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Review

Management of post-mortem examination in SARS-CoV-19 infections

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Summary
A brief overview on the management of autopsies during the SARS-CoV-19 epidemic is proposed. In particular, the point is made of the Italian laws on the subject, the characteristics required for the autopsy room and the sampling suggested for the histological examination.

Key words: SARS-CoV-19, autopsy, autopsy room, infectious risk

Introduction

The onset and rapid explosion of the epidemic in the first months of 2020 caught Italy, and the rest of the world, unprepared to deal with patient management and contagion containment.
Our aim is to examine the problems in the management of autopsies of patients who died from SARS-CoV-19 infection, with particular attention to the Italian legislation on safety for operators, the need for dissecting rooms and sampling.

Overview of the Italian laws on SARS-CoV-2 autopsies

Autopsies for diagnostic purposes is, still today, regulated in Italy with D.P.R. 10 September 1990, no. 285 "Approval of the mortuary police regulation". This was marginally supplemented by the Law 8 March 2017, n. 24, containing the "Provisions on the safety of care and of the assisted person, as well as on the matter of professional responsibility of healthcare professionals", a bridge rule between the ethical principle of guaranteeing the safety of care and patients and professional responsibilities of healthcare workers.
Even nowadays, despite the sophisticated diagnostic technologies available, there are discrepancies between clinical and autopsy diagnosis. For this reason, hospital autopsy still plays an important role in improving the quality and safety of care, but the physician requests autopsy in very limited cases compared to the number of deaths [1-3].
SARS-CoV-2 outbreak made autopsies more important. In fact, physician needed to acquire knowledge useful for the treatment, given the lack of knowledge on COVID-19 [4,5].

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Instead, especially at the onset of the pandemic and during the first wave, controversial provisions were issued by the Italian Ministry of Health.
On 20th March 2020 the WHO allowed COVID autopsy provided that: "Perform autopsies in an adequately ventilated room, i.e. at least natural ventilation with at least 160L/s/patient air flow or negative pressure rooms with at least 12 air changes per hour (ACH) and controlled direction of air flow when using mechanical ventilation" [6].
However, On April 2020, the Italian Ministry of Health (Circular "Emergency indications connected to the COVID-19 epidemic concerning the funeral, cemetery and cremation sector", revised on May 2020) recommended keeping SARS-Cov-19 autopsies to a minimum, even for lawsuit autopsy, advising the only external examinations of the corpses.
Subsequently, on 11 January 2021, the Ministry of Health, with Circular no. 818, promulgated other emergency indications concerning the funeral, cemetery, and cremation sector (that fully replaced the previous n. 11285 of 1/ 4/2020, n. 12302 of 8/4/2020, n. 15280 of 2/5/2020 and n. 18457 of 28/5/2020).
Given the uncertainty of the scientific foundations, the unpreparedness of the scientific community in this regard and the seriousness of the national and global situation, the provisions by the Italian Ministry of Health appeared controversial, with the commendable aim of safeguarding the health of professionals dedicated to sectoral activities, but at the same time making their task very difficult. Pathologists were debated between the pressing requests of clinicians to understand the causes of the numerous deaths and the solicitations of the Hospital Directors who pushed to comply the ministerial provisions.
In the meantime, the coroners, and pathologists, through their respective Scientific Societies, developed a document containing operational indications useful for the execution of lawsuit and diagnostic autopsies on 22 March 2020 [7]. The document, addressed to personnel potentially exposed to material, including bodily fluids, originating from cadavers in mortuary facilities and during the post-mortem procedure.
In many Hospitals, as in our department, for many months, the Pathologists proceeded on a case-by-case basis, asking the Hospital Director for authorization for each autopsy.

Management of the post mortem examination

During SARS-Cov-19 outbreak, to perform a diagnostic autopsy, was important to define a negative, suspect, probable and confirmed case of infection [8]. If a diagnostic autopsy is requested in a patient apparently SARS-CoV-2 negative, an oropharyngeal swab should be performed within two hours of death to assess the presence of infection from SARS-CoV-2, with a result that must be received within 24 hours of death.
These precautions are necessary to preserve the safety of the health workers involved and the quality of the service.
In any case, it is advisable to consider potentially infected body and take precautionary measures (disposable lab coat, mask and goggle visor, double gloves) to avoid any risk of contagion.
Histological examination, as well as from tissue samples during autopsy, can also be obtained from biopsies by core biopsy on multiple organs (lung, liver, kidneys, skeletal muscle). This approach could promote the collection of a greater number of samples from various deceased subjects, considering that the diagnostic autopsy can be performed only in specific autopsy rooms.
All personnel working in the postmortem room during the examination of a high infectious risk case need adequate training in autopsy techniques and safety procedures for these cases [9,10].
All those present in the sector room must be suitably equipped:

- disposable surgical gown that completely covers the arms, chest and legs;
- disposable plastic apron that covers the chest, trunk and legs;
- eye protection or non-ventilated flat visor;
- face mask to protect mouth and nose from splashes if a visor is not worn
- respiratory protection (N-95 or N-100 special disposable respirators or PAPR- powered air purifying respirator) to protect against aerosol

Autopsy room

Autopsies must be performed in structures that guarantee safety standards [11,12] (i.e. BSL3, see below). In fact, according to Italian law, biological agents can be divided into four risk groups based on:

1 infectivity, the ability of a microorganism to penetrate and multiply in the host (man/animal);
2 pathogenicity, the ability of a microorganism to produce disease following infection;
3 transmissibility and host spectrum, ability to be transmitted from a carrier or sick subject to a non-infected subject, presence of vectors, hygiene standards;
4 neutralization, availability of effective therapies or active or passive prophylactic measures to prevent disease, public health measures (water hygiene, tank, and vector control).

Risk Group 1. The risk group 1 (GR1) is for a low individual risk and a zero or low collective risk. It's for microorganisms that have little probability of causing disease in human subjects.

Risk Group 2. The Risk group 2 (GR2) includes moderate individual risk and low collective risk. GR2 pathogens can cause disease in humans and create a risk to workers. They have a low probability of spreading in the community. Effective prophylactic or therapeutic measures are usually available.

Risk Group 3. The risk group (GR3) foresees a high individual risk, but a low to moderate collective risk. These pathogens can cause serious disease in humans and create a serious risk to workers. There is a moderate probability of spreading in the community. Effective preventive or therapeutic measures are usually available for these pathogens as well. M. tuberculosis and MERS/SARS-CoV fall into this category.

Risk Group 4. In risk group 4 (GR4) both individual and collective risk are high. These pathogens can cause serious diseases in humans and a serious risk to operators. They also have a high risk of spreading to the community and effective preventative measures or treatments are usually not available. In this group there are Ebola and Lassa viruses.

According to WHO Laboratory biosafety manual (4th edition, 2020) [13] the laboratory standard is classified in biosafety levels (BSL) for exposure to pathogens, which generally correspond to the degree of risk of the pathogen.

Bio-safety level 1 (BSL1). Processing of material containing well-characterized infectious agents of minimal biological risk, not associated with disease in immunocompetent people. This level provides a basic level of containment with standard microbiological practices. Standard PPE (protective equipment) is required such as gown and gloves, eye protection in some cases. There are also non-specific facilities, such as controlled access, sinks for hand washing, hard-wearing floors and work surfaces that are impermeable and easy to clean and decontaminate, and adequate lighting.

Biosafety level 2 (BLS-2). Processing of material containing indigenous infectious agents of moderate biohazard present in the community, associated with human diseases of varying severity involves the processing of material containing.

In addition to the basic level specific practices are required: biohazard sign, restricted access to authorized worker, separate infectious waste disposal and an immunization program. Standard PPE: gown and gloves and for some procedures mask and goggles.

Biosafety Equipment: BSC-1/2 for procedures that may create aerosols/splashes.

Facility Requirements: Lockable doors, sink with hands-free operations, eyewash sink. Mechanical ventilation with air flow is recommended air to the inside without recirculation.

Biosafety level 3 (BLS-3). Processing of material containing GR3 infectious agents with possible airway transmission, associated with serious human diseases; processing of material with high concentrations of GR2 agents which can spread by aerosol.

This level requires a high level of containment and requires standard microbiological practices, specific practices whereby the laboratory supervisor controls access and handling of material under the fume cupboard as well as standard personal protective equipment such as a waterproof gown, hat, special footwear, shoe covers and respiratory PPE for some procedures. All PPE must be removed and decontaminated before leaving the laboratory.

Biosafety level 4 (BLS-4). Processing of material containing GR4 dangerous infectious agents with possible airborne transmission, associated with potentially lethal human diseases for which no vaccines or therapies are available. In Italy, only few centers have a BLS4 including INMI Spallanzani in Rome. In fact, the manipulation of the GR4 can be made under authorization from the Ministry of Health.

Sector table

The sector table must be equipped with aerosol containment systems, collection, and outflow of body fluids. It is easy to clean and made with waterproof surface and resistant to the chemicals used for sanitization.

Filtration is made with both specific activated carbon filters for Putrescine and Cadaverine and HEPA filters (with an efficiency of 99.997% on particles with a diameter of 0.3 micrometers with an autonomy of 8-14 months for activated carbon filters and 4-5 years for the HEPA ones).

Management of the autopsy sampling

Sampling is a fundamental moment of autopsy examination. In SARS-CoV-2 patients it must also be carried out keeping in mind biosafety and infection control [14].

If not performed during hospitalization, the collection of an upper respiratory tract (nasopharyngeal and oropharyngeal) swab is recommended. During autopsy, is also recommended the collection of a lower respiratory tract swab in tracheal tract. In fact, in a cohort of intubated COVID-19 patients, viral load was considerably greater in endotracheal than in nasal samples [15]. Swab must be stored specimens at 2-8°C for up to 72 hours after collection or at -70°C or below for a longer storage.

Lung sampling

There are no guidelines regarding the sampling of whole lungs from autopsy in the literature, but it is recommended a minimum of three section of lung parenchyma and one section of airway [14]. According to published data, in cases of suspected lung infection, lung tissue was recovered from autopsy between 1 and 16 days after the death of the patient. Lungs should be weighed, photographed, and a median of 19 lung tissue blocks, including subpleural and central areas, should be obtained [16].

The samples taken for histological examinations had to be immediately fixed with 10% formalin or glutaraldehyde for electron microscopy and, at the end of the autopsy or diagnostic finding, the sectional room should be thoroughly washed with sodium hypochlorite solution or phenol.

In absence of guidelines, at the University of Bologna we used the same protocol for explant lung evaluation, taking 3 samples per lobe and one at the hilum (17 samples) and all the lesions clearly visible or palpable during the examination. A similar protocol has been adopted by the Pathologists of the University of Padua [17].

For histological analysis, all tissue specimens were fixed in 10% buffered formalin, as well as 2.5% glutaraldehyde fixation for electron microscopy. Some centers have also suggested storing fresh tissue in RNA-later.

Hematoxylin and eosin staining is done on every block as the first examination, and further stains, including PAS, Gram, Warthin Starry, and Grocott staining, are done on demand to draw attention to microorganisms on selected blocks. Histochemical is also useful for the evaluation of DAD lesions, in particular PAS for the jaline membrane and Azan-Mallory trichrome for coagulopathy and fibrosis. Samples for electron microscopy were regarded as a secondary diagnostic test employing an electron transmission microscope [18].

The immunohistochemical evaluation included: a wide-spectrum cytokeratin (AE1/AE3), TTF-1, and p40 to highlight the lung parenchyma architecture and rule out malignancy; CD68, CD4/CD8 for lymphoid infiltrate and CD31 and ERG to highlight capillaries; it could also be useful to add antibodies against human cytomegalovirus (CMV), and Herpes Simplex Virus types 1 and 2 (HSV-1 and 2) to differentiate the lung infections.

Immunohistochemistry for novel antibodies, such as TMPRSS2, and ACE2, could be done in an attempt to identify distinct patterns of expression that could be connected to infection with SARS-CoV-2, some studies reported interesting results for TMPRSS2 and ACE2 (antibodies EPR3861 and EPR44352, respectively) [19], as well as microthrombi could be easily identify with CD61 (clone 2F2, Leica Biosystems, IL) [16].

Further, cut tissue slices for virus detection with real-time reverse transcription-PCR assays are used for the qualitative detection of SARS-CoV-2 nucleic acids in tissue sections cut at a 10-micron thickness; an endogenous internal control enables verification of the caliber of the sample material extracted. Additionally, a real-time PCR test might be used to quantify the presence of CMV, Epstein-Barr virus (EBV), and human herpesvirus 6 (HHV-6) in the specimens of human DNA (hDNA) to distinguish the cause of infection [19,20].

It is also important including among ancillary technique the detection of SARS-CoV-2 in tissue. In fact, this is possible using various methods, including PCR, ISH, IHC, and FISH. According to the literature, while RT-PCR achieves a sensitivity and specificity of 97% in FFPE tissue, ISH manages high levels of specificity (100%) with acceptable sensitivities (36-87%). Instead, the use of IHC achieves low levels of sensitivity (31-85.7%) and specificity (53.3-100%) [21]. These data are also in agreement with our experience, especially regarding the detention of low levels of viral loads.

Heart sampling

Cardiac involvement in patients with SARS-CoV-2 has been much debated at the clinical level and, marginally, at the autopsy level [22]. There are no criteria for heart sampling of SARS-CoV-2 infected patients. Generally, especially in centers without a cardio-pathology unit, autoptic hearts are sampled based on experience and habits.

At our center, hearts of SARS-CoV-2 infected patients, as in all autopsies, were sampled according to Society for Cardiovascular Pathology guidelines [23]. This extensive sampling makes it possible to evaluate all degrees of myocardial damage from these patients [24].

Sampling central nervous system

Several neurological symptoms have been described in SARS-CoV-2 infected patients, while the exact tissue damage mechanism is still under debate. To better examine morphological alterations it is suggested to sample a standard set of brain regions: the whole brain stem, basal ganglia, thalamus hippocampus, pre-rolandic and post-rolandic gyrus, frontal (parasaggital), temporal (T2) and occipital lobes (calcarine sulcus). In addition, the olfactory bulbs, and tracts up to the lateral olfactory stria [25,26].

Sampling other organs

In the literature the involvement of many other organs in SARS-CoV-2 patients is described, in particular liver [27-30], hematopoietic system and spleen [25,29,31], kid-

ney [27,29,32], adrenal gland [33,34] and even testis [35]. For these reasons we suggest sampling all organs, because even a small alteration can have its clinical significance in all diseases, but especially in an emerging pathology.

Conclusions

The SARS-CoV-19 pandemic caught us unprepared but had the ''merit" of exposing clinicians and pathologists to large amounts of cases of infectious lung injury, allowing us to expand our understanding of the pathogenesis and course of acute lung injury.
Moreover, the outbreak taught us a lot about the management of infectious diseases not only from a clinical point of view, but also in the management of infectious autopsies promoting the revision and improvement of the laws on this matter.

Conflicts of interest

The authors have no conflicts of interest to declare that are relevant to the content of this article.

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Authors' contributions

All authors critically revised the literature, discussed the data, wrote and critically reviewed and revised this paper.

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