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A descriptive study of syphilitic uveitis in patients treated at tertiary hospitals in Johannesburg

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Background: Syphilitic uveitis is a 'great mimicker' with a myriad of manifestations resembling other forms of inflammation in the eye. A large percentage of patients with syphilitic uveitis in South Africa have HIV co-infection and their clinical features and serological results may be confounded by the presence of HIV.

Aim: This study aimed to describe the clinical features of patients treated for syphilitic uveitis at two tertiary hospitals in Johannesburg.

Setting: The study was conducted at the ophthalmology departments of two tertiary hospitals in Johannesburg.

Methods: A retrospective descriptive case series of patients admitted for treatment of syphilitic uveitis at Charlotte Maxeke Johannesburg Academic Hospital and Chris Hani Baragwanath Hospitals.

Results: From 01 January 2015 to 30 June 2020, 25 patients (44 eyes) were admitted for syphilitic uveitis treatment. Vitritis was the most common sign in 54.5% of the patients (n = 24 eyes) and 23 of these eyes were of HIV positive patients. Anterior chamber cells were in 43.1% of the patients (n = 19 eyes), posterior synechiae in 36.3% (n = 16 eyes), optic disc swelling in 31.8% (n = 14 eyes), pigmentary retinopathy in 18.1% (n = 8 eyes) and ciliary injection in 18.1% (n = 8 eyes). Optic disc swelling was observed in 57.1% (n = 4 eyes) of HIV negative patients. There was an improvement in visual acuity (VA) in 64.3% of eyes (n = 27) and no change in VA in 35.7% (n = 15) of eyes. No deterioration in post-treatment VA was documented.

Conclusion: Majority of the patients admitted for syphilitic uveitis had posterior segment signs, which should prompt a diagnosis of syphilis. The treatment of syphilitic uveitis leads to an improvement in VA.

Contribution: This work contributes to our understanding of syphilitic uveitis presentation in South African hospitals.

Keywords: African; South Africa; syphilis; posterior uveitis; vitritis; posterior placoid chorioretinopathy; HIV.

Introduction

Syphilis is a systemic infection caused by the spirochete *Treponema Pallidum* and is characterised as having four stages, namely primary, secondary, latent (early and late) and tertiary.[1,2,3,4,5] Ocular syphilis constitutes inflammatory eye diseases caused by the same bacteria and is known as a 'great mimicker' as it can present in any form including, interstitial keratitis, uveitis including anterior uveitis, intermediate uveitis, retinal vasculitis, chorioretinitis, optic neuritis, papillitis and optic nerve gumma.[1,6] A high clinical suspicion is therefore important in diagnosing ocular syphilis, which can occur at any stage of the infection, owing to its long-term complications in the eye as well as other parts of the central nervous system. Syphilis is predominantly sexually acquired and an increasing number of cases has been reported in recent years.[1,2,7,8,9,10] South Africa has an estimated 13.7% of its population that is living with HIV and the number of people infected increased from an estimated 3.8 million in 2002 to 8.2 million in 2021.[11] Relatively there has been an increase in the number of syphilis cases in HIV positive patients.[1] A large percentage of our patients with syphilitic uveitis have HIV co-infection and their clinical features and serological results may be confounded by the presence of HIV.

Aims

This study aims to describe the clinical features of syphilitic uveitis in patients treated at tertiary hospitals in Johannesburg, South Africa.

Research methods and design

This study was a retrospective descriptive case series of patients admitted for treatment of syphilitic uveitis at Charlotte Maxeke Johannesburg Academic Hospital (CMJAH) and St Johns Eye Hospital (SJEH) at Chris Hani Baragwanath Hospital, Johannesburg, between 01 January 2015 and 30 June 2020. The admission records of the ophthalmology wards were reviewed for the aforementioned period for patients admitted for unilateral or bilateral 'uveitis', 'panuveitis', 'neurosyphilis', 'neuroluetic disease' and 'bilateral swollen discs'. These records were analysed to identify patients admitted to CMJAH and SJEH for intravenous antibiotic treatment on account of a diagnosis of syphilitic uveitis.

The patients' demographics, presenting symptoms and signs, laboratory investigations and visual outcomes were recorded. Classification of uveitis in each eye was according to the Standardisation of Uveitis Nomenclature (SUN) Working Group criteria.

Syphilis testing is routinely performed as part of part of uveitis workup in both the hospitals. The reverse sequencing testing algorithm is performed and includes treponemal serological testing (Treponema pallidum Antibody [TPAB] test), followed by non-treponemal testing, which is the rapid plasma reagin (RPR) test if the former was reactive. The cerebrospinal fluid (CSF) is tested for Venereal Disease Research Laboratory (VDRL), lymphocyte count and protein levels in all patients who present with posterior segment involvement (intermediate, posterior or panuveitis) in the presence of a positive syphilis serology.

Ethical considerations

Ethical approval to conduct the study was granted by the Human Research Ethics Committee, University of the Witwatersrand (M200833). Due to the study being retrospective in nature, the data was obtained from patient records. Permission was obtained from the Medical Advisory Board and Chief Executive Officer of the relevant hospital during the phase of protocol submission. Patients were given numerical identifiers and their names and surnames were not used during data collection in order to maintain confidentiality.

Results

From 01 January 2015 to 30 June 2020, 25 patients were admitted for intravenous antibiotic treatment on account of a diagnosis of syphilitic uveitis, 10 patients were admitted to CMJAH (40.0%) and 15 to SJEH (60.0%). All patients were of African ethnicity and the majority (76.0%, *n* = 19) were in 30–49-year age group. Gender-wise, 56.0% of the patients (*n* = 14) were males and 44.0% (*n* = 11) females. Table 1 illustrates demographic data and clinical history of the study population.

Most patients 76.0% (*n* = 19) had symptoms in both eyes. Blurred vision was the most common symptom in 68.0% (*n* = 17) of the patients, followed by pain in 28.0% (*n* = 7) and photophobia in 16.0% (*n* = 4).

There were 19 patients (76.0%) with bilateral eye disease and 6 (24.0%) with unilateral eye disease; 44 eyes of 25 patients were therefore included in the study. The commonest uveitis category was posterior uveitis in 31.8% (*n* = 14) of eyes, panuveitis was present in 25.0% (*n* = 11) of eyes, anterior and intermediate uveitis were present in 25.0% (*n* = 11) and 18.2% (*n* = 8), respectively. The LogMar visual acuity (VA) at presentation ranged from 0.0 to 4.0 and was recorded for all except 2 eyes documented to have anterior uveitis. Table 2 demonstrates the pre-treatment LogMar VA of 42 eyes according to uveitis category.

Of the 42 eyes for which VA was recorded, 10 (23.8%) had a good VA (0.0–0.3), 13 (31.0%) had a moderate VA (0.4–0.9) and most eyes (*n* = 19, 45.2%) had a poor LogMar VA of 1.0 or worse. All eyes belonging to HIV negative patients had a poor VA (*n* = 7 eyes), the HIV status of 1 patient with bilateral

TABLE 1: Demographic data and clinical history of study population.

Characteristics	No. of patients	%
Age groups (years)		
< 30	3	12.0
30–39	12	48.0
40–49	7	28.0
> 50	3	12.0
Gender		
Males	14	56.0
Females	11	44.0
Symptoms		
Bilateral	19	76.0
Unilateral	6	24.0
Nature of symptoms†		
Blurred vision	17	68.0
Pain	7	28.0
Photophobia	4	16.0
Red eyes	3	12.0
Floaters	1	4.0
Other	1	4.0
History of HIV		
Known positive	17	68.0
Known negative	4	16.0
Unknown	4	16.0
History of syphilis		
No previous history	24	96.0
Known history	1	4.0

†, Patients may have presented with more than one symptom.

TABLE 2: Pretreatment LogMar visual acuity according to uveitis category.

Uveitis classification	Total (*n*)	LogMar visual acuity categories					
		Good visual acuity (0.0 to 0.3)		Moderate visual acuity (0.4 to 0.9)		Poor visual acuity (≥ 1.0)	
		n	%	*n*	%	*n*	%
Anterior*	9	2	22.2	2	22.2	5	55.5
Intermediate	8	0	0.0	4	50.0	4	50.0
Posterior	14	7	50.0	2	14.3	5	35.7
Panuveitis	11	2	18.2	4	36.4	5	45.5
Total	**42**	**11**	**26.2**	**12**	**28.6**	**19**	**45.2**

*, The visual acuity for 1 patient with bilateral anterior uveitis was not documented.

posterior uveitis was not recorded (*n* = 2 eyes) and the remaining eyes belonged to HIV positive patients (*n* = 35 eyes).

While 68.0% (*n* = 17) of the patients had a background history of HIV, following blood investigations, 80.0% (*n* = 20) were confirmed HIV positive, 16.0% (*n* = 4) were HIV negative and 4.0% (*n* = 1) remained unknown. Of those who were HIV positive, 6 patients (30.0%) had a CD4 count > 350 cells/microlitre (μL), while 12 patients had a CD4 count < 350 cells/μL and 2 patients did not have a CD4 count recorded. The median viral load, which was only available for 30.0% (*n* = 6) of patients was 5645 copies/mL (range 126–217 000).

Table 3 represents the clinical signs in all 44 study eyes according to anterior and posterior segments of the eye.

Vitritis was the most common sign present in 54.5% (*n* = 24 eyes), 23 of these eyes were of HIV positive patients. The vitritis ranged from 1+ to 3+ grading according to the SUN classification and 70.8% of these eyes belonged to patients with a CD4 count < 350 cells/μL. Other common signs were AC cells in 43.1% (*n* = 19 eyes) followed by posterior synechiae in 36.3% (*n* = 16 eyes), optic disc swelling in 31.8% (*n* = 14 eyes), pigmentary retinopathy in 18.1% (*n* = 8 eyes) and ciliary injection in 18.1% (*n* = 8 eyes). Of those eyes belonging to HIV negative patients, the commonest sign was optic disc swelling observed in 57.1% (*n* = 4 eyes). The HIV negative patients displayed more posterior segment signs including pigmentary retinopathy in 2 eyes (28.6%) and retinal vasculitis in 2 eyes (28.6%). The median intraocular pressure (IOP) was 12 mmHg (interquartile range [IQR]: 10 mmHg – 15 mmHg).

TABLE 3: Clinical signs in study eyes according to anterior and posterior segments of the eye.

Segment of eye	Total no. of eyes	HIV positive		HIV negative	
		n	%	*n*	%
Anterior Segment					
AC cells	19	18	94.7	1	5.3
Posterior synechiae	16	14	87.5	2	12.5
Ciliary injection	8	7	87.5	1	12.5
AC flare	6	6	100.0	0	0.0
Keratic precipitates	2	2	100.0	0	0.0
Koeppe nodules	1	1	100.0	0	0.0
Iris bombe	1	1	100.0	0	0.0
Posterior segment					
Vitritis	24	23	95.8	1	4.2
Optic disc swelling	14	10	71.4	4	28.6
Pigmentary retinopathy	8	6	75.0	2	25.0
Vasculitis†	6	2	33.3	2	33.3
Retinitis	0	0	0.0	0	0.0

†, The HIV status of 2 patients with vasculitis were not known.

Uveitis complications included cataract in 25.0% (*n* = 11), ocular hypertension in 9.3% (*n* = 4), macula oedema in 4.6% (*n* = 2), epiretinal membrane in 11.3% (*n* = 5) and other complications in 6.8% (*n* = 3) of eyes; 47.7% (*n* = 21) of eyes were not reported to have any complications.

Table 4 summarises the serum and CSF results of the study patients relevant to the diagnosis of syphilitic uveitis according to HIV status.

The serum tests conducted included a treponemal test, Treponema Pallidum Haemagglutination Assay (TPHA), which was positive in all 25 patients. The non-treponemal test conducted was the RPR test, which was positive in 17 (68.0%) patients, 14 (82.4%) of which were HIV positive and 3 (17.6%) were HIV negative. The median RPR titre was 1:32 (IQR: 1:32 – 1:256). The CSF protein was raised above 45 mg/dL in 13 (52.0%) patients (9 [69.2%] HIV+ and 3 [23.1%] HIV–, 1 [7.7%] HIV status unknown). The CSF lymphocytes were raised above 5 cells/uL in 5 (20.0%) patients (all HIV+) and the CSF VDRL was positive in 5 (20.0%) patients (all HIV+). The HIV negative group did not have raised CSF lymphocytes and all HIV negative patients also had a negative CSF VDRL result.

Table 5 summarises the treatment used in all patients according to HIV status.

The systemic antibiotic used to treat 76.0% (*n* = 19) of patients was intravenous ceftriaxone. The median duration of treatment was 14 days. Topical corticosteroids were used to treat 52.2% (*n* = 23) of eyes. Regional corticosteroids were not used. Oral corticosteroids were used in 64.0% (*n* = 16) of patients with a median dose of 60 mg daily (IQR: 47.5 mg – 60 mg). Intravenous corticosteroids were used in 4.0% (*n* = 1) of patients.

TABLE 4: Serum and cerebrospinal fluid results of study patients according to HIV status (*N* = 25).

Specimen results	All patients *n*	HIV positive (*n* = 20)		HIV negative (*n* = 4)		HIV unknown (*n* = 1)	
		n	%	*n*	%	*n*	%
Serum tests							
Serum treponemal test (TPHA)							
TPHA reactive	25	20	80.0	4	16.0	1	4.0
Serum non-treponemal test (RPR)							
RPR reactive†	17	14	82.4	3	17.6	0	0.0
RPR non-reactive	7	5	71.4	1	14.3	1	14.3
CSF Abnormalities							
CSF protein > 0.45 g/uL	13	9	69.2	3	23.1	1	7.7
CSF lymphocytes > 5	5	5	100.0	0	0.0	0	0.0
CSF VDRL positive‡	5	5	100.0	0	0.0	0	0.0

Note: The median Rapid Plasma Reagin Test titre was 1:32 (interquartile range: 1:32 – 1:256).

CSF, cerebrospinal fluid; RPR, Rapid Plasma Reagin Test; TPHA, Treponema Pallidum Haemagglutination Assay.

†, the RPR result was not recorded for 1 HIV positive patient; ‡, CSF VDRL was not available for 1 HIV negative patient.

TABLE 5: Treatment used in patients according to HIV status (N = 25).

Variable	All patients	HIV positive (n = 20)		HIV negative (n = 4)		HIV unknown (n = 1)	
	n	n	%	n	%	n	%
IV antibiotic treatment							
Penicillin G	6	4	66.7	2	33.3	0	0.0
Ceftriaxone	19	16	84.2	2	10.5	1	5.3
Corticosteroid treatment†	19	16	84.2	2	10.5	1	5.3

†, Corticosteroid treatment included oral, topical, intravenous corticosteroids either as individual treatment or a combination thereof.

TABLE 6: LogMar visual acuity and visual acuity change according to immune status of eyes.

Visual acuity	All eyes		HIV positive eyes		HIV negative eyes		HIV unknown	
	n	%	n	%	n	%	n	%
Pre-treatment								
0.0–0.3	11	26.2	9	81.8	0	0.0	2	18.2
0.4–0.9	12	28.6	12	100.0	0	0.0	0	0.0
1.0 or worse	19	45.2	12	63.2	7	36.8	0	0.0
Change								
Post-treatment								
No change	15	35.7	10	66.7	3	20.0	2	1.3
Increase VA (> 2 lines)	27	64.3	23	70.0	4	14.8	0	0.0
Decrease VA (> 2 lines)	0	0.0	0	0.0	0	0.0	0	0.0

VA, visual acuity.

The LogMar VA and VA change according to immune status of eyes is presented in Table 6.

While 19 eyes (45.2%) had a poor pre-treatment VA of 1.0 or worse, 28 (66.7%) had a VA of 0.0–0.3 after completion of antibiotic treatment. There was an improvement in VA (> 2 lines) in 64.3% of eyes (n = 27) and no change in VA (< 2 lines change) in 35.7% (n = 15) of eyes. Of those with no change in VA, 53.3% (n = 8) had a good pre-treatment VA. None of the eyes had a deterioration in VA.

Discussion

The number of cases of syphilis is said to have been increasing since 2001 in the United States according to the Centers for Disease Control (CDC).[6] A higher rate of antenatal syphilis was found in sub-Saharan Africa when compared to other global regions in 1990–1999 and 2008.[2] Syphilis more commonly affects the eyes in the late latent and tertiary stages of syphilis; therefore, delaying treatment may result in an increase in the number of syphilitic uveitis cases.[6]

Ocular syphilis is reported to occur in the fourth decade in most studies, which is in keeping with our study where 48.0% of patients belonged to the 30–39 year age group.[5,9,12,13] In patients with HIV, ocular syphilis is described to occur at an earlier age.[1,12] While our population constituted a majority of HIV co-infected individuals (80.0%), they still presented at a comparable age to other studies. This may reflect a delay in treatment because of access to tertiary healthcare in our public health setting. A male predominance has been documented in other studies, with men who have sex with men being the largest contributor.[1,9,12,13,14] The gender representation in this study is similar in men and women and may be accounted for by different sexual practices and gender roles in Johannesburg, which was not specifically explored in our study. Our population is also solely representative of black individuals in contrast to other studies, some of which had a Caucasian predominance and others where African-Americans made up the majority.[6,12]

Treponema pallidum may affect any part of the eye, although the posterior segment of the eye is more commonly involved and anterior segment inflammation rarely occurs in isolation.[8,9,12] In addition, posterior uveitis followed by panuveitis were the most common uveitis classifications in keeping with other global and South African studies.[1,6,8,9,10,12,13] A retrospective study by Lapere et al. in South Africa re-iterated that posterior segment inflammation was more common than anterior segment inflammation (57.1% vs 38.0%, respectively).[2]

As reflected in our study, vitritis was the most common ocular sign and isolated anterior uveitis was only present in 11 of 44 eyes (25.0%). Anterior chamber cells (43.2%) and posterior synechiae (36.4%) were the other overall common signs in our population. Most of the eyes with isolated anterior uveitis belonged to patients who were co-infected with HIV. This is contrary to the prospective study by Mathew et al. reporting that patients with HIV co-infection were less likely to have isolated anterior uveitis.[12] The BOSS study conducted in the United Kingdom also reflected these common signs with vitritis in 65.1% of eyes and anterior uveitis signs in 26.0% of patients being reported as the two commonest clinical signs.[12]

Optic nerve involvement was reported in 78.0% of eyes in a study by Klein et al. with manifestations including isolated optic disc oedema with or without uveitis, optic atrophy and optic neuropathy.[5] Gumma may also occur on the optic disc.[5,7] Of the 14 eyes in our study that had optic nerve involvement, isolated disc swelling was present in only four eyes belonging to two patients, other eyes had an associated uveitis or retinal vasculitis. Optic nerve involvement appears to be a common sign as it was also reported as one of four most common signs

by Mathew and Pratas, and also as papillitis in a third of patients in a study by Fonollosa et al.[9,12,13] The HIV co-infection was not correlated with optic nerve manifestations according to Klein, concurring with two HIV negative patients (three eyes) in our study also having optic disc swelling.[5]

Posterior placoid chorioretinopathy is reported to be a distinctive finding in ocular syphilis.[3,4,7] It was not specifically documented as a finding in any of our study patients. The vast presence of vitritis may have impeded good visualisation of the posterior pole or it may have been encompassed in the description of 'pigmentary retinopathy'. It is described clinically as fine pigmentary changes within a discrete oval or circular area in the posterior pole, which represents outer retinal and inner choroidal inflammation.[3,7] In addition, OCT findings and other imaging studies were not included in this study. The OCT reveals disruption of the ellipsoid zone and small amounts of subretinal fluid.[7] The findings were initially thought to exclusively occur in immunocompromised patients; however, other studies have shown that it also occurs in patients who are not co-infected with HIV.[3]

All patients in our study had a positive TPAB, 68.0% had a positive RPR and 32.0% (n = 7) of patients (one HIV–) had a negative RPR but were treated for syphilitic uveitis. This is in keeping with another study in the United States where two-thirds of patients were found to have a positive RPR.[6] A South African based study was found to have 93.8% of patients with a positive TPAB and RPR and those with a negative RPR had CSF findings in keeping with neurosyphilis.[2] Of the RPR negative patients in our study, four patients had CSF findings consistent with neurosyphilis, while three patients had normal CSF composition and negative CSF VDRL results. Atypical serologic responses are known to occur in patients co-infected with HIV. While both treponemal and non-treponemal tests appear to be reliable in most patients with HIV, false positive results occur in non-treponemal tests because of the presence of a polyclonal gammopathy and possible coexistent anticardiolipin antibodies. Rarely, seronegative syphilis may occur in immunocompromised patients who are unable to elicit an adequate antibody response, and this may explain the findings in these three patients.[15] The three patients with negative laboratory findings on both serum and CSF were treated with antibiotics and oral corticosteroids, and visual improvement was attained in two of the patients.

Patients with HIV also tend to have higher titres in non-treponemal tests as compared to immunocompetent patients.[12,15] The median titre in other studies with predominantly HIV positive patients was 1:128.[12,15] While the median RPR titre in our study was 1:32(IQR: 1:32 – 1:256), there were eight patients with a titre greater than the median and seven of these patients were HIV positive with a low CD4 count ranging from 35 cells/uL to 256 cells/uL (IQR 80–172 cells/uL).

A lumbar puncture was performed in all patients in our study in accordance with CDC recommendations at the time of the study that all patients with syphilitic uveitis require a lumbar puncture.[3,16] The importance of lumbar puncture in patients with syphilitic uveitis was elucidated in a local study by Reekie et al where 45.6% of patients had a lumbar puncture and 25.8% of these patients showed features of neurosyphilis and were therefore at risk of long-term consequences.[17] There exists a strong association between HIV and neurosyphilis with as many as 83.0% of patients with syphilitic uveitis and HIV having abnormal lumbar puncture results.[3,10,13,14] This is in keeping with our results where CSF lymphocytes were raised in 5 (20.0%) patients and the CSF VDRL was positive in 5 (20.0%) patients (all HIV+). The HIV– group did not have raised CSF lymphocytes nor a positive CSF VDRL result and only 3 (23.1%) patients had a raised CSF protein. Visual acuity outcomes are reportedly not influenced by CSF results.[9] Owing to the finding that RPR has a good correlation with CSF findings, a lumbar puncture is now only recommended for patients with ocular syphilis who have neurological findings.[18,19]

Although 42.5% (19 eyes) had a pre-treatment LogMar VA of 1.0 or worse, 64.3% of eyes had an improvement of >2 lines in VA. After treatment with antibiotics, 83.3% (n = 35) of patients had a VA between 0.0 and 0.8 in our study. The BOSS study reported that 92.1% of eyes had a post-treatment VA of 0.3 or better and another study in the United Kingdom found that 92.0% of eyes had a visual improvement or complete recovery.[8,12] Better visual outcomes have been found in patients waiting a mean of 15 days as compared to a mean of 61 days before seeking treatment.[9] This may explain the inferior VA results obtained in our study where access to tertiary healthcare and ophthalmic consultation is inequitable among different communities. While some studies found that the VA outcomes were worse in patients with HIV and syphilis, others reported no difference in final VA between HIV positive and HIV negative patients, as found in our study.[8,9,12] Presenting VA has no influence on the final VA outcome.[8,9,12]

Limitations

The limitation of this study lies in its nature of being retrospective with the quality of data being highly dependent on record keeping. The small sample size also limited our ability to perform statistical analyses. The data are reflective of in-patient admission recordings only and the treatment and VA outcomes during follow up could not be documented. Although our study is solely representative of black African population, no definitive racial differences have been documented and the results can therefore be extrapolated to other populations.

Conclusion

This study contributes to the minimal research conducted in sub-Saharan Africa on syphilitic uveitis. The resurgence of syphilis makes it important to perform investigations for detecting *T. pallidum* in the differential diagnosis of ocular inflammation.[6] While syphilis is known as a the 'great imitator', the common risk factors for HIV and syphilis in

our setting and the clinical findings of posterior segment inflammation and vitritis highlighted in this study should prompt a diagnosis of syphilis. A delay in diagnosis of ocular syphilis could result in poor clinical outcomes and ocular and systemic complications. The treatment of uveitis secondary to syphilis infection is easily accessible and leads to improvement in VA, which is most relevant in the younger population that it is currently affecting.

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Competing interests

The authors declare that they have no financial or personal relationships that may have inappropriately influenced them in writing this article.

Authors' contributions

K.R. and M.A.M. contributed equally to this research article.

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Data availability

The data that support the findings of this study are available from the corresponding author, K.R., upon reasonable request.

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