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Acanthamoeba, fungal, and bacterial keratitis: a comparison of risk factors and clinical features

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Abstract

Purpose—To determine risk factors and clinical signs that may differentiate between bacterial, fungal, and acanthamoeba keratitis among patients presenting with presumed infectious keratitis.

Design—Hospital-based cross-sectional study.

Methods—We examined the medical records of 115 patients with laboratory-proven bacterial keratitis, 115 patients with laboratory-proven fungal keratitis, and 115 patients with laboratory-proven acanthamoeba keratitis seen at Aravind Eye Hospital, Madurai, India, from 2006–2011. Risk factors and clinical features of the three organisms were compared using multinomial logistic regression.

Results—Of 95 patients with bacterial keratitis, 103 patients with fungal keratitis, and 93 patients with acanthamoeba keratitis who had medical records available for review, 287 (99%) did not wear contact lenses. Differentiating features were more common for acanthamoeba keratitis than for bacterial or fungal keratitis. Compared to patients with bacterial or fungal keratitis, patients with acanthamoeba keratitis were more likely to be younger and to have a longer duration of symptoms, and to have a ring infiltrate or disease confined to the epithelium.

Conclusions—Risk factors and clinical examination findings can be useful for differentiating acanthamoeba keratitis from bacterial and fungal keratitis.

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Keywords

risk factors; disease attributes; India; corneal ulcer

Introduction

Acanthamoeba keratitis is a relatively rare, difficult-to-treat infection of the cornea that can result in severe vision loss. Studies have identified several risk factors for acanthamoeba keratitis, including contact lens wear, orthokeratology, water exposure, and certain contact lens solutions.[1–5] Although most acanthamoeba keratitis research has been conducted in industrialized countries, acanthamoeba keratitis also occurs in developing countries, often in non-contact lens-wearing individuals.[6,7]

Acanthamoeba keratitis is frequently misdiagnosed as herpetic or fungal keratitis, and subsequently treated incorrectly, which can lead to poor outcomes.[8] Case series of acanthamoeba keratitis have identified several important clinical signs, such as pseudodendrites, perineural infiltrates, and ring infiltrates.[9,10] However, we are unaware of any studies that have compared the clinical findings of acanthamoeba keratitis with those of bacterial and fungal keratitis. Clinical signs can be especially useful for differentiating the cause of infectious keratitis when microbiological testing is not available—which is frequently the case in developing countries. In this study, we compare the risk factors and clinical signs of laboratory-proven bacterial, fungal, and acanthamoeba keratitis cases from a tertiary eye care hospital in south India, in an attempt to improve differentiation of these forms of keratitis.

Methods

We obtained approval for this retrospective cross-sectional study from the Committee for Human Research at the University of California, San Francisco, and from the Institutional Review Board at Aravind Eye Hospital, Madurai. The research adhered to the tenets of the Declaration of Helsinki.

We identified all cases of smear- or culture-proven acanthamoeba keratitis from the microbiology database at Aravind Eye Hospital, Madurai, India, from January 2006 to June 2011. As controls, we identified a random sample of fungal and bacterial keratitis cases, matched to acanthamoeba keratitis cases based on the year of presentation (i.e., the number of fungal and bacterial cases chosen for a particular year was the same as the number of acanthamoeba cases detected that year). During this period of time, results of cultures and smears showed a fungal organism in approximately 35% of keratitis cases, a bacterial organism in 20%, and a parasitic organism such as acanthamoeba in 1%.[11] Using a review of the literature as a guide, we pre-specified certain risk factors and diagnostic signs to be of interest and extracted information on these variables from the patient's medical record using a standardized data collection form, masked to the identity of the organism. We were able to mask data extractors by having a separate chart reviewer cover all references to the microbiological diagnosis with adhesive paper. We recorded information on demographics, medical history, visual acuity at presentation, and clinical examination at presentation. We used only clinical information documented before microbiological evaluations were performed (i.e., clinical examinations were masked to laboratory results). Note that medical records could not be located for all patients listed in the microbiological database.

Microbiological methods for the Aravind Ocular Microbiological Laboratory have been described previously.[12] In general, all patients with presumed infectious keratitis undergo corneal scraping for smear and culture. Gram staining and potassium hydroxide (KOH) wet

mount are routinely performed for all smears. Routine culture media include sheep's blood agar, chocolate agar, potato dextrose agar, and brain-heart infusion broth without gentamicin. For ulcers in which acanthamoeba is suspected clinically and/or when smears are KOH-positive for amoebic cysts, further corneal scrapings are performed for culture on non-nutrient agar overlaid with *Escherichia coli*.

We created univariate multinomial logistic regression models with causative organism as the response variable (acanthamoeba, bacteria, or fungus), and each of the baseline risk factors or clinical features as the explanatory variable. Stromal infiltrate size was calculated as the geometric mean of the longest diameter and its perpendicular extent, as recorded in the medical record. For the purposes of this study, feathery infiltrate borders indicate that the words "feathery" or "fluffy" were documented in the medical record. Satellite lesions indicate that the word "satellite" was written in the chart, whereas multifocal lesions indicate that multiple discrete lesions were drawn. In general, ophthalmologists at the study site use the term satellite lesion to refer to a smaller infiltrate adjacent to a larger main infiltrate. All satellite lesions were by definition also classified as multifocal. Pseudodendrite indicates that the word "pseudodendrite" or "dendrite" was written in the medical record. We realize that the pseudodendrite is an ill-defined entity but use that term herein since it has been widely used in the acanthamoeba keratitis literature. Visual acuity was converted to logMAR units. We assessed for overall differences between the 3 organisms with a likelihood ratio test, and performed pairwise comparisons for any variables with $P<0.001$. To account for potential confounding, we entered all variables into a multivariate multinomial logistic regression model. We used a backwards stepwise algorithm for model selection, removing variables with the highest likelihood ratio test until all variables had a P-value <0.01. We kept variables with a $P<0.01$ in the multivariate model to account for important confounders, but only declared as statistically significant those variables with $P<0.001$.

Results

From January 2006 to June 2011, a total of 115 acanthamoeba keratitis cases were listed in the microbiological database, of which 93 (81%) had medical records available for review. We randomly selected 115 bacterial and 115 fungal keratitis cases from the same time period, and were able to identify microbiological and medical records for 95 (83%) of the bacterial cases and 103 (90%) of the fungal cases ($P=0.16$). Organisms were generally detected on both the smear and culture (Table 1). Bacterial cases were most commonly caused by *Streptococcus pneumoniae* (36/95, 38%) and *Pseudomonas aeruginosa* (28/95, 29%); fungal ulcers were most commonly caused by *Fusarium species* (32/103, 31%) and *Aspergillus species* (26/103, 25%); see Table 2.

Risk factors and clinical characteristics for each of the 3 classes of organisms are summarized in Table 3, along with the omnibus P-values from the univariate multinomial logistic regression models that assessed for overall differences between the 3 organisms. Pairwise comparisons for those risk factors and clinical features with evidence of an overall difference (defined as $P<0.001$) are shown in Table 4.

In pairwise comparisons, there appeared to be more differentiating features of acanthamoeba keratitis than for either bacterial or fungal keratitis. Risk features of acanthamoeba keratitis that were significantly different from both fungal keratitis and bacterial keratitis included younger age, longer symptom duration, prior use of topical antibiotics, and presence of a ring infiltrate (Table 4). Risk factors associated with bacterial keratitis relative to fungal or acanthamoeba keratitis included older age and lack of prior topical antibiotic use.

In the multivariate model, several features of acanthamoeba keratitis were significantly different from both fungal keratitis and bacterial keratitis (Table 5). Patients with acanthamoeba keratitis were younger than patients with bacterial keratitis or fungal keratitis, and had a longer duration of symptoms before being treated. In terms of clinical signs, acanthamoeba keratitis was more likely to have disease confined to the epithelium and a ring infiltrate. The multivariate model revealed fewer discriminating features for either bacterial or fungal keratitis; only age was significantly different among all 3 organisms, with older age a risk factor for fungal keratitis relative to acanthamoeba keratitis, and for bacterial keratitis relative to both fungal and acanthamoeba keratitis (Table 5).

Discussion

In this study of primarily non-contact lens-wearers, we found several risk factors and clinical features that helped to distinguish acanthamoeba keratitis from keratitis due to bacteria or fungi. Compared with bacterial or fungal keratitis, acanthamoeba keratitis was more likely to occur in younger patients and in patients with a longer duration of symptoms, and was more likely to have a ring infiltrate and disease confined to the epithelium.

Ring infiltrates have been described starting with the earliest case reports of acanthamoeba, with most larger series reporting this finding in at least one-third of cases (Table 6). Ring infiltrates have also been reported in fungal corneal ulcers as well as pseudomonas keratitis.[13–15] We found that while ring infiltrates did occur in fungal and bacterial keratitis, this finding was 9–11 times more likely to indicate acanthamoeba keratitis. It is unclear why ring infiltrates would be more common in keratitis due to acanthamoeba. It is possible that the immune ring is simply an indicator of prolonged untreated infections, which would be consistent with the longer duration of symptoms in the acanthamoeba group of this and other studies.

Patients with acanthamoeba keratitis were younger than those with fungal or bacterial keratitis. This is consistent with a previous study from South India.[16] The average age of patients with acanthamoeba keratitis in this study is similar to previous series (Table 6), though most of the patients in those series were contact lens-wearers, who might be expected to be younger than non-contact lens-wearers. We can only speculate why patients with acanthamoeba keratitis are younger than those with bacterial or fungal keratitis in south India. One possible explanation is that older patients are more likely to have ocular surface disease, which is thought to be a risk factor for bacterial corneal ulcers but has not typically been reported as a risk factor for acanthamoeba keratitis.[17,18]

In this study, acanthamoeba keratitis was associated with a longer delay until diagnosis compared with either bacterial or fungal keratitis. This is consistent with previous reports, and may be due to the subtle early findings of acanthamoeba keratitis.[9,19] Early on, acanthamoeba keratitis may involve only the corneal epithelium, and therefore a diagnosis of infectious keratitis may not initially be made. The current study supports this observation, since we found that disease confined to the epithelium was more common in acanthamoeba keratitis than either bacterial or fungal keratitis. In addition, the previous use of topical antibiotics was more common among acanthamoeba keratitis patients in this study, suggesting that a higher proportion of acanthamoeba patients were either referred from outside institutions or had self-treated their corneal ulcer, and presented only after the ulcer did not respond to therapy.

Satellite lesions have commonly been described as a characteristic feature of fungal keratitis.[20,21] Satellite lesions have also been reported to occur in acanthamoeba keratitis.[22–24] In this retrospective study, we found that clinicians documented satellite

lesions for both acanthamoeba and fungal keratitis cases, and at a similar frequency. Satellite lesions were not more common in fungal compared with bacterial keratitis, though this may be partly due to misclassification error due to the retrospective nature of the study. We further distinguished satellite lesions from multifocal lesions in this study, under the assumption that these represent distinct patterns. Acanthamoeba keratitis was more likely than either fungal or bacterial keratitis to have multifocal lesions, although this relationship was not statistically significant. Nonetheless, this is consistent with previous descriptions of multifocal or patchy stromal infiltration in acanthamoeba keratitis, and suggests that discrete small infiltrates should raise the suspicion for acanthamoeba keratitis.[25–28]

We did not detect any features to allow differentiation of fungal from bacterial keratitis in the multivariate analysis of this study, aside from the finding that patients with bacterial keratitis tended to be older. Previous studies comparing the clinical signs of bacterial and fungal keratitis have found that feathery, fluffy, or serrated infiltrate margins are a significant discriminating feature of fungal keratitis, but ring infiltration and satellite lesions are not.[21,29,30] Our results are consistent with this finding, although we did not document a statistically significant association between fungal keratitis and feathery infiltrate margins. The lack of association may be due to misclassification error during data extraction, or to an insufficient sample size. Previous studies have also identified a dry or raised or pigmented infiltrate to be associated with fungal keratitis, but the current study did not address these clinical features.[21,30]

Our results highlight the importance of microbiologic diagnosis for infectious keratitis. Although we identified several important clinical features that allow discrimination of acanthamoeba from bacterial or fungal keratitis, the vast majority of corneal ulcers seen in clinical practice are due to bacteria or fungi. For example, at Aravind only 1% of corneal ulcers are caused by parasitic organisms like acanthamoeba.[11] Thus, the inability to significantly discriminate fungal from bacterial keratitis based solely on the clinical appearance of the keratitis suggests that corneal scrapings are crucial for correct diagnosis and appropriate antimicrobial treatment. Furthermore, given the long treatment course for acanthamoeba keratitis, microbiologic evidence should be sought before committing a patient to many months of potentially toxic anti-amoebic therapy.

Besides the large number of acanthamoeba cases, a strength of this study is its comparison of the 3 major causes of infectious keratitis. In contrast, previous studies describing clinical features of infectious keratitis have generally consisted of a series of cases due to a single organism—with the exception of several studies that have compared bacterial and fungal keratitis.[21,29–31] There are also several limitations to this study. First, it was conducted in South India and contained relatively few contact lens wearers, which could limit its generalizability. However, the findings of this study generally support those from industrialized countries, arguing for broader generalizability. Regardless, this study is quite relevant for developing countries, which account for the vast majority of infectious keratitis.[32] Second, this is a retrospective study; clinicians did not use standardized data forms when examining patients. This may have resulted in misclassification error and likely underestimation of some risk factors and clinical signs; however, bias should be limited since the information used in this study was extracted from the first clinical visit, before culture results were known. Moreover, we went to great lengths to mask chart extractors to any mention of the causative organism, which should limit measurement bias on the part of the data extractors. Third, we did not include patients with herpetic keratitis, so cannot comment on discriminating features between acanthamoeba and herpetic keratitis. Fourth, we restricted this study to laboratory-proven cases. Although we intentionally included only laboratory-proven cases in order to reduce the possibility of misclassification bias, we acknowledge that this inclusion criterion may have resulted in selection bias by favoring

more severe or untreated ulcers. Fifth, the multivariate analysis should be interpreted with caution, since the limited number of events (i.e., keratitis cases) could have introduced additional bias in the early iterations of the backwards stepwise model selection process.[33] Finally, we are vulnerable to type I error because of the number of comparisons we have performed, though we should be partially protected from this by setting our significance level to 0.001.

In conclusion, in this study we identified risk factors and clinical features of acanthamoeba, fungal, and bacteria keratitis that may aid in early differentiation of the etiologic organisms of keratitis. An increased suspicion for acanthamoeba keratitis appears to be warranted in younger patients with many weeks of symptoms, and in patients with a ring infiltrate and disease confined to the epithelium. Culture and smear of corneal scrapings remain the most important ways to diagnose infectious keratitis. Nonetheless, the findings from this study may aid in early diagnosis before culture results are known, or in settings where a microbiological laboratory is unavailable.

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Table 1

Results of culture, Gram stain, and Potassium Hydroxide (KOH) wet mount from infectious keratitis specimens from a tertiary eye care center in South India

	Acanthamoeba Total = 93	Fungus Total = 103	Bacteria Total = 95
Culture-positive	85/92 (92.4%)	102/103 (99.0%)	94/94 (100%)
Gram-positive	79/92 (85.9%)	83/97 (85.6%)	76/93 (81.7%)
KOH-positive	67/75 (89.3%)	77/85 (90.6%)	3/58[a] (5.2%)

Proportion of tests with a positive result for the respective organism, stratified by final diagnosis; not all tests were performed for all ulcers so denominators for the tests do not necessarily match the total number of organisms.

[a]The 3 positive KOH results were *Nocardia spp*.

Table 2

Bacterial and fungal organisms isolated from a random selection of infectious keratitis patients, Aravind Eye Hospital, 2006–2011

Organism	Number (%)	
Bacteria		
Streptococcus pneumoniae	36/95	(38%)
Pseudomonas aeruginosa	28/95	(29%)
Nocardia species	6/95	(6%)
Staphylococcus aureus	4/95	(4%)
Staphylococcus epidermidis	4/95	(4%)
Diphtheroids	4/95	(4%)
Viridans group *streptococci*	3/95	(3%)
Streptococcus pyogenes	3/95	(3%)
Klebsiella species	2/95	(2%)
Moraxella catarrhalis	1/95	(1%)
Enterococcus species	1/95	(1%)
Atypical *Mycobacterium species*	1/95	(1%)
Acinetobacter species	1/95	(1%)
Aeromonas hydrophilia	1/95	(1%)
Culture negative (Gram positive cocci)	1/95	(1%)
Fungi		
Fusarium	32/103	(31%)
Aspergillus flavus	19/103	(18%)
Aspergillus fumigatus	7/103	(7%)
Curvularia	8/103	(8%)
Exerohilum species	4/103	(4%)
Bipolaris	3/103	(3%)
Scedosporium species	3/103	(3%)
Candida albicans	1/103	(1%)
Lasiodiplodia species	1/103	(1%)
Rhizopus species	1/103	(1%)
Cladosporium species	1/103	(1%)
Unidentified hyaline	17/103	(17%)
Unidentified dematiaceous	5/103	(5%)
Culture negative (KOH-positive)	1/103	(1%)

Table 3

Risk factors and clinical features of infectious keratitis from a tertiary eye care center in south India

Characteristic	Acanthamoeba (N=93)	Fungus (N=103)	Bacteria (N=95)	p[a]
RISK FACTORS				
Age, years; Mean ± SD	38 ±16	43 ±16	50 ±18	<0.001
Female gender, N (%)	41 (44%)	41 (40%)	29 (30%)	0.17
Symptom duration, days; Mean ± SD	33 ± 62	10 ± 13	13 ± 39	<0.001
Trauma, N (%)	55 (59%)	62 (60%)	60 (63%)	0.84
Vegetative trauma, N (%)	27 (29%)	32 (31%)	33 (35%)	0.70
Past ocular surgery, N (%)	5 (5%)	12 (12%)	22 (23%)	0.001
Cataract extraction	4 (4%)	9 (9%)	15 (17%)	0.03
Keratoplasty	0 (0%)	1 (1%)	2 (2%)	0.10
Other[b]	1 (1%)	2 (2%)	5 (5%)	0.19
Topical antibiotic use, N (%)	59 (63%)	48 (47%)	28 (29%)	<0.001
Topical antifungal use, N (%)	37 (40%)	34 (33%)	19 (20%)	0.01
Topical steroid use, N (%)	8 (9%)	6 (6%)	6 (6%)	0.89
Native medicine use,‡ N (%)	10 (11%)	11 (11%)	10 (11%)	1.00
Topical breast milk use, N (%)	3 (3%)	10 (10%)	7 (7%)	0.17
Topical castor oil use, N (%)	1 (1%)	4 (4%)	4 (4%)	0.33
Eye contact with tongue, N (%)	3 (3%)	1 (1%)	1 (1%)	0.43
Contact lens wear	3 (3%)	0 (0%)	2 (2%)	0.10
CLINICAL CHARACTERISTICS				
Visual acuity, logMAR; Mean ± SD	1.46 ± 0.61	1.18 ± 0.71	1.36 ± 0.66	0.009
Infiltrate size; Mean ± SD	5.6 ± 3.0	4.6 ± 3.1	4.6 ± 3.3	0.06
Stromal involvement in posterior 1/3	32 (34%)	36 (35%)	42 (44%)	0.29
Hypopyon, N (%)	36 (39%)	43 (42%)	52 (55%)	0.06
Pseudodendrites, N (%)	7 (8%)	2 (2%)	1 (1%)	0.04
Epitheliopathy only, N (%)	12 (13%)	2 (2%)	2 (2%)	0.001
Feathery edges, N (%)	5 (5%)	20 (19%)	7 (7%)	0.004
Satellite lesions, N (%)	4 (4%)	3 (3%)	0 (0%)	0.05
Multifocal lesions, N (%)	17 (18%)	10 (10%)	5 (5%)	0.02
Ring infiltrate, N (%)	28 (30%)	5 (5%)	4 (4%)	<0.001
Perineuritis, N (%)	3 (3%)	0 (%)	0 (0%)	0.03

[a] Overall comparison of the 3 groups in univariate multinomial regression

[b] Amniotic membrane (acanthamoeba group, N=1); retinal detachment repair (fungus group, N=1); dacryocystectomy (bacteria group, N=1); the remainder were unspecified.

Table 4

Risk factors and clinical characteristics of infectious keratitis due to acanthamoeba, fungus, and bacteria: univariate pairwise comparisons

	Odds Ratio (95% Confidence Interval)[a]		
Explanatory Factor	**Acanthamoeba vs. Bacteria**	**Acanthamoeba vs. Fungus**	**Fungus vs. Bacteria**
Risk Factors			
Age, per decade	**0.64 (0.53 to 0.77)**	**0.82 (0.69 to 0.97)**	**0.78 (0.66 to 0.92)**
Symptom duration, per week	**1.13 (1.02 to 1.25)**	**1.23 (1.08 to 1.40)**	0.92 (0.80 to 1.05)
Topical antibiotic use	**3.97 (2.16 to 7.29)**	**1.90 (1.07 to 3.36)**	**2.09 (1.16 to 3.76)**
Clinical Characteristics			
Ring infiltrate	**9.80 (3.28 to 29.3)**	**8.44 (3.10 to 23.0)**	1.16 (0.30 to 4.46)

[a] Univariate multinomial logistic regression with causative organism as the outcome; odds ratios are reported for acanthamoeba keratitis relative to a bacterial keratitis reference group and to a fungal keratitis reference group, and for fungal keratitis relative to a bacterial keratitis reference group; results with $P<0.05$ in bold

Table 5

Risk factors and clinical characteristics of keratitis caused by acanthamoeba, fungus, and bacteria: multivariate models

	Odds Ratio (95% Confidence Interval)[a]			
Explanatory Factor	**Acanthamoeba vs. Bacteria**	**Acanthamoeba vs. Fungus**	**Fungus vs. Bacteria**	**Omnibus P-value**
Risk Factors				
Age, per decade	**0.62 (0.50 to 0.78)**	**0.78 (0.63 to 0.95)**	**0.80 (0.67 to 0.96)**	<0.001
Symptom duration, per week	**1.10 (1.00 to 1.21)**	**1.17 (1.04 to 1.32)**	0.94 (0.83 to 1.07)	<0.001
Clinical Characteristics				
Visual acuity, per unit logMAR	**1.96 (1.10 to 3.49)**	**2.37 (1.37 to 4.08)**	0.83 (0.52 to 1.32)	0.005
Epitheliopathy only	**12.9 (2.45 to 67.6)**	**17.1 (3.24 to 89.9)**	0.75 (0.10 to 5.64)	<0.001
Multifocal lesions	**5.90 (1.87 to 18.6)**	**3.22 (1.24 to 8.39)**	1.83 (0.59 to 5.69)	0.004
Ring infiltrate	**11.0 (3.42 to 35.3)**	**9.26 (3.23 to 26.6)**	1.19 (0.30 to 4.65)	<0.001

[a] Multivariate multinomial logistic regression with causative organism as the outcome; odds ratios are reported for acanthamoeba keratitis with bacterial or fungal keratitis as the reference group, and for fungal keratitis with bacterial keratitis as the reference group; results with pairwise $P<0.05$ in bold

Table 6

Features of acanthamoeba keratitis from selected case series in different geographic regions

	EUROPE	NORTH AMERICA				ASIA				OCEANIA
	London 1993[9]	USA 1999[25]	Chicago 2008[34]	Philadelphia 2011[35]	Toronto 2012[36]	Hyderabad 2000[22]	Tirunelveli 2007[7]	Beijing 2006[37]	Singapore 2009[38]	Auckland 2010[39]
No. Eyes	77	87	72	59	42	39	33	20	43[a]	25
Culture/Smear positive	64%	50%	74%	53%	87%	100%	100%	100%	88%	60%
Risk Factors										
Mean age (y)	NR	33	29	34	34	37	NR[b]	26	26	40
Mean time to diagnosis (d)	25	68	NR[c]	39	11	NR[d]	NR[e]	42	29	41
Contact lens wear	89%	75%	89%	97%	93%	0%	0%	60%	100%	96%
Prior topical steroid	NR	35%	82%	69%	62%	NR	NR	NR	24%	56%
Clinical Characteristics										
Ring infiltrate	49%	29%	19%	32%	60%	41%	45%	30%	29%	32%
Perineuritis	41%	2%	22%	17%	38%	3%	NR	10%	45%	12%
Epitheliopathy only	37%	NR	38%	46%	NR	0%	0%	25%	NR	64%
Pseudodendrites	8%	NR	NR	NR	12%	3%	NR	NR	17%	NR
Hypopyon	26%	NR	NR	5%	7%	54%	27%	20%	NR	20%

NR=not reported

[a] Features reported as the proportion of patients (N=42)

[b] 33% were ≤ 40 years, 39% were 41–50 years, and 27% were > 50 years

[c] 61% diagnosed ≥ 3 weeks after start of symptoms

[d] 38% diagnosed ≥ 30 days after start of symptoms

[e] 66% diagnosed ≥ 7 weeks after start of symptoms