



RESEARCH NOTE

Patterns of ocular inflammation in patients with miliary tuberculosis [version 1; referees: 4 approved]

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Abstract

Background: Ocular morbidity associated with systemic tuberculosis is common. The clinical picture varies from anterior uveitis, intermediate uveitis and posterior uveitis to even panuveitis. There is little data on the correlation between specific systemic presentations and the ocular inflammation. We conducted a retrospective review of the ocular findings in the case records of patients admitted with a diagnosis of miliary tuberculosis. These patients were then referred for a more detailed ophthalmic evaluation.

Methods: We analysed the case records of patients with a clinical diagnosis of miliary tuberculosis over a 10-year period at Lilavati Hospital and Research Center, Mumbai.

Results: In total, 11 immunocompetent patients were identified. All 22 eyes showed normal findings on slit lamp examination. Dilated fundus examination showed single or multiple tubercles. In our cohort, the ocular findings were exclusively in the form of choroidal tuberculosis, either unilaterally or bilaterally. Slit lamp examination revealed no anterior segment inflammation.

Conclusions: We suggest that this pattern of choroidal/retinal tuberculosis in the absence of anterior and intermediate segment inflammation is specific for miliary tuberculosis and may be related to a specific immune response.

Open Peer Review

Referee Status:

	Invited Referees			
	1	2	3	4
version 1				
published 03 Apr 2017	report	report	report	report

- Jyotirmay Biswas**, Sankara Nethralaya India
- Reema Bansal**, Postgraduate Institute of Medical Education and Research India
- Somasheila I. Murthy**, LV Prasad Eye Institute India
- Padmamalini Mahendradas**, Narayana Nethralaya India

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Competing interests: No competing interests were disclosed.

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Introduction

Tuberculosis is a significant cause of uveitis, with published literature describing a spectrum of ocular inflammation that includes anterior uveitis, intermediate uveitis and posterior uveitis or even panuveitis in patients with different presentations of systemic tuberculosis. However, little data exists on the correlation between specific systemic presentations and any ocular inflammation that may co-exist.

Miliary tuberculosis is a specific systemic presentation that is commonly associated with ocular inflammation. We conducted a retrospective observational study of patients admitted with a diagnosis of miliary tuberculosis, to assess the specific patterns of any associated ocular inflammation.

Methods

The study was conducted at Lilavati Hospital (Mumbai, India), which is a private tertiary healthcare facility. The Institutional Ethics Committee of Lilavati Kirtilal Mehta Medical Trust Research Centre approved this study for publication (09/02/2017).

We defined miliary tuberculosis as “tiny, discrete, widespread and uniform-sized lung opacities 2 mm or less in diameter (millet grains) on X ray or CT scan”. We retrieved the records of matching patients from 2006–2016 and excluded records of patients with HIV infection, autoimmune disease or on immunosuppressive therapy.

As part of a regular protocol that recognizes the diagnostic value of fundoscopy, all patients with a probable diagnosis of miliary tuberculosis were referred for an ophthalmic evaluation. All patients or their next of kin provided written informed consent for an ocular evaluation. Following this consent, patients underwent assessment of best-corrected visual acuity, slit lamp examination, and dilated indirect fundus examination and intraocular pressure assessment with an applanation tonometer. Patients unable to undergo a full evaluation underwent dilated indirect fundus examination at the bedside but were scheduled to complete the evaluation once their systemic status had improved. All patients who gave their written informed consent underwent fundus photography or optical coherence tomography (OCT) studies for documentation. All patients underwent both tests.

The following additional data was retrieved from patient records: age, sex, findings of chest X rays, CT scans (chest, brain or abdominal) and laboratory data (complete and differential blood counts, mantoux testing, renal and liver function tests at the least). Microbiological data included blood cultures (aerobic, anaerobic, mycobacterial cultures) and cultures of sputum studies.

Results

In total, 11 immunocompetent patients were identified. These included 5 males and 6 females with ages ranging from 4 to 73 years (mean 42.5). All were ethnically Indian and their socioeconomic status varied from the indigent residing in high-density tenements/slums to the affluent. Sources of referral included transfer from neighborhood facilities or from family physicians.

The common modes of clinical presentation of miliary tuberculosis included persistent fever, (7 patients: 4 males and 3 females with ages ranging from 4–73 years) or sepsis (4 patients: 3 females and 1 male with ages ranging from 16–71 years). 6 patients underwent a detailed evaluation soon after admission. The remaining 5, who were significantly ill, underwent only dilated fundus examination at that time.

The eyes of all 11 patients were analyzed (22 eyes in total). All patients were visually asymptomatic. Visual acuity studies were available for 6 of the 11 patients and were normal with 6/6 best-corrected visual acuity. All 22 eyes gave normal findings (no cells/flare) on slit lamp examination. Dilated fundus examination showed single or multiple tubercles bilaterally in 7 patients and unilaterally in 4 patients. No vitritis or raised intraocular pressure was seen in any patient. (Table 1).

4 patients (3 females and 1 male, ages ranging from 16–71 years) gave consent for both fundus photography and OCT to be performed, and both tests were carried out.

Additionally, patients (2 females, 42 and 44 years old) had additional signs of acute respiratory distress syndrome (ARDS). 4 patients (3 men and 1 woman; ages ranging from 4–71) had central nervous system (CNS) granulomas found in the frontal, parietal or temporal regions.

A standard therapy of INH, rifampicin, ethambutol and pyrazinamide was given. Systemic steroids were used at the discretion of the treating physician. Follow-up was available for 3–12 months for 4 patients (3 female and 1 male, ages ranging from 16 to 71, mean 30.5) until the choroidal tubercles were healed.

The clinical and ocular data of these patients is available in Dataset 1¹.

Dataset 1. Clinical and ocular data of study patients

<http://dx.doi.org/10.5256/f1000research.11035.d155310>

Table 1. The clinical and ocular findings of patients with miliary tuberculosis in our cohort. ARDS: Acute Respiratory Distress Syndrome; CNS: Central Nervous System; RE: right eye; LE: left eye; BE: both eyes.

Sr.No	Age/Sex	Diagnosis	Vision (RE)	Vision (LE)	Anterior Segment	Posterior Segment
1	44/f	Miliary tuberculosis (ARDS)	NA	NA	Normal (BE)	Tubercles (BE)
2	42/f	Miliary tuberculosis (ARDS)	6/6	6/6	Normal (BE)	Tubercles (BE)
3	73/m	Miliary tuberculosis	NA	NA	Normal (BE)	Normal (RE) Tubercles (LE)
4	54/m	Miliary tuberculosis	NA	NA	Normal (BE)	Normal (RE) Tubercles (LE)
5	57/m	Miliary and CNS tuberculosis	6/6	6/6	Normal (BE)	Tubercles (BE)
6	4/f	Miliary and CNS tuberculosis	NA	NA	Normal (BE)	Tubercles (BE)
7	71/m	Miliary and CNS tuberculosis	6/6	6/6	Normal (BE)	Tubercles (BE)
8	16/f	Miliary tuberculosis	6/6	6/6	Normal (BE)	Tubercles (BE)
9	14/f	Miliary tuberculosis	6/6	6/6	Normal (BE)	Tubercles (BE)
10	16/f	Miliary tuberculosis	NA	NA	Normal (BE)	Normal (RE) Tubercles (LE)
11	71/m	Miliary and CNS tuberculosis	6/6	6/6	Normal (BE)	Normal (RE) Tubercles (LE)

Discussion

Of the 1.7 billion individuals infected with tuberculosis, only 10 % will develop an active infection in their lifetime, due to a protective immune response that can also be damaging to the tissues and is responsible for the clinical picture seen during active disease. The various clinical presentations are the result of a complex interaction between immune cells, secreted cytokines and varying combinations of systemic Th1 and/or Th2 responses.

Miliary tuberculosis accounts for 2% of all new cases of tuberculosis and approximately 20% of all extrapulmonary tuberculosis cases². It is a potentially fatal form of disseminated TB that follows from massive hematogenous dissemination. Its etiopathogenesis involves immune responses skewed towards a Th2 response that inhibits protective responses (granuloma formation), and this may permit widespread dissemination³.

The ocular correlates of the systemic picture have been less well studied. Mehta analyzed the PET/CT scans of 27 patients in total; 13 with anterior uveitis, 7 with intermediate uveitis, 6 with pan-uveitis, 2 with vasculitis and 1 with multifocal serpiginous-like choroidopathy. 14 showed metabolically active, largely mediastinal, lymphadenopathy, and lung parenchymal disease was only rarely seen. The author postulated that a specific immune response to mycobacteria in the target tissues was responsible for this pattern of disease; i.e. systemic lymph node tuberculosis with its ocular correlate in the form of uveitis, with marked anterior and intermediate inflammation⁴.

In our cohorts, who differ significantly in their systemic presentation from the previously mentioned study, the ocular findings were exclusively in the form of choroidal tuberculosis, either unilaterally or bilaterally. Slit lamp examination revealed a marked absence of anterior or intermediate segment inflammation. All the patients had evidence of tubercles, thus confirming the diagnostic role of funduscopy, but a larger cohort is needed to confirm the absence of anterior segment inflammation.

We suggest that this pattern of choroidal/retinal tuberculosis in the absence of anterior and intermediate segment inflammation is specific for miliary tuberculosis and may be due to a specific immune response. A larger study that assesses the CD4 and CD8 counts and the cytokine profile is needed to elucidate the exact nature of the immune response responsible.

Data availability

Dataset 1: Clinical and ocular data of study patients.

DOI, [10.5256/f1000research.11035.d155310](https://doi.org/10.5256/f1000research.11035.d155310)¹

Competing interests

No competing interests were disclosed.

Grant information

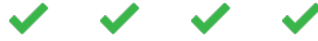
The author(s) declared that no grants were involved in supporting this work.

References

1. Mehta S: **Dataset 1 in: Patterns of ocular inflammation in patients with miliary tuberculosis: An observational study.** *F1000Research*. 2017.
[Data Source](#)
2. Sharma SK, Mohan A, Sharma A: **Miliary tuberculosis: A new look at an old foe.** *J Clin Tuberc Other Mycobact Dis*. 2016; **3**: 13–27.
[Publisher Full Text](#)
3. Sharma SK, Mohan A, Sharma A, *et al.*: **Miliary tuberculosis: new insights into an old disease.** *Lancet Infect Dis*. 2005; **5**(7): 415–30.
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4. Mehta S: **Observed Patterns of Systemic Disease on PET/CT Scan in Patients with Presumed Ocular Tuberculosis: Findings and Hypotheses.** *Ocul Immunol Inflamm*. 2016; 1–3.
[PubMed Abstract](#) | [Publisher Full Text](#)

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Current Referee Status:



Version 1

Referee Report 11 May 2017

doi:10.5256/f1000research.11903.r21514



Padmamalini Mahendradas

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1. The author has reported that the choroidal tubercle is a characteristic finding in cases of military tuberculosis in immunocompetent cases. Unlike other types of systemic tuberculosis (for example, pulmonary, lymphadenitis) which could be associated with several different ocular manifestations, it is interesting that choroidal tubercle is the only presentation observed in military tuberculosis.
2. Providing the fundus photographs and optical coherence tomography images of choroidal tubercles along with radiological images of military tuberculosis cases would add additional value to the manuscript.
3. The author has mentioned that systemic steroids were used at the discretion of the treating physician. Addition of treatment details in the Data set 1 will give a more clear picture regarding the management of individual cases to the readers.

Is the work clearly and accurately presented and does it cite the current literature?

Yes

Is the study design appropriate and is the work technically sound?

Yes

Are sufficient details of methods and analysis provided to allow replication by others?

Yes

If applicable, is the statistical analysis and its interpretation appropriate?

Not applicable

Are all the source data underlying the results available to ensure full reproducibility?

Partly

Are the conclusions drawn adequately supported by the results?

Yes

Competing Interests: No competing interests were disclosed.

Referee Expertise: Uveitis and ocular immunology

I have read this submission. I believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Referee Report 10 May 2017

doi:10.5256/f1000research.11903.r22605



Somasheila I. Murthy

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The study provides information on the patterns of ocular inflammation in patients with millitary tuberculosis over a 10-year period. The finding of choroidal tubercles in the presence of normal visual acuity and in the absence of associated anterior chamber inflammation or significant vitritis highlights the importance of screening posterior segment in patients with millitary tuberculosis. The examination can be easily done as a bed side procedure.

A few points mentioned below, if further analyzed, can help to improve the understanding of disease behavior in these patients.

1. All patients had choroidal lesions detected on fundus examination. It would have been better to know at what time points the patients were examined. Were any of these patients already on anti-tubercular therapy (ATT) at the time of presentation or were started on it only after the presentation.
2. The course and time of resolution of choroidal tubercles following initiation of ATT using OCT imaging at least in patients who were ambulatory will be an important addition.
3. Did any of the patients have persistent lesions after the completion of ATT requiring prolonged continuation of ATT or some additional form of treatment?

4. Did any of the patient have a resurgence of the disease following discontinuation of ATT, after an initial cure. Information regarding the recurrence pattern can further provide an insight into the etiopathogenesis of this manifestation.

Is the work clearly and accurately presented and does it cite the current literature?

Yes

Is the study design appropriate and is the work technically sound?

Yes

Are sufficient details of methods and analysis provided to allow replication by others?

Yes

If applicable, is the statistical analysis and its interpretation appropriate?

Not applicable

Are all the source data underlying the results available to ensure full reproducibility?

Yes

Are the conclusions drawn adequately supported by the results?

Yes

Competing Interests: No competing interests were disclosed.

I have read this submission. I believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Referee Report 21 April 2017

doi:[10.5256/f1000research.11903.r21512](https://doi.org/10.5256/f1000research.11903.r21512)



Reema Bansal

Department of Ophthalmology, Advanced Eye Center, Postgraduate Institute of Medical Education and Research, Chandigarh, Haryana, Punjab, India

1. The authors report the ocular profile of a rare but an important systemic disease, which adds relevant information to the literature. The study highlights the choroidal tubercles as hallmarks of miliary TB.
2. Providing fundus photographs would add value to the manuscript.
3. Four patients did undergo both fundus photography and OCT. But the authors haven't described the OCT findings in any of these.
4. Another reference may be added; Sharma *et al.* 2012.

References

1. Sharma SK, Mohan A, Sharma A: Challenges in the diagnosis & treatment of miliary tuberculosis. *Indian J Med Res.* 2012; **135** (5): 703-30 [PubMed Abstract](#)

Is the work clearly and accurately presented and does it cite the current literature?

Yes

Is the study design appropriate and is the work technically sound?

Yes

Are sufficient details of methods and analysis provided to allow replication by others?

Yes

If applicable, is the statistical analysis and its interpretation appropriate?

Not applicable

Are all the source data underlying the results available to ensure full reproducibility?

Yes

Are the conclusions drawn adequately supported by the results?

Yes

Competing Interests: No competing interests were disclosed.

Referee Expertise: Uveitis and Retinal diseases

I have read this submission. I believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Referee Report 18 April 2017

doi:[10.5256/f1000research.11903.r21905](https://doi.org/10.5256/f1000research.11903.r21905)



Jyotirmay Biswas

Vision Research Foundation, Sankara Nethralaya, Chennai, Tamil Nadu, India

Author reported the pattern of ocular lesions in patients with miliary tuberculosis. He analysed the record of the patients with the clinical diagnosis of miliary tuberculosis over ten years period seen in a hospital of Western India.

All the patients were immunocompetent, had normal anterior segment findings but fundus examination showed single or multiple tubercles in the choroid. This is a rare cohort of patients of miliary tuberculosis who have got an ophthalmic examination done.

It would have been better if authors could put some photograph of the fundus of these patients showing choroidal tubercles. We have studied 1005 patient of systemic tuberculosis in TB hospital in 1985 and found in 1.39% patients had ocular tuberculosis and only one patient had miliary tubercles in choroid (Biswas *et al.* 1996). New imaging system like optical coherence tomography particularly enhanced-depth and swept source of optical coherence tomography could show, the lesion location elegantly.

Interestingly these lesions are in the periphery, not in the macular area and the patients preserve good visual function. I feel this article will be good addition to ophthalmic tuberculosis and systemic tuberculosis literature.

References

1. Biswas J, Badrinath SS: Ocular morbidity in patients with active systemic tuberculosis. *Int Ophthalmol*. **19** (5): 293-8 [PubMed Abstract](#)

Is the work clearly and accurately presented and does it cite the current literature?

Yes

Is the study design appropriate and is the work technically sound?

Yes

Are sufficient details of methods and analysis provided to allow replication by others?

Yes

If applicable, is the statistical analysis and its interpretation appropriate?

Yes

Are all the source data underlying the results available to ensure full reproducibility?

Partly

Are the conclusions drawn adequately supported by the results?

Yes

Competing Interests: No competing interests were disclosed.

I have read this submission. I believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.
