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Pandemics and pathology: a reflection on influenza, HIV/AIDS and SARS (COVID-19) pandemic infections

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Abstract

The COVID-19 pandemic has reminded pathologists of our significant roles in the management and understanding of rapidly spreading and dangerous pathogens, from identifying the agent to characterizing the clinical pathology to managing the dead. Cellular pathology – through autopsy – has depicted the main features: viral pneumonitis, acute lung injury, organising pneumonia, secondary bacterial pneumonia, thrombophilia and infarction, and systemic inflammatory response syndrome with multi-organ failure. These are similar to another viral pandemic of the 20th century, H1N1 influenza; but contrast with the second major more complicated pandemic, that of HIV/AIDS. The outcomes of these infections are compared, along with seasonal influenza and SARS-1-CoV disease. Work to be done on COVID-19 includes characterisation of the emerging 'long COVID' syndrome, and monitoring the complications of therapies and vaccination programs.

Keywords autopsy; coronavirus; COVID-19; HIV; influenza; long covid; pandemic; pathology

Introduction

In 2020, the world has experienced a pandemic infection caused by a new virus, a SARS coronavirus. It has caused massive economic damage, occupied medical facilities in many countries to the exclusion of 'normal' or 'usual' diseases, significantly increased population mortality, and changed normal socio-cultural behaviours in a manner unprecedented in living memory. In this edition of *Diagnostic Histopathology* the clinical pathology of SARS-2 coronavirus (COVID-19) and its impact on diagnostic cellular pathology is depicted in four other articles. This paper places the SARS-2 disease in the context of other pandemic infections over the last century, and discusses some of the roles and responses of pathology in their management.

The WHO defines a pandemic simply as "the worldwide spread of a new disease". This does not exclude non-infectious diseases, though all current attention is on infections; and it has to be "new". Thus tuberculosis, which remains endemic and impossible to eradicate in all parts of the world, is not a pandemic; syphilis in the 16th century became pandemic, but is

also not new and is notably less virulent than when it first became prevalent.

One of the most obvious consequences of the COVID-19 pandemic, and its domination of the public domain, is the spotlight it has shown on many hitherto occult aspects of medicine. We are all 'experts' now: on epidemiology, vaccines, testing strategies, therapies, and on the subtle distinctions of dying *with* versus *of* COVID-19. Extraordinary has been the speed at which the scientific endeavours (including pathological identification and genetic sequencing of the virus) mushroomed. This was quicker than with SARS-1 coronavirus infection (about 4 months from first clinical recognition in 2002 to virus identification¹), and vastly faster than with HIV – that took 2 years from first recognition of a problem (1981) to virus identification, and a further 13 years (to 1996) until effective therapy was developed. For influenza, it was not until the early 1930s – more than a decade after the 1918-19 pandemic of H1N1 – that the virus was first identified in pigs and humans.

This speed of the science in 2020 has set a benchmark, against which all future pandemics will be measured.

The roles of pathology in pandemic infections

The roles of multi-disciplinary pathology in pandemic infectious diseases are many. They are grouped into three chronological phases, indicated in [Table 1](#). Of course, with the earlier 20th century influenzas and HIV/AIDS, this sequence was not followed since medical diagnostic technology, particularly for identifying virus infections, had not evolved to its current state with reliance upon molecular diagnostics. So with HIV/AIDS, the Middle Phase activities were in part accomplished before the agent was definitively identified in 1982. But from now on, with existing (and ever-improving) global infectious disease monitoring facilities, new pandemics should follow the phases.

The following pandemic infections are addressed: the influenzas, HIV/AIDS, and SARS-2 coronavirus (COVID-19) – including mention of H5N1 influenza, SARS-1 and MERS² coronavirus infections, which fortunately did not become pandemic. The focus is on some of the processes in [Table 1](#) as they apply to human *cellular pathology* practice. In particular: 1) a comparative overview of their clinical pathologies; 2) how autopsy pathology practice has managed and its codes of practice; and 3) what can cellular pathology will contribute, beyond what is already evident, to our knowledge of COVID-19 clinical pathology and public health.

COVID-19 infection and comparative pathology

For information on the tissue pathology and pathogenesis of the influenza and coronavirus infections, it is important to recognize the limitations of the material available to study. Mainly it is *autopsy* samples from people who have *died* of *severe* infection, and therefore represents the end of a spectrum of possible pathological abnormalities *plus* opportunistic infections in those who do not die rapidly *plus* the effects of therapy. That said, the earliest histological description of COVID-19 lung disease came opportunistically from study of lung removed electively for cancer.³ Many people during the 1918-19 H1N1 pandemic were autopsied,⁴ with histology still reviewable, as they were during the H1N1 pandemic in 2009-10,⁵ and seasonal influenza fatalities

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The roles of pathology (all disciplines) in a pandemic severe infection

Early phase	<p>Identification and characterisation of the infectious agent</p> <p>Generation and evaluation of diagnostic tests for the infection</p> <p>Drafting simple clinico-pathological case definitions or indicators of the new infectious disease</p> <p>Advising on health & safety issues around the treatment of patients with the disease</p>
Middle phase	<p>Roll-out and performance of diagnostic tests</p> <p>Detailed description of the clinical pathology, ie what the infection does to tissues, organ and how it results in disease and mortality</p> <p>Research into the pathogenesis of the disease</p> <p>Advising on health & safety issues around the post-mortem examination of patients who die with the disease</p> <p>Providing guidelines on how to perform autopsy examinations on those who die of and with the infection, recommending what diagnostic samples to take</p> <p>Advising on safe practices for those who remove and dispose of cadavers that contain the infection^a</p> <p>Diagnosing through autopsy who has died because of the infection versus with the infection; evaluating the impact of co-morbidities on the outcome of infection</p> <p>Contributing to vaccine development, including safety studies in animals and humans</p>
Late phase	<p>Monitoring, through autopsy, adverse effects of treatments and vaccines against the infection</p> <p>Monitoring through the autopsy the potential excess deaths from other causes as the pandemic impacts on normal diagnostic and life-saving therapeutic procedures</p> <p>Veterinary pathology study of possible sources of the infection in the wild and how they transmitted to humans</p> <p>Eternal population surveillance for the infection, in the living and the dead</p>

^a In 2007, the author attended a meeting of doctors, coroners, nurses, undertakers, religious leaders, and Home Office and public health officials to discuss what might happen if H5N1 influenza virus was introduced into the UK and became epidemic. The most memorable talking point was how to dispose of large numbers of bodies, of those dying with H5N1. A historian described how in both World Wars, mass graves were used to bury the dead, without apparent controversy, and queried whether this would be acceptable in the 21st century? Most participants at the meeting, particularly the religious leaders, were adamantly opposed to the idea

Table 1

are perennially autopsied. For SARS-1, the number of cases studied is less (fewer than 100 autopsies⁶), and for H5N1 there are <15 autopsy cases published.⁷ Tissue biopsies in life in COVID-19-related disease are uncommon outside renal biopsy. For HIV disease, in comparison, there is an ongoing mass of clinicopathological data derived from biopsies, fine needle cytology, and autopsy cases going back nearly forty years.

The main direct clinical and pathological features of COVID-19 infection are well known, and can be summarized⁸:

1. pneumonitis with acute lung injury, organising pneumonia, and lung fibrosis;
2. secondary bacterial pneumonia in some
3. systemic inflammatory response syndrome (SIRS) with haemophagocytosis (by marrow and splenic macrophages and liver Kupffer cells) and splenic white pulp atrophy – reflecting a cytokine storm.⁹
4. thrombophilia and tissue infarction, particularly affecting small vessels in the lungs and brain

In all these respects, COVID-19 resembles the influenzas (seasonal, pandemic and H5N1), SARS-1 and MERS infections.³⁸ There is much investigation into endothelial injury and pro-coagulant changes in the clotting cascades associated with COVID-19, but this thrombophilia is not a new feature, being noted in the earlier infections.

Much speculation around COVID-19 has gone into whether there are direct cardiac (myocarditic) and encephalitic syndromes. Encephalitis appears, uncommonly, as a clinical entity and there are very few convincing autopsy histological cases, in contrast to the thrombo-vasculopathy brain syndromes. The few examples of ‘myocarditis’ in the literature do not satisfy the stringent Dallas criteria for myocarditis, ie they seem to be a non-specific feature of SIRS, with interstitial inflammation only. The same comments apply to the influenzas, SARS-1 and H5N1 morbid anatomy studies. Coronary atherosclerosis, being a chronic process, is not affected by corona- or influenza viruses, and examples of plaque rupture seem to be coincidental rather than due directly to virus infection. Similarly there are no evident nephritis or hepatitis syndromes attributable to influenza and coronavirus direct infections.¹⁰

HIV is different, by way of its more complex and long term pathogenetic processes. The relatively limited range of clinicopathological consequences from the influenzas and coronavirus infections contrasts with the vast range encompassed within HIV disease. A list published in 2015 found >100 distinct entities caused by HIV-1 infection.¹¹ They range from acute infections associated with severely compromised cell mediated immunity, through malignant tumours associated with viruses such as EBV and HPV, direct inflammatory and cytotoxic effects of HIV on tissues, enhanced drug-related toxicity, immunopathological consequences of changing virus-host immunity balance through anti-retroviral therapy (ART), systemic inflammation (SIRS and multiorgan failure directly due to the virus), and unanticipated new syndromes of organ damage such as CD8 encephalitis.¹²

Of course, it is possible that COVID-19 infection is throwing up chronic clinicopathological complications of which we are not yet aware (see below). But these are unlikely to be the consequence of persistent viral infection; whereas in HIV, everyone who is infected is always infected as the virus is intractably latent

even when suppressed by antiretroviral therapy, and the infection always rebounds if therapy is stopped.

A final important point of comparison with influenza and coronavirus infections concerns perinatal transmission of HIV. Paediatric HIV disease differs from that in adults especially in central nervous system disease: the brain is growing whilst infected, and so there are complex neurodevelopmental pathologies to consider. Fetal corona- and influenza virus syndromes are yet to be described.

Table 2 highlights the impacts of co-morbidities and other standard risk factors on the outcomes of these pandemic infections. The higher risk for death from COVID-19 among non-white ethnic populations is of intense interest.¹³ There are two distinct issues: 1) is the higher mortality related to co-morbidities associated with different ethnic groups, their healthcare inequalities, and to differential opportunities for infection because of housing, transport and employment? 2) are there genetic or other biological factors that may predispose individuals to more severe disease and higher mortality related to COVID-19¹⁴? Research is ongoing, but the current opinion is that the first issue is the more important; autopsy pathology has an important descriptive role here (see below).

Post-mortem examinations in times of pandemic infection

Seasonal influenzas do not, and the 2009-10 H1N1 influenza pandemic did not, generate significant disinclination to performing autopsies; SARS-1 and H5N1 infections presented no deaths in the UK, and there was only one imported MERS fatality (who was not autopsied). However, HIV and COVID-19 deaths are both numerous and continue to present problems for mortuaries and post-mortem examinations. Despite an apparently uniform death-investigation service across England & Wales and theoretically uniform training of pathologists and anatomic pathology technologists (APTs), there is a range of attitudes to accepting HIV and COVID-19 cases for autopsy: from routine acceptance to blanket refusal to undertake such work. Curiously, some mortuaries are happy to do HIV work, but not COVID-19, and others take the opposite approach. For both infections, formal guidelines on safe working practices emerged rapidly.²⁰ But health risks are the quoted reason for refusal to do autopsies. Some COVID-19 guidelines on managing cadavers are extremely risk-averse,²¹ whilst a comprehensive review of global published guidelines wryly notes how they “vary greatly”.²²

To complicate matters with respect of COVID-19, the chief coroner (whose coroner colleagues commission the vast proportion of all autopsy work in England & Wales) rushed through guidance on post-mortem death certification and cadaveric examinations that made certification less stringent than before, and effectively reduced the number of all deaths, not just suspected or known COVID-19 infected, that came to autopsy. That imbalance has now mostly reversed, but there is still controversy over ascribing deaths to COVID-19 or with COVID-19 infection. Anecdotally, we now seem to be examining more COVID+ve cadavers where the relatives/doctors/coroners are particularly concerned over this distinction – and of course it is only with full autopsy (post-mortem CT scanning will not help) that it can be determined.

With 9 months of COVID-19 experience, we are now in the position to state that the risk of acquiring COVID-19 infection from an autopsy, when simple personal protective equipment (PPE) precautions such as FFP3 face masks are applied, is exiguous, despite autopsies being listed as ‘aerosol generating procedures’. Pathologists and APTs with COVID-19 are far more likely to have acquired it from social contacts away from the mortuary table – as always was the case with HIV infection, where only one pathologist is known to have become infected from an autopsy examination.²³ Cut-resistant gloves are the major PPE needed for HIV autopsies when the body has a significant viral load; in patients who were well-controlled on ART, there is essentially zero risk of being infected.

In terms of complexity of case analysis, COVID-19 and the influenzas are relatively simple compared with HIV deaths: the pathology is generally that of the aged, plus direct effects of COVID-19 on a limited number of organs, principally the lung plus the systemic effects of SIRS. HIV presents a vastly greater range of possible clinical pathologies. Because of the limited experience of the disease among pathologists, it is recommended that HIV autopsies be performed only by those who know about HIV (forensic scenarios, of course, excepted); such a stricture does not apply to influenza and coronavirus deaths.

Looking to the future and the likely emergence of new pandemic infections, it will be important for pathology to rapidly grasp the health and safety aspects of working with patients still alive and those who have died. This happened quickly after COVID-19 arrived with a triage approach,²⁰ and an appreciation that all cadavers might have the infection. In the long term, the impact of a pandemic infection depends on how long it lasts in the community: pandemic influenzas stopped in due course within a year or less (and SARS-1 rapidly stopped and never became pandemic), but HIV will continue for ever. And at the moment, we must assume that COVID-19 may be with us, as infectious as at the start, for ever. Whether vaccines will alter that remains to be seen; a vaccine against HIV seems unlikely, but there is optimism that COVID-19 vaccines might end this particular pandemic. Nonetheless, COVID-19 has changed how all autopsies are undertaken for at least the medium term, with enhanced levels of PPE overall.

Emerging co-epidemics and novel COVID-19 clinical pathologies

There is a significant role for morbid anatomy over the next years or decades of COVID-19 infection, and it concerns the documentation of the effects of therapies, interactions with other diseases, possible long term direct consequences of the virus, and possible lethal complications of the vaccines about to be rolled out (Table 1).

It is already evident from routine autopsy work in UK that COVID-19 prevents other diseases from being managed properly, ie death prevented, such as diabetic ketoacidosis and acute myocardial infarction.²⁴ Obviously the death toll from the COVID-19 pandemic is greater than just the numbers cited daily of those who died with recent infection, and autopsy pathology shed lights on this otherwise silent co-epidemic. Autopsy data are not, unfortunately, routinely fed into healthcare audits and

The impact of certain risk factors and co-morbidities on the outcome of the infections

Significant risk factors and co-morbidities	Seasonal influenza	Pandemic influenza (H1N1)	SARS-2 COVID-19	HIV
Age ¹⁵	Increased mortality >65 yrs; increased hospital admissions in young children (<2yrs)	Increased mortality in young adults (20–40 yrs)	Increased mortality with age; infants and children hardly affected	Without treatment, all age mortality universal; faster in infants
Sex	No difference	No difference	Male mortality higher	Female mortality higher
Ethnicity including BAME (Black, Asian, minority ethnic) ^{13,14,16}	Lower mortality among USA black and Hispanic patients	No differences in mortality rates	Mortality increased in black and asian patients, but causation uncertain	Only: HIVAN and CD8E, restricted to African ethnicity
Obesity	Increased mortality	Increased mortality	Increased mortality	No impact
Diabetes	Increased mortality	Increased mortality	Increased mortality	No impact
Pregnancy ^{17,18}	Some increase in maternal mortality	3rd trimester & peri-partum maternal mortality markedly increased	Not at higher risk of severe disease ^a	Increased maternal mortality due to untreated HIV/AIDS
Effects on fetus ¹⁸	Fetus rarely infected to cause organ damage	Fetal impact through maternal disease	None yet described	25% rate of mother-to-child transmission if mother not on anti-retroviral therapy
Learning difficulties ⁵	No data	Mortality increased	Anecdotal indication of increased mortality	No data
Genetic susceptibility ^{15,19}	Increased risk of hospital admission with certain transmembrane polymorphisms	No data	Under investigation	Well-defined subgroups with cell receptors resistant to infection; HIVAN

HIVAN, HIV-associated nephropathy; CD8E, CD8 + T-cell encephalitis.

^a However, review highlighted confusion and delays around managing peripartum women with respiratory distress with known or possible COVID-19.¹⁹

Table 2

outcome analyses, but accuracy in the evaluation of dying of versus with COVID-19 is an essential dataset for estimating excess mortality associated with this (and any future) pandemic.²⁵ Similarly, it is important for pathologists to consider the ethnicity of patients they examine, for the epidemiological reasons given above. That said, this is not straightforward as there are complications and inconsistencies in ascribing race or ethnicity to the deceased,²⁶ as a result of which many pathologists simply omit this feature in their external descriptions.

Diabetes

COVID-19 has a significant and complex relationship with diabetes, both types 1 & 2. From the outset of the pandemic, having type 2 diabetes was seen to incur a higher mortality compared with age, ethnicity and BMI-matched patients without diabetes. The mechanisms are still being investigated, and similar outcomes are known in other coronavirus and influenza infections.

Then there are the indirect effects of COVID-19. Known diabetics on therapy found it difficult to maintain their usual controlling medications because of COVID-related restrictions. And new patients found it difficult to engage with medical services, some dying of hyperglycaemic ketoacidosis before they could be diagnosed with diabetes (²⁷ and personal observations from autopsy cases).

Lastly there appears to be a precipitation of type 1 diabetes and/or a worsening of known type 2 diabetes directly due to COVID virus infection; this emerges from diabetologists who have noted in 2020 a marked increase in severe diabetes presentations with no other evident explanation. This is probably not due to infection of pancreatic beta cells by COVID-19²⁸ but the scenario is under investigation.

Other diseases

Research into the negative impact of COVID-19 on the survival of patients undergoing cancer treatments²⁹ and surgical treatments, both elective and emergency,³⁰ highlights the heightened complication rates and mortalities, compared with patients not so infected. A treatment complication noted in many publications has been internal haemorrhage, associated with the thromboprophylaxis regimes used to counter the thrombophilia. These are areas where pathologists become involved in retrospective audit analyses, and we need to examine and investigate such patients with more than average care.

Regarding HIV and COVID-19 co-infection, there seems to be little impact on the effectiveness of routine ART care, and the only autopsy report, in a patient recently HIV-diagnosed, found the expected COVID-19 lung pathology from which he died.³¹

Long COVID syndrome

Some patients do not recover well from COVID-19 and experience chronic symptoms of fatigue, breathlessness, muscle weakness, joint pains, mental confusion, and other problems affecting all the major organs.^{32,33} What is going on in this 'long COVID' syndrome is unclear pathogenetically, but it bears some similarities to other post-viral syndromes,³⁴ and to the experiences of patients diagnosed with chronic fatigue syndrome/myalgic encephalitis (CFS/ME). In the latter, there is little if any anatomical pathological abnormality to see, rare exceptions being some neuropathological case reports,^{35,36} and the current

focus is on nervous system abnormalities and immune dysregulation. Conversely, all patients with long COVID will have had definite pathological lesions during the acute phase of COVID-19 infection, but not a documented encephalitis. Viral RNA is absent from cerebrospinal fluid, but antibodies are sometimes found.³⁷ However there have to date been no reported tissue pathology examinations in long COVID patients that would help clarify the underlying processes.

If this new syndrome is going to become as numerically important as many believe,³² pathology has an obligation to collect and collate tissue histology data, as it arrives from in-life organ biopsies and from the inevitable autopsy procedures that will happen in the future. In turn, this could also throw some light on CFS/ME. There have been calls to establish organ tissue banks for CFS/ME,³⁵ and consideration could be given to doing the same for opportunistically available tissues from patients with long COVID.

Summary and conclusions

The basic clinical pathology of COVID-19 infection has been described, but there is important work in anatomical pathology to be done on the emerging long COVID syndrome, the effects of therapies on COVID disease, interactions with non-infectious chronic diseases, and monitoring any complications of vaccination programs. This infection has many similarities to pandemic influenza, but differs from the more complicated clinical pathology of HIV/AIDS. The COVID-19 pandemic has highlighted the contribution that autopsy pathology still makes in modern medicine. ◆

Practice points

- Performing autopsies on COVID-19 patients is a safe and useful procedure.
- Care must be taken to distinguish the direct effects of COVID-19 from co-morbidities and their relative contributions to a death.
- Opportunities to examine tissue pathology in patients suffering from the long COVID syndrome should be taken, to help understand this emerging problem.

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