Journal Club vom 21.9.2015

Healthcare-associated prosthetic heart valve, aortic vascular graft, and disseminated *Mycobacterium chimaera* infections subsequent to open heart surgery

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Eur Heart J 2015; doi:10.1093/eurheart/ehv342. July 17, 2015

Background / Introduction

- A growing number of reports of cardiosurcical site infections due to non-tuberulous mycobacteria (NTM) have been reported, all isolates were fast-growing mycobacteria.
- In 2013 the authors published two cases (PVE and bloodstream infection) with *M. chimaera* (slowly growing, belongs to the *M. avium*-complex).
- During an outbreak at the Zurich Heart Center, *M. chimaera* was cultured from air sampling in the operating theatre and from water tanks of heater-cooler units serving the heart-lung machine. Similar fingerprints indicated that patients were infected during operation due to airborne transmission of microorganisms sprayed from the ventilation outlet of the heater-cooler unit (HCU) ***(Sax H. et al. Prolonged outbreak of Mycobacterium chimaera infection after open-chest heart surgery, CID 2015:61 (1 July).***
- Six cases were identified in Zürich, and 4 cases in Freiburg (DE), Zwolle and Rotterdam. On 30 April 2015, an alert was published by the European Centre for Disease Prevention and Control (ECDC).
- The aim of the study is a comprehensive description of the clinical manifestations and outcome to these 10 cases. In addition exposure criteria and case definitions are presented for this novel disease entity.

Methods

Exposure criteria: Former open-heart surgery and implantation of cardiocascular implant
Clinical criteria: PVE, Prosthetic vascular graft infection, or disseminated infection

Case definition
1 Confirmed cases
Cases including exposure and clinical criteria and *M. chimaera* proven by culture or PCR identification from invasive samples of the cardiac surgery site.

2 Probable cases
Cases including exposure and clinical criteria. In addition detection of *M. chimaera* or *M. avium*-complex in blood and/or extracardiac tissue cultures.

Case finding

- Mycobacterial culture are not part of the routine workup in cardiavascuslar infections.
- 1 case: positive histopathology followed by genus-specific PCR
- Remaining cases: Broad-range bacterial PCR (part of 16S rRNA gene) of cardiac tissue, bone or positive blood culture for mycobacteria

Detection of *M. chimaera*

- Mycobacterial culture using MGIT 960 and Middlebrook 7H11 agar plates
- Direct broad-range bacterial PCR and sequencing
- Antimicrobial susceptibility testing with MGIT 960 with TB Exist module (strains from Zürich)

Clinical investigations

- Comorbitities quantified with Charlson index
- ASA score, type of operation, extracorporeal circulation time, modified Duke criteria were assessed
- Treatment failure: death due to uncontrolled infection or if patient showed a positive *M. chimaera* culture despite antimicrobial therapy for at least 3 months

Results

Population at risk and prevalence

From August 2008 to May 2012, a total of 3706 cardiovascular procedures with extracorporeal circulation were conducted.

- 6 disseminated *M. chimaera* cases were identified (0.16%)
- 4 additional cases (1 from Freiburg (DE), 2 from NL, and 1 pediatric case from Rotterdam (NL)

Patient characteristics

- 9 confirmed cases and 1 probable case (Table 1)

Manifestations of disease

- Fever, shortness of breath, fatigue, weight loss
- Splenomegaly, other physical findings unspecific
- In all patients anaemia: lymphocytopenia and thrombocytopenia
- In all patients: Elevated CRP, LDH, transaminases, and creatinine

Confirmed cases
Cardiac manifestations
Five cases with PVE, two with PVGI and one with myocarditis
Child: infection of prosthetic band and mycotic aneurism of pulmonary artery.

All diagnoses after cardiosurgical reintervention with culture or PCR.
Delayed diagnosis between index surgery and detection of *M. chimaera*: 21 months, range, 5-40

Extracardiac manifestations
Six of nine with extracardiac manifestations prior to cardiac m.: bone infections, cholestatic hepatitis, nephritis or blood stream infection.

Antimicrobial therapy

Targeted therapy with clarithromycin or azithromycin, rifabutin or rifampicin, ethambutol, plus/minus amikacin, or moxiflocacin.
Time course in **Figure 2**. Overview of antimicrobial drugs and susceptibilities in **Table 2**.

Outcome

At least eight patients with therapy failure according to our definition. Five patients died, four due to uncontrolled *M. chimaera* infection.

Discussion

- As of February 2015, 10 heart surgery patients form 4 hospitals in 3 different countries with disseminated *M. chimaera* infection.
- Source of infection: most probably airborne contamination during operation with *M. chimaera*
- Unspecific clinical manifestation after a very long incubation time
- Delayed diagnosis because mycobacterial culture is not part of routine diagnostic workup
- Outcome is very poor despite surgical reintervention and long-term antimicrobial therapy
- In 8 of 16 Swiss hospitals, 1 of 1 German hospital, and 8 of 8 Dutch hospitals, *M. chimaera* was found in the HCU
- Ongoing whole genome sequencing indicates a match between patient isolates and air samples
- For mycobacterial blood culture, the BacTec myco Lytic/F or the isolator tubes should be used multiple times on separate days
- *M. chimaera* isolates were uniformly susceptible to clarithromycin. A combination of clarithormycin, rifabutin, and ethambutol was used for basis of treatment

Important implications:

1 Inclusion of *M. chimaera* infection in differential diagnosis of patients with previous cardiac surgery and extracorporeal circulation.

2 HCUs are a potential source of *M. chimaera* and have to be identified and avoided. Recommendations tor prevention of these infections are strongly warranted.

3 These infections are recalcitrant to classic therapy due to intrinsic antibiotic resilience, challenging infection sites (e.g. bone) and biofilm formation on implants.

15.9.2015 / DG