cannot grow (Cordero-Coma et al., 2010). These bacilli can potentially remain embedded in the necrotized environment for a long period of time until they are phagocytosed by another macrophage (Cordero-Coma et al., 2010). The presence of natural killers (NK) plays a relevant role at this stage as they can activate macrophages and cause a small amount of bacillary destruction (Abebe, 2012). Neutrophils, which were previously thought to have a bactericidal effect when apoptotic also contribute this process by inducing necrosis in the extracellular matrix, and curtailing bacterial dissemination, contributing to the formation of a granulomatous structure that is regarded to support sudden cellular entrance (Abebe, 2012). In this granulomatous structure, approximately 10% of monocytes are disclosed to become dendritic cells (DCs), which, once infected, migrate towards the regional lymph nodes where
they present M. tuberculosis antigens and induce the proliferation of specific T lymphocytes (Chen & Kolls, 2013). These lymphocytes, mainly type 1 CD4 with some type 1 CD8, then migrate towards the infection site, where they are considered to recognize the infected macrophages and activate them by IFN γ or cause their death by necrosis or apoptosis, thus controlling the bacillary load. This process is regarded to be faster for immune hosts as they already have memory T lymphocytes, thus allowing a faster generation of effector T cells (Chen & Kolls, 2013). Another process, which is considered the removal of cellular debris by macrophages, which progressively become filled with lipid bodies to become foamy macrophages (FM), takes place simultaneously (Silva Miranda et al., 2012). The slow pace of bacillary growth is disclosed in a discrete pathological process at the beginning of the infection (Silva Miranda et al., 2012). In the experimental murine model, where infection is induced with a low-dose aerosol, infected lungs are shown to have a very limited and transient localized increase in the cellularity between the epithelia and the lamina propria rather than granulomatous lesions in the first three weeks post-infection despite the fact that the bacillary load increases up to 105 CFU (Calderon et al., 2013). Granuloma formation is considered to depend entirely on TNF production by the infected macrophages and T cells, as well as the integrity of all ligands and receptors of the TNF family (Heuts et al., 2013). Sustained TNF signaling is disclosed to maintain the necessary local chemokine gradients to hold the cells in close apposition, thus favoring the activation of infected macrophages (Allie et al., 2013). Aqueous cytokine and chemokine analyses have shown that subjects with TRU who respond to anti-TB therapy do not have an active ocular tuberculosis infection, but rather an autoimmune-related ocular inflammation that may be triggered by TB (Ang et al., 2012a). Higher levels of interleukin-6, interleukin-8, interferon-gamma, and interferon-gamma-induced protein 10 have been disclosed in the aqueous analysis of the patients with TRU (Ang et al., 2012a).

3 Clinical Manifestations of Tuberculosis Related Uveitis

TB in the eye is considered to associate with a wide spectrum of clinical manifestations (Bouza et al., 1997; Rodriguez et al., 1996). Definitive diagnosis of confirmed ocular tuberculosis is reported to be daunting due to the difficulty of getting ocular samples for microbiologic or histologic evaluation. High awareness of ocular manifestations is considered as important for the diagnosis of ocular tuberculosis (Vyas, 2009). The diagnosis of presumed ocular tuberculosis (POTB) is based on the clinical signs of tuberculosis uveitis associated with a history or signs and symptoms of pulmonary or extra pulmonary tuberculosis (Lara & Ocampo, 2013). The common clinical presentations are reported as anterior granulomatous uveitis, vitritis, choroiditis, choroidal tubercles, multifocal choroiditis, occlusive vasculitis, rarely serpiginous-like choroiditis, subretinal abscesses or suspected ocular tumors (Manousaridis et al., 2013). Anterior uveitis associated with tuberculosis has also been reported as non-granulomatous with broad-based posterior synechia formation (Lara & Ocampo, 2013). Anterior granulomatous uveitis might be associated with bilateral central interstitial keratitis (Kamal et al., 2013). POTB might also present only with low grade anterior chamber activity (Manousaridis et al., 2013). Rarely hypopyon associated anterior uveitis might occur (Chatziralli et al., 2012). Focal, nodular, diffuse or necrotizing scleritis with or without keratitis have also been disclosed in patients with POTB (Manousaridis et al., 2013). Although scleritis is considered as a rare condition associated with POTB, anterior nodular non-necrotizing scleritis is revealed as the most common scleral involvement. Anterior scleritis has also been reported as associated with extensive posterior synechia (Ang et al., 2012b).
Nodular episcleritis with pain, redness and blurred vision has been disclosed in POTB (Bathula et al., 2012). Necrotizing scleritis associated with recurrent erythema nodosum related to an immune reaction of delayed hypersensitivity type IV to various antigenic components of mycobacteria has been reported in patients with no history of pulmonary or systemic disease, and 50% of no evidence of pathology on chest X-ray (Pedroza et al., 2010). Necrotizing scleritis might also be associated with peripheral ulcerative keratitis in POTB (Gupta et al., 2008). Isolated posterior scleritis is reported as a rare condition associated with POTB (Gupta et al., 2003; Sharma et al., 2010). Very rarely, posterior scleral granuloma mimicking choroidal melanoma has been reported in POTB (Velasco e Cruz et al., 2011). Posterior segment inflammation associated with POTB is reported to include intermediate, posterior, or panuveitis (Chu & Hui, 2010). Multifocal chorioretinitis presented with transient visual disturbances is another manifestation of posterior segment inflammation due to tuberculosis (Baha et al., 2009; Anna et al., 2013). Multifocal serpiginoid choroiditis is described in patients particularly from TB-endemic regions presenting fundus changes similar to serpiginous choroiditis but also showing evidence of active TB and/or the presence of mycobacterial DNA in the aqueous humor (Nazari Khanamiri & Rao, 2013). Multifocal outer retinal and inner choroidal inflammation is considered as a marker of intraocular TB even in a non-endemic area. The lesions are described as multifocal, irregular in shape, very numerous, widespread, noncontiguous to the optic disc, often asymmetrical and often demonstrating both active and resolved areas simultaneously (Gan & Jones. 2013). Tubercular serpiginous-like choroiditis is reported predominantly affecting the young to middle-aged man, and it is associated with moderate to severe vitreous inflammation unlike serpiginous choroiditis (Bansal et al., 2012). Retinal periphlebitis in multiple quadrants of the retina and choroiditis lesions might occur simultaneously (Nayak et al., 2011). Choriocapillaritis is regarded as another posterior segment manifestation of POTB. It has similar features of acute multifocal posterior placoid pigment epitheliopathy (APMPPE), but it shows smoldering relentless evolution monitored by indocyanine green angiography (De Luigi et al., 2012). Isolated retinal vasculitis with pulmonary tuberculosis characterized by multiple retinal hemorrhages, vascular sheathing, and a yellowish retina associated with the sign of xanthopsia has also been described (Roh et al., 2011). Macular edema in patients with POTB is reported to cause significant visual impairment (Al-Mezaine et al., 2008). Three patterns of macular edema: diffuse, cystoid and serous retinal detachment which is the most common type were described. Optical coherence tomography is considered useful in monitoring the efficacy of treatment in patients with macular edema (Al-Mezaine et al., 2008). Patients who are immunosuppressed or HIV infected are reported to develop active mycobacterial disease in the eye leading to rapid destruction of the ocular structures (Babu et al., 2006; Nwosu, 2008). Ocular TB in AIDS is considered to occur even at CD4+ cell counts greater than 200 cells/microl (Babu et al., 2006). Choroidal tuberculosis characterized by choroidal granuloma has been reported in patients with HIV and miliary tuberculosis.

4 Diagnosis and Differential Diagnosis of Tuberculosis Related Uveitis

With absence of proper diagnostic standard, it usually leads to missed diagnosis, misdiagnosis, and delayed diagnosis of POTB which is considered to result in severe consequences such as vision loss, blind, and even eye enucleation (Tabbara, 2013). However, POTB is considered a diagnostic challenge (Vos et al., 2013). A history of TB contact, abnormalities on chest X-ray, extraocular manifestations of TB associated with good response to anti-tuberculosis therapy (ATT) are marked as helpful parameters for the diagnosis of POTB (Vos et al., 2013). Tuberculosis skin test (TST) is considered to determine the
immune response to the Bacille Calmette Guerin (BCG) strain of Mycobacterium (American Thoracic Society, 2000). This immune response is reported to develop if the individual has active TB or had exposure to TB in the past or received the BCG vaccine against TB. The immune response is considered a delayed type sensitivity reaction of memory T-cells sensitized prior to the purified protein derivatives of the bacterium (American Thoracic Society, 2000). The TST test is reported to be in clinical use primarily to identify latent TB infection in persons at risk of progression to active disease, and to support the diagnosis of active TB disease (Huebner et al., 1993). However, the TST might be an imperfect marker of TB infection since it has been reported that 10-25% of persons with active TB have a negative TST result (Holden et al., 1971; Nash & Douglass, 1980). On the other hand, persons with a positive TST are considered less likely to have a disseminated disease (Colditz et al., 1994). In general, it has been found that persons with TST ≥ 15 mm were less likely to have military or combined pulmonary and extrapulmonary disease, and more likely to have cavitary pulmonary disease relative to the non-cavitary pulmonary disease (Auld et al., 2013). TST is also reported to be influenced by the HIV status and birthplace of the person. Persons with HIV, and US-born persons without HIV who have a TST ≥ 15 mm are considered to have more likely cavitary pulmonary disease while foreign-born persons without HIV who have a TST ≥ 15 mm are significantly less likely to have cavitary pulmonary disease (Auld et al., 2013). The TST is reported to be insensitive in immunocompromised persons because of the high rates of anergy, and false-positive results in persons who have BCG vaccination (Ahmed & Karter, 2004).

In vitro assays that measure effector T cell response to stimulation of early secretory antigen target-6 (ESAT-6) and culture filtrate protein-10 (CFP-10) antigens from Mycobacterium tuberculosis, called interferon gamma release assays (IGRAs) are reported to be more effective in immunosuppressed population, and also reported that they are not affected by previous vaccination with BCG (Mori, 2009). There are three commercially available IGRAs including T-SPOT.TB (Oxford Immunotec United Kingdom), Quantiferon Gold (Celletis USA) and Quantiferon In-tube (Celletis USA) (Winthrop et al., 2008). T-SPOT.TB is considered a type of ELISPOT assay which counts the number of anti-mycobacterial effector T-cells that produce interferon (IFN) gamma in a sample of blood (Meier et al., 2005). T-SPOT.TB assay is regarded to give an overall measurement of the host immune response against mycobacteria which might reveal the presence of either active or latent infection with Mycobacterium tuberculosis (Huebner et al., 1993). This test is reported to be not affected by the previous BCG vaccine and previous infections with non-tuberculous mycobacterium (Ang et al., 2013). Based on these facts, T-SPOT.TB test is considered more specific but less sensitive than TST that is recommended to use in preference to the TST in low-TB prevalence populations (Holden et al., 1971). It has been also recommended to use both T-SPOT.TB and TST in conjunction to increase the likelihood diagnosis of POTB (Lalvani & Pareek, 2010). T-SPOT.TB is considered helpful either to rule-in or to rule-out active TB in immunocompromised patients from intermediate TB burden regions (Jung et al., 2012). The Quantiferon-TB Gold test is considered as an enzyme linked immunosorbent assay (ELISA) which measures the amount of IFN gamma in the sample of blood after the effector T-cells are stimulated with ESAT-6 and CFU-10 antigens (Bellete et al., 2002). A combination of the Quantiferon-TB Gold and TST tests rather than solo test are recommended in endemic areas for TB, such as India, Asia, and Western urban multi-ethnic population (Baby et al., 2013). The sensitivity (S) and specificity (Sp) of the TST and Quantiferon–TB Gold are disclosed not differentiating significantly as S 87% vs. 90% and Sp 85% vs. 82% (Liorenç et al., 2013). The limiting factors for the combining the tests in these areas are reported the higher cost, technical issues, and inability to distinguish active and latent TB (Baby et al., 2013). The use of 18(F) fluorodeoxyglucose positron emission tomography/CT in quantiferon-TB Gold positive patients
with POTB is recommended to identify the size and metabolic activity of the hilar and mediastinal lymph nodes and pulmonary lesions and to find out whether these lesions are appropriate for biopsy (Doycheva et al., 2011). The Quantiferon-TB Gold In-tube (QFT-G-IT) test is considered as a third generation of IGRAs which measures the IFN gamma concentration of blood in tube after stimulating the effector T-cells by ESAT-6, CFP-10 and Tb7.7 (p49) peptide antigens (Streeton et al., 1998). It has been reported that QFT-G-IT has a consistent specificity of > 99% in low risk individuals and a sensitivity as high as 92% in individuals with active disease, depending on setting and extend of disease (Moon & Hur, 2013). QFT-G-IT is considered to have advantages when combined with TST in immunosuppressed patients especially in older patients with a negative TST and in BCG vaccinated patients with a positive TST (Garcia-Gasalla et al., 2013). It is reported to prevent unnecessary treatments and toxicities related to a false-positive TST result (Garcia-Gasalla et al., 2013). The sensitivities of QFT-G-IT, T-SPOT-TB and TST to rule out active TB in immunosuppressed patients are revealed as 11.1%, 40% and 25% respectively (Jung et al., 2012). Since the IGRAs have limitations to differentiate latent TB from active infection nucleic acid amplification techniques (NAAT) have emerged as an important tool for rapid and accurate diagnosis of TB (Boehme et al., 2007). NAAT-based diagnostic methods mostly use a single target Mycobacterium genome (IS6110) for the amplification and detection of tuberculosis (Sarmiento et al., 2003). It has been reported that IS6110 is absent in 10-40% Mycobacterium tuberculosis isolates in endemic areas like India that likelihood increases the false-negative tests (Das et al., 1995; Sarmiento et al., 2003).

A low sensitivity (37.7) has been reported with NAAT (IS6110) in ocular samples from POTB patients (Arora et al., 1999). An alternative approach is considered to use multi-targeted PCR using three targeted genes specific including IS6110, MPB64 and Pab which are specific for Mycobacterium tuberculosis (Sharma et al., 2013). Presence of TB DNA in the ocular fluid is considered suggesting presence of Mycobacterium infection within the eye, but does not differentiate the clinical picture from an immune response to mycobacterial antigens being loaded from the retina pigment epithelial (RPE) cells or somewhere else from the body. Thus, multi-targeted PCR cannot differentiate between active and latent TB infection. Besides, multi-targeted PCR positivity has been reported in POTB patients groups with both active and latent TB infections (Sharma et al., 2013). Several acid-fast bacteria localized within the necrotic RPE cells has been demonstrated (Rao et al., 2006). This finding is considered to support the possibility of tubercular uveitis as an immune response to these sequestered bacteria within the RPE cells (Rao et al., 2006). Several studies revealed the presence of Mycobacterium tuberculosis genome in the vitreous samples of patients with retinal vasculitis so-called Eales’ disease and chronic or recurrent choroiditis (Bhuibhar et al., 2012, Singh et al., 2012). Multifocal serpiginoid choroiditis characterized by multifocal lesions that are noncontagious to the optic disc and showing serpiginoid spread associated with vitreous inflammation has been described (Bansal et al., 2012; Nazari Khanamiri & Rao, 2013; Vasconcelos-Santos et al., 2010). The distinction between serpiginous choroiditis and multifocal serpiginoid choroiditis is considered crucial to avoid unnecessary ATT for serpiginous choroiditis (Bansal et al., 2012; Nazari Khanamiri & Rao, 2013).

5 Therapeutic Approach of Presumed Ocular Tuberculosis

ATT is considered highly effective and for both confirming the diagnosis and resolving the inflammatory process, and it is recommended to be initiated for cases with a clinical suspicion of POTB. It is also
reported that ATT has additional advantages, such as preventing latent-tuberculosis reactivations due to immunosuppressive therapy, and decreasing the number and/or severity of uveitis relapses (Cordero-Coma et al., 2013). Early referral is recommended for patients who are not responding appropriately to anti-inflammatory therapy (Patel et al., 2013). Patients diagnosed after 500 days after initial ocular symptoms are reported to be more likely losing their vision (Patel et al., 2013). The initial prescribed ATT is reported to include 4 drugs: isoniazid, rifampicin, pyrazinamide and ethambutol (Blumberg et al., 2005). The minimum length for the treatment of drug-susceptible TB with a rifampin-based regimen is revealed 6-9 months (Blumberg et al., 2005). The recommendations for treatment of LTBI in both HIV-infected and HIV-uninfected patients are reported to include isoniazid for 9 months as the preferred regimen, or isoniazid for 6 months based on the local program condition, rifampin and pyrazinamide for 2 months or rifampin for 4 months (Cohn, 2000). In patients with either proven or POTB in the absence of constitutional or respiratory symptoms, elevated inflammatory markers, or an abnormal chest X-ray, a minimum of 6 month of ATT is suggested (Manousaridis et al., 2011; Sanqhvi et al., 2011). However, it is reported that it may not be effective in patients having complications such as, retinal vasculitis with vitreous hemorrhage, branch retinal vein occlusion, persistent macular edema, choroidal scar and optic atrophy (Yasaratne et al., 2010). Topical or systemic anti-inflammatory therapy in conjunction with ATT is indicated for patients with hypopyon uveitis, interstitial keratitis, phylectenular keratitis, tubercular serpiginous-like choroiditis, tuberculosis-related choriocapillaritis, focal choroiditis and chorioidal and brain tuberculoma associated with miliary tuberculosis (Bansal et al., 2012; Bogadhi & Le Hoanq, 2000; Chatziralli et al., 2012; De Luigi et al., 2012; Kamal et al., 2013; Manousaridis et al., 2013; Takakura et al., 1998). Paradoxical worsening of patients condition after initiating ATT are described as Jarisch-Herxheimer reaction to the therapy (Bogadhi & Le Hoanq, 2000; Takakura et al., 1998). The prompt resolution of this allergic reaction with systemic steroid treatment has been reported in these patients (Cheung & Chee, 2009; Neunhöffer et al., 2013). Anti-inflammatory therapy in conjunction with ATT is considered to prevent worsening of the existing lesion in the eye, recurrence of the disease, and paradoxical reactions (Basu & Das, 2010).

References


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