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Mycobacterium Chimaera: Clinical and medico-legal considerations starting from a case of sudden acoustic damage

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ABSTRACT

Mycobacterium Chimaera is a microorganism that can cause nosocomial infections particularly in patients undergoing cardiac surgery. The specific case presented herein shows an original clinical presentation of the infection: sudden unilateral deafness as a result of septic embolization. Medico-legal experts appointed by the court in a civil liability dispute analyzed the case and submitted their expert opinion. This article analyzes the peculiar and innovative aspect of professional liability that can be attributed to the healthcare facility and the manufacturer of the equipment used in the operating room from a medical-legal point of view.

1. Introduction

Mycobacterium Chimaera (MC) belongs to the large family of non-tuberculous mycobacteria (NTM), also known as environmental mycobacteria, because they are distributed in the ecosystem, especially in the aquatic system. It was first reported in 2004 when, through molecular testing in patients affected by respiratory problems, researchers showed the existence of an organism with hybrid characteristics, between *M. avium* and *M. intracellulare*, hence the name "*chimaera*". MC is generally not dangerous for humans and it causes, after a variable incubation-period of 3–72 months, non-specific symptoms such as fatigue, fever and weight loss. However, recent evidence suggests that it is responsible for disseminated syndromes like other mycobacteria. To date, the extent of the global epidemic is not precisely understood and no effective therapy exists. Despite its tendency to spontaneously resolve, since 2014 MC has been identified as a possible cause of infections in patients who have undergone open-chest heart surgery with exposure to contaminated heater-cooler units (HCUs) [1]. In these situations, infections have a poor prognosis and a sustained cure remains uncertain. Despite treatment with at least three active antibiotics, combined in many cases with revision surgery, to date, in the broadest published case series, the mortality rate was approximately 50% [2]. This high rate in cardiac surgery is a consequence not only of the fact that these infections are recalcitrant to classic antimycobacterial therapy and show an intrinsic antibiotic resilience, but above all because infectious aggregates are formed in sites which are difficult to treat due to the biofilm formation. This occurs especially on the cardiovascular implants [3].

Subsequent retrospective investigations, starting in 2011, have also highlighted many other similar cases in Switzerland, Germany, the Netherlands and the United Kingdom, suggesting increased surveillance efforts and outbreak investigations in Europe [4–6]. In 2017, the Italian Ministry of Health initiated a new health plan against multi-resistant bacteria that included particular recommendations for the surveillance of MC. Since 2011 the number of global infection cases due to MC is more than 180, 10 of which occurred in Italy.

It is currently supposed that MC may be present in the aerosol coming from the HCUs water tanks which regulate blood temperature during extracorporeal circulation. However, the low incidence of MC infections after extracorporeal circulation suggests that contamination depends on a set of circumstances relating to the device, operating room, type of operation and the patient's health. In fact, in certain situations MC can cause endocarditis, disseminating through the production of emboli, and sometimes even pneumonia [7]. Due to its late and non-specific presentation, the diagnosis of MC infections is challenging and depends on molecular analysis for DNA r-PCR or 16s r-RNA, which is not part of the routine diagnostic work-up [8].

In this study, we will present, for the first time, an interesting case of prosthetic valve endocarditis with auditory complications caused by cerebral ischemic injuries due to embolic dissemination. In addition, we will highlight the medico-legal aspects related to the assessment of medical liability in this particular case of nosocomial infection.

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2. Case report

In 2015, a 46-year-old man underwent mitral valve replacement surgery, performed using minimally invasive techniques, due to a serious insufficiency. The intra- and post-operative period were regular with good functional recovery. Approximately six months later, for the first time, the patient began to notice a recurrent fever, fatigue, abdominal pain and weight loss, and was thus admitted in November 2016. During hospitalization, through imaging tests, his physicians detected an endocarditic vegetation at the level of the mitral annulus, which required a valve replacement operation, and multiple embolic repetitions at the pulmonary, hepatic and pancreatic level, initially attributed to sarcoidosis. Further investigations revealed a partial detachment of the posterior portion of the mitral prosthetic ring caused by the endocarditic vegetation, and moderate-severe cardiac insufficiency (FE $<$ 60%). Additionally, *M. Lentiflavum* nucleic acid was detected in hepatic tissues, leading physicians to start therapy with rifabutin, ethambutol and clarithromycin.

In February 2017, he presented with sudden and permanent deafness characterized by focal alterations of the centrum semiovale, as evidenced by the cerebral Magnetic Resonance Imaging (MRI), which were compatible with embolic ischemic events. The continuation of antibiotic therapy led to a partial resolution of the affected organs within approximately 30 days. In June 2017, physicians conducted new molecular tests and identified the presence of *Mycobacterium Chimaera*, and decided to continue antibiotic therapy with ethambutol and clarithromycin. When the infection was stabilized, the patient underwent valve replacement surgery.

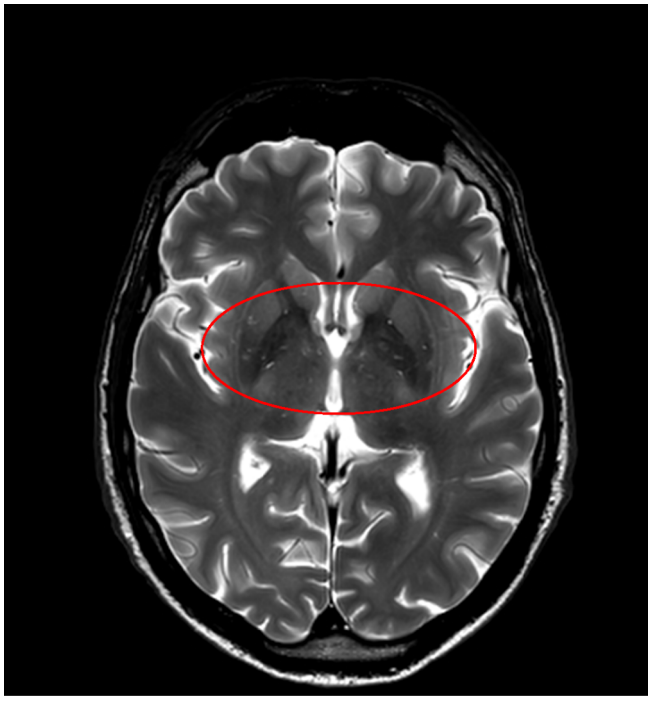

Fig. 1. Cerebral Magnetic Resonance Imaging sequence Turbo Spin Eco Sense which shows minute focal points of altered signal in the white matter of the semi-oval centers (red area).

3. Discussion

Infectious endocarditis due to NTM is a rare event. In fact, the British Public Health System estimated that the risk of contracting this disease is less than 1 in 10,000 patients (based on data collected between 2004 and 2014 in the UK, the rate is estimated at 0.39 cases per 10,000 people/year and 0.17-3 cases per 1000 procedures/year) [9]. However, to date, more than 100 cases of endocarditis have been reported worldwide as a result of MC blood infections due to environmental contamination.

In the case in question, we can confirm that the embolic vegetation was caused by the dissemination of MC. In fact, other organic or infectious causes of embolism can be excluded as the patient was protected by antibiotic therapy against bacteria that can cause endocarditis, and the timing of manifestation is representative of the growth trend of MC and incompatible with other microorganisms. Initially, the mycobacteria was mistakenly identified as M. Lentiflavum due to the fact that these mycobacteria belong to the same group and also because of a diagnostic error, considering that a culture for mycobacteria is not part of the hospital's routine diagnostic work-up.

Several observational studies suggest that MC is transmitted by the aerosol generated in contaminated HCU devices used in cardiac surgery. After a lag time of between months and years from exposure to HCUs, prosthetic material-associated endocarditis generally presents with the same clinical characteristics as cardiac functional alteration, systemic non-specific signs or symptoms and multiple sites of infections due to embolic dissemination [2,10].

In particular, we found a recent case series that describes the spectrum of ocular alterations [11] or encephalitis due to disseminated MC infections in patients undergoing cardiac surgery [12] but we did not find any cases of otological brain injuries. Therefore, the peculiarity of this case stems from the auditory dysfunction due to focal alterations, evidenced by cerebral MRI (Fig. 1). The diagnosis of permanent deafness was confirmed by a subsequent audiometric test.

The criteria for attributing sudden unilateral deafness to recent ischemia produced by septic emboli appear to have been met. Other causes of deafness such as trauma, ototoxic drugs or nerve injuries can be excluded. On the contrary, the MRI shows minute focal points of altered signal in the white matter of the semi-oval centers, which, compared with the diffusion weighted imaging sequence, proved to be sensitive in assessing in acute the extent of damage caused by edema due to a cerebrovascular episode compatible with recent embolic ischemia. This element highlights the systemic embolization that reached the brain and the anterior inferior cerebellar artery (AICA), which led to cochlea and acoustic nerve damage causing total hearing loss.

Owing to the difficult diagnosis of this infection, many authors suggest a high level of clinical suspicion in patients with cardiac prosthetic material, previous cardiac surgery and signs and/or symptoms of disseminated disease, without a clear causative pathogenesis. The analysis of the case in question demonstrates that deafness, as well as any dysfunction of the Central Nervous System, may be an important indication of the cerebral dissemination of MC.

This aspect is also important in cases where the operative access is obtained by means of minimally invasive techniques, as in this specific case. Although exposure to the open chest is reduced, contagion is nevertheless possible.

Furthermore, from a medico-legal point of view [13], it is essential to analyze the peculiarities of MC infections compared to other nosocomial infections. As occurs in the majority of nosocomial infections, there is often a relationship between MC infections and the incomplete execution of disinfection and/or maintenance procedures performed by hospital staff and, in these situations, contamination is certainly proof of organizational deficiency in the hospital.

However, this is not always the case. In fact, as a result of some inspections executed by the FDA of Sorin Group/Livanova production sites in the USA in 2015, some researchers, in 2019, performed a genetic and microbiological analysis on HCUs from various countries around the world [14] and found the same bacterial strain, proving that the contamination, in some cases, started in the assembly stages. In particular, the HCU used in the present case was also assembled by the Sorin Group and, a few years after the fact, we learnt that the cardiac surgery department had requested the HCUs be replaced due to contamination.

Therefore, in these situations, a case-by-case medico-legal evaluation must be carried out in order to identify the source of the nosocomial infection and to establish the liability of the contamination and the related personal injuries.

In the present case, a court case has been filed for financial compensation for damages caused by the infection. This is one of the first lawsuit in Italy for this type of situation. To date, the patient is particularly asthenic, unable to work, deaf in the ear and has to continue drug therapy with antimycobacterial drugs (rifabutin and ethambutol) to keep the infection contained. The presiding judge appointed a panel composed of a medico-legal expert and an infectious disease specialist. The two specialists have analyzed the case and submitted their expert opinion, which we shall report in brief.

MC contamination can occur at any time, both at the production site and at the hospital. Regular, thorough hospital decontamination procedures are the only way to reduce the potential for contamination, proving that the instrument is not already contaminated and that the biofilm is not already present and does not prevent complete disinfection. There is general data on the presence of MC contamination at the production site. In the specific case in question, however, it is not possible to define where the contamination of the machine by extracorporeal circulation occurred, since the microorganism can be present both at the hospital and at the production site. Approximately three months before the events of the cardiac surgery in question, the Sorin Group carried out the programmed annual disinfection, but there is no documentation relating to the periodic disinfections required by the manufacturer that must be performed by the hospital. Many months before the intervention, the Italian Ministry of Health and Sorin LivaNova published and distributed repeated and updated field safety notices on mycobacterial risks during cardiac surgery and on disinfecting and cleaning HCUs, including the recommended action to take. It is therefore not possible to consider the risk unknown by the hospital authorities. However, given the nature of mycobacteria infections, even the most careful hospital disinfection procedures might not have prevented contamination with any certainty.

Definitely in light of these technical considerations, the need for specific medico-legal analysis is evident.

The considerations to which the experts appointed in this case have come not represent an unchangeable paradigm of civil liability in similar cases; on the contrary, it is clear that in terms of liability, results can differ depending on the characteristics of each individual case. However, we believe that this report is particularly useful both from a clinical point of view, due to the particular presentation of the disorder, and from a medico-legal point of view for describing the parameters that are used for the evaluation and therefore provide initial support to those who will have to deal with this new aspect of professional medical liability in the future.

4. Conclusion

Systemic MC infections are very important both from a clinical and medico-legal point of view. This specific case demonstrates that in patients with a history of cardiac surgery and signs of disseminated disease, such as cerebral injuries of unknown origin, especially visual deficits and/or deafness, MC infection must be considered. On the other hand, the potential detection of an HCU contamination at the production site changes the typical evaluation of medical liability where the manufacturing companies are sometimes involved, and requires a careful case-by-case analysis to identify the eventually liable parties. Legal medicine is central to this important assessment and must ascertain, if possible, the origin of the infection, the hospital's responsiveness to the alerts issued by the health authorities and the manufacturer, and the actual damages caused by the infection.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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