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Результаты лечения больных с серпигинозными и серпигинозно-подобными хориоидитами

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Treatment Outcomes Of Patients With Serpiginous And Serpiginous-Like Choroiditis

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РЕФЕРАТ

Цель. Представить клинические результаты применения различных иммуномодулирующих средств и/или препаратов противотуберкулезной терапии (ПТТ) у больных серпигинозным хориоидитом (СХ) и серпигинозно-подобным хориоидитом (СПХ).

Материал и методы. Ретроспективно в исследование были включены 18 глаз 10 пациентов, получавших различные иммуномодулирующие препараты. Средний возраст пациентов составил 53,2±12,1 года. Средний период наблюдения – 47,4±46,8 месяца.

Результаты. Восемь из десяти пациентов получали стероиды и иммуномодулирующее лечение. Если у пациентов был активный или латентный туберкулез, они также получали ПТТ. Четыре пациента на-

ходились в ремиссии при приеме адалимумаба. Интравитреальная инъекция бевацизумаба была проведена двум пациентам с хориоидальной неоваскуляризацией, связанной с СХ.

Вывод. Основные методы лечения СХ и СПХ являются противоречивыми. В то время как кортикостероиды рекомендуются при острой форме заболевания, иммуномодулирующие средства важны для предотвращения рецидивов. В случае доказанного латентного или активного туберкулеза необходимо добавлять в схему лечения ПТТ. Адалимумаб может быть полезен для предотвращения рецидивов у пациентов, которые трудно поддаются традиционному иммуномодулирующему лечению.

Ключевые слова: Адалимумаб, противотуберкулезная терапия, серпигинозный хориоидит, серпигинозноподобный хориоидит. ■

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ABSTRACT

Purpose. To present the clinical outcomes of different immunomodulatory agents and/or antitubercular therapy (ATT) in patients with serpiginous choroiditis (SC) and serpiginous-like choroiditis (SLC).

Material and methods. Eighteen eyes of ten patients who were treated with different immunomodulatory agents were retrospectively enrolled in the study. Mean age of the patients was 53,2±12,1 years. Mean follow-up period was 47,4 (±46,8) months.

Results. Eight of ten patients received steroids and immunomodulatory treatment. If patients had active or latent tuberculosis, they also re-

ceived ATT. Four patients were in remission with adalimumab. Intravitreal bevacizumab injection was applied to two patients who had choroidal neovascularisation associated with SC.

Conclusion. As a result, main treatment modalities of SC and SLC are controversial. While corticosteroids are recommended in the acute form of disease, immunomodulatory agents are important to prevent relapses. In case of proven latent or active tuberculosis, ATT has to be added to treatment regimen. Adalimumab may be beneficial to prevent relapses in patients with recalcitrant to conventional immunomodulatory treatment.

Key words: adalimumab, antitubercular therapy, serpiginous choroiditis, serpiginous-like choroiditis. ■

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INTRODUCTION

Serpiginous choroiditis (SC) and serpiginoz-like choroiditis (SLC) are similar uveitic entities on the same spectrum but with different clinical morphologic features and different etiologies. Serpiginous choroiditis is an uncommon, chronic, progressive and recurrent posterior uveitis that affects primarily choriocapillaris, retinal pigment epithelium and photoreceptor layers. It often involves both eyes asymmetrically [1].

Idiopathic noninfectious choroiditis that has radial extension from peripapillary region with geographical pattern is named as serpiginoz choroiditis; while uveitis with similar morphological involvement with an infectious origin is named as serpiginoz like choroiditis or multifocal serpiginoz choroiditis. In SLC, the most common infectious agent is Mycobacterium tuberculosis. Since antitubercular therapy (ATT) does not cause any regression in choroidal lesions it is assumed that active tuberculosis (TB) is not the direct cause of SLC. But, ATT may prevent recurrences in SLC patients [2]. Differential diagnosis of SC and SLC is important for treatment plan and prognosis [3, 4]. While corticosteroids and immunomodulatory agents are used in SC, antimicrobial drugs to causative agent are added to treatment regimen in SLC.

According to Turkey National Tuberculosis Surveillance Study, incidence of TB in Turkey showed decreasing trend with respect to previous years and the case rate was 21 per 100,000 people between 2005 and 2011. But there is still a higher incidence of latent TB compared to developed countries [5].

PURPOSE

The aim of this study to present the clinical outcomes of different immunomodulatory agents and/or ATT in patients with SC and SLC.

PATIENTS AND METHODS

Patients diagnosed with SC or SLC, and using different immunomodulatory agents between January 2008 to January 2019 were retrospectively en-

Characteristics	n=10
Age, years (\pm SD)	53,2 \pm 12,1
Female	5
Bilateral disease	8
Previous history of tuberculosis	0
PPD > 5 mm	5
Normal chest X-ray	6
Serpiginous choroiditis	7
Serpiginous-like choroiditis	3

rolled in the study. Patients were between the age of 25 and 73 years, and followed for at least three months after the beginning of immunomodulatory agents and/or ATT. The study was approved by the Ethics Committee of Uludag University School of Medicine and adhered to the tenets of the Declaration of Helsinki.

Patients with characteristic clinical findings consistent with SC or SLC and who regularly received their medications were included in the study. After diagnosis, all patients had undergone purified protein derivative (PPD) test and/or positive interferon-gamma release assay test (IGRA; Quantiferon-TB Gold, ELISPOT), chest X-ray (CXR) and consultation of pulmonologists for determining the existence of active or latent TB. Patients without proper medical records were excluded.

All patients underwent a detailed ophthalmologic examination which included best corrected visual acuity, slit lamp and fundus examination. Best corrected visual acuity was measured using Snellen charts at first and final clinical visits and the data was then converted to minimal logarithmic angle resolution (logMAR). In addition, fundus photography, optical coherence tomography and fluorescein angiography images were evaluated. Retinal images and degree of inflammation were assessed.

Data including age, sex, homecity region in Turkey and history of previous TB were then extracted from the clinical records of the patients. Details

of the treatment as oral steroids, steroid sparing agents and ATT were noted. Occurrence of choroidal neovascularisation (CNV) was noted with treatment approach.

RESULTS

A total of 18 eyes of 10 patients were included in the study. The mean age of the patients was 53,2 \pm 12,1 years. Five patients (50%) were female. Two patients (20%) had unilateral disease. Three patients were from east regions of Turkey, while seven patients were coming from west regions of Turkey. Demographic features of patients are given in Table 1.

All patients exhibited multiple lesions in layers of choriocapillaris, retinal pigment epithelium and photoreceptor, due to choroidal inflammation. In three eyes the lesions were spreading from the peripapillary area to the periphery. In three eyes the lesions were diffuse in the posterior pole while twelve patients had only macular lesions.

In one (10%) patient, there was panuveitis at the time of presentation, while other nine (90%) patients had presented with primarily chorioretinal involvement without inflammatory flare or cells. Detailed information about clinical features and treatment are shown in Table 2.

At presentation, eight patients (80%) had active disease while two patients (20%) were in inactive phases. Eight

Table 2

Clinical features and treatment modalities of the patients

Patients	Age	Sex	Diagnosis	Side	PPD (mm)	CXR	ATT	Starting Steroid Treatment	First SSA	Second SSA	CNV	Follow up (months)
1	55	M	SC	OU	-	N	-	Systemic	MA	-	-	24
2	47	F	SC	OD	21	N	+	Systemic	C+AZA	ADA	-	18
3	63	M	SC	OU	20	N	+	Systemic	AZA	ADA	-	18
4	45	M	SLC	OU	28	Pathologic	+++	Systemic + IViDex	ADA	-	-	9
5	25	M	SC	OU	0	N	-	IViDex	***	***	-	3
6	56	F	SC	OD	5	Pathologic	-	Systemic	ADA	-	-	54
7	52	F	SLC	OU	18	Pathologic	+++	Systemic	AZA	MMF+IFN	-	132
8	55	F	SLC	OU	20	Pathologic	+++	Systemic	AZA	-	-	72
9	61	M	SC	OU	-	N	-	Subtenon	IVi RBZ	-	+	132
10	73	F	SC	OU	-	N	-	-	IVi BVZ	-	+	12

ADA: Adalimumab, AZA: Azathiopurine, BVZ: Bevacizumab, ATT: Antituberculosis Treatment, C: Cyclosporine, CXR: Chest X-Ray, CNV: Choroidal Neovascularisation, Dex: Dexamethasone Implant, F: Female, IFN: Interferon, Ivi: Intravitreal, M: Male, MA: Mycophenolic Acid, MMF: Mycophenolate Mofetil, OD: Oculus Dexter, OS: Oculus Sinister, OU: Oculus Uterque, RBZ : Ranibizumab SC: Serpiginous Choroiditis SLC: Serpiginous Like Choroiditis, SSA: Steroid Sparing Agent, PPD: Tuberculin Skin Test

*Isoniazid

**Combined treatment of two months of Isoniazid, Ethambutol, Rifampicin, Pyrazinamide followed by 4 months of Isoniazid and Rifampicin

***Treatment was suggested but patient refused.

patients received corticosteroids with various systemic and local administration routes. Three of them treated with starting pulse doses (1000 mg) of intravenous steroid since they had severe, vision threatening and active phase of disease. Four patients also received oral steroid treatment in a starting dose ranging from 16 to 80 mg/day and it was gradually tapered. One patient was treated with only subconjunctival dexamethasone since he had very mild activation of previous foci of chorioretinitis. Intravitreal dexamethasone implant had been injected in two patients together with systemic steroids. Two patients who had no active inflammation on presentation did not receive steroid therapy. However one of them was treated with mycophenolic acid since 20 years without recurrence.

Any of the patients had history of known previous TB or known contact with active TB. All patients had undergone testing for TB and five of them showed evidence of latent or active TB

(five patients with positive PPD results, while two patients had negative interferon γ analysis).

Six patients (60%) had normal CXR images while four patients had various abnormal signs. One of them had cavitary lesions in CXR and then he had diagnosed with both pulmonary and extrapulmonary TB. Besides that, three of them had nonspecific CXR findings.

Five patients (50%) who had showed evidences of active or latent TB were received ATT. Two of them were given only isoniazid prophylaxis since they had shown no signs of pulmonary TB with CXRs. Other three patients were treated with multiple antitubercular drugs which were composed of two months of isoniazid, pyrazinamide, rifampicin and ethambutol and followed by four months of rifampicin and isoniazid. One patient had pulmonary TB, one patient had urogenital TB with «Mycobacterium Other Than Tuberculosis» (MOTT) and other patient had high PPD result with history of living in

endemic area. In the patient with urogenital TB with MOTT, combination of trimethoprim sulfamethoxazole, clindamycin and ciprofloxacin treatment had been started following ATT.

Two of 10 patients developed CNV during the course of their follow up period and they were treated with intravitreal anti-vascular endothelial growth factor (VEGF). They both respond well to intravitreal treatment with regression of fundus and OCT findings.

Oral steroid sparing agents like mycophenolic acid, cyclosporine and azathiopurine were used as first line treatment in four patients after steroid therapy. In three patients, uveitis were recalcitrant to conventional immunomodulatory agents and they were changed to interferon or adalimumab. Clinical remission was achieved in all patients and no patient had active uveitis at latest follow up.

Best corrected visual acuity of patients measured at initial and final visits are shown in Table 3.

DISCUSSION

In classical SC, funduscopy findings are typical for the diagnosis but to start to immunomodulatory treatment, infectious causes must be excluded. Negative history of TB contact, negative PPD, negative syphilis serology and a normal CXR are sufficient for diagnosis of SC in non-endemic area for TB [4].

Choroidal involvement in TB related uveitis is possibly correlated with inflammatory balance of patient's immune system activity and activity of TB bacilli (Fig. 1). Choroidal granuloma, multifocal choroiditis, serpiginous-like choroiditis, ampiginous choroiditis and acute posterior multifocal placoid pigmentary epitheliopathy (APMPPE)-like lesions are possible forms of TB related choroidal involvement. The Collaborative Ocular Tuberculosis Study (COTS)-1 [5] included 245 patients with tubercular uveitis from 25 centers. In COTS-1 it was reported that SLC was clearly the most prevalent phenotype (113 patients, 46.1%), particularly in Asia Pacific region. However in West regions (Europe, America and Africa) SLC was less prevalent while the most common involvement was choroidal tuberculoma [6].

If any of the following atypical features like multifocal choroidal lesions, unaffected peripapillary choroid, floating cells in the anterior chamber and vitreous cavity are present, the patient should be investigated for infectious agents like TB, syphilis and Herpesviruses [4]. In this particular study, PPD and CXR were tested in every patient who had classical fundus findings in the time of presentation. In patients with higher than 5 mm test results in PPD and with suspected TB related lung lesions in CXR, the ATT had been started in addition to systemic corticosteroid and immunomodulatory treatment.

Patients may be present with different symptoms like floaters, metamorphosis, scotomas and blurry vision. Visual acuity may range from 10/10 to counting finger (CF) depending on the location and extension of lesions. Occasionally visual field defects could occur although visual acuity is better. In SC, main sight threatening factor is foveal involvement. In this manner, focus of choroiditis might directly involve the fovea or extrafoveal lesions might com-

Table 3

Best corrected visual acuity of patients during the follow-up time		
	Initial visual acuity (OD/OS)	Final visual acuity (OD/OS)
SLC		
Pt 4.	1,0/1,0	0,8/1,0
Pt 7.	0,1/NOP	0,3/NOP
Pt 8.	CF/CF	CF/CF
SC		
Pt 1.	0,3/0,1	0,3/0,1
Pt 2.	0,1/1,0	0,8/1,0
Pt 3.	0,5/0,7	0,6/1,0
Pt 5.	0,9/0,5	1,0/0,8
Pt 6.	0,4/0,9	0,8/0,6
Pt 9.	CF/1,0	CF/0,1
Pt 10.	0,3/0,1	0,3/0,3

SLC: Serpiginous Like Choroiditis, SC: Serpiginous Choroiditis Pt: Patient (Decimal by Snellen)

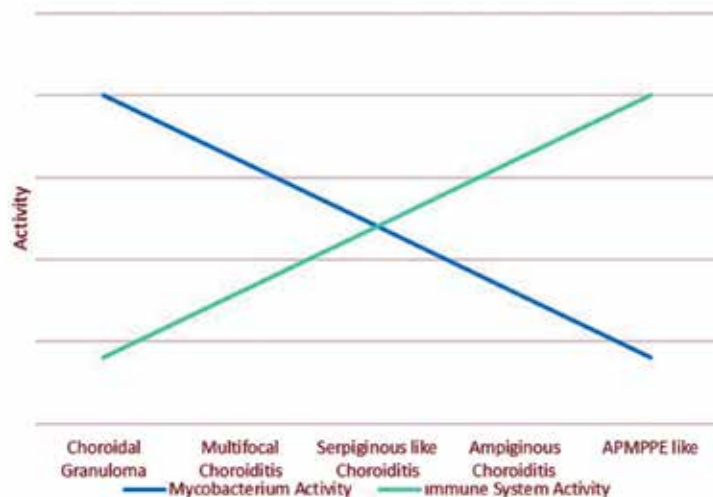


Fig. 1. Spectrum of choroidal involvement in tuberculosis

plicated with central vision threatening CNV [4, 7]. In SC, the prevalence of CNV is 10-25% and generally occur on the margin of healed and inactive chorioretinal lesions. Choroid, Bruch membrane or outer retinal ischemia secondary to choriocapillaris inflammation might play a role in the pathogenesis of CNV. The CNV could be associated with active or healed lesions. Early onset antiinflammatory treatment could decrease the incidence of CNV [3]. In our study, there were two patients with CNV and they were 61 and 73 years old.

Both patients had administered to our clinic years after the initiation of disease. They had inactive disease and did not receive any immunomodulatory treatment. One of the patients with CNV had been treated with 6 doses of intravitreal ranibizumab monthly and the other one had been treated with 3 doses of intravitreal bevacizumab monthly (Fig. 2). Since their choroiditis were inactive, no immunomodulatory treatment had been started.

Since autoimmune mechanisms could play a major role in the patho-

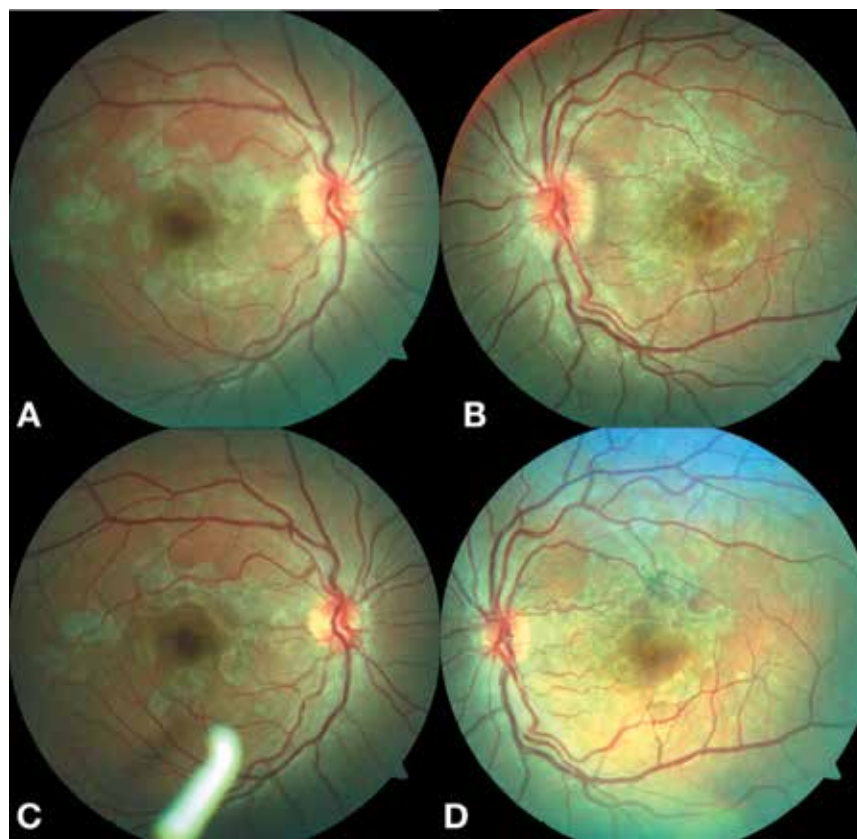


Fig. 2. Twenty five years old, male patient with serpiginous-like choroiditis in presentation with active lesions, mild vitritis and optic disc edema in right eye (A) and left eye (B). One month after bilateral intravitreal dexamethasone implant, noted that regression of lesions, vitritis and optic disc edema in right eye (C) and left eye (D)

genesis of SC, the main treatment of the disease is immunosuppression. Although, high dose corticosteroid treatment generally limits the acute chorioid lesions, they are ineffective to preventing the relapses. Immunomodulatory drugs are needed to prevent relapses. In some patients, relapses are self-limited and can heal without treatment. There is no consensus on optimal drug therapy for disease remission and the duration of immunomodulatory treatment [8]. In this particular study, high dose prednisone treatment had been started to seven patients with active chorioretinal lesions, one patient had additional intravitreal dexamethasone implant to systemic treatment. In one patient with bilateral active macular chorioretinal lesions, the empirical treatment had been started and bilateral intravitreal dexamethasone implant had been implanted without waiting for the test results since the results could take a while (Fig. 3). Active

serpiginous chorioretinal lesions had been regressed in both patients with intravitreal dexamethasone implant. Dexamethasone intravitreal implant may be an effective treatment option to control active serpiginous lesions in patients in whom increased systemic corticosteroid therapy is contraindicated [9]. Similarly, Jain et al [10] reported that sustained-release intravitreal dexamethasone is a safe and efficacious adjunctive anti-inflammatory therapy for TB-associated serpiginoid patients with contraindication for systemic corticosteroids or requiring supplemental anti-inflammatory therapy.

Christmas et al [11] reported all of the thirteen patients who didn't receive immunomodulatory treatment or treated with steroid therapy alone had relapses while in six patients who received immunomodulatory treatment, only two of them had relapses. So, to prevent relapses and to avoid possible side effects of steroid treatment, im-

munomodulatory treatment should be added to treatment regimen in patients with SC and SLC. In our study, five patients received azathiopurine, mycophenolic acid and cyclosporine. Among these five patients, three patients had relapses during the course of immunomodulatory treatment. Conventional agents were switched to adalimumab in two patients and interferon in one patient. Additionally, in two patients with severe and sight threatening uveitis, adalimumab had been started as a first line steroid sparing agent. So, four of eight patients (50%) who received immunomodulatory treatment were in remission with adalimumab. Similarly, patients with chronic uveitis recalcitrant to immunomodulatory agents, the adalimumab treatment was found effective [12, 13]. But it was suggested that adalimumab could be ineffective in acute and refractory disease [14].

In our study, we applied subconjunctival interferon α 2a in one patient who had not shown enough response to conventional immunomodulatory agents and systemic agents were contraindicated due to systemic side effects. This treatment modality was found beneficial and it was reported as a case report in 2011 [15].

Some limitations in our study, such as limited number of patients, variable follow up periods, not given a standard therapy to all patients and being retrospective in nature should be taken into account. However, there is no consensus on treatment protocol in this disease spectrum. Treatment modality of choice varies on fundus findings, foveal involvement, concomitant systemic diseases and presence of latent or active TB. In the light of this information, we believe that our study is of value because of single center results of various treatment approaches in this relatively rare disease spectrum.

CONCLUSION

Serpiginous choroiditis is recurrent, progressive, asymmetrical and bilateral inflammation of choriocapillaris and RPE.

As a result, etiopathogenesis and treatment approach of the SC and SLC is still controversial. Autoimmune or idiopathic mechanisms thought to be in-

volved in SC. But it is believed that SLC is associated with TB. Effective treatment approach is corticosteroids and then immunomodulatory agents but in case of latent TB, the ATT should be added to regimen. In patients with relapses despite use of conventional immunomodulatory agents, adalimumab is thought to be an effective choice. But large prospective studies are needed.

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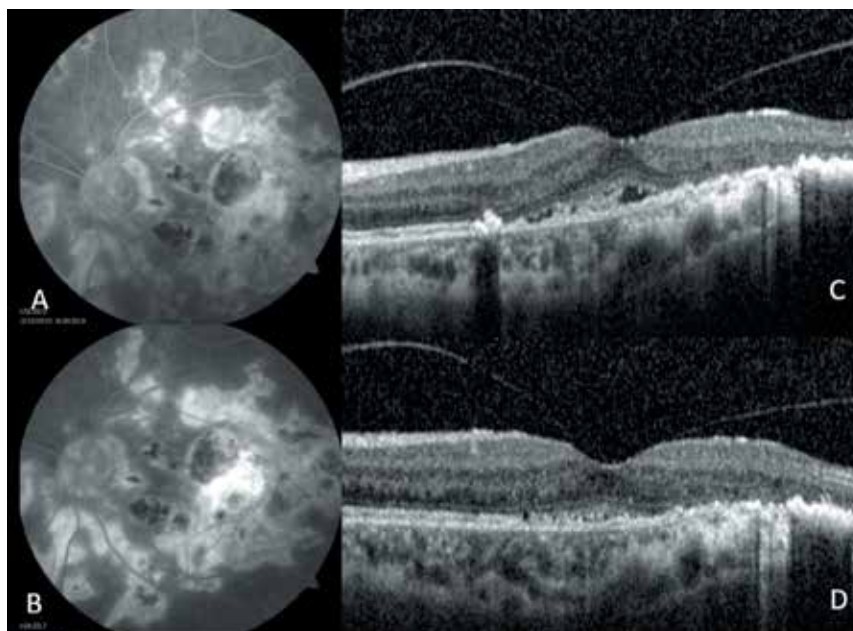


Fig. 3. Sixty one years old male with serpiginous choroiditis associated choroidal neovascularization (CNV) in his left eye. Early phase of florescein angiography (FA) (A); late phase of FA with CNV staining (B); optical coherence tomography findings in left eye with patches of chorioretinal scars, and vitreomacular adhesion and subretinal fluid (C); resolution of subretinal fluid after one dose of intravitreal ranibizumab (D)