The global *Mycobacterium chimaera* outbreak

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Summary

Infections due to *Mycobacterium chimaera* associated with a heater-cooler device used during the open-heart surgery have been reported worldwide. These cases represent the first outbreak caused by a non-tuberculous mycobacterium at a global level. Salient features of the infection are long latency and high mortality. Different aspects of the *M. chimaera* outbreak, from the first detected cases to the present burden are reviewed in this study. Although the source has been found and thwarted, new cases continue to be detected due to the late manifestation of symptomatology. The treatment remains poorly effective and mortality is around 50%.

Introduction

Mycobacterium chimaera is a slowly growing species belonging to the *Mycobacterium avium* complex (MAC). Previously known as ITS1-sequevar MAC-A, it was raised to species rank in 2004 by a polyphasic approach (50). It is actually distinguishable from other MAC members by unique sequences in the 16S rRNA gene and in the internal transcribed spacer (ITS) interposed between the 16S and the 23S rRNA; conversely, at phenotypic level, it presents a HPLC mycolic acid pattern not found in other MAC members. The name chimaera (the mythological creature made up of parts of three different animals) was assigned due to the apparent mix of genetic features characterizing the species. Out of 12 strains investigated for the species description, seven proved to be responsible for pulmonary disease according to the ATS criteria (1), a finding that led the authors to hypothesize higher pathogenic power in comparison with other MAC members (50). However, this hypothesis has not been confirmed by other studies (8,39).

M. chimaera has been frequently isolated from water and is able to form biofilm (55).

Very recently phylogenomic analyses have suggested more appropriate the classification of *M. chimaera* at subspecies level with the name *M. intracellulare* subs. *chimaera* (47).

Several commercially available DNA probe systems are unsuitable for identification of *M. chimaera*, GenoType Mycobacterium CM (Hain Lifescience, Germany) and AccuProbe M. intracellulare (Hologic, USA) misidentify *M. chimaera* as *M. intracellulare* (49). With INNO LiPA Mycobacteria (Fujirebio, Belgium), *M. chimaera* hybridizes with the probe MIN-2 (48,49); GenoType NTM-DR (Hain Lifescience) identifies *M. chimaera* as such.

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The beginning of the story

Two fatal cases of *M. chimaera* infection were reported in Zurich (Switzerland) (2), from patients with history of cardiac interventions in 2013. In one case *M. chimaera* was isolated from both an explanted prosthetic valve and blood culture; in the other, it has grown from bone marrow, blood cultures, urine and tracheal swabs. The strains isolated from the two patients revealed a close relation at genotypic level, while differed from any other strain of *M. chimaera* grown from various sources in the hospital of Zurich. Epidemiological investigations allowed to detect further retrospective cases and led to the implementation of surveillance procedures consisting in culturing for mycobacteria water and air samples collected in operating rooms (36).

The heater-cooler device

The heater-cooler unit (HCU) is a device used in open-chest surgical interventions to adjust the blood temperature during extracorporeal circulation. HCU has two circuits, the cold one for cardioplegia and the warm one for the blood; the circulating water acts as heat exchanger and does not come into contact with the patient. A fan present in the HCU provides air circulation.

Among the multiple environmental samples collected in the operative rooms at Zurich Hospital (36) some grew in culture *M. chimaera*: from the water of five HCUs and from the air exhausted

by one HCU. Such findings, in addition to having verified that HCU circuits were not airtight, led to hypothesize the emission from the HCUs of aerosolized *M. chimaera* potentially capable of infecting the surgical area.

Despite the replacement of the HCUs with others, brand new, and the use of frequently changed filtered water, environmental cultures did not steadily convert to negative and, at different times, *M. chimaera* regrew (37). Very soon emerged that HCUs of a specific brand and model (LivaNova, 3T, Germany) were involved and their early contamination, during production in factory, appeared likely (21,45). Starting from September 2014 LivaNova implemented a novel decontamination procedure at the end of the production cycle and provided customers with updated instructions recommending periodic decontaminations of the devices. Only in a few cases *M. chimaera* grew from water collected in HCUs of other brands but none was a source of outbreak.

The spreading of the outbreak

Following the first report in Switzerland many others were published in Germany (19), Australia (32,34,44),United Kingdom (13,40), Canada (10,22,29), Denmark (46), USA (4-6,23,27,30,35,41), Poland (24), Italy (11,15), Cina (14,56) and Spain (3).

The solution of the mystery

An epidemiological study (53) recently gathered 250 *M. chimaera* strains including 21 clinical isolates associated with HCU use during cardiothoracic surgery and others from patients without history of open-heart interventions, as well as environmental strains from water and air collected at LivaNova factory and in hospitals, both from HCUs and from drinking water. All the strains underwent whole genome sequencing and a phylogenomic tree was built based on single nucleotide polymorphisms. The strains grouped into eight clusters: all those from the 21 HCU-related patients belonged to Group 1, while the remaining clinical strains were dispersed across the tree. A more in-depth cluster analysis split Group 1 in 11 subgroups. Subgroup 1.1 included, along with 20 out of 21 clinical isolates above mentioned, most of the strains isolated from water at LivaNova factory and from air sampled in hospitals, close to working HCUs. The very high clonality of the strains of Subgroup 1.1 proves the evidence of the contamination of HCUs in LivaNova, with only one case (the HCU-associated clinical strain not clustering within Subgroup 1.1) of contamination of the device at hospital level. More recently, also the *M. chimaera* strains involved in an outbreak at Hong Kong Hospital proven to belong to the Subgroup 1.1 (56).

The disease

The case definition requires: detection of *M. chimaera* from invasive specimen, history of open-heart surgery and compatible clinical presentation (40).

Subjects who underwent a surgical intervention requiring cardiopulmonary bypass in the five years prior onset of symptomatology, with valve replacement or reconstruction and aortic vascular graft, are at high risk of infection. The disease is characterized by long latency and mortality may be as high as 60% (40). Initial symptoms are fever, fatigue and weight loss. Endocarditis and infection, either disseminated or localized at prosthetic vascular graft or sternotomy wound, are the most common manifestations. Other presentations include hepatitis, nephritis, splenomegaly, chorioretinitis, osteomyelitis and bone marrow involvement with cytopenia (17). Development of non-necrotizing granulomatous tissue is frequent.

The optimum treatment is unknown; as for other mycobacterial infections, drugs association is required. In most cases the regimen recommended for pulmonary MAC infection has been adopted: macrolide plus rifampicin and ethambutol (20). The biofilm formation is the most common factor responsible for treatment failure; in such cases a second surgery with replacement of prosthetic material is the only way out (25).

Microbiological diagnosis

The blood culture is the diagnostic test of choice. It is characterized by good sensitivity but the collection of two or three samples is recommended because of possible intermittent bacteraemia. In case of new surgery, the culture of explanted materials and/or biopsies is mandatory (16). In asymptomatic subjects, the history of surgery with exposition to 3T HCU should warrant blood culture testing.

Some of the commercial methods for identification of mycobacteria are not suited for definition of *M. chimaera* (26), therefore every identification as *M. intracellulare* or MAC must be checked by sequencing of 16S rRNA or ITS.

Environmental sampling

Mycobacterial cultures should be performed on air and water samples collected in operating rooms while the HCU is working (16). For air sampling proper instrumentations are commercially available which suck selected air volumes (½ m^3 is recommended) and throw particulate, including bacteria, on the surface of an agar plate (selective Middlebrook 7H11 is suggested). The air should be collected close to (30 cm approx.) the air exhaust of the operating HCU. Water samples should be collected both from patient's circuit and cardioplegia circuit (1 L each). The samples, once concentrated (by centrifugation or, preferably, by filtration) should be decontaminated, using either the standard NALC-2% NaOH method, or cetylpyridinium chloride 0.005%, before inoculation onto solid and liquid media for mycobacteria. Home-made methods for molecular detection of *M. chimaera* have also been developed (3,57).

Measures to mitigate transmission risk

Having understood that HCU is involved in *M. chimaera* outbreaks, a number of risk mitigation measures have been implemented in hospitals. The most widely adopted include: replacement of 3T HCUs produced before September 2014 with new ones and displacement of HCU outside the operating room (7). When impossible, it should be located distant from the operating table with the air exhaust as closer as possible to the room air suction exhaust.

HCU maintenance and decontamination must comply with the instructions for use in force since September 2014 (9,12,33,52).

Replacement of HCU internal tubing with evidence of biofilm is recommended and the water in the tank should be changed weekly using filtered water (18).

A written procedure should be implemented recording which individual HCU has been used in each intervention, to make possible, in case of later infection, to trace the device involved (31).

Not always such measures allowed eradication of *M. chimaera* (37); however, they could prevent new cases (54).

The hospital staff should be aware that, although the cases of *M. chimaera* outbreak were all linked to HCUs of a single brand, every non-airtight device with water reservoir can potentially become a vehicle of infections when used within operating rooms (43,51,54).

Retrospective cases detection

Due to different signs and symptoms of *M. chimaera* infection, a large number of health specialists (infectious diseases, cardiology, rheumatology, ophthalmology, haematology, pulmonology), together with primary care providers, have been alerted worldwide by national health authorities to maintain high level of attention for patients with a history of surgery with cardiopulmonary bypass and presenting with deep infections of unknown origin or with granulomatous disease sarcoidosis like (16,17,28). Noteworthy is that a misdiagnosis of sarcoidosis often leads to start steroid treatment, thus causing a worsening of the disease (10,15).

A measure implemented in many countries consists in contacting the subjects meeting the exposition criteria (open heart surgery with use of a 3T HCU manufactured before September 2014) making them aware of risks and instructing them on how to recognize compatible signs and symptoms (38).

As for the 10 countries with the higher burden of open-heart surgery, 156-282 new cases/year have been recently estimated (42).

A national survey reported seven cases of *M. chimaera* infection following aortic or valvular surgery performed in Italy in 2017. The risk of infection was calculated 0.4-1 every 1000 interventions; median latency was two years, while mortality for patients requiring a new surgery was 50% (11).

Even in the best scenario of a prompt implementation of the risk mitigation measures in early 2016, several new cases are expected to emerge in the next two years.

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