

# Phlyctenular Eye Disease: A Reappraisal

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**Purpose:** Phlyctenular keratoconjunctivitis is a nonspecific allergic response in the cornea and/or conjunctiva to a variety of distinct conditions. Tuberculosis as an etiological association is being supplanted by staphylococcal infection and worm infestation in developed countries. Our aim was to determine the relative frequency of the various known etiological factors of phlyctenular keratoconjunctivitis, and the clinical profile of the disease as it exists today in India, a country where tuberculosis is still highly prevalent.

**Cases:** This is a prospective study of 112 consecutive patients with phlyctenular eye disease seen over a 2-year period.

**Observations:** In 86 patients (76.7%), phlyctenular eye disease was associated with tuberculosis. Worm infestation was found in 14 patients (12.4%), whereas 7 (6.2%) had staphylococcal blepharitis. Thirteen patients had evidence of multiple etiology, of which one causative factor was always tuberculosis. When tuberculosis was the only association, 37% patients had severe lesions, whereas only 11.5% patients without tuberculosis had such lesions. When tuberculosis along with another etiological factor was present, the incidence of severe lesions increased to 84.6%. Recurrence on follow-up was seen in three patients who were already on multidrug therapy for tuberculosis, and two who had tubercular allergy.

**Conclusions:** Our study shows that tuberculosis is still a major cause of phlyctenular eye disease in India. Severe lesions are more common in patients with tuberculosis, especially when another etiological factor is associated. Recurrences are more common in patients with tuberculosis. Corneal lesions are less extensive than described in the literature and are no longer a significant cause of blindness. **Jpn J Ophthalmol 2000;44:146–150** © 2000 Japanese Ophthalmological Society

**Key Words:** Keratoconjunctivitis, phlycten, phlyctenular eye disease.

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## Introduction

Phlyctenular keratoconjunctivitis (PKC) represents an allergic cell-mediated response within the conjunctiva and/or cornea to some antigen to which it has become sensitized.<sup>1</sup> In the past, tuberculo-protein was thought to be the main antigen responsible for phlyctenular eye disease (PED); however, other proved antigens include staphylococcal products<sup>2–4</sup> and worm infestations,<sup>5–7</sup> the relative prevalence of which are reported to be on the rise.<sup>8</sup> Conjunctival phlyctens are usually transient and asymptomatic,

but corneal phlyctens can occur in various forms and are occasionally of sufficient severity to cause visual impairment.<sup>9</sup>

Early and effective multidrug therapy has resulted in a world wide leveling off or decline of tuberculosis (TB) in industrialized countries.<sup>10</sup> In India, however, the reported incidence of new cases is 1 in 1,000 and the prevalence of bacteriologically confirmed disease is 4 cases per 1,000.<sup>11</sup> The last large comprehensive study of PKC was in Alaskan natives in 1951.<sup>9</sup> Subsequently, although a few patients with nontubercular PKC have been reported,<sup>2–4</sup> there is little information in the world literature on the present status of tubercular PKC. In our institution, we still see a large number of PKC patients. In this context, the present study was conducted to determine the relative frequency of the various known etiological

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Received: January 6, 1999

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factors of PKC and the clinical profile of patients seen in an urban hospital in a developing country.

### Materials and Methods

This prospective study included 166 consecutive PED patients seen by the authors between April 1994 and March 1996. The age, sex, history of exposure to TB, ocular symptoms, and systemic complaints, if any, were recorded on a specially prepared proforma. Visual acuity on Snellen's chart, the number, stage, and location of phlyctens, presence of old scars, and history and number of recurrences were noted. Lid margin and conjunctival swabs for bacteriologic examination were taken from all patients with evidence of blepharitis or conjunctivitis. Three stool examinations for ova and cysts, a chest x-ray, fine needle aspiration cytology (FNAC) of enlarged lymph nodes, blood counts with erythrocyte sedimentation rate (ESR), and the Mantoux test were done in each case. Serological tests to aid in the diagnosis of TB, staphylococcal infection, or worm infestation were not conducted as they are not available at our institution, and most of the patients could not pay for private testing.

Patients considered to have definite evidence of TB disease were those with characteristic pulmonary lesions on x-ray, positive FNAC findings, or those already on antitubercular treatment. Ulceration on Mantoux testing or induration  $\geq 15$  mm was taken to indicate TB allergy. Patients who had a first-degree relative with TB disease were taken to have a positive family history. A positive Mantoux test with or without raised ESR ( $>20$  mm in the first hour by the Westergren method) and/or a positive family history of TB were taken as indirect evidence of TB. Patients with at least one out of three stool examinations positive for worm cysts or ova were taken to have worm infestation. Patients with clinical evidence of lid margin or conjunctival infection, confirmed microbiologically, were taken to have infective blepharitis or conjunctivitis. Patients with more than one disease were taken to have mixed etiology.

After investigation, patients were treated, regardless of etiological association, with topical steroid-antibiotic combination drops (dexamethasone 0.01% and chloromycetin 0.5%) and the response to treatment was noted. Associated conditions were treated simultaneously; systemic TB was treated with four drugs: Rifampicin, Isoniazid, Ethambutol, and Pyrazinamide, according to the weight of the patient, for 2 months, followed by the first two drugs for an additional 4 months. Patients with indirect ev-

idence of TB who had more than one recurrence on follow-up were also given antitubercular treatment according to the same regime. Mebendazole, 100 mg twice a day for 3 days, was used to treat worm infestation. Staphylococcal disease was treated with topical antibiotic ointment, applied twice a day, in accordance with the antibiotic sensitivity report. Fifty-four patients, who either did not submit to the investigations or did not report back for follow-up, were excluded from the study. The remaining 112 patients were followed up for recurrences for a period ranging from 6 months to 1 year (mean  $9.11 \pm 1.96$  months) and the following data pertain to these patients.

### Results

Of the 112 patients, 58 (51.8%) were men and 54 (48.2%) were women. Their ages ranged from 3 to 38 years for those having phlyctens associated with TB and from 3 to 25 years in the other patients. The maximum incidence in both groups was between 5 and 15 years of age; 86.4% of tubercular phlycten cases and 81.8% of nontubercular phlycten cases occurred before the age of 15 years.

Direct or indirect evidence of tubercular etiology was seen in 86 patients (76.7%, Table 1). Definite evidence of TB was found in 56/86 patients (36 had active and 20 had healed TB). In 22/86 patients there was evidence of tubercular allergy with or without raised ESR, whereas 2/86 patients had family history of pulmonary TB in one or both parents.

Worm infestation was detected in 14 patients (12.4%) on stool examination. The most common was *Ascaris lumbricoides* ( $n = 11$ ). There were 2 cases of *Ankylostoma duodenale* and 1 of *Enterobius vermicularis*. All 14 patients had elevated ESR. Four patients had worm infestation, as well as an association with TB (Table 1).

In 7 patients (6.2%), staphylococcus infection was isolated in culture from lid margins. Of these, 4 patients also had active TB, and another 2 had a family history of tuberculosis TB (Table 1).

Other associated conditions were vestibulitis of the nose and past history of *Herpes zoster* ophthalmicus (Table 1). In 15 PKC patients no associated disease could be determined.

The most common site of TB was pulmonary (33/56). Among extrapulmonary sites, cervical lymphadenitis was the most common (20/56). Four patients had TB at more than one site. In 1 patient treated in the past for TB, the site of the current infection could not be determined.

As shown in Table 2, 42.7% patients of PED pre-

**Table 1.** Concomitant Diseases in 86 Patients with Tubercular Etiology of Phlyctenular Eye Disease

	Alone	With FH	Worm Infestation	Staph Blepharitis	Healed HZO	HSV Vestibulitis	Total
TB disease*	32	18	–	4	1	1	56
TB allergy†	13	8	–	–	–	1	22
FH	2	–	4	2	–	–	8

TB: Tuberculosis, FH: Family history of TB, Staph: Staphylococcal, HZO: herpes zoster ophthalmicus, HSV: herpes simplex virus.

\*Radiological or cytological evidence of TB or past history of TB.

†Mantoux test  $\geq 15$  mm after 24 hours with or without raised erythrocyte sedimentation rate and without evidence of TB disease.

sented during the first attack; 57.3% had a history of recurrent attacks. The most common site of phlycten, regardless of etiology, was limbal. Palpebral phlyctens were rare, seen in only 2 patients with recurrent phlycten. Corneal phlycten was more common in recurrent cases, especially when the patient had TB alone or TB along with another condition. Thirty-four patients (30.4%) had corneal involvement in the form of superficial keratitis with vascularization ( $n = 4$ ), fascicular ulcers ( $n = 8$ ), wedge-shaped fascicular scars ( $n = 6$ ), limbal scars ( $n = 14$ ) and indolent marginal corneal ulcers ( $n = 2$ ). Secondary infection or corneal perforation was not seen. The lesions were unilateral in 58.9% and bilateral in 41.1% of the patients (Table 3). Single phlycten in one eye was the commonest presentation (40.2%). Multiple phlyctens in one or both eyes was more common in tubercular patients (30.4%) as compared with patients with mixed etiology (8.0%) or nontubercular patients (6.3%, Table 3).

Severe lesions, such as corneal or multiple and bilateral phlyctens, were seen in 43 patients (38.4%,

Table 4). Of these, 28 were associated with TB alone, 1 with staphylococcal blepharitis alone, and 11 with mixed etiology. In 3 patients, the cause could not be determined.

#### Response to Treatment

Response to treatment with antibiotic-steroid combination drops was excellent. The duration of treatment varied from 3 days to 3 weeks. Delay in onset of response resulting in prolonged duration of treatment was seen in 7 patients, all of whom had severe lesions. Of these, 4 patients had both TB and staphylococcal infection, and in 3, the etiology could not be determined. Only 5 of the 112 patients showed recurrence during the study period; 3 of them were on antitubercular treatment, and 2 were positive for TB allergy. The latter were put on antitubercular treatment during the follow-up period. Visual impairment of between 6/9 to 6/24 was seen in 17 patients (15.2%). There was no case of unilateral or bilateral blindness resulting from phlycten.

**Table 2.** Sites of Phlycten, Number of Attacks and Etiology of Phlyctenular Eye Disease

Site		TB Only	Non-TB Only	Mixed Etiology*	Etiology Unknown	Total
Limbal	First attack	34	6	4	8	52
	Recurrence	32	6	8	6	52
Bulbar	First attack	6	–	–	–	6
	Recurrence	4	–	–	2	6
Palpebral	First attack	–	–	–	–	0
	Recurrence	–	–	–	2	2
Corneal	First attack	6	–	–	–	6
	Recurrence	15	1	10	2	28

TB: tuberculosis.

\*TB along with another predisposing condition.

**Table 3.** Etiology and Number of Phlycten at Presentation

No. of Phlycten	TB Only	Non-TB Only	Mixed Etiology*	Unknown Etiology
Unilateral				
Single	23	10	3	9
Multiple	17	–	–	4
Bilateral				
Single	16	–	1	–
Multiple	17	1	9	2
Total	73	11	13	15

TB: tuberculosis.

\*TB along with another predisposing condition.

### Discussion

Phlyctenular eye disease is seen in the first two decades of life.<sup>9</sup> In this series, the highest incidence was in the 5- to 15-year age group (>80.0%). The strong preponderance of women described by other authors<sup>1,9,12</sup> was not borne out in this study, where the disease more commonly involved men. Although this may be a true male predominance, it might actually represent the greater frequency with which boys, compared with girls, are brought to a hospital in our country.

Phlyctenular keratoconjunctivitis was seen in patients with both active and healed TB and also in patients already on multidrug therapy for TB (6 patients before the onset of the study and 3 patients during the study period). The most common sites of TB were lungs and cervical lymph nodes. These two are also the most frequent sites of TB in the general population. Evidence of tubercular allergy without signs of active or healed TB was seen in a large number of patients (n = 22). Any hypersensitivity to tuberculo-protein even without tubercular disease is known to cause PKC.<sup>1,9,12</sup>

Worms have been implicated in the etiology of PKC by various authors.<sup>5,6,7,12</sup> In this study, where

the only associated condition was helminthiasis, the phlyctens were limbal in location and the patients had a history of one or no recurrence. Phlyctens associated with TB and helminthiasis were corneal and limbal in location and all these patients had a history of recurrences. All our patients with worm infestation showed excellent response to Mebendazole and local antibiotic-steroid eye drops, with no recurrences in the follow-up period.

Staphylococcal products, proved antigens in experimental studies,<sup>13</sup> induce a PKC that differs slightly in clinical behavior from that caused by TB. Staphylococcal-induced disease occurs in relatively older individuals, causes less photophobia and shows a relative lack of response to steroids.<sup>8</sup> Although, in our series (7 patients) there was no difference with reference to age of occurrence; these patients were more symptomatic, and all had severe lesions when compared with the patients with TB alone (28/73 patients). However, since 6/7 of the patients with staphylococcal PKC also had TB or history of contact with a TB patient, it is suggested that the severity of lesions is related to the presence of more than one antigen. This is further borne out by the fact that in the 13 instances where there was more than one etiological factor, 11 patients (84.6%) had severe lesions, as opposed to 32/99 patients (32.3%) with single/unknown etiological factor. Only 1 patient had staphylococcal blepharitis alone, and although this patient had severe lesions, no generalization can be made on the basis of a single case. Further clinical studies and animal experiments may help shed light on the relationship between severe lesions and multiple etiology. A higher incidence of history of recurrent attacks and multiple phlycten in one or both eyes was seen in the tubercular patients as compared with the nontubercular. Low-dose oral tetracycline on a long-term basis has been found to be effective in treating recalcitrant cases of staphylococcal PKC.<sup>2</sup> However, all our patients responded to local steroid-antibiotic

**Table 4.** Severe Lesions of Phlyctenular Eye Disease and Etiology

Lesions	TB Alone	Staph Alone	Mixed Etiology*				Unknown Etiology
			Worms + FH	Staph + Active TB	Staph + FH	HSV + TB Allergy	
Corneal	22	1	4	2	2	1	2
Bilateral and multiple (none corneal)	6	–	–	2	–	–	1

TB: Tuberculosis, Staph: staphylococcal blepharitis, FH: family history of TB, HSV: herpes simplex virus vestibulitis.

\*TB along with another predisposing condition.

combination drops. None of the patients with staphylococcal PKC showed recurrence on follow-up, as opposed to 5 patients in the tubercular group.

The possible etiological role of other conditions like vestibulitis of the nose and healed *Herpes zoster* ophthalmicus could not be assessed, as they were present in only a few patients. Besides, all these patients had direct or indirect evidence of TB so that the presence of these other conditions may not have been contributory.

Limbal phlycten is the most common and most characteristic manifestation reported in the literature.<sup>9,12,14</sup> In this series, 104/112 patients had limbal phlycten, presenting as single or multiple lesions in one or both eyes. They occurred alone or in association with corneal lesions but rarely with bulbar ones. Photophobia and tearing were common symptoms, though not as severe as in corneal phlycten. Mild conjunctival discharge was seen in most of the patients, but severe mucopurulent conjunctivitis was seen in only 4 patients. Atypical phlyctenulosis has been described in severe conjunctival inflammation in which a primary bacterial conjunctivitis apparently activates a latent phlyctenulosis,<sup>14</sup> and these 4 cases may have been representative of this.

Bulbar lesions present with mild symptoms of irritation and redness, sometimes so mild and transient that they are ignored. Palpebral phlyctens are rare<sup>9</sup> and have been described in the upper palpebral conjunctiva as a row of phlyctens<sup>9,14</sup>. In this series, they were seen in only 2 patients in the lower palpebral conjunctiva near the lid margin. Both cases were associated with multiple attacks and persisted for a longer time despite treatment. One case was associated with indolent corneal ulcer.

Keratoconjunctivitis is rarely seen in the first attack. Six patients in this series had corneal phlycten in the first attack. It is possible that earlier conjunctival attacks were transient or asymptomatic and not noticed by the patients.

While multiple etiological factors were frequently associated with severe PED in this study, 64.3% of the severe lesions were seen in association with TB alone. This suggests the important role of TB in the etiology of severe lesions. An association with TB has been found in 76.7% patients with PED in this study. These findings underscore the point that, although the response to treatment of phlyctens is good, as documented herein, it is by no means enough to treat only the phlycten. Every patient presenting with PED, even a mild, first attack, must be investigated for TB; this should include a survey of all close family members. Early diagnosis of TB is bound to help the pa-

tient, especially in areas where mortality from TB is high. This study has also brought out the frequency with which it is possible to find more than one etiological factor. Thus, especially in the case of severe lesions of PKC, the finding of one etiological association should not mean the search is over.

Visual impairment due to the presence of corneal opacities in the pupillary area was observed in 17 patients. However, no patient progressed to blindness, as none of the corneal lesions developed secondary bacterial infection or perforation.

This report, which highlights the etiology, clinical features, course, and magnitude of phlyctenular eye disease as it exists in India today, should prove to be beneficial to ophthalmologists working in those parts of the world where TB is no longer a major health problem. The effects of the HIV pandemic on the magnitude and course of PED, when cases of TB are expected to increase and the immune response to fall, cannot be predicted at this stage.

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