Open Forum Infectious Diseases

BRIEF REPORT

Corynebacterium kroppenstedtii Is an Emerging Cause of Mastitis Especially in Patients With Psychiatric Illness on Antipsychotic Medication

Sally C. Y. Wong,[1,2] Rosana W. S. Poon,[1,2] Jonathan H. K. Chen,[1,2] Herman Tse,[2] Janice Y. C. Lo,[3] Tak-Keung Ng,[4] Jonathan C. K. Au,[4,a] Cindy W. S. Tse,[6] Ingrid Y. Y. Cheung,[6] Man-Ting Yuk,[6] Wei-Kwang Luk,[5] and Kwok-Yung Yuen[1,2]

[1]Queen Mary Hospital, Hong Kong; [2]The University of Hong Kong; [3]Centre for Health Protection, Department of Health, Hong Kong; [4]Princess Margaret Hospital, Hong Kong; [5]Tseung Kwan O Hospital, Hong Kong; and [6]Kwong-Wah Hospital, Hong Kong

This retrospective study of patients with *Corynebacterium kroppenstedtii* infections revealed a predominance of mastitis and a potential association with psychiatric illnesses. At least one third of our patients with *C kroppenstedtii* mastitis had psychiatric illness, and >92% received antipsychotic medications. Drug-induced hyperprolactinemia may be an important modifiable risk factor in these patients.

Keywords. *Corynebacterium kroppenstedtii*; granulomatous mastitis; infection; antipsychotics agents; hyperprolactinaemia.

Corynebacterium kroppenstedtii is a lipophilic *Corynebacterium* first described in 1998 after isolation from a sputum specimen [1]. Association with breast conditions, especially recurrent granulomatous mastitis (GM), was noted subsequently [2–4]. Occasional reports of bacteremia and a single report of prosthetic valve infection have also been described [2, 5]. However, knowledge on risk factors associated with *C kroppenstedtii*, clinical presentations, and significance remained incomplete. In this study, we analyzed the clinical, microbiological, and investigative findings from 42 patients with *C kroppenstedtii*.

METHOD

The database of a reference laboratory in Hong Kong was searched retrospectively for *C kroppenstedtii* isolated from clinical specimens between January 2009 and January 2015. The isolates were identified as *C kroppenstedtii* by phenotypic characteristics [1], matrix-assisted laser desorption/ionization-time-of-flight mass spectrometry ([MALDI-TOF MS] Bruker Daltonics, Bremen, Germany) MALDI Biotyper version 3.1 with reference library version 5.0.0.0 plus an in-house-enhanced database against *C kroppenstedtii* [6], and an in-house one-tube nested quantitative polymerase chain reaction (qPCR) targeting *C kroppenstedtii*-specific sialidase gene, *nanI*, using primers (CKOut-F-TCGACGTTGAAGACGCCACCACCATCAC CGAT, CKOut-R-GGGGGCATCGGCGATGGTGAGTTCCT; CKIn-F-CCAATGGCACAGCATCG, CKIn-R-GAACGTCGGCAAGAAATGC) and CKPb (FAM-CACCAAGTTTTATCTCGACGGGTACCA-3IABkFQ) (GenBank accession no. ACR18588) [7]. The target, *nanI*, is specific for *C kroppenstedtii* with no in silico or in vitro cross-reactivity against other *Corynebacterium* spp. Additional information on laboratory identification is available in the Supplementary Material. Clinical data were retrieved from case records and hospital information system for analysis.

Statistical Analysis

Mann-Whitney *U* test was used to compare patients' data as appropriate. A *P* value of <.05 is considered statistically significant. All statistical analysis was performed using SPSS version 20.

RESULTS

From 2009 to 2015, 46 strains of *C kroppenstedtii* were isolated (42 patients), including 41 breast-related samples and 5 nonbreast-related specimens. The age ranged from 20 to 90 (median 39 years), and 39 were female. Good identification to species (score of ≥2.0) and genus level (score ≥1.7 to <2.0) was noted in 28 and 7 isolates by MALDI-TOF MS, respectively, and all 46 isolates were *nanI* qPCR positive.

Corynebacterium kroppenstedtii in Breast-Related Specimens

The 41 breast-related *C kroppenstedtii* strains (37 patients) included 27 aspirates/biopsies and 14 wound swabs. *Corynebacterium kroppenstedtii* was found as pure culture in 39 specimens; 1 breast aspirate collected from a lactating woman and 1 swab of nipple discharge from a 5-month postpartum patient yielded additional scanty *Acinetobacter* sp and coagulase-negative *Staphylococcus*, respectively. Three patients have multiple specimens, collected at least 1 month apart, yielding *C kroppenstedtii*.

Histological analyses were available from 29 of the 37 patients. Noncaseating granulomatous inflammation was observed in 11 patients, whereas nonspecific inflammatory changes were noted in others. Granulomatous inflammation was found in patients

Received 11 February 2017; editorial decision 1 May 2017; accepted 4 May 2017.

[a]Present affiliation: Tseung Kwan O Hospital, Hong Kong.

Correspondence: K.-Y. Yuen, MBBS, FRCPath, FHKAM (Pathology), MD, Carol Yu Centre for Infection, Department of Microbiology, The University of Hong Kong, Queen Mary Hospital, 102 Pokfulam Road, Pokfulam, Hong Kong Special Administrative Region, China (kyyuen@hku.hk).

Open Forum Infectious Diseases®

DOI: 10.1093/ofid/ofx096

with longer duration of symptoms compared with patients with nongranulomatous inflammation, although the difference was not statistically significant (median, 30 vs 14 days; $P = .099$). Age, underlying conditions, clinical presentation, treatment, and recurrences were not significantly different between the 2 groups.

Nine of the 11 patients with GM were investigated for acid-fast bacilli (AFB) (smear for AFB in 4 patients; smear and culture for AFB in 5 patients), and all were negative for AFB. Smear and culture for AFB were also performed in 13 of the 26 patients with non-GM, which were again negative.

Clinical characteristics of the 37 patients are summarized in Table 1. The only patient presented without breast lesions was a breastfeeding mother with left breast mastitis, where *C kroppenstedtii* was isolated from pus expressed from her nipple.

Past medical and psychiatric histories were available from 35 of the 37 patients. Four patients had pituitary tumor. Thirteen patients (37%) were diagnosed with a psychiatric illness, with schizophrenia being the commonest. Drug history was available from 12 of the 13 patients, and all regimens included antipsychotic drugs associated with hyperprolactinemia. Two patients with schizophrenia had concurrent pituitary tumor.

History of antibiotic use and other interventions were available from 34 and 33 patients, respectively. Exact dates of antibiotics were available in 15 patients, where 5 patients were receiving antibiotics at the time, or within 1 week before specimen collection. Overall, β-lactam antibiotics were the most commonly used antibiotics. At least 15 patients underwent more than 1 invasive intervention. Follow-up data were available from 20 of the 37 patients, and 3 of the 6 patients with recurrence had a psychiatric illness.

Corynebacterium kroppenstedtii in Other Specimens

Corynebacterium kroppenstedtii were isolated from 3 blood cultures, 1 Tenchkoff exit site swab, and 1 sputum. Patients with *C kroppenstedtii* bacteremia were 80, 82, and 90 years old, 2 were male, and all presented with low-grade fever with no obvious foci. They received ceftriaxone, vancomycin, and ampicillin-clavulanate, respectively. All 3 patients recovered fully. *Corynebacterium kroppenstedtii* was also isolated from Tenckhoff exit site in a 31-year-old male patient with Tenckhoff exit site infection. He recovered after 3 weeks of oral ampicillin. One 64-year-old male had dry cough, weight loss, and consolidative lung lesion despite multiple courses of antibiotics including levofloxacin, piperacillin-tazobactam, and metronidazole. The clinical significance of *C kroppenstedtii* in his sputum specimen was doubtful.

Table 1. Clinical Characteristics of Patients With *Corynebacterium kroppenstedtii* Isolated From Breast-Related Specimens

Characteristics	N = 37 (All Female)	
Age (median, range), years	36, 20–52	
Clinical Presentation		
Laterality		
Left	16/37	
Right	15/37	
Bilateral	6/37	
Duration of symptoms before presentation (median), days	2–180 (30)[a]	
Palpable breast abnormality	35/36 (97%)	
Pain	16/36 (44%)	
Discharge	5/36 (14%)	
Laboratory Test Results		Reference Range
White cell count (range, median), $\times 10^9$/L	6.6–18 (9.6)	3.89–9.93
Absolute neutrophil count (median), $\times 10^9$/L	2.5–13.9 (7.2)	2.01–7.42
Lymphocyte count (median), $\times 10^9$/L	1.2–3.4(1.9)	1.06–3.61
Past History		
History of recurrent abscesses	10/35 (29%)	
Diabetes/impaired glucose tolerance	5/35 (14%)	
Hypertension	2/35 (6%)	
Pituitary tumor (macro- or microadenoma)	4/35 (11%) 3 with evidence of hyperprolactinaemia	
Psychiatric history	13/35 (37%)	
Schizophrenia	9	
Bipolar affective disorders	3	
Substance abuse with drug-induced psychosis	1	
Psychiatric medication	12/12[b]	
Pregnancy history		
Pregnant	1 (3rd trimester)	
Within 12 months postpartum	3	
Management		
Antibiotics	31/34	
Aspiration only	13/33	
At least 1 I&D	13/33	
Aspiration and I&D	4/33	
Resection of lesion	3/33	
Steroids	0/34	
Outcome		
Recovered	14/20 (duration of follow-ups: 1 to 12 months, median 3 months)	
Recurrence	6/20	

Abbreviations: I&D, incision and drainage.

[a]Data available from 32 patients.

[b]Number of patients on medications with known association with hyperprolactinemia: 6 risperidone, 3 haloperidol, 2 chlorpromazine, 2 fluoperazine, 1 flupenthixol, 1 olanzapine, 1 paroxetin. Number of patients on medications with no known association with hyperprolactinemia: 8 trihexophenidyl, 1 aripiprazol, 1 clonazepam. Eleven patients are on more than 1 psychiatric medications.

NOTE: Denominators denote the number of patients with details available for analysis.

DISCUSSION

To the best of our knowledge, our study included the largest cohort of patients with *C kroppenstedtii* infection. The predominance of breast-related specimens (89%) is consistent with previous reports of its potential association with mastitis and abscesses [2–4, 8].

Several additional findings were noted. First, psychiatric illnesses were seen in 37% of patients with *C kroppenstedtii*-related

mastitis/abscesses. This is significantly higher than the local prevalence of (1) 8.97% in the female population with mixed anxiety and depressive disorders and (2) 2.5% of psychotic disorders in Hong Kong [9, 10]. These patients also appeared to have a higher risk of recurrence of mastitis/abscesses. Although *C kroppenstedtii*-related GM has been described in 2 patients with psychiatric illnesses [11], our finding involving more patients put forward a cogent argument for the potential association between the 2. We suspected that antipsychotic-induced hyperprolactinemia is the unsuspected culprit, which was also postulated in the case report [11]. Hyperprolactinemia has also been reported in patients with "idiopathic" GM [12, 13]. It is likely that some of these idiopathic GM were *C kroppenstedtii*-related but were misdiagnosed as idiopathic because routine culture methods do not reliably isolate this slow-growing organism. Prolactin was thought to induce ductal ectasia and milk stagnation, predisposing patients to GM. Moreover, the proinflammatory effect of prolactin was observed in bovine mammary epithelial cells, through induction of nuclear factor κ-light-chain enhancer of activated B-cell signaling pathway [14]. It is unfortunate that serum prolactin level was not performed in most of our patients. Although further research is required to establish the exact role of hyperprolactinemia in *C kroppenstedtii*-related mastitis/abscesses, we believe that prolactin level should be routinely checked in these patients, to identify patients who may benefit from withdrawal of prolactin-inducing drugs. Besides drug-induced hyperprolactinemia, other potential contributing factors, eg, behavioral and personal hygiene, cannot be excluded and deserve further investigations.

Second, a spectrum of histopathological appearance is observed in our patients. Granulomatous inflammation was seen more frequently in patients with prolonged symptoms, implying a possible common etiology between nongranulomatous and GM.

Our study is limited by the retrospective nature of data retrieval. First, investigations to exclude other GM-associated pathogens, in particular dimorphic fungi and *Mycobacterium tuberculosis* (MTB), were not performed in all patients. Nonetheless, histoplasmosis and blastomycosis previously related to GM are extremely rare in our locality. For MTB, of the 11 patients with GM potentially suggestive of MTB, smear or culture of AFB was performed in 9 patients, and all yielded negative results. The only patient with subsequent right cervical tuberculous lymphadenitis was believed to be irrelevant, because 2 years lapsed between the resolution of left breast abscess and MTB lymphadenitis. Second, exact dates of antibiotics were only available in 15 patients. Hence, we cannot assess whether antibiotic use shortly before or at specimen collection could have selected towards isolation of *C kroppenstedtii*. Nonetheless, a metagenomic analysis of microbiota in breast specimens taken before antibiotic treatment also revealed a predominance of *Corynebacterium* spp, especially *C kroppenstedtii*, among patients with nonlactating GM [15]. Their finding supported that *C kroppenstedtii* plays a role in GM. Thirdly, prolactin level was not tested in most of our patients; hence, the role of drug-induced hyperprolactinemia in *C kroppenstedtii*-related mastitis and psychiatric illness remained speculative. Finally, potential diagnostic bias of GM in women with psychiatric illness cannot be excluded in our study. Future study comparing prevalence of psychiatric illnesses in patients with *C kroppenstedtii* and non-*C kroppenstedtii* mastitis/abscesses is required.

CONCLUSIONS

In conclusion, our finding strengthened the association of *C kroppenstedtii* with breast diseases. Further study is warranted to confirm the association among *C kroppenstedtii*, mastitis/abscesses, and psychiatric illnesses. Finally, we propose that serum prolactin level should be routinely checked in all patients with *C kroppenstedtii*-related mastitis/abscesses.

Supplementary Data

Supplementary materials are available at *Open Forum Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Acknowledgments

We thank Griffon C. P. Wong, Tiffany H. Y. Leung, and Vivian C. M. Lam (Department of Microbiology, The University of Hong Kong) for assistance with the microbiological investigations.

Financial support. This work is partly funded by the Consultancy Service for Enhancing Laboratory Surveillance of Emerging Infectious Disease for the Hong Kong Special Administrative Region, Department of Health; the Hui Hoy and Chow Sin Lan Charity Fund Limited.

Potential conflicts of interest. All authors: No reported conflicts of interest.

All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

References

1. Collins MD, Falsen E, Akervall E, et al. *Corynebacterium kroppenstedtii* sp. nov., a novel corynebacterium that does not contain mycolic acids. Int J Syst Bacteriol **1998**; 48:1449–54.
2. Paviour S, Musaad S, Roberts S, et al. *Corynebacterium* species isolated from patients with mastitis. Clin Infect Dis **2002**; 35:1434–40.
3. Bernard KA, Munro C, Wiebe D, Ongsansoy E. Characteristics of rare or recently described corynebacterium species recovered from human clinical material in Canada. J Clin Microbiol **2002**; 40:4375–81.
4. Goh Z, Tan AL, Madhukhumar P, Yong WS. Recurrent *Corynebacterium kroppenstedtii* breast abscess in a young Asian female. Breast J **2015**; 21:431–2.
5. Hagemann JB, Essig A, Herrmann M, et al. Early prosthetic valve endocarditis caused by *Corynebacterium kroppenstedtii*. Int J Med Microbiol **2015**; 305:957–9.
6. Freiwald A, Sauer S. Phylogenetic classification and identification of bacteria by mass spectrometry. Nat Protoc **2009**; 4:732–42.
7. Tauch A, Schneider J, Szczepanowski R, et al. Ultrafast pyrosequencing of *Corynebacterium kroppenstedtii* DSM44385 revealed insights into the physiology of a lipophilic *Corynebacterium* that lacks mycolic acids. J Biotechnol **2008**; 136:22–30.
8. Taylor GB, Paviour SD, Musaad S, et al. A clinicopathological review of 34 cases of inflammatory breast disease showing an association between corynebacteria infection and granulomatous mastitis. Pathology **2003**; 35:109–19.
9. Lam LC, Wong CS, Wang MJ, et al. Prevalence, psychosocial correlates and service utilization of depressive and anxiety disorders in Hong Kong: the Hong Kong Mental Morbidity Survey (HKMMS). Soc Psychiatry Psychiatr Epidemiol **2015**; 50:1379–88.

10. Chang W, Wong C, Lam L, et al. *Prevalence, Psychosocial and Physical Health Correlates of Psychotic Disorders in Hong Kong: The Hong Kong Mental Health Morbidity Survey. Schizophrenia Bulletin, 2015*. Oxford University Press; **2015**; pp s135.
11. Kutsuna S, Mezaki K, Nagamatsu M, et al. Two cases of granulomatous mastitis caused by *Corynebacterium kroppenstedtii* infection in nulliparous young women with hyperprolactinemia. Intern Med **2015**; 54:1815–8.
12. Lin CH, Hsu CW, Tsao TY, Chou J. Idiopathic granulomatous mastitis associated with risperidone-induced hyperprolactinemia. Diagn Pathol **2012**; 7:2.
13. Nikolaev A, Blake CN, Carlson DL. Association between hyperprolactinemia and granulomatous mastitis. Breast J **2016**; 22:224–31.
14. Boutet P, Sulon J, Closset R, et al. Prolactin-induced activation of nuclear factor kappaB in bovine mammary epithelial cells: role in chronic mastitis. J Dairy Sci **2007**; 90:155–64.
15. Yu HJ, Deng H, Ma J, et al. Clinical metagenomic analysis of bacterial communities in breast abscesses of granulomatous mastitis. Int J Infect Dis **2016**; 53:30–3.