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CASE REPORT

COVID-19 Associated Bacteremia with *Chryseobacterium indologenes* Co-Harboring bla_{IND-2}, bla_{CIA} and bla_{CcrA}

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Abstract: We report a COVID-19 case with carbapenem resistant *Chryseobacterium indologenes* bacteremia. Whole genome sequencing identified the presence of bla_{IND-2}, bla_{CIA} and bla_{CcrA}. To our knowledge, this is the first report of *Chryseobacterium indologenes* complicating COVID-19 and the detection of bla_{CcrA} in *C. indologenes*. The presence of bla_{CcrA} in *Chryseobacterium* was overlooked previously may related to substantial sequence divergence with the original allele in *Bacteroides fragilis*. Antimicrobial resistance (AMR) is a challenge to global health in the age of COVID-19 pandemic. Further study and surveillance of underlying mechanisms is needed.

Keywords: COVID-19, SARS-CoV-2, *Chryseobacterium indologenes*, resistance

As the COVID-19 pandemic continues, bacterial co-infections are reported globally and attributed to significant mortality. Secondary bacterial infections could occur in more than 50% of fatal COVID-19 patients.[1] Considerable increase in antimicrobial resistance (AMR) in associated with heavy use of broad-spectrum antibiotics in COVID-19 patients was expected and multidrug-resistant (MDR) bacterial co-infections were reported.[2] The prevalence of carbapenem resistance in COVID-19 bacterial co-infection cases was reported higher than 90%.[1] About AMR, different resistant pattern had been classified, including MDR, extensively drug-resistant (XDR), pandrug-resistant (PDR), usual drug-resistant (UDR) and newly difficult-to-treat resistance (DTR).[3] The crush of COVID-19 pandemic with increasing AMR deserved close monitor.

Chryseobacterium indologenes, a non-fermenting, non-motile gram-negative bacillus, belongs to the genus *Chryseobacterium* and was previously named as *flavobacterium indologenes*. It is distributed in nature, found in soil, plants, and water. *C. indologenes* has become one of nosocomial pathogens, often associated with immunocompromised and indwelling device in recent decades.[4] *C. indologenes* frequently exhibit resistance to penicillin, cephalosporins and carbapenems.[5] It has been assumed the AMR of *C. indologenes* is caused by class A β-lactamase bla_{CIA} and class B carbapenem-hydrolyzing β-lactamase bla_{IND}. The bla_{IND} and bla_{CIA} were the predominant AMR gene in *C. indologenes* and the bla_{IND} and bla_{CIA} co-harboring *C. indologenes* were also reported.[6] Although *C. indologenes* has become one of healthcare-associated infections (HAI) pathogen, there are few reports about *C. indologenes* infection associated with COVID-19. Here, we reported a COVID-19 patient with superimposed *C. indologenes* bloodstream infection. Genomic analysis further revealed the *C. indologenes* co-harboring three β-lactamases gene, bla_{IND-2}, bla_{CIA} and bla_{CcrA}.

A 58-year-old Taiwanese male was admitted due to COVID-19, diagnosed by reverse transcriptase polymerase chain reaction viral nucleic acid test. Bilateral pneumonia complicated with oxygenation failure developed on admission day 1. Recurrent fever to 38.6°C on 10th day after admission. Blood cultures yielded Gram-negative bacilli and was identified as *C. indologenes* by MALDI-TOF MS (BioMérieux). The susceptibility test, determined by VITEK®2 (bioMérieux),

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Table 1 Minimum Inhibitory Concentration (MIC) of the *C. indologenes* Strain C205

Antibiotic	MIC	Interpretation
Piperacillin/tazobactam	⩾128	R
Ceftazidime	=32	R
Ceftriaxone	⩾64	R
Cefepime	⩾32	R
Imipenem	⩾16	R
SMX+TMP	⩽20	S
Gentamicin	=8	I
Amikacin	⩾64	R
Ciprofloxacin	⩾4	R
Tigecycline	=4	I

revealed the *C. indologenes* isolate was resistant to piperacillin/tazobactam, ceftazidime, ceftriaxone, cefepime, imipenem, amikacin, gentamicin, ciprofloxacin, tigecycline (Table 1). The report was conducted according to the guidelines of the Declaration of Helsinki, and approved by the Institutional Review Board of Taichung Veterans General Hospital (CE20261A).

The whole genome of this *C. indologenes* strain (designated strain as C205) was sequenced using Nanopore sequencing (GridIon, R9.4 flowcells). The genome was assembled by Flye and the errors were corrected by Homopolish. The antibiotic resistant genes were annotated by NCBI AMRFinderPlus and Hidden Markov Models (HMM) search was used. Whole-genome sequencing, assembly, and resistome analysis identified two metallo β-lactamases ($bla_{\text{IND-2}}$ and bla_{CcrA}) and one extended-spectrum β-lactamase (bla_{CIA}) in the chromosome (Figure 1). All the sequencing data have been deposited in GenBank under Accession CP085529. bla_{CcrA} in *Chryseobacterium* has not been reported previously. Further investigated did not identify mobile genetic elements at either upstream nor downstream of the bla_{CcrA} in *C. indologenes* C205, suggesting a possibility of vertical transmission. Subsequent search of bla_{CcrA} in the NCBI database confirms it was also presented in the chromosomes of other *C. indologenes* strains and many species of *Chryseobacterium* (e.g., *C. lactis, C. phosphatilyticum*, and *C. carnipullorum*). No *C. indologenes* growth in the sputum culture of this case. Indwelling central venous catheter was considered as risk factor and infection source of *C. indologenes* bacteremia in this case. The patient was treated with trimethoprim-sulfamethoxazole (TMP-SMX) and discharged under clinical stable condition.

To the best of our knowledge, this is the first report COVID-19 associated bacteremia with *C. indologenes* co-harboring $bla_{\text{IND-2}}$, bla_{CIA} and bla_{CcrA}. Considering secondary bacterial co-infections with AMR attributed to increasing mortality during previous pandemics,[2] COVID-19 patients superimposed bacterial infection with MDR pathogen deserved more investigation.

The bla_{CcrA} has not been reported in *Chryseobacterium*. The CcrA, belonging to metallo-β-lactamase, was initially identified in a clinical isolate of *Bacteroides fragilis* TAL3636.[7] CcrA enzyme strongly hydrolyzed cefoxitin and carbapenems, but not the monocyclic β-lactam. CcrA enzyme was inhibited by tazobactam but not clavulanic acid or sulbactam. Our investigation indicated the bla_{CcrA} is not only found in our strain but also vertically transferred in many species of *Chryseobacterium*. The presence of bla_{CcrA} in *Chryseobacterium* was overlooked in previous studies because of substantial sequence divergence with the original allele in *B. fragilis*. Therefore, the homology-based search of antibiotic-resistance genes would miss this β-lactamase.

In conclusion, we reported the first case of co-harboring $bla_{\text{IND-2}}$, bla_{CIA} and bla_{CcrA} in a *C. indologenes s*train isolated from a COVID-19 patient with bacteremia. The interrelationship between SRAS-CoV-2 and AMR represents a public health concern globally.

Author Contributions

All authors made a significant contribution to the work reported during the conception, study design, execution, data acquisition, analysis, interpretation, drafting, and revising, or critically reviewing the article. All authors gave their final

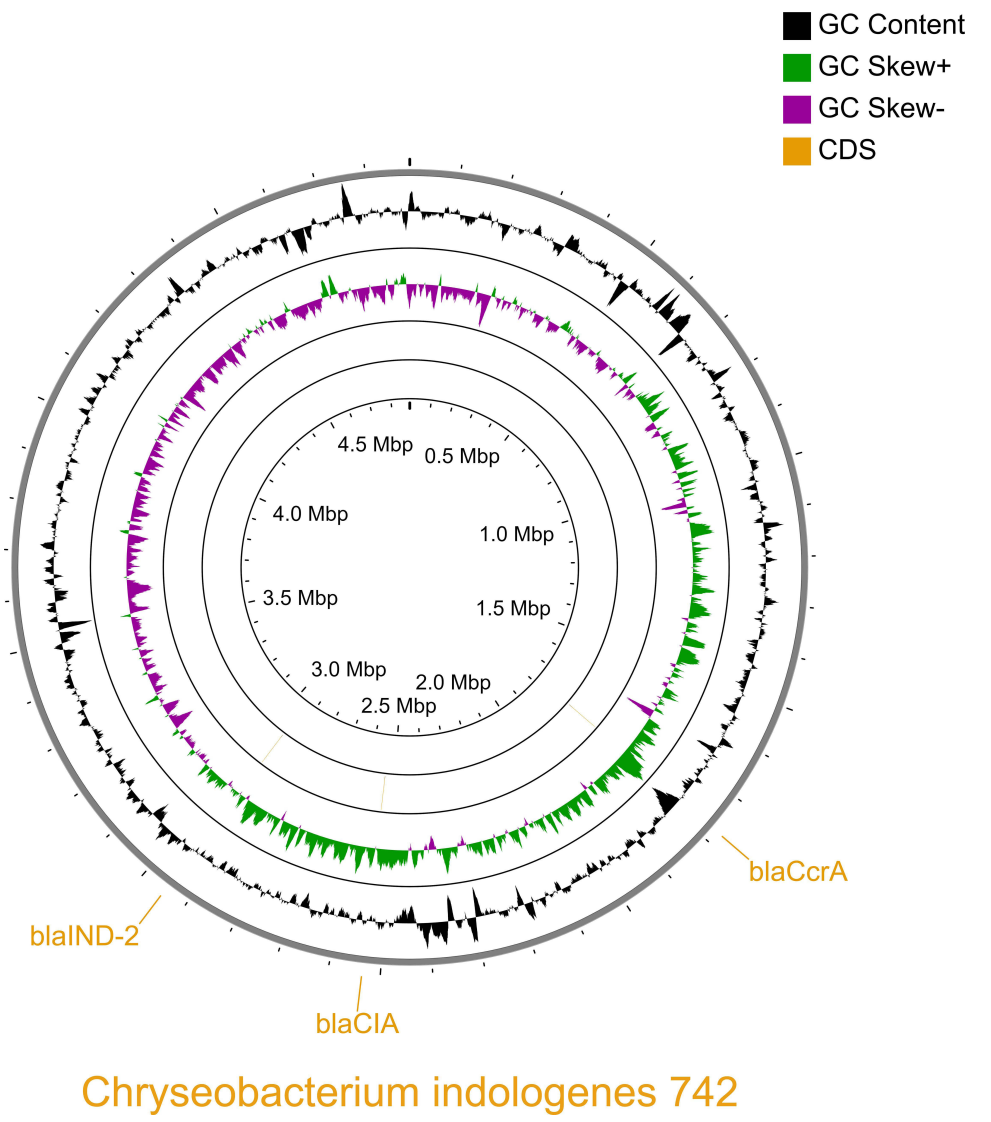

Figure 1 Circular maps of the chromosome of *C. indologenes*. The outermost ring highlights the CDS loci of three beta lactamases: bla_{IND-2}, bla_{CIA}, and bla_{Ccra}. The following inner ring depicts the GC content (black). The two remaining inner rings show the GC skew on the forward and reverse strands (purple/green).

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Disclosure

All authors report no conflicts of interest relevant to this work.

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