Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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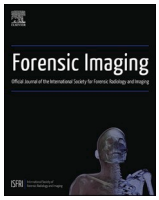

Virtual autopsy in SARS-CoV-2 breakthrough infection: a case report

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ABSTRACT

It is well documented that COVID-19 vaccines are effective tools for limiting the pandemic. Unfortunately, as is true for all vaccines, SARS-CoV-2 infection in vaccinated individuals is still possible.

We present an autopsy case of SARS-CoV-2 infection after vaccination (“breakthrough infection”) in an elderly man with several comorbidities where post-mortem CT scan was performed. The death was histologically attributed to cardio-respiratory arrest due to ischemic heart failure related to superinfected COVID-19 pneumonia and pre-existing comorbidities. For the first time in the literature, PMCT imaging related to a fatal, autopsy case of breakthrough SARS-CoV-2 infection is reported. PMCT of the lungs, in accordance with histopathological results, showed few signs of COVID-19 pneumonia, large area of consolidation in the right lower lobe, interpreted as bronco-pneumonic focus, and hypostasis.

These findings were well-correlated with the previously reported literature about both PMCT and clinical CT imaging of the lungs in non-vaccinated individuals with early COVID-19 pneumonia and about pulmonary clinical CT imaging in COVID-19 pneumonia in breakthrough SARS-COV-2 infections.

Further studies are needed to cover the whole spectrum of PMCT lung imaging in fatal breakthrough SARS-CoV-2 infection, however, this case represent a first step for exploring this difficult challenge during SARS-CoV-2 pandemic using virtual autopsy.

Introduction

A breakthrough SARS-CoV-2 infection is defined as the detection of severe acute respiratory SARS-CoV-2 ribonucleic acid (RNA) or antigen in a respiratory specimen collected from a person who is vaccinated with either a primary series or a primary series plus a booster dose [1]. Indeed, fully vaccinated individuals can still develop SARS-CoV-2 infection and symptomatic COVID-19 disease [2], especially elderly patients with comorbidities [3–5]. However, it has been demonstrated that the risk of infection is much lower among vaccinated individuals, and, in case of breakthrough infection, the vaccination reduces the disease severity [6–15].

From a forensic point of view, in those died with SARS-CoV-2 infection it is crucial to evaluate what was the cause of the death and, in particular, to assess the specific causal role played by the infection [16]. This inferential process is often complex and may require a multidisciplinary approach including radiological examination.

Computed tomography (CT) imaging findings in COVID-19 disease in pre-vaccination era, especially of the lungs, have been widely reported and discussed in the literature [17–24]. Conversely, imaging data

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of patients with breakthrough infections have been rarely reported [25].

Post-mortem CT (PMCT) has been proposed as a useful tool in SARS-CoV-2 pandemic, as a pre-autopsy screening tool for SARS-CoV-2 infection in cadavers, to increase the quantity of post-mortem data during pandemic peak with reduction of infection risk for operators [26–40], and an instrument for assessing the severity of COVID-19 pneumonia with good histopathological correlation [27].

In this case report, we present a forensic case of breakthrough SARS-CoV-2 infection, with special focus on PMCT imaging and on the correlation between autopsy results, histopathological analysis, and radiological data.

Case description

An 86-year-old male was transported to the Emergency Department of a hospital after a syncopal episode associated with abdominal pain and diarrhea.

The patient reportedly suffered from ischemic heart disease, severe type 2 diabetes, hypertension, and benign prostatic hypertrophy. Moreover, few years before he had a transient ischemic attack. He received two doses of BNT162b2 (Pfizer-BioNTech) mRNA vaccination (the last dose seven months before admission) and he was fully vaccinated because the third dose was still not available for the elderly at that time. Laboratory tests at admission showed modest increase in C reactive protein and creatinine. Ante-mortem CT examination documented two faint areas of ground glass opacity (GGO) in the left lower lobe and oropharyngeal swab tested positive for SARS-CoV-2 infection. Being affected by COVID-19, the patient was treated accordingly (i.e., with Clexane, Tazocin, Sodium Chloride, Pantorc, Lasix, Rocefin, Paracetamol, Novorapid).

Despite the appropriate treatment, the clinical condition of the patient did not improve, leading to his death about three weeks after the hospital admission.

A public prosecutor requested a forensic multidisciplinary team (two pathologists and a forensic radiologist) to investigate whether the infection was the cause of the death and if the hospital physicians could be considered liable for it. Both the PMCT and forensic autopsy were performed at the Section of Legal Medicine of Università Cattolica del Sacro Cuore (Rome, Italy).

PMCT imaging

A PMCT scan was performed before the autopsy [41] using a 16-slice scanner (Philips Medical Systems, Best, The Netherlands), with the following parameters: slice acquisition 1.25 mm, pitch 0.5, rotation time 0.5 s, tube voltage 120 kVp, tube current-time 400 mAs/rotation. No contrast medium was administered. Image reconstruction was obtained at a slice thickness of 1 mm (0.6 mm increment), with soft tissue and sharp bone kernel. PMCT of the lungs in this case showed scant non-dependent on gravity areas of GGO, with peripheral distribution in both upper lobes, multiple areas of consolidations, the largest with scant air bronchogram in the right lower lobe, and dependent on gravity densities (Fig. 1). No other relevant alterations were documented on PMCT.

Forensic autopsy and histopathological examination

Post-mortem swabs of the rhino-pharyngeal/tracheal tract and both lungs were performed and tested positive for SARS-CoV-2.

At the autopsy, all organs appeared swollen. In particular, the lungs (right: 650 g, left: 400 g) appeared emphysematous at their apexes and congested at their bases.

Biopsies were performed on the whole lung parenchyma, and targeted biopsies were performed on areas highlighted by PMCT as of pathological significance (both upper lobes, right lower lobe). At the histopathological analysis, lungs showed congestion and edema, emphysema, multiple foci of polymorphonuclear cells, signs of intravascular coagulation and multinucleated giant cell with viral inclusions, findings attributed to broncho-pneumonic and COVID-19 pneumonia foci (Fig. 2). Moreover, signs of diabetic nephropathy and of ischemic heart disease, represented by small vessel amyloidosis (confirmed with Congo red staining and the apple-green birefringence at polarized light) and subendocardial myocytolysis (Fig. 3) were reported.

Hence, according to the pathologists report, death was caused by an ischemic heart failure due to superinfected COVID-19 pneumonia and patient comorbidities. Being the association of COVID-19/superinfection/comorbidities the main cause of the death and since it had been adequately treated, the hospital physicians were not considered liable for the patient death.

Discussion

In this paper, we report the autopsy case of an elderly man with severe comorbidities infected by COVID-19 who died seven months after having received the second dose of mRNA vaccination.

In this case, PMCT of the lungs showed scant non-dependent on gravity areas of GGO, with peripheral distribution in both upper lobes, multiple areas of consolidation, the largest with scant air bronchogram in the right lower lobe, and dependent on gravity densities.

The few non-dependent on gravity areas of GGO were interpreted as the expression of scant signs of COVID-19-related interstitial pneumonia.

According with the previous PMCT studies of Filograna et al. [27,35] in non-vaccinated individuals, these pulmonary alterations can be attributed to scant involvement of the lungs by SARS-COV-2 infection. In the two individuals reported by Filograna et al. [27] with this imaging pattern the histopathological results confirmed the imaging suspect of early infection and histologically the cause of death was attributed to a

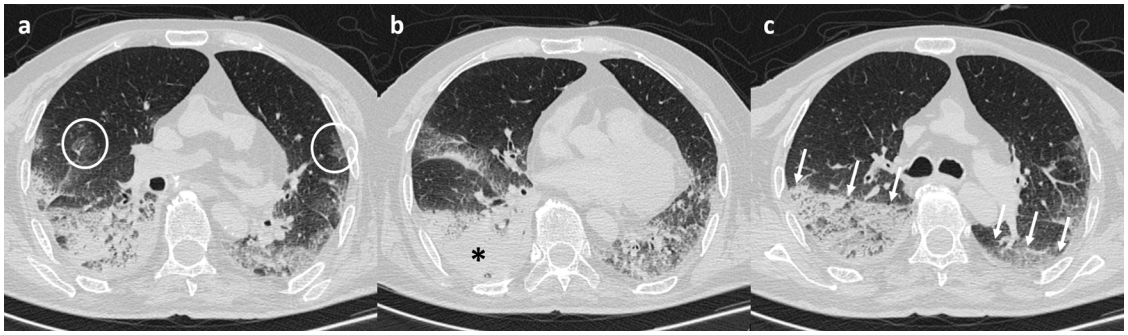

Fig. 1. Axial PMCT images at the level of the thorax, lung window. Scant non-dependent on gravity areas of GGO, with peripheral distribution in both upper lobes are better visible in (a) (circled), multiple areas of consolidations, the largest in the right lower lobe is showed in (b) (asterisk), and dependent on gravity densities are better appreciable in (c) (arrows).

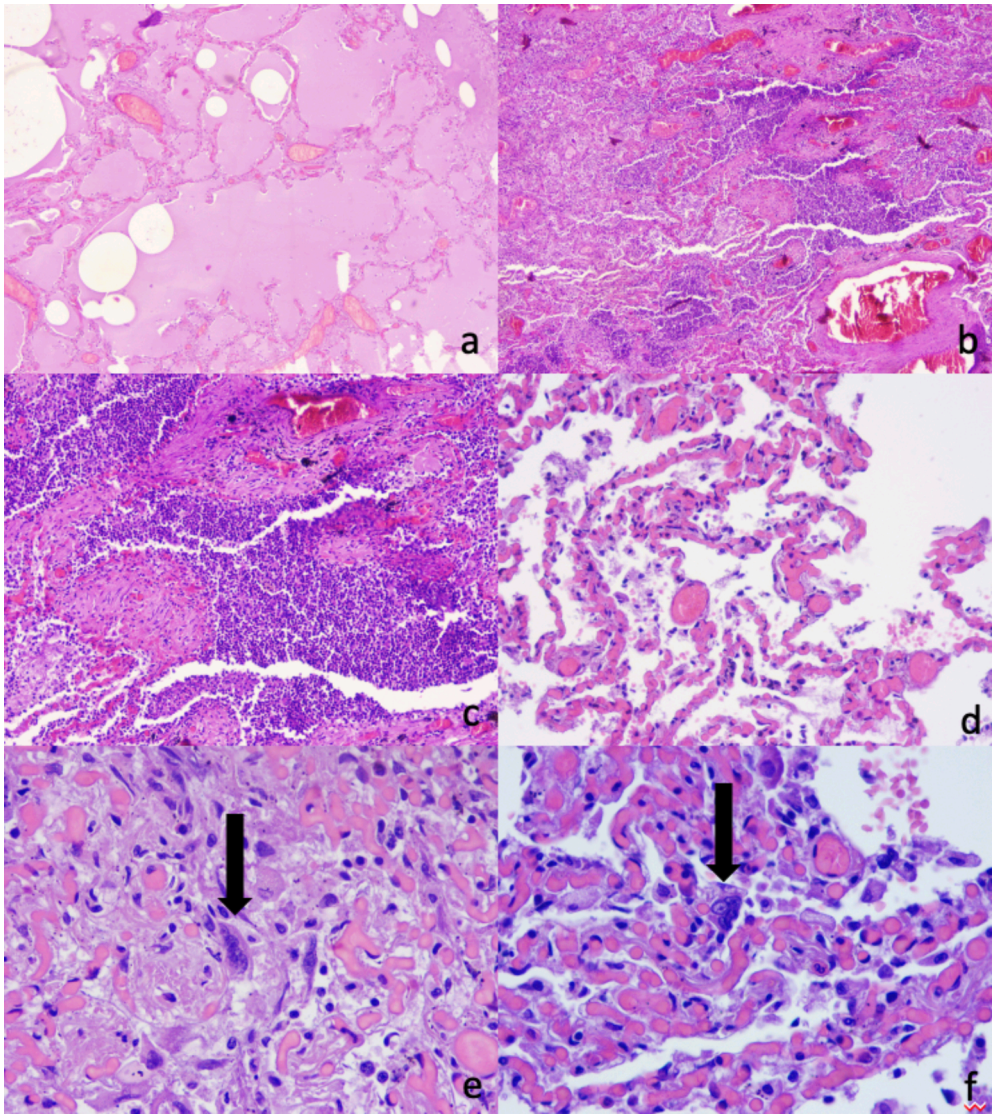

Fig. 2. Histological findings: (a) congestion, oedema and emphysema (hematoxylin and eosin staining, 4 × magnification); (b and c) multiple broncho-pneumonic foci of polymorphonuclear cells (hematoxylin and eosin staining, (b) 4× magnification, (c) 10x magnification); (d) intravascular coagulation (hematoxylin and eosin staining, 20× magnification); (e and f) multinucleated giant cell with viral inclusions (hematoxylin and eosin staining, 40× magnification).

cause different by COVID-19 disease.

This interpretation is in line with clinical literature about CT appearances of COVID-19 pneumonia at early stages or in scant lung involvement by COVID-19 [42].

Moreover, accordingly, some recent studies [25,43], who studied imaging features of COVID-19 breakthrough infections, demonstrated that CT findings in such populations are commonly mild.

The dependent on gravity densities found in this case, according to previously reported evidence [26,44], can be interpreted as the imaging expression of parenchymal hypostasis. Furthermore, according to previous studies about PMCT in COVID-19 pneumonia, we retain that these pulmonary post-mortem alterations might have masked some other areas of GGO related to lung SARS-CoV-2 infection, as they were described in the CT performed 20 days before death.

Regarding the large area of consolidation with scant air bronchogram in the right lower lobe, among the smaller, we retain that it might be interpreted as the result of a bronchopneumonia at the same level, in accordance with histopathological analysis results. In fact, histologically this diagnosis was reached because the intra-alveolar and peribronchial neutrophilic multifocal infiltrates characteristic of bacterial broncho-pneumonia were found, as typically occurs, more extensive than observed during acute diffuse alveolar damage, eventually related to COVID-19 pneumonia, which usually exhibits diffuse but less intense interstitial and mild intra-alveolar neutrophil accumulations [45,46].

It is well known that bacterial superinfections, in particular pneumonias or broncho-pneumonias, can complicate COVID-19 [47–49]. Particularly, bacterial superinfections were reported in –8% and –16% of hospitalized and critically ill patients affected by COVID-19, respectively [49]. In the review paper of 2021 on fatal cases of COVID-19 disease, Clancy et al. [47] it was concluded that bacterial superinfections in the lungs were evident at postmortem examination in 32% of persons who died with COVID-19, but they were uncommonly the cause of death (16% of patients with potential bacterial infections for whom a cause of death was assigned in the studies examined in the review).

In this case reporting of the 86-year-old male affected by breakthrough SARS-COV-2 infection, death was histologically attributed to cardio-respiratory arrest due to ischemic heart failure in a patient with COVID-19 pneumonia with lung bacterial superinfection and pre-existing comorbidities like hypertension and type 2 diabetes. Hence, COVID-19 pneumonia can be considered to have been the main factor leading to the death of the subject.

The most common cause of death in fatal COVID-19 infection in the

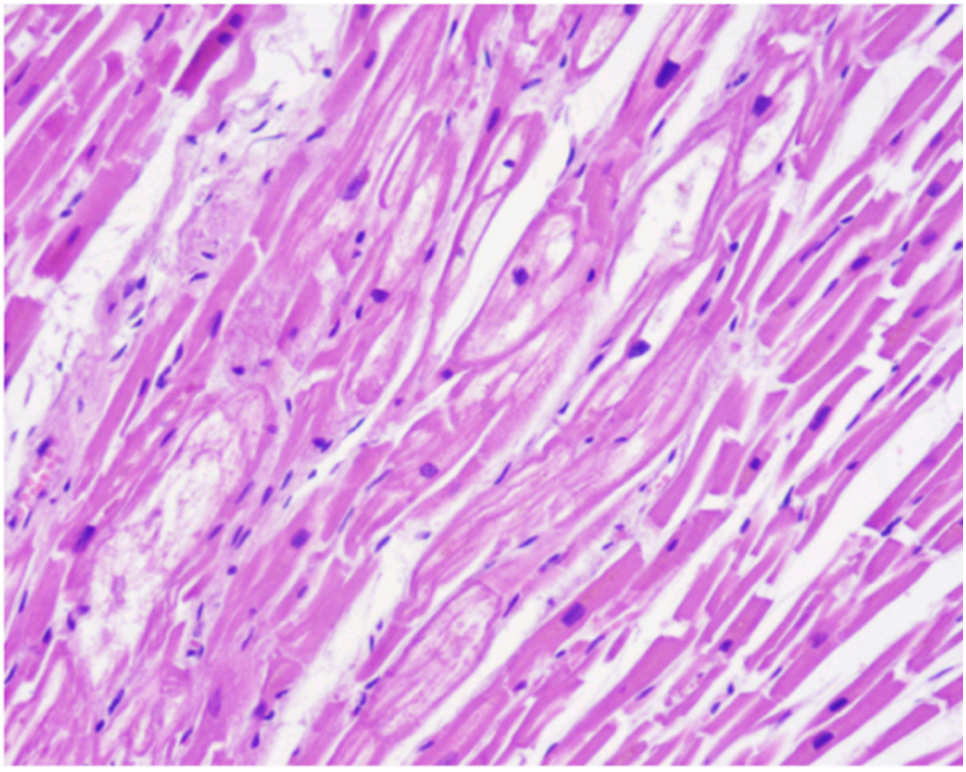

Fig. 3. Histological findings: subendocardial myocytolysis (hematoxylin and eosin staining, 20 × magnification).

pre-vaccination era was acute respiratory distress syndrome (ARDS) caused by diffuse alveolar damage, often complicated by cardiopulmonary and other organ failure [50–52].

Some studies have published data about the cause of death in fatal cases of breakthrough SARS-CoV-2 infection [2,3,15]. A study from 2021 included patients fully vaccinated with Pfizer/BioNTech and the mortality rate was 22%, death occurring in individuals with a high rate of co-morbidities predisposing to severe COVID-19 disease, including hypertension (71%), diabetes (48%), congestive heart failure (27%), chronic kidney and lung diseases (24% each) [15]. The cause of death was not specified in this paper.

Furthermore, diabetes was the most common comorbidity found in 17.1% of the deaths, followed by hypertension in the study of Verma et al. [3] assessing comorbidities and vaccination status of COVID-19-related deaths at a Tertiary Care Center of Western India.

A study about COVID-19 cases where fully vaccinated persons with an outcome of death were characterized [2] demonstrated that only 3% of this study population died. Moreover, in accordance with the case reported, those who died were older (median age 82 years), more commonly male (51%), more likely to have at least one underlying health condition associated with risk for severe disease (64%). The most common underlying pathology among patients who died were diabetes (44%), and chronic renal disease (37%). Regarding the cause of death, among the deaths, 78% were classified as COVID-19-related in this study [2]. Moreover, of the death certificates available for review in this study [2], a total of 76% cases listed COVID-19 in the chain of events leading to the immediate cause of death (68%), or listed it as a contributing condition (8%). Thus, the ascertained cause of death of the case here presented is in accordance with these evidences, although it is difficult to attribute an exact weight to breakthrough SARS-CoV-2 infection, due to the evidence of bacterial superinfection, and many comorbidities.

A limitation of the study is that neither the viral linage was isolated, nor the viral load was measured, because not part of the routine forensic procedures.

Nevertheless, a recent study [2] revealed that there were no differences in outcomes in patient subgroups with different viral lineage.

Conclusions

This is the first case reported in the literature where PMCT findings aid the diagnosis of a fatal case of SARS-CoV-2 breakthrough infection whose death was histologically attributed to cardio-respiratory arrest due to ischemic heart failure in a patient with COVID-19 pneumonia with lung bacterial superinfection and pre-existing comorbidities.

In this case, targeted biopsies and histological analysis with topographical accuracy were performed and a good correlation between radiological and histopathological results was found. Moreover, the reported PMCT findings resemble those of non-vaccinated cadavers where COVID-19 was not histologically ascertained as the main cause of death, and of patients with COVID-19 pneumonia of early stages or with COVID-19 pneumonia in breakthrough SARS-COV-2 infections.

Further studies are needed to cover the whole spectrum of PMCT lung imaging in fatal breakthrough SARS-CoV-2 infection, however, this case represent a first step for exploring this new and difficult challenge for post-mortem investigations with virtual autopsy during SARS-CoV-2 pandemic.

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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