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Case Report

Dying at home during the SARS-CoV-2 endemic: The importance of defining the exact mechanism of death

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ABSTRACT

Introduction: Coronavirus Disease 2019 (COVID-19) has become endemic in Europe thanks to the presence of less deadly and more infectious variants and to the existence of a significant portion of unvaccinated people among the general population. SARS-Cov-2 related deaths are probably going to fade in the next years, but Covid-19 should still be considered a potential cause of death in the out-of-hospital setting in the next future.

Material and methods: Three (3) cases of unexpected death at home are here presented. Each case has been investigated with the same methodological approach: death scene investigation (DSI), complete autopsy with histology, immunohistochemistry, RNA in situ hybridization for SARS-CoV-2 spike protein in lung tissue, toxicology and microbiology.

Results and Discussion: All three cases had a COVID + post-mortem nasopharyngeal swab. Histology and immunohistochemistry revealed a SARS-CoV-2 lung involvement in only two of the cases (Cases 2 and 3), while a septic bacterial pneumonia was found in Case 1, where RNA-in situ hybridization for viral spike protein showed no reactivity in pneumocytes. The integration of all postmortem evidence allowed to attribute a different role of SARS-Cov-2 in the determinism of the death.

Conclusion: In the current post-pandemic context, SARS-CoV-2 remains a possible cause of death when investigating out-of-hospital unexpected deaths. Since a positive post-mortem swab does not automatically imply a COVID-19-related death, histology and immunohistochemistry are helpful for identifying SARS-CoV-2 lung involvement and, therefore, its potential active role in the determinism of death.

1. Introduction

Coronavirus Disease 2019 (COVID-19) spread worldwide from March 2020 and the World Health Organization (WHO) soon declared it as a pandemic. In 2020, COVID-19 has been the second leading cause of death in England, Wales, France and the third leading cause of death in several other countries, including the U.S. [1]. In Europe, the restrictive measures, the introduction of vaccines, and the more infectious but less deadly SARS-CoV-2 variants led COVID-19 fall into an endemic phase, with a decrease in COVID-19 related hospitalizations and intensive care unit admissions. Most recently, on May 2023, more than three years into the pandemic, the WHO declared that COVID-19 is no longer a "Public Health Emergency of International Concern" while emphasising that it remains a global health threat. Indeed, WHO's Emergency Committee established that COVID-19 should now be considered a well-established and ongoing disease, depicting a situation of rather stable prevalence, instead of the typical infection waves that characterized the pandemic from the early 2020 to the late 2021. This does not mean that the pandemic itself is over; indeed, although the global emergency has finished, COVID-related deaths might still occur.

COVID-19 represents an infectious disease caused by the SARS-CoV-2 virus, which can affect a wide range of systems and organs, particularly the respiratory system. Pulmonary damage due to SARS-CoV-2 can lead to severe acute respiratory syndrome, which represents the most prevalent cause of death in patients affected by COVID-19. Several studies have investigated coronavirus related organ damages and the local and systemic complications, in order to identify common traits or pathognomonic findings that would allow the pathologists to reconstruct the exact mechanisms of death. In the literature, the lungs are described as the main organs affected by severe COVID-19. Gross examination of the lungs showed a heavy and firm parenchyma, with patchy or diffuse areas of consolidation and severe congestion and

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oedema [2,3]. The most commonly reported pulmonary histological finding is diffuse alveolar damage (DAD) [4,5], which is characterized by an acute phase with oedema and hyaline membranes, followed by an organizing phase with alveolar septal fibrosis and type II hyperplasia [2,6–8]. DAD described in COVID-19 shows a substantial overlap with DAD from other causes [9]. Severe capillary congestion, intra-alveolar haemorrhages, desquamation and squamous metaplasia have also been described [10]. Pulmonary microvasculature is also affected ranging from platelet-rich thrombi in capillaries and small vessels to thrombosis of large arterial vessels [11–13]. Other relevant features are the increase of intravascular megakaryocytes and perivascular inflammatory infiltrations with a variable cell composition [14].

In the forensic context, an eventual role of SARS-CoV-2 in causing the death could have important legal consequence under both criminal and tort law, including any hypotheses of medical liability. Even if COVID-19 now stepped into a post-pandemic phase, since many people are still dying with or from COVID-19, it is presumable that forensic pathologists will have to continue dealing with COVID-19 related deaths.

Several post-mortem studies performed on COVID-19 cases are currently available in the literature, but establishing the potential role of the viral infection in the determinism of death sometimes remains a tricky issue for the forensic pathologist and it is made even more difficult if the body is found at home without any information on the clinical history.

We here present three cases of unexpected death at home exhibiting a COVID + post-mortem nasopharyngeal swab, investigating the eventual causal role of SARS-CoV-2 in the determinism of the death.

2. Material and methods

Three cases underwent death scene investigation (DSI) performed according to the most recent procedures endorsed by the European Council of Legal Medicine [15].

Subsequently, post-mortem external and internal examinations were performed according to recently published guidelines for forensic autopsy in suspected SARS-CoV-2 infected bodies [16–17].

Post-mortem testing for SARS-CoV-2 RNA in nasopharyngeal and bronchoalveolar swabs [18] was performed using real-time reverse transcription polymerase chain reaction (RT-PCR).

During autopsy, tissue specimens were collected from the central nervous system, heart, lungs, kidneys and spleen and fixed in 10 % buffered formalin, dehydrated, paraffin-embedded, and stained with Haematoxylin and Eosin (HE). Periodic acid-Schiff (PAS) and immunohistochemical stains for CD61 and Thyroid Transcription Factor-1 (TTF-1) were performed in lung sections. RNA in situ hybridization (RNA-ISH) for SARS-CoV-2 spike protein-encoding RNA was performed in each case (only lung sections) following Borczuk AC et al. [19]. In addition, in Case 1, a Gram stain was performed in lung sections.

Toxicology was performed on urine and peripheral blood, including a general unknown screening for drugs of abuse through liquid chromatography coupled to mass spectrometry (LC-MS); blood alcohol concentration was determined through head space gas chromatography coupled to a flame ionization detector (HS-GC-FID); blood carboxyhaemoglobin (COHb) was determined using gas chromatography coupled to mass spectrometry (GC–MS).

Table 1
Summary of autopsy, histology, immunohistochemistry, microbiology and toxicology findings.

Case	Macroscopic findings	Histology, Immunohistochemistry, RNA in situ hybridization for SARS-CoV-2 (RNA-ISH)	Microbiology and Toxicology	Cause of death
Case 1	Cachectic state Advanced abdominal green stain Pressure ulcer on sacral region Lung with air blisters	Septic emboli in brain vessels Granulocytic inflammatory lung infiltration No reaction for PAS, CD61 and TTF1 in lung sections No reaction for RNA-ISH in pneumocytes or hyaline membranes	SARS-CoV-2 swab + COHb 6,4%	Respiratory failure due to sepsis and bacterial pneumonia
Case 2	Severe obesity Lung oedema Hepatomegaly	Hepatic steatosis Intra-alveolar proteinaceous-type oedema Increased number of megakaryocytes in the pulmonary vessels Lymphocytic infiltration in the alveolar septaPlatelet-rich thrombi in the small pulmonary vessels (CD 61 +)Hyperplasia of type II pneumocytes (TTF1 +)Focal hyaline membranes in the alveolar septa (PAS +) RNA-ISH reaction in probable type II pneumocytes and hyaline membranes	SARS-CoV-2 swab + COHb 6,0% BAC 1,12 g/L	Respiratory failure due to SARS-CoV-2 related interstitial pneumoniae
Case 3	Severe obesity Brain oedema Severe cardiomegaly Coronary arteries with stenosing sclerotic plaques Oedematous and dense lung parenchyma Hepatomegaly Polivisceral congestion	Hepatic steatosis Myocardial sclerosis Non-obstructive coronary artery plaques Diffuse intra-alveolar oedema with focal area of proteinaceous-type oedema Increased number of megakaryocytes in the pulmonary vessels Lymphocytic infiltration in the alveolar septaPlatelet-rich thrombi in the small pulmonary vessels (CD 61 +)Hyperplasia of type II pneumocytes (TTF1 +)Focal hyaline membranes in the alveolar septa (PAS +) No reaction for RNA-ISH in pneumocytes or hyaline membranes	SARS-CoV-2 swab + Toxicology testing -	Respiratory failure due to SARS-CoV-2 related interstitial pneumoniae and acute heart failure in pre-existing chronic ventricular dysfunction

3. Case reports

3.1. Case 1

Main autopsy, histology, microbiology, and toxicology findings are reported in Table 1 and Fig. 1. Almost three years after the start of the COVID-19 pandemic, the corpse of a 68-year-old man (body height: 160 cm; weight: 65 Kg) was found in the kitchen of an apartment belonging to a protected structure for homeless and needing people. He shared his dwelling with another man, who was found dead in his bedroom on the same day (Case 2, reported below).

Upon our arrival the body was lying supine on the floor, scattered with filth and garbage. Examination of the body revealed fixed purple hypostases distributed on the supine decubitus, rigor mortis on both upper and lower limbs and greenish discoloration of the skin over the right iliac fossa. The body temperature was equal to the environmental one. Traumatic injuries were not detected, except for a pressure ulcer over the sacral region. The ambient measurement of carbon monoxide was negative.

3.1.1. Autopsy, microbiology and toxicology findings

A forensic autopsy was performed 3 days after the body was found. The distribution of post-mortem lividities was comparable to that found at death scene investigation, while rigor mortis was absent. The corpse displayed putrefactive changes and a reduction of the body mass, with extremely low adipose tissue and hypotrophic muscles. The only sign of trauma was the presence of a sacral pressure ulcer affecting the subcutaneous tissues. At autopsy moderate poli-visceral congestion was observed, more evident in the lungs. Moreover, multiple blisters filled with gaseous material were detected over the lung surface. The lungs weighed 785 g (right) and 830 g (left). Post mortem swab specimens collected during autopsy tested positive for SARS-CoV-2. Blood and urine toxicology tested negative for ethanol, opiates, cocaine and metabolites, cannabinoids, amphetamines/methamphetamines. Blood COHb concentration was 6,4%.

3.1.2. Histology, immunohistochemistry, and RNA-ISH

Lung sections displayed multifocal oedema and marked intra-alveolar infiltration of granulocytes. Immunohistochemistry for PAS and CD61 showed no reactivity. Immunohistochemical staining for TTF-1 showed no hyperplasia of the type II pneumocytes. RNA-ISH for viral spike protein did not show reactivity in pneumocytes. The Gram stain did not reveal any bacterial colonies in the examined lung sections. Multiple septic brain emboli were observed.

3.2. Case 2

At the same time as the body of Case 1 was discovered, another one was found lying supine on the bed in a bedroom of the same apartment. The body belonged to a 48-year-old man (body height: 174 cm; weight: 105 Kg). Examination of the body revealed fixed pink-red hypostasis consistent with the position in which the body was found, absence of

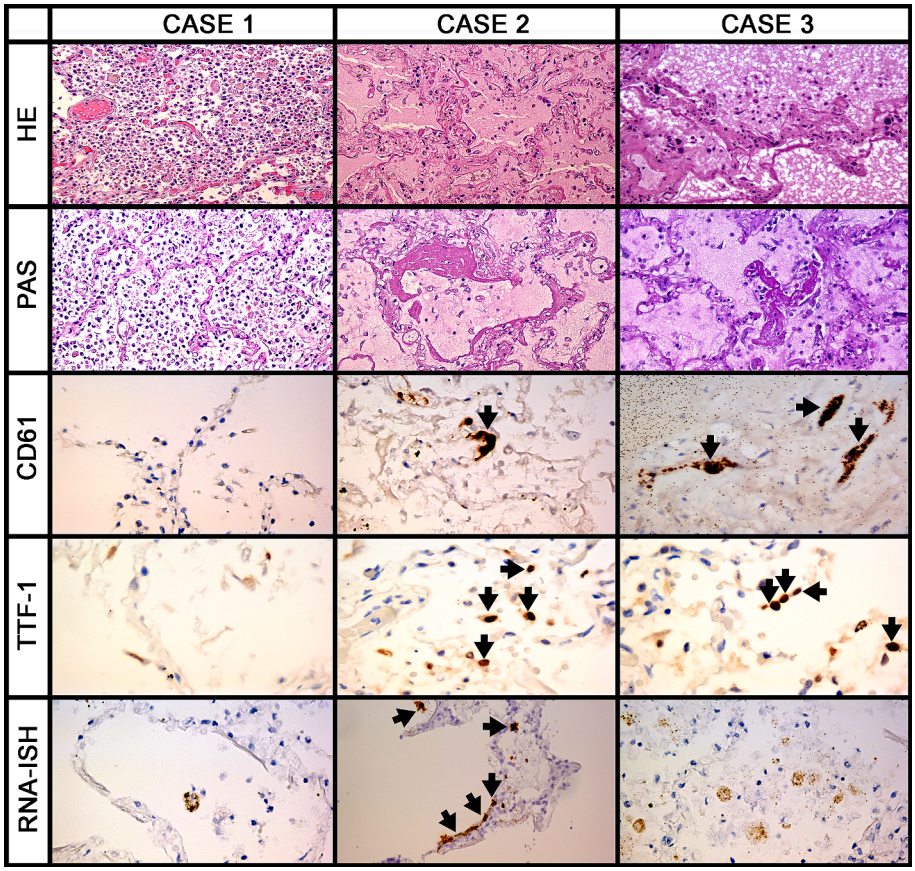

Fig. 1. Main pulmonary histological findings of the three reported cases. HE sections display dense aggregates of neutrophil granulocytes within the alveolar lumen in Case 1 (x200) and interstitial lymphocytic infiltrate associated with intra-alveolar proteinaceous-type oedema in Case 2 and in Case 3 (x200). PAS staining highlights diffuse hyaline membranes in Case 2 and in Case 3 (x200). In Case 1 no hyaline membranes were detected (x200). Platelet-rich microthrombi are highlighted by CD61 immunohistochemical stain within the alveolar septa in Case 2 and in Case 3 (x400, black arrows). In Case 1 platelet-rich microthrombi were not detected (x400). Hyperplasia of type II pneumocytes were highlighted by TTF-1 in Case 2 and in Case 3 (x630, black arrows). In Case 1 hyperplasia of type II pneumocytes was not detected (x630). RNA-ISH for viral spike protein showed reactivity in areas of hyaline membranes and in probable type II pneumocytes in Case 2 (x200, black arrows). RNA-ISH did not show reactivity for pneumocytes in Cases 1 and 3 (X400).

rigor mortis, body temperature equal to the environmental one and greenish discoloration of the skin over the right iliac fossa. On the floor close to the bed several blood-stained paper tissues were found. On a night table in the same room different kind of medication boxes and blisters, such as paracetamol, ramipril, atenolol, omeprazol, ketoprofene and nimesulide, were observed.

3.2.1. Autopsy, microbiology and toxicology findings

A forensic autopsy was performed 3 days after the body was found. At external examination severe obesity was noted as well as red liquid material leaked from the oral cavity. The internal examination revealed lung oedema and liver hypertrophy with yellow and small nodules all over its surface. The lungs weighed 1100 g (right) and 845 g (left); the liver weighed 4500 g. Post mortem swab specimens collected during autopsy tested positive for SARS-CoV-2. Blood and urine toxicology tested negative for opiates, cocaine and metabolites, cannabinoids, amphetamines/methamphetamines. Blood alcohol concentration (BAC) was 1,12 g/L. Blood COHb concentration was 6,0%.

3.2.2. Histology, immunohistochemistry, and RNA-ISH

Lung showed diffuse alveolar damage (DAD). PAS stain highlighted focal hyaline membranes in the alveolar septa, TTF-1 revealed type II pneumocyte hyperplasia and immunostaining with CD61 showed platelet-rich thrombi in the pulmonary microvasculature. Focal areas of intra-alveolar proteinaceous-type oedema, an increased number of megakaryocytes and a scattered septal lymphocytic infiltrate were also observed. RNA-ISH showed reactivity in areas of hyaline membranes and in probable type II pneumocytes. Histology of the liver revealed a diffuse steatosis.

The third case involved a 60-year-old woman (body height: 162 cm; weight: 120 Kg) who presented with symptoms suggestive of SARS-CoV-2 infection. After testing positive to SARS-CoV-2 rapid antigenic swab, she was treated at home with paracetamol. The following evening her husband, worried about the woman's health due to aggravated conditions and comorbidities (diabetes, severe obesity and hypertension), tried unsuccessfully to call the territorial health service. The woman was found dead in her bed early in the morning.

3.2.3. Autopsy, microbiology and toxicology findings

A forensic autopsy was performed 4 days after the death to identify the cause of death and any medical liability hypotheses. At external examination severe obesity was noted as well as red liquid stains leaked from the nostrils and the oral cavity. Forensic autopsy revealed swelling and oedema of the brain, severe cardiomegaly (weight: 795 g) with extended and stenosing sclerotic plaques in coronary vessels, hardening and oedema of the lungs, greasy and enlarged liver and polivisceral congestion. The lungs weighed 840 g (right) and 790 g (left); the liver weighed 1350 g. Post-mortem swab specimens collected during autopsy confirmed positivity for SARS-CoV-2. Blood and urine toxicology tested negative for ethanol, opiates, cocaine and metabolites, cannabinoids, amphetamines/methamphetamines.

3.2.4. Histology, immunohistochemistry, and RNA-ISH

Lung showed diffuse alveolar damage (DAD). PAS stain highlighted focal hyaline membranes in the alveolar septa, TTF-1 revealed type II pneumocyte hyperplasia and immunostaining with CD61 showed platelet-rich thrombi and in the pulmonary microvasculature. Diffuse intra-alveolar oedema with focal areas of proteinaceous-type oedema, increased number of megakaryocytes and scattered septal lymphocytic infiltrate were also observed. RNA-ISH for viral spike protein did not show reactivity in pneumocytes or areas of hyaline membranes.

Myocardial bridges, diffuse non-obstructive coronary artery plaques and severe myocardial sclerosis with large scarring areas were found. Histology of the liver revealed a diffuse steatosis.

4. Discussion

Suspecting a COVID-19-related death may be easy when comprehensive circumstantial data and a thorough medical history are present. Differently, finding corpses at home with no clinical information may lead to several challenges for the forensic pathologist, who has to reconstruct the exact mechanism and time of death of the victim. Therefore, in a stable prevalence COVID-19 context in which the disease is now well-established, it is necessary to consider SARS-CoV-2 infection as a potential cause of death even in an out-of-hospital setting, using a systematic post-mortem approach.

Regarding Cases 1 and 2, an accidental drug and/or CO intoxication or a traumatic death were initially hypothesized by the Public Prosecutor.

Since the two corpses were found in the same home and the post-mortem interval (PMI) was assessed to be very similar, COHb intoxication had also to be considered. After toxicology, due to the presence of low COHb in peripheral blood, the hypothesis of a fatal CO intoxication was rejected. Moreover, the low blood alcohol concentration in Case 2 and the absence of other psychoactive substances in body fluids of both cases seemed to exclude a fatal intoxication, pointing towards a natural death to be investigated through autopsy, histology and immunohistochemistry.

Concerning case 3, clinical and circumstantial data suggested an active role of SARS-CoV-2 infection in the determinism of death. Since in case 3 death occurred in a patient with multiple comorbidities, being managed at home by the general practitioner, the Public Prosecutor asked for a forensic autopsy to verify any potential medical liability in the determinism of death.

Even if different causes of death were initially hypothesized, we used the same methodology to investigate all cases (see Material and Methods).

In Case 1, autopsy revealed a sepsis probably originating from the lung; in particular, cachectic state, poli-visceral congestion, marked accumulation of neutrophils within the alveoli and multiple septic brain emboli, consistent with a septic pneumonia were found. On the other hand, the presence of SARS-CoV-2 lung involvement was excluded through histology, immunohistochemistry, and RNA-ISH. Case 1 did not show any signs of DAD and/or pulmonary microvascular thrombosis. Moreover, extremely advanced putrefactive changes were found in the lungs (lung surface scattered with putrefactive blisters), consistently with the evidence of a septic state, which as well-known can accelerate putrefaction [20]. Although patients affected by COVID-19 seem to exhibit an increased risk of lung bacterial infection [21,22], above all when hospitalized in an Intensive Care Unit, the pathogenesis of bacterial co-infection or super-infection in SARS-CoV-2 is incomplete. For influenza, it has been postulated that viral damage of epithelial cells in the lower airway, coupled with mucociliary dysfunction, facilitate binding to cell surfaces of pathogenic bacteria aspirated from the nasopharynx [23]. Whether this mechanism applies to SARS-CoV-2 remains to be determined [21,23]. In Case 1, there was no necroscopic evidence of damage to epithelial cells in the lower airway and also the lungs did not show any clear signs of damage referrable to COVID-19 disease. Moreover, RNA-ISH showed no reaction in pneumocytes confirming the absence of COVID-19 in the lungs; therefore, no evidence of a direct causal relationship between SARS-CoV-2 infection and death could be detected.

Cases 2 and 3 have several traits in common. Both subjects displayed risk factors for a severe COVID disease, such as obesity, heart and liver disorders, diabetes and hypertension [24,25]. In both cases, at gross examination, the lungs were oedematous and hardened. At histology, they exhibited diffuse alveolar damage (DAD) prevalently staged at the exudative phase. This non-specific pathological finding has commonly been reported in SARS-CoV-2-related deaths [2,6–7,26], being an expression of the alveolar-capillary membrane injury during the viral infection. Additionally, a relevant number of intravascular

megakaryocytes were observed through CD61 immunohistochemical staining; this finding is consistent with several autoptic studies reporting an increase of megakaryocytes in COVID-19 patients with DAD [27]. Beside alveolar damage, pulmonary microvasculature involvement was also observed in cases 2 and 3, where platelet-rich thrombi were found in small and medium lung vessels. The presence of micro-thrombi in the lungs of SARS-Cov-2 infections has often been reported [28]. As regards cases 2 and 3, the identification of DAD in addition to CD61 positivity for platelet-rich thrombi and megakaryocytes, TTF1 positivity for hyperplastic type II pneumocytes and PAS positivity for hyaline membranes allowed to identify with a degree of high probability a SARS-CoV-2 related alveolo-capillary injury. In Case 2, RNA-ISH showed reactivity for viral spike protein in probable type II pneumocytes and areas of hyaline membranes, strengthening the causal relationship between the viral infection and the fatal interstitial pneumoniae. In Case 3, RNA-ISH did not detect SARS-CoV-2 RNA genome fragments in the examined lung sections, suggesting a cleareance of the virus in the presence of lung damage.

As a result, due to the integration of all post-mortem findings, the most probable cause of death in Case 1 was a respiratory failure due to a bacterial pneumonia with sepsis, while in Case 2, a respiratory failure due to a SARS-CoV-2 related interstitial pneumonia (confirmed also by RNA-ISH). In Case 3, the overlapping between pulmonary damage, although with no reactivity at RNA-ISH for the viral spike protein, and cardio-pathological abnormalities (severe cardiomyopathy, acute visceral congestion, acute pulmonary oedema) evidenced during the postmortem examination, allowed to identify a combination of acute heart failure in pre-existing chronic ventricular dysfunction and acute respiratory failure due to a SARS-CoV-2 pneumonia as the most probable cause of death. Therefore, in Case 3, SARS-CoV-2 played a co-causal role in the determinism of death.

This manuscript describes three autoptic cases of SARS-CoV-2 infection; in only two of them COVID 19 played a demonstrable causal or co-causal role in the determinism of the passing.

According to WHO international guidelines, a death from SARS-CoV-2 is a “death resulting from a clinically compatible illness, in a probable or confirmed COVID-19 case, unless there is a clear alternative cause of death that cannot be related to COVID disease” [29].

In a forensic setting, this definition is clearly insufficient. An evidence of SARS-CoV-2 infection implies for the forensic pathologist the need for further investigation aimed at identifying any COVID-related organ damages and reconstructing the exact mechanism of death.

Although COVID-19 no longer constitutes a “Public Health Emergency of International Concern” and there is currently an endemic phase, when a corpse is found at home (or in another extra-hospital setting), the pathogen-related death should be still considered. Even if the preliminary investigations can lead to the suspect of a different cause of death, a complete post-mortem examination should be performed in order to properly recognize the exact physiopathology of the passing. Bronchoalveolar and nasopharyngeal swabs should be always collected; however, positivity to the swab-test should not be considered confirmatory of a SARS-CoV-2 related death. The attribution of a causal or co-causal role to SARS-CoV-2 requires the identification of an adequate pathogen-related organ damage, which can be confirmed only through histology and/or immunohistochemistry.

Compliance with Ethical Standards

This is case study has been performed in accordance with international ethical standards and national laws. No funding was received.

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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