Diagnosis of prosthetic mitral valve endocarditis due to *Tropheryma whipplei* Using Next-Generation Sequencing of Plasma

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Background

Tropheryma whipplei is a gram-positive bacillus that causes Whipple's disease, a protean multisystem syndrome classically characterized by arthralgias, chronic diarrhea, malabsorption and weight loss. *T. whipplei* infection has a wide spectrum of clinical manifestations including gastrointestinal, musculoskeletal, neurologic, dermatologic and cardiac. Endocarditis has been diagnosed in a small number of patients. Diagnosis is usually accomplished by histopathology on resected valvular tissue or GI tract biopsy with a compatible cardiac course. Next-generation sequencing (NGS) of microbial cell-free DNA (mcfDNA) in plasma offers a rapid, non-invasive means of diagnosis of this rare cause of culture-negative endocarditis.

Methods

Microbial cell-free DNA was extracted from plasma and NGS was performed by Karius in its CLIA certified/CAP accredited laboratory (Redwood City, CA). Human sequences were removed and the remaining sequences aligned to a curated database of over 1,000 pathogens. Organisms present above a predefined statistical significance threshold are reported and quantified in DNA molecules per microliter (MPM).

Results

An adult male with prior tissue aortic and mitral valve replacements presented with worsening congestive heart failure. Echocardiography revealed a thickened mitral valve with a small mobile vegetation and severe mitral stenosis. An exhaustive infectious blood culture and serologic evaluation was negative. Karius testing detected *T. whipplei* at 766 MPM within two days of sample receipt (8 days after sample acquisition). The normal range for *T. whipplei* is 0 MPM based on a cohort of 684 healthy individuals. Blood PCR for *T. whipplei* was confirmatory (ARUP Laboratories, Salt Lake City, UT with a turnaround time of 21 days).

Clinical Parameters of Case of *T. whipplei* infection diagnosed by NGS of plasma mcfDNA

Parameters	Values
Age and Gender	Adult male
Presenting symptoms	Exertional dyspnea
Antecedent symptoms	None
Tmax/Fever at presentation	99.8°F Tmax, otherwise afebrile
Hgb/Hct	8.4/27.5
WBC with %N	8.7 with 83%
Platelets	188,000
PT/PTT	PT 33.2 INR 3.3 No PTT
ESR mm per hr/CRP md per dL	ESR 49 CRP 7.9 mg/dl
Albumin	3.8
Blood culture result	9 sets negative for bacteria
Sites/organ systems involved: Heart	Heart
Imaging results	Pulmonary edema CT chest/abd/pelvis otherwise negative
Abx pretreatment duration prior to Karius Test	Vancomycin/ceftriaxone for 4 days
Choice of antibiotics after Karius Test	Ceftriaxone/moxifloxacin
Karius Test result	*Tropheryma whipplei* 766 MPM RR 0 MPM (turnaround ~ 2 days)
Other infectious disease testing, result and turnaround time:	*T. whipplei* to ARUP on 2 occasions (turnaround ~21 days) Negative tests: *Histoplasma* and *Blastomyces* antigens, CF and ID antibodies, Fungitell assay, *Coxiella* serology, *Bartonella quintana* PCR, *Brucella* antibodies, Rickettsial antibodies, Blood PCR for CMV, EBV and BKV, *Legionella* antibody

MPM – molecules of microbial cell-free DNA/microliter; RR – reference range based on the 97.5th %ile in a cohort of 684 healthy individuals

Conclusion

NGS for mcfDNA in plasma offers a rapid, non-invasive method for identifying *T. whipplei*. To our knowledge, this is the first report using NGS of plasma mcfDNA to diagnose prosthetic valve endocarditis due to *T. whipplei*.