Corynebacterium kroppenstedtii is an emerging cause of mastitis especially in patients with psychiatric illness on anti-psychotic medication

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Running Title: Risk factors for C. kroppenstedtii mastitis.

Keywords: Corynebacterium kroppenstedtii; human; infection; mastitis; breast abscesses; granulomatous mastitis; antipsychotics agents; hyperprolactinemia.
Abstract

This retrospectively study of patients with Corynebacterium kroppenstedtii infections revealed a predominance of mastitis, and 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.
Introduction

*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. Here, 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 (Bruker Daltonics, Germany) MALDI Biotyper version 3.1 with reference library version 5.0.0.0 plus in-house enhanced database against *C. kroppenstedtii* (6), and an in-house one-tube nested quantitative PCR (qPCR) targeting *C. kroppenstedtii*-specific sialidase gene, *nanI*, using primers (CKOut-F-TCGACGTTGAAGACGCCACCACCACCACCGAT, CKOut-R-GGGGGCATCGGCGATGGTGAAGTTCC, CKIn-F-CCAATGGCACAGCATCG, CKIn-R-GAACGTCGGGCAAGAAATGC) and CKPb (FAM-CACCAAGTTTATCTCGACGGTACCA-31ABkFQ) (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 < 0.05 is considered as statistically significant. All statistical analysis was performed using SPSS v.20.
Results

From 2009 – 2015, 46 strains of *C. kroppenstedtii* were isolated (42 patients), including 41 breast-related samples and five non-breast-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.

*C. kroppenstedtii* in breast-related specimens

The 41 breast-related *C. kroppenstedtii* strains (37 patients) included 27 aspirates/biopsies, and 14 wound swabs. *C. kroppenstedtii* was found as pure culture in 39 specimens; one breast aspirate collected from a lactating woman, and one 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 one month apart, yielding *C. kroppenstedtii*.

Histological analyses were available from 29 of the 37 patients. Non-caseating granulomatous inflammation was observed in 11 patients, whereas non-specific inflammatory changes were noted in others. Granulomatous inflammation was found in patients with longer duration of symptoms compared with patients with non-granulomatous inflammation, although the difference was not statistically significant (median 30 days vs. 14 days, p value = 0.099). Age, underlying conditions, clinical presentation, treatment, and recurrences were not significantly different between the two 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), all were negative for AFB. Smear and
culture for AFB were also performed in 13 of the 26 patients with non-granulomatous mastitis, 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, 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 one week prior to specimen collection. Overall, beta-lactam antibiotics were the commonest antibiotics used. At least 15 patients underwent more than one invasive intervention.

Follow-up data was available from 20 of the 37 patients, three of the six patients with recurrence have a psychiatric illness.

*C. kroppenstedtii* in other specimens

*C. kroppenstedtii* were isolated from three blood cultures, one Tenckhoff exit site swab and one sputum. Patients with *C. kroppenstedtii* bacteremia were 80, 82 and 90-year-old, two were male, and all presented with low grade fever with no obvious foci. They received ceftriaxone,
vancomycin and ampicillin-clavulanate, respectively. All three patients recovered fully. *C. kroppenstedtii* was also isolated from Tenckhoff exit site in a 31-year-old male patient with Tenckhoff exit site infection. He recovered after three 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.
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 8.97% in the female population with mixed anxiety and depressive disorders, and 2.5% of psychotic disorders in Hong Kong (9-10). These patients also appeared to have a higher risk of recurrence of mastitis/abscesses. While *C. kroppenstedtii*-related GM has been described in two patients with psychiatric illnesses (11), our finding involving more patients put forward a cogent argument for the potential association between the two. 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’ since 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, pro-inflammatory effect of prolactin was observed in bovine mammary epithelial cells, through induction of nuclear factor kappa-light-chain enhancer of activated B cells signaling pathway (14). Unfortunately, serum prolactin level was not performed in our patients. While 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, in order to identify patients who may benefit from withdrawal of prolactin-inducing drugs. Besides drug-induced hyperprolactinemia, other
potential contributing factors, e.g. 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 non-granulomatous and granulomatous mastitis.

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 nine and all
yielded negative results. The only patient with subsequent right cervical tuberculous
lymphadenitis was felt to be irrelevant, as two year has lapsed between the resolution of left
breast abscess and MTB lymphadenitis. Secondly, exact dates of antibiotics were only available
in 15 patients. Hence, we cannot assess if 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 non-lactating GM
(15). Their finding supported that C. kroppenstedtii plays a role in GM. Thirdly, prolactin level
was not tested in 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.
In conclusion, our finding strengthened the association of *C. kroppenstedtii* with breast diseases. Further study is warranted to confirm the association between *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.
Funding

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CONFLICT OF INTEREST

None declared.
Reference


Table 1: Clinical characteristics of patients with *Corynebacterium kroppenstedtii* isolated from breast-related specimens.

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>N=37 (all female)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (median, range), years</td>
<td>36, 20-52</td>
</tr>
</tbody>
</table>

**Clinical presentation**

<table>
<thead>
<tr>
<th>Laterality</th>
<th>16/37</th>
</tr>
</thead>
<tbody>
<tr>
<td>Left</td>
<td></td>
</tr>
<tr>
<td>Right</td>
<td>15/37</td>
</tr>
<tr>
<td>Bilateral</td>
<td>6/37</td>
</tr>
</tbody>
</table>

Duration of symptoms before presentation (median), days 2 – 180 (30)*

<table>
<thead>
<tr>
<th>Palpable breast abnormality</th>
<th>35/36 (97%)</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Pain</th>
<th>16/36 (44%)</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Discharge</th>
<th>5/36 (14%)</th>
</tr>
</thead>
</table>

**Laboratory test results**

<table>
<thead>
<tr>
<th>Laboratory test results</th>
<th>Reference range</th>
</tr>
</thead>
<tbody>
<tr>
<td>White cell count (range, median), ( \times 10^9 /L )</td>
<td>6.6 – 18 (9.6) ( 3.89 – 9.93 )</td>
</tr>
<tr>
<td>Absolute neutrophil count</td>
<td>2.5 – 13.9 (7.2) ( 2.01 – 7.42 )</td>
</tr>
<tr>
<td>Past history</td>
<td></td>
</tr>
<tr>
<td>History of recurrent abscesses</td>
<td>10/35 (29%)</td>
</tr>
<tr>
<td>Diabetes/impaired glucose tolerance</td>
<td>5/35 (14%)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>2/35 (6%)</td>
</tr>
<tr>
<td>Pituitary tumor (macro- or micro-adenoma)</td>
<td>4/35 (11%) 3 with evidence of hyperprolactinaemia</td>
</tr>
<tr>
<td>Psychiatric history</td>
<td>13/35 (37%)</td>
</tr>
<tr>
<td>Schizophrenia</td>
<td>9</td>
</tr>
<tr>
<td>Bipolar affective disorders</td>
<td>3</td>
</tr>
<tr>
<td>Substance abuse with drug-induced psychosis</td>
<td>1</td>
</tr>
<tr>
<td>Psychiatric medication</td>
<td>12/12†</td>
</tr>
<tr>
<td>Pregnancy history</td>
<td></td>
</tr>
<tr>
<td>Pregnant</td>
<td>1 (3rd trimester)</td>
</tr>
</tbody>
</table>
Within 12 months postpartum | 3
---|---

**Management**

| Antibiotics | 31/34 |
| Aspiration only | 13/33 |
| At least one 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 |

*Data available from 32 patients.

†Number of patients on medications with known association with hyperprolactinemia: 6 risperidone, 3 haloperidol, 2 chlorpromazine, 2 fluoperazine, 1 flupenthixol, 1 olanzapine, 1 paroxetine; number of patients on medications with no known association with hyperprolactinemia: 8 trihexophenidyl, 1 aripiprazol, 1 clonazepam. Eleven patients are on more than one psychiatric medications.

**Footnote**: denominators denote the number of patients with details available for analysis.