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Ocular Involvement in Autoimmune Connective Tissue Disorders- A Prospective Observational Study Using Optical Coherence Tomography

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Abstract

Background: Autoimmune connective tissue disorder (ACTD) are chronic, inflammatory diseases, with very a broad and varied clinical presentation. Due to the generalized and chronic nature the disease influences all aspects of patient's quality of life. Ocular involvement may be an early and sometimes presenting manifestation in some cases of ACTD. Ocular changes have an adverse effect on quality of life. The severity of ocular involvement may also be an indicator of severity of systemic disease activity and may warrant a more detailed investigation of visceral involvement. This study aimed at recording the prevalence of ocular manifestations in different ACTDs and to assess the utility of a novel technique like OCT in assessing the posterior segment involvement.

Material and methods: We conducted a cross-sectional observational study in a tertiary care hospital in North India. Patients attending Dermatology outpatient and admitted in ward were recruited and subjected to a thorough evaluation. This included a complete history, a complete physical examination including general physical examination and mucocutaneous examination. Relevant hematological and biochemical investigations, skin biopsy for histopathology for hematoxylin and eosin staining, direct immunofluorescence and muscle biopsy, when indicated. A detailed Ophthalmological evaluation was done including visual acuity, Color vision, Tests for dry eye, Slit lamp examination, Ocular surface staining with fluorescein, Intraocular pressure by applanation tonometry, Detailed Fundus examination, Retinoscopy, Fluorescein angiography, if indicated, Optical coherence tomography.

Results: In our study population, 22(64.7%) patients had Systemic Sclerosis, 11(32.4%) had SLE and 1 patient had Dermatomyositis. Ocular involvement was seen in 41.2% patients. Anterior segmentinvolvement (29.4%) was more common than posterior segment involvement (11.7%). Eye lid changes were the most common finding (26.4%), followed by Glaucoma (17.6%). Decreased central macular thickness (CMT) was the most common posterior segment abnormality

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(8.82%). Ocular involvement was seen in 12 systemic sclerosis patients (54.54%) (n=22) whereas 2 patients (18.18%) had ocular involvement in the SLE subgroup (n=11.In SSc patients, anterior segment abnormalities included eyelid stiffness (40.9%), ciliary madarosis (27.27%), glaucoma (27.27%), dry eye (9.09%) and anterior uveitis (4.54%). Posterior segment abnormalities included central macular thinning (13.63%) and retinal arteriolar attenuation (4.54%). In SLE subgroup, only 2 patients (18.18%) had ocular involvement in the form of posterior subcapsular cataract and decreased visual acuity.

Conclusion: We recommend that patients with ACTD should be actively assessed for ocular involvement and a complete ocular examination should be routinely performed as it can have an impact on the disease severity and quality of life in patients with ACTD. Optical Coherence Tomography (OCT) is a non-invasive diagnostic technique that renders an in vivo cross-sectional view of the retina. Individual retinal layers can be visualized and calculation of the retinal thickness at the centre of the macula (central macular thickness [CMT]) can be done. Thus. OCT may aid in early detection of posterior segment involvement.

Keywords: ***Autoimmune connective tissue disorders (ACTD); Systemic sclerosis (SSc); Systemic lupus erythematosus (SLE); Optical coherence tomography (OCT)***

1. Introduction

Autoimmune connective tissue disorders (ACTD) are characterized by immune mediated damage to self-antigens resulting in cutaneous and systemic damage. The most common diseases in this group includes Polymyositis, Dermatomyositis, Rheumatoid arthritis (RA), Systemic sclerosis, Sjogren's syndrome, Systemic lupus erythematosus.

ACTDs have a strong female preponderance. Worldwide, the prevalence of Rheumatoid arthritis is about 1%; systemic lupus erythematosus (SLE) is estimated between 15 and 50 per 100000 population, systemic sclerosis ranges from 280 cases per million (in the US) to 13-48 cases per million in the UK [1].

The most common systemic involvement is pulmonary, renal and cardiac. Ocular inflammation seen in connective tissue diseases can affect any part of the eye from the conjunctiva, cornea and sclera anteriorly to the retina and choroid posteriorly. Ocular involvement can occur in well-established ACTD, however sometimes it may be a heralding manifestation [2]. Involvement of cornea and posterior segment can be threatening for visual acuity. The incidence, severity, and course of uveitis and scleritis in ACTDs is variable. Many factors may contribute to the natural history of the disease, including gender, the underlying systemic disease, and the extent of the inflammatory process.

A detailed assessment of ocular involvement includes visual acuity, colour vision, tear film assessment, slit lamp examination, fundus examination. Special investigations like fluorescein angiography may be done in selected cases. Optical Coherence Tomography (OCT) is a non-invasive diagnostic technique that gives an in vivo cross-sectional view of the retina. OCT utilizes a concept known as inferometry to create a cross-sectional map of the retina that is accurate to within 10-15 microns. It helps in early detection of posterior segment involvement in ACTD so that early intervention can be done. This study aimed at recording the prevalence of ocular manifestations in different ACTDs and to assess the utility of a novel technique like OCT in assessing the posterior segment involvement.

2. Methods

A cross-sectional observational study was conducted from 2020 to 2021 in a tertiary care hospital in North India. All patients >12 years of age, who fulfilled the standard diagnostic criteria of an autoimmune connective tissue disorder (SLE, rheumatoid arthritis, progressive systemic sclerosis, dermatomyositis, mixed connective tissue disorder) attending the Dermatology outpatients department and admitted in ward and willing to give informed consent were included in the study.

Pregnant and lactating females, patients with previously documented ocular disease attributable to a systemic cause other than ACTD and patients who did not give informed consent were excluded.

A total of 34 patients were included in the study. After an informed written consent, recruited patients were subjected to a thorough evaluation. This included a complete history, general physical examination and mucocutaneous examination. Relevant hematological and biochemical investigations, special disease specific investigations, skin biopsy for histopathology for hematoxylin and eosin staining and special staining for mucin, direct immunofluorescence and muscle biopsy, if indicated. A detailed Ophthalmological evaluation was done including visual acuity, Color vision, schirmer's test for dry eye, Slit lamp examination, Ocular surface staining with fluorescein, Intraocular pressure by applanation tonometry, Detailed Fundus examination, Retinoscopy, Fluorescein angiography when indicated and Optical coherence tomography.

Ethical clearance was taken from the institutional ethical committee.

2.1 Statistical analysis

Data was entered on Microsoft excel to prepare the master chart. After the data cleaning, master chart was exported to SPSS (Statistical package for social sciences) version 20.0 for analysis. Frequencies in each category were computed and descriptive statistics were applied. Appropriate tests of significance (Chi-square test, Fisher's exact test, Mann-Whitney U test) were applied to compare the groups, and $p<0.05$ was taken as significant.

3. Results

A total of 34 patients were included in the study which included 22 patients with Systemic sclerosis (SSc), 11 patients with Systemic lupus erythematosus (SLE) and 1 with Dermatomyositis. The mean age of study population was 30.12 years ± 11.95 with a range of 13-60 years. There were 5 males and 29 females with a F:M ratio of 5.8:1.

In Systemic sclerosis patients, 7 patients (31.81%) had limited cutaneous involvement, and 15 patients (68.18%) had diffuse cutaneous involvement. Raynaud's phenomenon and skin sclerosis was seen in all SSc patients (100%) (n=22). Other cutaneous findings included microstomia (95.45%), increased pigmentation (90.90%), Sclerodactyly (90.90%), salt and pepper pigmentation (72.72%), digital 62 pits/scars (72.72%), digital tip ulceration (36.36%), and calcinosis cutis (36.36%). Gastrointestinal involvement was present in all SSc patients (100%), whereas lung involvement was seen in 50% (n=11) of patients. One patient with diffuse cutaneous SSc had cardiac involvement in the form of pulmonary hypertension detected on 2D echo (TABLE 1).

TABLE 1. **Clinical features in systemic sclerosis patients.**

Clinical features	Total patients (n=22)	Limited SSc (n=7)	Diffuse SSc (n=15)
Raynaud's Phenomenon	22	7	15
Skin sclerosis	22	7	15
Increased pigmentation	20	5	15
Salt and pepper pigmentation	16	3	13
Microstomia	21	6	15
Digital pits/scars	16	2	14
Digital tip ulcers	8	0	8
Sclerodactyly	20	5	15
Calcinosis cutis	8	0	8
Pulmonary symptoms	11	2	9
Gastrointestinal symptoms	22	7	15
Cardiac involvement	1	0	1

In SLE patients, all patients had fever (100%) followed by oral ulceration (90.90%), joint pain (81.81%), Discoid rash (72.72%), malar rash (54.54%), non-scarring alopecia (54.54%) and Papulosquamous lesions (54.54%). Hematological abnormalities like autoimmune hemolytic anemia, pancytopenia, leukopenia were seen in 10 patients (90.9%), whereas Renal, pulmonary and neuropsychiatric involvement was seen in 5 patients (45.45%), 3 patients (27.27%) and 1 patient (9.09%) respectively (TABLE 2).

Ocular involvement was seen in 14 patients (41.2%) out of 34 patients (TABLE 3). Ocular involvement was more commonly seen in systemic sclerosis patients (n=12) whereas only 2 patients in the SLE subgroup had ocular involvement (TABLE 4). In the 14 patients with ocular involvement, anterior segment involvement was seen in 10 patients (29.4%) and 4 patients (11.7%) had posterior segment involvement. Anterior segment involvement presented with eye lid changes as the most common finding

in 9 patients (26.4%), followed by Glaucoma seen in 6 patients (17.6%) which was diagnosed by measuring intraocular pressure by using non-contact tonometry (NCT) (TABLE 5).

TABLE 2. **Clinical features in SLE patients.**

Clinical features	Number of patients
Fever	11
Non scarring alopecia	6
Photosensitivity	4
Oral ulcers	10
Malar rash	6
Discoid rash	8
Raynaud's phenomenon	3
Papulosquamous lesions	5
Vasculitis	4
Joint pain	9
Hematological abnormality	10
Renal involvement	5
Pulmonary involvement	3
Neuropsychiatric involvement	1

TABLE 3. **Distribution of Ocular Involvement.**

Ocular involvement		Frequency	Percent
Absent		20	58.8
Present	**Anterior segment**	10	29.4
	Posterior segment	4	11.7
Total		34	100.0

TABLE 4. **Distribution of all Ocular abnormalities among different ACTDs.**

	ACTD (n=34)	**SSc (n=22)**	**SLE (n=11)**	**Dermatomyositis (n=1)**
Best corrected visual acuity (BCVA)	7	5	2	0
Color vision	0	0	0	0
Intra Ocular Pressure (IOP)	6	6	0	0
Schirmer's Test	2	2	0	0
Tear Film Break Up Time	2	2	0	0
Slit lamp examination findings	2	1	1	0
Fundus Findings	1	1	0	0
Retinoscopy Findings	0	0	0	0
OCT Findings	3	3	0	0

TABLE 5. **Distribution of anterior segment abnormalities.**

Manifestation	**No. of patients(n=10)**
Eye lid stiffness	9(26.4%)
Ciliary madarosis	6(17.6%)
Dry eye	2(5.8%)
Keratitis	0(0.0%)
Anterior uveitis	1(2.9%)
Posterior subcapsular cataract	1(2.9%)
Glaucoma	6(17.6%)
Total	10(29.4%)

In patients with posterior segment involvement, central macular thinning detected on OCT was the most common finding seen in 3 patients (8.8%), 1 patient (2.9%) showed retinal arteriolar attenuation (TABLE 6).

TABLE 6. **Distribution of posterior segment abnormalities.**

Manifestation	No. of patients (n=4)
Posterior uveitis	0(0.0%)
Central macular thinning	3(8.8%)
Retinal arteriolar attenuation	1(2.9%)
Vitreous hemorrhage	0(0.0%)
Total	4(11.7%)

In the functional assessment decreased visual acuity was seen in total 7 patients (20.7%) (5 SSc and 2 SLE).

4. Discussion

Autoimmune connective tissue disorders (ACTD) are chronic, inflammatory diseases, with varied clinical presentations. Due to generalized and chronic nature, the disease affects all aspects of patient's life and compromises quality of life. Ocular involvement may be an early and severe manifestation in some patients with ACTD [2]. Additionally, visual morbidity has an adverse effect on quality of life. Ocular involvement may also be an indicator of severity of systemic disease activity and may warrant a more detailed investigation of visceral involvement. In the present study, we recorded the prévalence of ocular manifestations in patients with ACTD.

Patients with Systemic sclerosis, SLE and Dermatomyositis formed the study population. A strong female preponderance was observed in the study subjects (M: F=5.8:1), which is as expected.

In present study, ocular involvement was seen in 14 (41.2%) patients. In a study by Rai et al. [3]. ocular involvement was seen in 37 (74%) patients out of 50 patients with connective tissue diseases (Rheumatoid arthritis, Ankylosing spondylitis, Systemic Lupus Erythematosus, Sarcoidosis, Systemic Sclerosis, Sjogren's Syndrome, Behcet's Disease and Seronegative Spondyloarthropathy). In our study, anterior segment involvement was seen in 10 (71.4%) patients out of the 14 affected patients and posterior segment involvement was seen in 4 (28.6%) patients. These findings are consistent with Rai et al. [3] in which anterior segment was more common (81.08%) than posterior segment involvement.

In Systemic Sclerosis group, out of 22 patients, 12 patients (54.54%) had ocular involvement, of which anterior segment involvement was seen in 9 (40.9%) patients compared to posterior segment involvement which was seen in 4 (18.18%) patients. This was higher as compared to the study by Rai et al [3]. in which ocular involvement was seen in only 2 (20%) out of the 10 SSc patients. This may be attributed to the higher mean MRSS score (16.82) as compared to the study by Rai et al.(mean

MRSS=13.46).

In another study by Gomes et al. [4] out of the 45 SSc patients, ocular involvement was seen in 33 (77.2%) patients, of which anterior segment involvement wasseen in 23 patients (51.1%) and posterior segment was seen in 14 patients (31.1%). Anterior segment involvement was seen in the form of eyelid changes including eyelid stiffness (n=9(40.9%)) and ciliary madarosis (n=6(27.27%)), glaucoma (n=6(27.27%)), dry eye (n=2(9.09%)) and anterior uveitis (n=1(4.54%)). Posterior segment abnormalities in the form of central macular thinning (n=3(13.63%)) and retinal arteriolar atténuation (n=1(4.54%)) were observed.

Eyelid skin changes in SSc have been well documented in the literature. These changes are due to sclerosis of the eyelid connective tissue and occur most commonly in patients in with more extensive skin involvement (i.e., diffuse cutaneous SSc) [5]. Dry eye disease (DED) is considered to be the most common ocular manifestation of SSc. Fibrosis-related impairment of the lacrimal gland secretion can cause a quantitative lack of the precorneal tear production. Moreover, chronic blepharitis and Meibomian gland dysfunction (MGD) can result in further tear film abnormalities [6].

Glaucoma occurs due to an aberrant immune system has been shown to play a pathogenic role in optic nerve damage. An increased prevalence of monoclonal gammopathy, retinal immunoglobulin deposition, elevated serum titres of autoantibodies to optic nerve, and retinal antigens have been reported in patients with glaucoma. Thus, heat shock protein antibodies may have a pathogenic role for retinal cell death in glaucoma [7].

Generalized vasculopathy plays an important role in the pathomechanism of SSc, and this fact is particularly supported by the large portion of cases with microvascular abnormalities in the retina and choroid [8]. The major pathology of lupus retinopathy is attributed to vasculopathy, most commonly, microangiopathy. It is thought to be an immune complex- mediated vasculopathy. There are three types of direct retinal damage by lupus: microangiopathy, severe Vaso occlusion and vasculitis [9].

In 11 SLE patients, only 2 (18.18%) patients had ocular involvement which was lower in comparison to study by Turk et al (31%) [10] and Uribe-Reina et al. (43%) [11]. Ocular involvement was seen in the form of posterior subcapsular cataract and decreased visual acuity.

Optical Coherence Tomography (OCT) is a non-invasive imaging modality that provides an in vivo cross-sectional view of the retina. It utilizes a concept known as inferometry to create a cross-sectional map of the retina that is accurate to 10-15 microns. Individual retinal layers can be visualized and calculation of the retinal thickness at the centre of the macula (central macular thickness [CMT]) can be done.

Vasculopathy in SSc is known to occur in multiple target organs such as the skin, the heart and kidney [12]. The choroid is the most vascularized tissue of the eye, supplying oxygen and metabolites to the outer retinal layers, constituted by the

photoreceptor layer of the retina as well as the retinal pigment epithelium. Measuring sub-foveal choroidal thickness with EDI-OCT is of particular interest, as it has been shown to correlate with ocular perfusion pressure [13].

Central macular thickness (CMT) has been studied in 3 reports. In a case report by E. Esen et al. [14] it was reported that CMT was significantly thinner in SSc patients when compared with those of healthy controls. In another study of 34 SSc patients and 31 healthy controls by Aydin et al. [15] the mean CMT was lower than healthy controls but was not statistically significant. Each of these reports showed a trend towards a decrease in CMT. In a study by Liu et al. [16] central macular thickness was assessed in 15 neuropsychiatric SLE (NPSLE) patients, 14 non NPSLE patients and 15 healthy controls, no significant difference was found in CMT of NPSLE and Non NPSLE patients. However, CMT in SLE patients was lower than the healthy controls. Fang et al, conducted a cross-sectional study in Chinese SSc patients and concluded that retinal thickness and superficial vascular density was decreased in SSc patients as compared to normal population 17].

To the best of our knowledge, there are no similar studies in Indian population.

OCT is useful in the diagnosis of many retinal conditions. OCT can be particularly helpful in diagnosing macular hole, macular pucker/epiretinal membrane, vitreomacular traction, macular edema and exudates, detachments of the neurosensory retina, detachments of the retinal pigment epithelium (e.g., central serous retinopathy or age-related macular degeneration).

In present study, we used SD-OCT to measure the central macular thickness and observed that out of 22 SSc patients, 3 patients had decreased central macular thickness (CMT). These patients did not have any ocular symptoms but had lung involvement in the form of interstitial lung disease.

We did not find any difference in CMT in SLE patients which may be due to the small sample size

5. Conclusion

Patients with ACTD should be actively assessed for ocular involvement and a complete ocular examination should be routinely performed as it can have an impact on the disease severity and quality of life in patients with ACTD. Optical coherence tomography (OCT), which is a non-invasive modality to assess posterior segment and it may be associated with more severe visceral involvement. Patients presenting with pulmonary involvement should undergo an early OCT and a detailed ocular examination so as to detect, treat and prevent grave ocular complications like macular hole formation and retinal detachment. Further studies incorporating a larger number of patients are required to further evaluate our preliminary findings.

6. Conflict of Interest

None.

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