Special Focus, Uvea, Original Article

Pattern of uveitis from a tertiary eye care center in Himalayan belt of North India

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Purpose: To study the clinical characteristics of uveitis in patients presenting to a tertiary care institute in the northern part of India, predominantly serving the population of Himalayan belt. **Methods:** In this retrospective descriptive case series, data of 141 eyes of 102 patients diagnosed between January 2019 and January 2021 were analyzed. Patients were diagnosed, named, and meshed as per the Standardization of Uveitis Nomenclature. A panel of investigations (systemic and ocular ancillary investigations) were done, which was individualized according to the clinical picture. **Results:** The mean age of presentation was 39.1 ± 14.62 years. A male predominance (62.7%) was noted. Unilateral presentation was seen in 61.8% of patients. Specific etiological diagnosis was not reached in 56.7% of cases. The incidence of infectious and noninfectious uveitis was 23.4% and 19.9%, respectively. The frequency of anterior, intermediate, posterior, and panuveitis was 23.4%, 11.3%, 46.8%, and 18.5%, respectively. Posterior uveitis was the most frequent anatomical location (46.8%). Tuberculous uveitis was the most common definitive etiology irrespective of location (18.5%). Anterior, intermediate, and posterior uveitis were more frequently idiopathic in origin. Sympathetic ophthalmitis was the most common cause for panuveitis. **Conclusion:** Uveitis significantly affected the working age group population. Despite the evolution of diagnostic investigations, etiology remained unknown in many cases of uveitis. Infectious etiology was more common. Posterior uveitis as the most frequent anatomical location in our study may be attributed to the tertiary care referral bias.

Access this article online

Website: www.ijo.in

DOI: 10.4103/ijo.IJO_2159_21

Quick Response Code:

Key words: Anterior Uveitis, intermediate uveitis, panuveitis, posterior uveitis, uveitis

Uveitis is broadly defined as the inflammation of uveal tract, which may also be accompanied by inflammation of adjacent ocular structures like the retina, sclera, cornea, vitreous, and optic nerve. Its prevalence is estimated to be 730 per 1,00,000 population in India.[1] The incidence of uveitis among the patients visiting tertiary care institutes in India as estimated by the studies in North and South India has been shown to be 1.31% and 0.8%, respectively.[2,3] The disease per se, complications, and treatment, all can contribute to the visual morbidity, accounting for about 25% of blindness in developing countries.[4-7] Both infectious and noninfectious etiological factors cause uveitis. However, the etiology remains unknown in a majority of cases. Owing to the multitude of etiology, the internationally accepted classification system of uveitis as per the current International Uveitis Study Group (IUSG) Classification system is based on anatomical location of inflammation rather than the etiology.[8] Etiology and clinical presentation of uveitis may vary depending upon the population, genetic make-up, environmental factors, and many other factors including available medical and laboratory facilities.

Over the years, multiple studies across the world have shown changing trend in the clinical profile, pattern, and etiology with time, India being no exception to it.[2,9-11] Improvement in diagnostic facilities, better understanding of ocular immunology, relatively new emerging agents, and eradication of certain infectious agents have contributed to this evolving trend. A dedicated baseline study to analyze the clinical presentation, etiology, and demographic association of uveitis in any geographic area would help to arrive at a correct etiological diagnosis by a tailored approach specific to that area. An unfocused laboratory screening would be an inefficient, time-consuming process and an economic burden to the patient. Hence, the current study was undertaken with an aim to understand the clinical characteristics of uveitis in patients presenting to our institute, which is recently established and predominantly caters to a resource-constrained sub-Himalayan population.

Methods

The study was conducted as a retrospective analysis of records of patients diagnosed with uveitis in our institute between January 2019 and January 2021. Naming and meshing of these patients were done as per the guidelines

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Received: 17-Aug-2021 Revision: 22-Oct-2021
Accepted: 11-Jan-2022 Published: 28-Apr-2022

Cite this article as: Pandurangan S, Samanta R, Kumawat D, Sood G, Devi TS, Agrawal A. Pattern of uveitis from a tertiary eye care center in Himalayan belt of North India. Indian J Ophthalmol 2022;70:1642-7.

of Standardization of Uveitis Nomenclature (SUN).[12] Investigations were tailored individually for every patient based on demography, anatomical location, and pattern of uveitis. The investigations included complete blood count (CBC), erythrocytic sedimentation rate (ESR), tuberculin skin test (Mantoux), interferon-gamma release assay (IGRA), venereal disease research laboratory (VDRL) test, *Treponema pallidum* hemagglutination assay (TPHA), serum angiotensin converting enzyme (ACE), rheumatoid factor (RF), serum antinuclear antibody (ANA), anti-neutrophil cytoplasmic antibody (ANCA) testing, viral markers, Toxoplasmosis, Rubella, Cyctomegalovirus, Herpes simplex virus (TORCH), Human Leukocyte antigen B-27 (HLA-27; flow cytometric assessment on peripheral blood), dengue NS-1 antigen, CD-4 cell count, chest X-ray, and contrast-enhanced computed tomography (CECT) thorax. Ophthalmic ancillary investigations like fundus photography, fundus autofluorescence image, fundus fluorescein angiography (FFA), optical coherence tomography (OCT), and ultrasound B scan of eye were done as and when required. A total of 102 patients (141 eyes) were enrolled during this period. The diagnoses of ocular tuberculosis, sarcoidosis, and acute retinal necrosis (ARN) were made according to the diagnostic criteria as described in literature.[13-16] Intraocular tuberculosis (IOTB) was further classified into confirmed, probable, and possible IOTB.[13] Sarcoidosis-associated uveitis was subclassified into definite, presumed, and probable ocular sarcoid as per the revised international classification system published in literature.[14] Endophthalmitis of any etiology was excluded. Appropriate consultation with other specialty departments including general medicine, pediatric medicine, pulmonary medicine, and rheumatology department was done in selected cases. The term "idiopathic uveitis" was used when a specific etiological cause could not be determined despite laboratory and imaging investigations. Statistical analysis was done using the SPSS v23 software. Wilcoxon test, Chi-squared test, and Fisher's exact test were used to find the correlation and for comparison of variables. A P value of <0.05 was taken as significant.

Results

The mean age of the study population was 39.1 ± 14.6 years; 6.9% were less than 18 years of age, 83.3% belonged to the 18–60 years age group, and 9.8% were more than 60 years of age. Sixty-four patients (62.7%) were male and 38 were female (37.3%). Unilateral presentation was seen in 63 patients (61.8%) and bilateral presentation in 39 patients (38.2%). A significant association (P = 0.004) was noted between laterality and anatomical location of uveitis in the present study. Unilateral presentation was more commonly seen in patients with anterior uveitis and bilateral presentation in patients with panuveitis. This association was not significant in posterior and intermediate uveitis. Specific etiology was attributed to 61 eyes (43.3%), out of which infectious etiology was seen in 33 eyes (23.4%) and noninfectious etiology in 28 eyes (19.9%). Eighty eyes contributing to 56.7% of eyes with uveitis were termed "idiopathic" as no specific etiology could be established. Of the 141 eyes with uveitis, 33 (23.4%) were anterior uveitis, 16 (11.3%) were intermediate uveitis, 66 (46.8%) were posterior uveitis, and 26 (18.5%) were panuveitis. An acute course was seen in 78 eyes (55.3%), chronic course in 33 eyes (23.4%), and recurrence in 30 eyes (21.3%).

Anterior uveitis patients were further classified as granulomatous (10 eyes, 30.3%) and nongranulomatous (23 eyes, 69.7%) clinically. In anterior uveitis, 13 eyes (39.4%) were idiopathic. HLA-B27–associated anterior uveitis was the most common etiological diagnosis seen in nine eyes (27.3%). Fuch's heterochromic iridocyclitis was seen in three eyes (9.1%), and sarcoid-associated anterior uveitis was seen in one of the fellow eyes with sarcoid-associated panuveitis. Tuberculous anterior uveitis was the only infectious cause of anterior uveitis seen in six eyes (18.2%) in the present study. Juvenile idiopathic arthritis (JIA)-associated anterior uveitis was seen in one child of 15 years of age.

In intermediate uveitis, specific diagnosis was not reached in 10 eyes (62.5%). Tuberculous uveitis accounted for the remaining six eyes (37.5%) with intermediate uveitis.

In posterior uveitis, 51 eyes (77.3%) had uveitis of idiopathic origin. IOTB was seen in eight eyes (12.1%). Among the three eyes (4.6%) of three patients with ocular toxoplasmosis, only one patient was reactive for IgM antibodies of *Toxoplasma*. Though the remaining two patients were positive for IgG antibodies, the diagnosis of ocular toxoplasmosis in these patients was made on the basis of focal active retinochoroiditis with overlying vitritis and a positive therapeutic response to intravitreal clindamycin with dexamethasone and oral cotrimoxazole. One case of dengue microvasculopathy presenting as foveolitis was seen in a patient with dengue NS-1 antigen positivity. One human immunodeficiency virus (HIV)-positive patient presented with ARN. Though polymerized chain reaction (PCR) test for aqueous sample could not be performed due to nonavailability, the patient was treated with systemic acyclovir therapy and the lesions regressed completely with the therapy. Progressive outer retinal necrosis (PORN) was diagnosed in one patient, who on investigation was found to be HIV reactive. The patient was started on antiretroviral therapy (ART). Cytomegaloviral (CMV) retinitis in one patient was also diagnosed clinically, though viral PCR from ocular fluids was not available.

Among the panuveitis cases, specific etiological diagnosis could not be reached in six (23.1%) out of 26 eyes. Among the infectious etiology, IOTB was seen in six eyes (23.1%). Among the noninfectious etiology, sympathetic ophthalmitis was seen in 10 eyes (38.4%) and sarcoidosis in four eyes (15.4%). A summary of the demographic, clinical, and etiological characteristics of uveitic patients is given in Table 1.

Of the 26 eyes with IOTB, 21 (80.8%) were possible IOTB and five (19.2%) were probable IOTB based on the classification system proposed by Gupta *et al*.[13] There was no clinically significant association noted between the location of uveitis and IOTB in the present study. Table 2 shows the characteristics of IOTB in the present study.

Of the three patients with sarcoidosis, one patient was subclassified as presumed ocular sarcoid and the other two were subclassified as probable ocular sarcoid as per the classification system.[14]

The overall pattern of posterior segment involvement was also analyzed separately and is presented in Table 3. The most frequent pattern was vasculitis (30 eyes, 21.3%).

Table 1: Summary of demographic, clinical and etiological characteristics of uveitic patients

Characteristics	Mean±SD || median (IQR) || min.–max. || frequency (%)
Age (years)	39.14±14.62 || 39.50 (27.75-50.00) || 15.00-72.00
Age group	*n*=102
<18 years	7 (6.9%)
18-60 years	85 (83.3%)
>60 years	10 (9.8%)
Gender	*n*=102
Male	64 (62.7%)
Female	38 (37.3%)
Laterality	*n*=102
Unilateral	63 (61.8%)
Bilateral	39 (38.2%)
Course	*n*=141
Acute	78 (55.3%)
Chronic	33 (23.4%)
Recurrent	30 (21.3%)
Location	*n*=141
Anterior	33 (23.4%)
Intermediate	16 (11.3%)
Posterior	66 (46.8%)
Pan	26 (18.5%)
Etiology	*n*=141
Idiopathic	80 (56.7%)
IOTB	26 (18.5%)
Sympathetic ophthalmitis	10 (7.1%)
HLA-B27	9 (6.4%)
Sarcoid	5 (3.6%)
Fuch's	3 (2.1%)
Toxoplasma	3 (2.1%)
Herpes	2 (1.4%)
CMV	1 (0.7%)
Dengue	1 (0.7%)
JIA	1 (0.7%)
Type of etiology	*n*=141
Idiopathic	80 (56.7%)
Infectious	33 (23.4%)
Noninfectious	28 (19.9%)

CMV=cytomegalovirus, HLA-B27=human leukocyte antigen B27, IOTB=intraocular tuberculosis, IQR=interquartile range, JIA=juvenile idiopathic arthritis, SD=standard deviation

Fifty-one uveitic eyes (36.1%) had some associated ocular complications at the time of presentation. The presenting complaint in most of the posterior uveitis patients was related to complications, the most common being retinal neovascularization and vitreous hemorrhage (21 eyes, 14.9%). Various complications seen in the present study are described in Table 4.

Four uveitic eyes with associated scleritis were also noted. One had anterior uveitis associated with anterior scleritis and three had posterior uveitis associated with posterior scleritis.

Discussion

Comparing the present study with the previous studies, certain similarities and differences in the trend and pattern of uveitis were noted. A male predominance shown in previous studies from India[3,5,10,17] has been attributed to the fact that males seek medical attention more often than females and the socioeconomic habits place them at a high risk of exposure to infectious agents. In developed countries, usually, an equal gender distribution or a slight female predominance is reported.[18-20] In the present study, there was a male predominance.

Mean age of presentation of uveitis in the present study (39.14 ± 14.62 years) was comparable with other Indian studies, in which the range was between 30 and 60 years.[2,5,12,13,19] Pediatric uveitis accounted for about 5%–10% of all uveitis cases,[11,21-24] which in the present study accounted for 6.8% of all uveitis cases. Of the seven eyes with pediatric uveitis, JIA and IOTB were found to be the cause in one each, while the rest were idiopathic in origin. Posterior uveitis was common, followed by anterior uveitis among the pediatric population in the present study. Few Indian studies[11,23] showed anterior uveitis to be the most common location, while one study[24] showed intermediate uveitis to be more common. We did not have any case of intermediate or panuveitis among the pediatric population during our study period. Pediatric uveitis differs from adult uveitis in that the pediatric patients have a higher ocular morbidity, risk of amblyopia, and complications of long-term steroid therapy and immune suppression therapy.

Frequent unilateral presentation in anterior uveitis and bilateral presentation in intermediate and panuveitis has been documented in many studies[3,4,25] and a similar pattern is noted in our study also. With regards to the anatomical location, studies across India have uniformly shown anterior uveitis to be the most common anatomical location encountered in clinical practice, following which either posterior or panuveitis has been noted. Intermediate uveitis was the least frequently encountered site of ocular inflammation.[3,4,5,17,26-28] But posterior uveitis was more common in our institute (46.8%), followed by anterior uveitis (23.4%). Posterior uveitis has been reported to be the most common location in a few studies from tertiary care centers outside India.[4,18] This may be due to tertiary care referral bias, while the other reason could be a higher prevalence of infectious agents affecting the posterior segment, such as *Toxoplasma*, tuberculosis, CMV, and onchocerciasis, in developing countries.[20] Moreover, posterior uveitis may be associated with greater visual morbidity, which explains the higher frequency seen at tertiary institutes. Additionally, the overall number of retinal vasculitis patients (21.3% of all uveitis patients) in our cohort was quite higher than in other Indian studies. We believe all of the above factors might have contributed to the higher number of posterior uveitis cases in our study.

Though a number of studies from India[9,10,27] that have compared the changing trend of uveitis have documented a significant increase in cases with specific etiological diagnosis, still 30%–60% of cases remain to be idiopathic in origin. In the present study, 56.7% of cases were idiopathic. The relatively higher number of idiopathic cases in our study could be due to multiple factors like unavailability of sophisticated molecular

Table 2: Distribution of subclassification of IOTB

IOTB	Location				
	Anterior	Intermediate	Posterior	Pan	Total
Possible	4 (66.7%)	4 (66.7%)	7 (87.5%)	6 (100.0%)	21 (80.8%)
Probable	2 (33.3%)	2 (33.3%)	1 (12.5%)	0 (0.0%)	5 (19.2%)
Total	6 (100.0%)	6 (100.0%)	8 (100.0%)	6 (100.0%)	26 (100.0%)

IOTB=intraocular tuberculosis

Table 3: Frequency of various patterns of posterior segment involvement in uveitis

Pattern	No. (%)
Vasculitis	30 (21.3%)
Choroiditis	
Serpiginous-like choroiditis	21 (14.9%)
Focal choroiditis	2 (1.4%)
Serpiginous choroiditis	2 (1.4%)
Neuroretinitis	7 (4.9%)
Choroidal granuloma	2 (1.4%)
Choroidal tubercles	1 (0.7%)
Retinitis	
ARN	1 (0.7%)
PORN	1 (0.7%)
Toxoplasma retinitis	3 (2.1%)
CMV retinitis	1 (0.7%)
Foveolitis	1 (0.7%)
Subretinal abscess	1 (0.7%)
Posterior uveitis associated with scleritis	3 (2.1%)

ARN=acute retinal necrosis, CMV retinitis=cytomegaloviral retinitis, PORN=progressive outer retinal necrosis

Table 4: Frequency of various complications seen in uveitis patients in the present study

Complications	No. (%)
Any	51 (36.2%)
CC	11 (7.8%)
Glaucoma	2 (1.4%)
CME	13 (9.2%)
RD	3 (2.1%)
RNV/VH	21 (14.9%)
CNV	2 (1.4%)
ERM	2 (1.4%)
BSK	2 (1.4%)
RVO	1 (0.7%)
RAO	1 (0.7%)

BSK=band-shaped keratopathy, CC=complicated cataract, CME=cystoid macular edema, CNV=choroidal neovascularization, ERM=epiretinal membrane, RAO=retinal artery occlusion, RD=retinal detachment, RNV/VH=retinal neovascularization/vitreous hemorrhage, RVO=retinal venous occlusion

laboratory investigations as the institute is newly set up. Many patients belonged to a difficult geographic terrain with limited laboratory resources.

In developing countries, infectious etiology accounts for 30%–50% of the total cases.[3,20] IOTB tops the list in most of the studies, followed by viral etiology, *Toxoplasma*, syphilis, and leprosy in variable proportions.[4,9,10,20] The most common specific infectious etiology diagnosed in our study was IOTB (18.4%), which is similar to most of the previous studies.[1,2] The pathogenesis of IOTB being immune response to the tuberculous bacilli, which is frequently a paucibacillary type, makes the demonstration of bacilli in the intraocular fluids a rarity. *Toxoplasma*-associated posterior uveitis has been the frequently diagnosed infectious uveitides in India, next to IOTB in a majority of the Indian studies.[2,5,9] *Toxoplasma* retinitis was the second most common infectious uveitis, accounting for 2.1% of cases. The other infectious etiology noted among the patients of Himalayan belt included herpes-associated retinitis, dengue, and CMV.

Considering the noninfectious causes of uveitis, in a global perspective, HLA-B27–associated anterior uveitis is less frequent in Asian countries when compared to the western countries. Incidence of acute anterior uveitis in the general population is found to be 0.2%, while in HLA-B27–positive population, the incidence is 1%.[4] In the present study, HLA-B27–associated uveitis accounted for about 6.4% of cases. In many instances, ophthalmologists may be the first to suspect the disease entity. Three of the nine patients who were positive for HLA-B27 had symptoms of ankylosing spondylitis, which on further investigation and specialty consultation confirmed the same. The frequency of diagnosis of Fuch's heterochromic iridocyclitis ranged between 1% and 30%.[3,5,10,22,25] Fuch's iridocyclitis accounted for 2.1% of uveitis cases in the present study. Sarcoidosis as a cause of uveitis has been considered a rarity in developing countries. However, recent studies have shown an increasing trend of diagnosing sarcoidosis in developing countries and tuberculosis has been implicated in the pathogenesis of sarcoidosis in some studies.[29,30] Sarcoidosis manifesting as panuveitis in India varies from 1% to 21%. In the current study, sarcoid-associated uveitis accounted for 3.6% of cases. In the present study, of the five eyes with sarcoid-associated uveitis, four presented as panuveitis and one presented as anterior uveitis.

Analysis of etiology with respect to the anatomical location of uveitis gave the following results. Of the anterior uveitis cases, 39.4% were of idiopathic origin in our study, which is comparable to other studies globally, where the proportion of anterior uveitis of unknown etiology ranged from 38% to 88%.[4,31] HLA-B27–associated anterior uveitis was more common followed by tubercular anterior uveitis in our study, while studies from India have shown tubercular anterior uveitis to be a more common etiology for anterior uveitis.[5,9,10,17,27]

Intermediate uveitis, which is the least common form of clinically seen uveitis, is often of idiopathic origin (60%–

Table 5: Comparison of pattern of uveitis found between the present study and in other Indian studies

Study		Dogra *et al.*[2]	Borde *et al.*[5]	Palsule *et al.*[32]	Das *et al.*[27]	Biswas *et al.*[9]	Present study
Geographic location		North India	Central India	Western India	Northeast India	South India	Himalayan belt
Total cases		1912	210	198	343	352	141
Gender distribution (%)	Male	56.6	51	44.4	60.9	56	62.7
	Female	43.4	49	55.6	39.1	44	37.3
AU (%) Most common causes of AU		43.04 Idiopathic (41.7%) followed by tubercular AU (37.7%)	47.1 Idiopathic (37.4%) followed by herpes related (18.8%)	41.4 Idiopathic (53.7%) followed by HLA-B27 associated (29.3%)	41.39 HLA-B27 associated (40.8%) followed by idiopathic (25.3%)	35.22 Idiopathic (37.4%) followed by HLA-B27 associated (30%)	23.4 Idiopathic (39.4%) followed by HLA-B27 associated (27.3%)
IU (%) Most common causes of IU		10.66 Idiopathic (44.6%)	31.9 Idiopathic (77.6%)	16.7 Idiopathic (69.7%)	23.61 Idiopathic (50.6%)	30.11 Idiopathic (51.9%)	11.3 Idiopathic (62.5%)
PU (%) Most common causes of PU		24.6 IOTB (48.5%) followed by idiopathic (36.6%)	12.8 Idiopathic (25.9%) followed by IOTB (22.2%)	20.7 Idiopathic (31.7%) followed by IOTB (19.5%)	16.3 IOTB (37.5%) followed by Toxo (14.3%)	25 IOTB (35%) followed by Toxo (20.4%)	46.8 Idiopathic (77.3%) followed by IOTB (12.1%)
Panuveitis (%) Most common cause of panuveitis		16.2 IOTB (29%)	8.1 Idiopathic (29.4%)	21.2 Idiopathic (42.9%)	18.6 IOTB (29.7%)	9.6 VKH (55.9%)	18.5 Sympathetic ophthalmitis (38.4%)
Overall idiopathic cases (%)		39.4	48	49.5	26.2	33.8	56.7
Overall most common infectious etiology		IOTB	IOTB	IOTB	IOTB	IOTB	IOTB
Overall most common noninfectious etiology		HLA-B27–associated uveitis	Spondyloarthropathy	HLA-B27–associated uveitis	HLA-B27–associated uveitis	HLA-B27–associated uveitis	Sympathetic ophthalmitis and HLA-B27–associated uveitis

AU = anterior uveitis, HLA-B27 = human leukocyte antigen B27, IOTB = intraocular tuberculosis, IU = intermediate uveitis, PU = posterior uveitis, VKH = Vogt-Koyanagi-Harada Disease

100% of cases).[1,4] In the present study, 62.5% of cases with intermediate uveitis were of idiopathic origin. Rest (37.5%) of the cases in which specific etiology was found were of tubercular origin. Frequent causes of intermediate uveitis in India have been IOTB and sarcoidosis.[1,2,11] In our study, a specific etiology could not be reached in a maximum number of cases with posterior uveitis (77.3%). IOTB was the most common specific diagnosis reached in 12.1% of posterior uveitis cases, followed by toxoplasmosis in 4.6% of cases. A specific diagnosis was made in maximum number of cases with panuveitis (76.9%) in the present study. Noninfectious etiology was more common in panuveitis, which included sympathetic ophthalmitis and sarcoid-associated panuveitis. Comparison of uveitis pattern between the presented study and other Indian studies has been represented in a table [Table 5].

A limitation of this study is the significant tertiary care center referral bias, which led to a greater number of posterior uveitis cases presenting with complications. Nonavailability of specific PCRs for infective etiology diagnosis might have led to a higher number of idiopathic cases. Though higher number of IOTB cases (presumed and probable IOTB) have been diagnosed in the present study, there were no confirmed IOTB cases, as histopathologic examination and confirmation from ocular or extraocular sites could not be performed due to logistic reasons. Since the institute has been recently set up, some of the sophisticated laboratory investigations are yet to be fully functional. The small sample size, which is a major limitation, was due to decrease in the number of cases due to coronavirus disease 2019 (COVID-19) pandemic.

Conclusion

The present study gives a broad overview of uveitis patients and serves as a benchmark for the pattern of uveitis in this sub-Himalayan terrain. This study also emphasizes further need for increased stepwise utilization of molecular and histopathologic tests after preliminary baseline investigations to confirm the etiopathogenesis.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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