

THE SUCCESS OF CORTICOSTEROID THERAPY FOR VISUAL OUTCOME AND CHOROIDAL TUBERCLE REGRESSION ON PARADOXICAL REACTION IN TUBERCULOUS LYMPHADENITIS

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Abstract

Paradoxical reaction is worsening effect of pre-existing lesion or development new lesion. Commonly occurred in extrapulmonary tuberculosis, about 20-30% in tuberculous lymphadenitis, showed by development of posterior uveitis like choroidal tubercle. A 32-year-old man presented with sudden loss vision and central scotoma on his left eye 1 day before admission. The patient got anti therapy tuberculosis by pulmonologist in one month previously for his tuberculous lymphadenitis. Our examinations revealed tuberculosis infection with swollen disc and choroidal tubercle that affected the worsening of visual acuity until 2/60 in the left eye. Based on clinical picture and history of treatment before, we decided the patient had paradoxical reaction. Topical and oral corticosteroid therapy with continuation of anti-tuberculosis therapy referred significant improvement toward visual outcome until 20/20 and posterior pole condition on 4 months. Paradoxical reaction in tuberculous lymphadenitis is not well understood, it may caused by bacterial spreading or hypersensitivity responses. Corticosteroid therapy with continuation of anti-tuberculosis therapy recommended to help improvement visual acuity by reducing inflammation and hypersensitivity response in patient tuberculous lymphadenitis with paradoxical reaction. This is proved by improvement visual acuity and choroidal tubercle regression in our patient. Intraocular lesion can be caused by paradoxical reaction in tuberculous lymphadenitis. Early diagnosed and early corticosteroid therapy may help to sight saving.

Keywords: choroidal tubercle; paradoxical reaction; tuberculous lymphadenitis

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Introduction

Tuberculosis is a chronic, infectious disease, caused by *Mycobacterium tuberculosis*, which is characterized by necrotic granulation tissue in response to these germs. The disease is transmitted quickly to vulnerable people and the body's endurance is weak. It is estimated that a tuberculosis sufferer to 1 in 10 people around him. Tuberculosis is a disease that disrupts human resources and generally affects people with low socioeconomic groups (Nizar, 2017).

Tuberculosis is one of the biggest health problems worldwide. The disease is also the highest cause of death and morbidity in developing countries, such as Indonesia (Perawat & Pasien, 2018).

Currently infectious diseases, tuberculosis (TB) is still a concern of the world and no country is free of TB. The death and pain rate from the germ 'Mycobacterium tuberculosis' is still high. In 2009, 1.7 million people died from TB, and one-third of the world's population had contracted TB, most of whom were of productive age, 15–55 years old. Global Report 2009 (WHO) showed in 2008 Indonesia was ranked the 5th most TB sufferers in the world after India, China, South Africa and Nigeria or decreased from third after India and China in 2007 (Izza & Roosihermatie, 2013).

Tuberculosis (TB) is an airborne infectious disease that leading cause of mortality and morbidity worldwide, including in Indonesia (Ghuri et al., 2019). Caused by *Mycobacterium Tuberculosis* (MTb) which treated by anti tuberculosis therapy (ATT) for certain period. However, in some patients who receiving ATT can occur paradoxical reaction. Paradoxical reaction means worsening in pre-existing clinical or radiological tuberculous lesion or new lesion was developed in patient who showed an initial response or improvement with treatment (Ganesh, Abraham, & Sudharshan, 2019).

Intraocular reaction on paradoxical reaction showed commonly as posterior uveitis, like as choroidal tubercles, subretinal abscess or serpiginous-like choroiditis (Goel, 2015), (Agarwal & Shrivastav, 2017). MTb is an obligate aerob acid microorganism that affects high oxygen tension and high blood supply area like choroid (uveal tract) in the eye (Goel, 2015), (Dalvin & Smith, 2017). Different with intraocular tuberculosis, visual complication in extraocular described rarely occur as a result of a paradoxical reaction during ATT (Goel, 2015). This case report will describes a patient with tuberculous lymphadenitis, showed development of choroidal tubercle in posterior pole as part of a paradoxical reaction and have good visual outcomes after corticosteroid therapy during anti-tuberculosis therapy.

Research Methods

This was an observational prospective study was conducted at Makassar, from September 2019 to Mei 2020. The patient presented with complain of sudden loss of vision and central scotoma on his left eye, then underwent detailed history, general examination, anterior and posterior segment examination. The patient was administered with corticosteroid oral (methylprednisolone) by ophthalmologist after diagnosed. Clinical response, visual acuity and choroidal tubercle was assessed at 1, 2, 3 and 8 months followup. All data were collected and processed anonymously (Ata et al., 2020).

Results

A 32-year-old man presented with sudden loss vision and central scotoma on his left eye 1 day before admission. On examination, his visual acuity (VA) was 20/20 in the right eye and 2/60 in the left eye. Slitlamp examination for anterior segment including intraocular pressure and pupils were within normal limits. Fundus

examination of right eye appeared normal, but in the left eye revealed a swollen disc optic nerve and choroidal tubercle. (**Figure 1**).

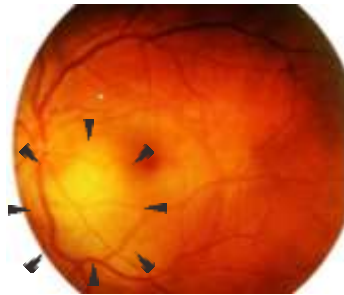


Figure 1. Choroidal tubercle on first fundus examination



Figure 2. Optical coherence tomography scan showing subretinal fluid

Two month earlier, there was history of cough, dyspnea, recurrent middle-grade fever, malaise, unexplained weight loss, and developed supraclavicular lymphadenopathy which painless and tenderness, there was no history of other systemic disease. Internist did physical examination to him, sputum examination, and chest X-Ray, then he was diagnosed tuberculosis and referred to pulmonologist. Pulmonologist did fine-needle aspiration biopsy to his gland, and diagnosed with tuberculous lymphadenitis (**Figure 3**). He was started on standard four-regimen anti tuberculosis therapy planned, consisting of rifampicin 600 mg once daily, isoniazid 450 mg once daily, pyrazinamide 1.5 g once daily and ethambutol 800 mg once daily for one month previously.

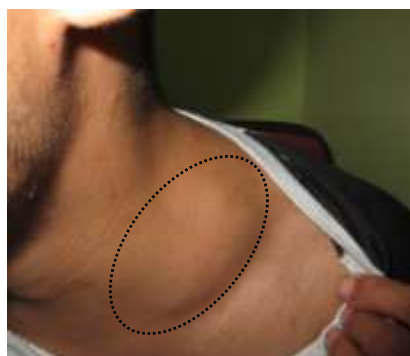


Figure 3. Swollen of supraclavicular gland

Based on the clinical picture, evidence of confirmed active extra-pulmonary tuberculosis, and history of tubercular treatment before, a diagnosis of left ocular tuberculosis was made by ophthalmologist. The patient was diagnosed to have paradoxical worsening following ATT based on complaints of visual worsening, no ocular findings at the time of diagnosis but choroiditis tubercular developed on initial ATT. Thus, the patient was administered with fluorometholon eye drops 5 times per day, vitamin C 1 tablet per day and corticosteroid oral (methylprednisolone) starting dose given was 1.0 mg/kg body weight then gradually tapered every week depending on visual acuity improvement and decreasing of choroidal tubercle.

After 1 month treatment with corticosteroid, the BCVA on left eye was 20/150. Fundus Examination of left eye result swollen disc of optic nerve and decreased of choroidal tubercle size in perimacula.

2 months under corticosteroid treatment, BCVA on the left eye more increased to 20/30 and central scotoma was dissolve. Fundus examination showed minimal tubercle on perimacula (**Figure 4A**). 1 month later, BCVA showed very satisfying result, the patient got 20/20 for both eyes. However on his fundus examination leaved minimal scarred on perimacula (**Figure 4B**).

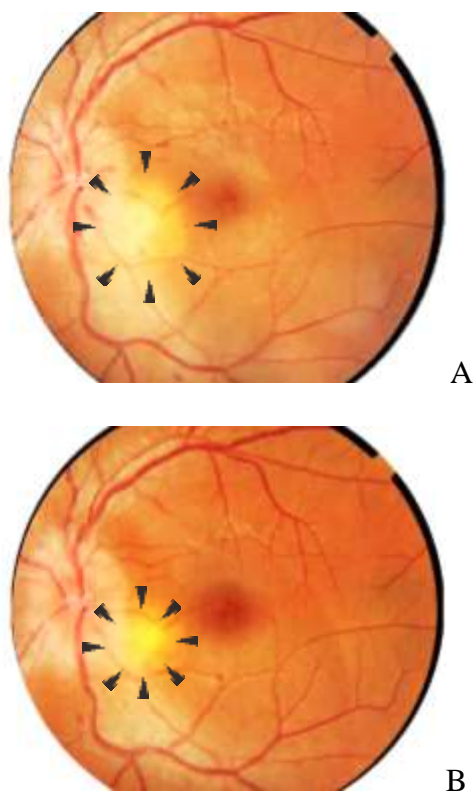


Figure 4.

(A) Funduscopy control on 2 months after corticosteroid therapy showed minimal tubercle on perimacula. (B) Scarred on perimacula showed regression of lesion on 3 months after corticosteroid therapy

This clinical picture was maintained for 8 months with no recurrences marked from stability of visual acuity and no worsening in fundus examination with continuation of ATT. Although, the treatment by ophthalmologist have been finished, anti therapy tuberculosis by pulmonologist have to continued up to 9 months to maximized anti-tuberculosis therapy.

Discussions

Tuberculosis is a multi-organs disease caused by the obligate aerobic acid fast bacilli *Mycobacterium tuberculosis* (MTb). Mainly, TB affects the lungs, but it may have various extrapulmonary infection including ocular. Hematogenous and lymphatic spread of MTb bacilli is mainly theory why extrapulmonary tuberculosis occurred **6**. Lymphadenitis is the most commonly form of extrapulmonary tuberculosis which has a peak age of onset of 20-40 years (Dalvin & Smith, 2017), (Agarwal & Shrivastav, 2017).

Culturing MTb from a specimen obtained from the patient help a doctor to get diagnosis. In superficial tuberculous lymphadenitis, fine-needle aspiration (FNA) biopsy of affected lymph nodes is the first-line diagnostic technique. However, if the FNA examination results are inconclusive, excisional biopsy may be useful because it has the highest sensitivity and both sensitivities (82.4%–100%) till specificities (94%–100%) were increased when fine needle aspiration (FNA) and PCR were combined in the diagnosis of tuberculous lymphadenitis (Ramirez-Lapausa, Menendez-Saldana, & Noguerado-Asensio, 2015),(Lee, 2015). In our patient, diagnosed was made by pulmonologist from FNA that got purulen inflammation on microscopic examination, suggestive tuberculous, therefore pulmonogist diagnosed the patient was suffered tuberculous lymphadenitis and not did biopsy anymore. Tuberculin skin test (TST) was not performed in this case because it has low sensitivity and specificity. Interpretation of TST reactivity can be show false positive by cross-reactivity with previous BCG vaccination or latent tuberculosis infection in those living in endemic areas including in Indonesia (Agarwal & Shrivastav, 2017).

A six-month to nine-month regimen (two months of isoniazid, rifampicin, pyrazinamide, and ethambutol, followed by four to seven months of isoniazid and rifampicin) is recommended as initial therapy for all forms of extrapulmonary tuberculosis (Ghuri et al., 2019), (Agarwal & Shrivastav, 2017), (Golden & Vikram, 2005).

Paradoxical reaction (PR) in which worsening of existing disease or new lesions developed, occur more frequently in extrapulmonary tuberculosis (20–30% with tuberculous lymphadenitis) than pulmonary tuberculosis (Ganesh et al., 2019), (Goel, 2015), (Agarwal & Shrivastav, 2017), (Singh, Rahman, Kumar, & Anila, 2013). This phenomenon is not well understood but it has been attributed to host immunologic reactions, with possible mechanisms including delayed hypersensitivity response, decrease immunosuppression mechanisms, and a response to MTb antigens (Agarwal & Shrivastav, 2017), (Singh et al., 2013), (Chahed et al., 2017).

In this case, the patient came with sudden blurred vision up to 2/60 and central scotoma in his left eye. This case represent a paradoxical reaction in a month with tuberculous lymphadenitis, presenting with posterior uveitis, specifically choroidal tubercle. Choroidal tubercle presenting as yellowish lesions, discrete with ill-defined borders, may occur from liquefaction necrosis within a caseating granuloma that may contain acid-fast bacilli and can develop in patients with disseminated tuberculosis (Agarwal & Shrivastav, 2017), (Dalvin & Smith, 2017). Bacteria-laden macrophages appeared when a caseous lesion erodes into the blood vessels or the lymphatic channels then carrying the bacteria to the eye, where the organisms may persist and initiate an immune-mediated response (Ganesh et al., 2019), (Sharma, Thapa, & Lavaju, 2011). If it seen in a tuberculosis of endemic area should raise a strong suspicion of ocular tuberculosis associated uveitis (Agarwal & Shrivastav, 2017).

Although, intraocular disease in this case may caused by secondary hematogenous or lymphatogenous spread, direct local extension and hypersensitivity responses from existing infection in the body can also result in intraocular findings (Dalvin & Smith, 2017). Optic neuropathy may also develop due to a hypersensitivity response to antigen. The manifestations of involvement of the optic nerve may be papillitis, optic neuritis, or papilledema as like occurs in this patient (Agarwal & Shrivastav, 2017).

Steroids are recommended in other forms of extrapulmonary tuberculosis. This patient got steroid treatment that expected help to limiting the damage of the ocular tissues, resulting more rapid improvement to reducing inflammation and also preventing a delayed hypersensitivity response to the tubercular antigen (Agarwal & Shrivastav, 2017), (Chahed et al., 2017). Methylprednisolone was given in a dose of 1.0 mg/kg given for 1 week, then tapered off every week, according to the response to the treatment. The result of adding corticosteroid for 4 months during continuation of anti-tuberculosis therapy, got a maximal visual outcomes untill 20/20 and showed regression of choroidal tubercle. Serial fundus photographs help documenting appearance of new lesions as well as studying the regression of lesions. The healed lesions show scarred areas with chances of good visual recovery (Sharma et al., 2011).

The diagnosis of a paradoxical reaction was made, based on the exclusion of other diseases, adequate adherence to anti-tuberculosis therapy (intraocular disease progressivity was noted on anti-tuberculosis therapy alone), and the dramatic response to corticosteroids. On the other hand, if this is not a paradoxical reaction but treatment failure, steroids would exaggerate the infection further (Goel, 2015), (Gogia, Venkatesh, Garg, Takkar, & Sheemar, 2019). Early time institution of therapy can lead to restoration of vision and may prevent irreversible vision loss (Alvarez, Roth, & Hodge, 2009).

Conclusion

Paradoxical reaction occur more frequently in extrapulmonary tuberculosis that can affected to intraocular lesions. The mechanisms is not too unclear, but it is thought

to result from host immunologic reactions, with possible mechanisms including delayed hypersensitivity response, decrease immunosuppression mechanisms, and a response to mycobacterial antigens. Steroids are recommended to solve paradoxical reaction to help limiting the damage of the tissues, resulting more rapid improvement to reducing inflammation and also preventing a delayed hypersensitivity response to the tubercular antigen. Timely treatment of therapy, anti-tuberculosis therapy and corticosteroid also can lead sight saving for the patient.

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