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CHEST RADIOLOGY

Severe acute respiratory syndrome (SARS), Middle East respiratory syndrome (MERS), influenza, and COVID-19, beyond the lungs: a review article

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Abstract

Background In the past 20 years four major viral infectious diseases outbreaks caused hundreds of thousands of deaths worldwide: SARS, Influenza H1N1, MERS, and COVID-19. They all present clinically initially as upper and lower respiratory tract infections and may progress to multi-organ failure.

Methods This study was a systematic review of literature conducted in September 2020 to study extra-pulmonary complications of SARS, FLU, MERS, and current COVID-19. We carried out a systematic search using the keywords in online databases of PubMed, EMBASE, and Google Scholar until June 2020.

Objective This article aims to review the most common extra-pulmonary manifestations of SARS, Influenza, MERS, and COVID-19.

Discussion Several studies have reported extra-pulmonary conditions in patients diagnosed with SARS, Influenza, MERS, and COVID-19, either by direct viral injury or from the systemic response to the initial infection.

Conclusion SARS, Influenza, MERS, and COVID-19 have all been associated with dysfunction of kidneys, endocrine system, neuromuscular symptoms, perinatal complications, and myocardial injury**.** Progression from pulmonary disease to a systemic condition has a poor outcome and can result in multi-organ failure.

Keywords COVID-19 · SARS · MERS · FLU · Extra-pulmonary · Complications · Pneumonia

Introduction

Recently severe acute viral infections have caused significant death toll globally through four major pandemics in the past 20 years. The severe acute respiratory syndrome (SARS) first appeared in 2002 and caused 774 deaths worldwide. In 2009 a new H1N1 influenza A virus caused another pandemic, affecting 60.8 million people and causing 12,469 deaths only in the USA. In 2012, a new coronavirus (MERS-CoV) was recognized to cause the Middle East respiratory syndrome (MERS) that presented with more than 30% mortality (858 reported deaths) and spread to 27 countries. In December 2019, a new coronavirus (SARS-CoV-2) surged in China, causing the current COVID-19 pandemic. The high viral infectivity caused the disease to spread throughout the world rapidly. More than 7.76 million cases in more than 188 countries, resulting in more than 429,000 deaths, have been reported to the present day. This article aims to review extra-pulmonary complications associated with these four viral outbreaks. Although the recent H1N1 pandemic was associated with only one type of influenza virus, the annual seasonal infectious epidemics make this a viral infection that is worth studying in a more comprehensive way.

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Methods

This study was a review of literature conveyed in August 2020. The authors studied the extra-pulmonary complications of SARS, FLU, MERS, and current COVID-19.

By systematic search of keywords in online databases of PubMed, EMBASE, and Google Scholar two independent researchers retrieved the most relevant peer-reviewed papers by titles and abstracts published in English until August 2020. The papers of non-human studies, suspicious of duplicated results, and papers with unavailable full texts excluded from our study. Finally, two independent researchers evaluated the quality of selected articles and the bias risk. In either case of discrepancy, a third independent researcher resolved the differences in viewpoints.

Extra-pulmonary complications

Renal abnormalities

MERS and SARS have been associated with acute kidney injury (AKI), possibly caused by virus tropism for the kidneys and secondary damage due to systemic inflammation and hypotension. In a retrospective study of 536 patients with a diagnosis of SARS, 6.7% presented with acute renal failure, of which eventually 91.7% died [1]. In another retrospective study with 30 patients diagnosed with MERS, eight (26.7%) patients developed AKI, and 15 (50%) showed proteinuria [2]. According to this study, older patients had higher incidence of AKI.

Direct involvement of kidneys by influenza viruses is a subject of debate. However, renal involvement in children with influenza A infection as a part of multiple organ dysfunction has been described in the past, suggesting that secondary injury is the most common pathophysiology of the renal disease [3]. Myoglobinuria and renal injury have been described as culprits in some case series [4, 5]. Disseminated intravascular coagulation (DIC) and rhabdomyolysis were considered the cause of renal injury in one case series of influenza A patients, although the authors also discussed the difficulty in proving a direct involvement of kidneys in viral infections [6]. A more recent retrospective study by Dovč et al. [7] showed an AKI incidence of 71.4% of critically ill influenza patients, with 25% of acute renal failure and 28.6% overall mortality rate.

MERS-CoV infection usually causes severe extra-pulmonary organ dysfunction, and most patients present with shock, acute kidney injury, and thrombocytopenia [8]. The exact mechanism of renal dysfunction is not well understood; however, studies have shown viral tropism for kidney cells ex vivo, suggesting MERS-CoV could induce apoptosis in the kidney [9, 10].

Pei et al. studied data from 333 patients hospitalized with COVID-19 pneumonia and showed that 75.4% demonstrated kidney injury [11]. Su et al. reported kidney abnormalities in 26 autopsies of patients with COVID-19 from which nine patients had clinical signs of kidney injury. The most significant findings were proximal tubule lesion, loss of brush border, and necrosis [12].

Endocrine system

Patients recovered from SARS have shown lipid and glucose metabolism abnormalities, with elevated levels of lysophosphatidylinositol (LPI) and phosphatidylinositol (PI), according to a study from Wu et al. [13]. As these lipids are involved in insulin metabolism, these changes could cause glucose metabolism abnormalities, increasing glucose tolerance, and insulin release.

Another study by Yang et al. found that SARS-related coronavirus can cause damage to the kidney, heart, lung, and endocrine part of the pancreas, likely due to increased expression of angiotensin-converting enzyme (ACE) receptors. In this study more than 50 percent of the patients became diabetic during hospitalization for the SARS-CoV infection. They suggested that coronavirus might enter the pancreas via ACE2 receptor causing acute islet cell dysfunction and hence reduces insulin release, leading to acute hyperglycemia and transient type 2 diabetes mellitus [14].

SARS has also been implicated in hypocortisolism and hypothyroidism in a group of 61 survivors of the viral infection. According to the authors, it might be due to a transient hypophysitis or direct hypothalamic effect caused by the virus [15].

Aloysius et al. described a case of severe acute pancreatitis in a patient diagnosed with COVID-19 [16]. Another case series reported on acute pancreatitis associated with SARS-CoV-2 diagnosis. According to Hadi et al. two patients presented with elevated plasma amylase and image signs of acute pancreatitis. The authors hypothesized that direct viral invasion might be associated with enzyme activation, autodigestion, complement system activation, microcirculation disturbance, and necrosis [17].

One of the authors of this article reports on a case from his hospital in which a patient with a confirmed diagnosis of COVID-19 presenting with ground glass opacities on chest CT, also presented with concomitant abdominal pain and increased levels of amylase, and was later diagnosed with acute pancreatitis (Fig. 1).

Although the present data are sparse, patients with adrenal insufficiency may be at higher risk of medical complications and mortality in the case of COVID-19 infection. European Society of Endocrinology recommends timely

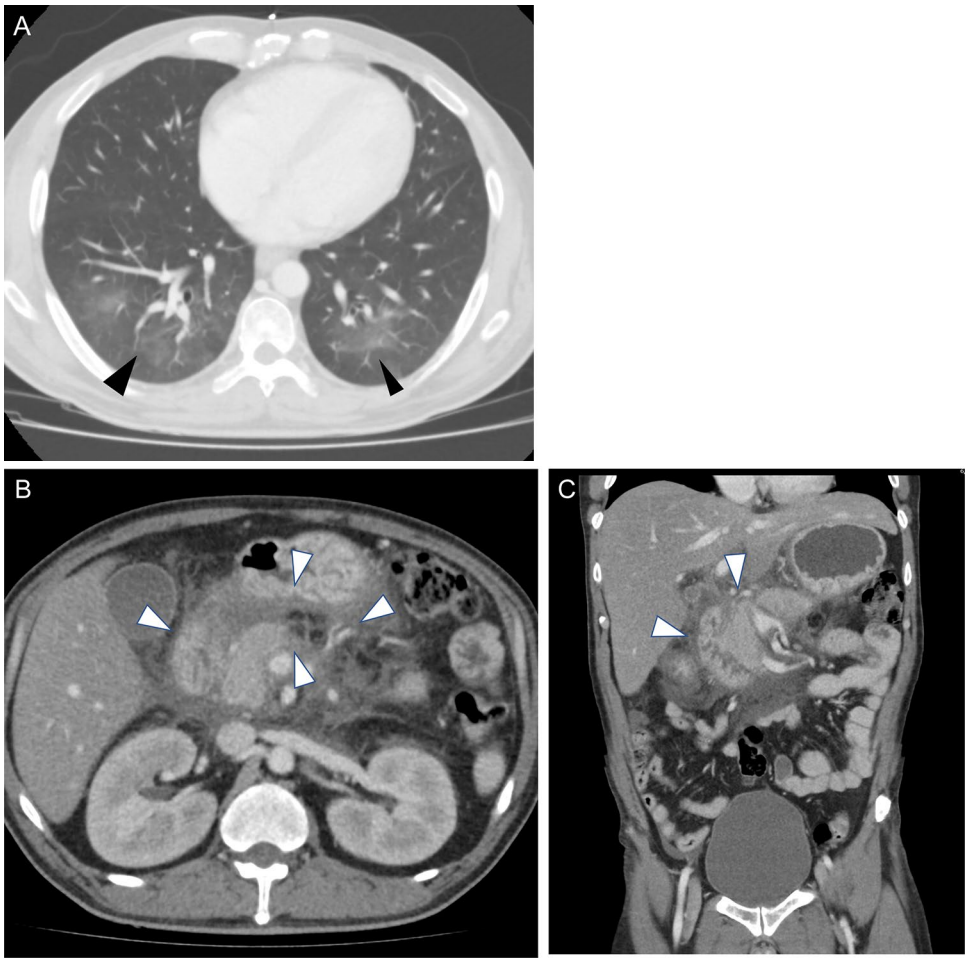

Fig. 1. Forty-year-old male presented to the emergency department with abdominal pain. Bilateral peripheral ground glass opacities are identified involving bilateral lung bases (**a**), the RT-PCR proven positive for COVID-19. Severe pancreatic edema and peripheral fat stranding are noted, in keeping with pancreatitis (**b, c**). The patient's serum amylase was above 1000

modification of the replacement treatment in these patients, when minor symptoms of infection appear, by at least doubling the usual doses of glucocorticoids so as to avoid adrenal crisis [18].

Undernourished patients diagnosed with COVID-19 infection may also be under higher risk of malnutrition due to the increased inflammatory body response and increased nutrient requirements. According to the European Society of Endocrinology a dense diet and adequate vitamin D supplementation must be offered for critically ill patients, with possible enteral or even parenteral nutrition if necessary [18].

Liver injury

Studies have reported a variety of liver abnormalities caused by SARS and MERS, including mild to moderately elevated transaminases, hypoalbuminemia, mild steatosis, congestion, and necrosis [19]. Chau et al. reported percutaneous liver biopsies in three patients that showed hepatocyte infection by SARS-CoV and elevated transaminases. The investigators found a marked accumulation of cells in mitosis and apoptosis [19]. The possible mechanism of invasion is through angiotensin-converting enzyme 2 (ACE2) receptors that are abundantly expressed on endothelial cells of the liver [20].

As found in SARS-infected patients, MERS causes mild inflammation in the liver. Still, the mechanism of entering the cell is different through other types of cell receptors (DDP-4), which also has high expressivity in hepatocytes [20, 21]. Liver function abnormalities associated with COVID-19 have also been described [22].

Neurological and muscular abnormalities

Coronaviruses can invade the nervous system causing a wide range of clinical neurological complications, which can be achieved by several routes, including trans-synaptic transfer, direct invasion via the olfactory nerve, endothelium, or migration across the blood–brain barrier [23]. Tsai et al. described neuromuscular symptoms in patients diagnosed with SARS: two patients presented motor-predominant peripheral nerve disorders, one developed myopathy, and another developed neuropathy and myopathy. All patients had clinical improvement and good outcome on follow-up [24]. Another case series reported three

patients with SARS that developed rhabdomyolysis during treatment. However, all received succinylcholine for muscle blockade during ICU treatment, which might have influenced as a causative agent [25]. Influenza infection has also been associated with the development of myositis in 3% of affected children involving most commonly the calf muscles, with high blood concentration of creatine phosphokinase [26]. Peripheral neuropathy has also been described in patients with SARS, and critical illness polyneuropathy should be considered as the cause [27].

Cerebral infarction may be associated with SARS, according to a case series of 206 patients, of which five developed ischemic strokes, although only two had previous risk factors [28]. The cause is unknown, although the use of intravenous immunoglobulin might be associated with this outcome [29, 30]. Other hypothesized mechanisms could be a vasculitis or a hypercoagulable state [31, 32].

MERS has also been associated with the development of intracerebral hemorrhage as a result of thrombocytopenia, Disseminated Intravascular Coagulation (DIC), platelet dysfunction, and polyneuropathy after long ICU treatment, according to a case report by Algahtani et al. [33].

Encephalitis may be associated with influenza viral infection. However, it is difficult to isolate the virus from the brain or cerebrospinal fluid. Morishima et al. reported 148 cases of influenza-associated encephalitis during the seasonal epidemic of 1998–1999, in which 87.8% were caused by type A virus, most patients were children less than 5 years, and the major signs were altered consciousness and convulsions. The mortality rates were high (31.8%), with rapid progression of symptoms and poor outcomes [34]. McCullers reported a case of a 6-year-old girl with influenza B infection and neurological sequelae. The patient presented with excessive somnolence that evolved to delirium and akinetic mutism [35]. Different types of encephalitis have been reported following influenza B infection [36]. The patient presented with lethargy, mutism, and the ECG showed slowed background activity. MRI was performed, and there was diffusion restriction and T2 hyperintensity on the corpus callosum and peripheral white matter. Cerebrospinal fluid was normal [36].

Protheroe et al. encephalitis postinfluenza A demonstrated hypodense lesions within the thalami and pons on head computed tomography and signal alterations in the pons on MRI in one case [37]. Yoshikawa studied 20 patients with influenza-associated encephalitis/encephalopathy during four seasons in Japan and found that clinical presentation varied among patients. They divided the patients according to the clinical presentation between those resembling Reye's syndrome, those that presented with shock symptoms and those with pontine, cerebellar, and brain stem symptoms. According to the authors, the high level of cytokines in these patients presented could be associated with neurological symptoms [38].

Regarding the current COVID-19 pandemic, several studies describe neurological symptoms and complications. Headache, anosmia, hypogeusia are frequently early symptoms of coronavirus infections [39]. Cerebral ischemia occurs probably due to viral invasion of endothelium resulting in vasculitis, coagulopathy, and thrombosis. Seizures, encephalopathy, meningitis, myelitis, Guillain-Barré, Miller-Fisher have also been described [39]. Invasion of the medullary cardiorespiratory center by coronavirus-2 might be responsible for refractory respiratory failure in critically ill patients [40].

Facial paralysis can also occur following SARS-CoV-2 infections [41]. Morassi et al. reported six cases of patients with a diagnosis of COVID-19 that developed stroke during treatment, although all patients but one had pre-existing vascular risk factors. The outcome was poor, with five patients dying and one remaining severely neurologically affected [42].

Patients infected with COVID-19 have also presented symptoms of cranial peripheral neuropathy like internuclear ophthalmoparesis and oculomotor palsy [43]. It is important, though, to be aware that many neurological symptoms described in patients with these viral infections are non-specific and have considerable overlap with other severe infections and generally there is no definitive confirmation of viral infection in the CSF of patients with SARS-CoV-2 [44].

Recent radiological reports added increasing evidence of central nervous system abnormalities in patients infected with SARS-CoV-2, particularly white matter signal alterations [45] that could involve the corpus callosum [46], but also several examples of acute necrotizing encephalopathy [47], acute ischemic infarcts [45, 48], microhemorrhages [49], basal ganglia abnormalities [50], encephalomyelitis, and meningitis, as well as cranial nerve and spinal nerve root abnormalities [51], highlighting the importance of neurological surveillance specially in critically ill patients [52].

Cardiovascular abnormalities

There is limited literature regarding cardiovascular involvement from SARS-CoV-1 infection, with some anecdotal data of patients with acute coronary syndrome, myocardial infarction, transient diastolic dysfunction, hypotension, bradycardia, transient cardiomegaly, and one postmortem study that showed thromboembolic disease [53–57]. Cardiovascular involvement in MERS also has limited systematic information. Most of the published works are from case reports or about the prevalence of comorbidities in affected patients [58]. Increased troponin and image signs of myocarditis were described in one case report [59].

Table 1 Summary of main extra-pulmonary manifestations of SARS, Influenza, MERS, and COVID-19

Organ/system	Condition	Main finding	Method
Kidney	Acute kidney injury	Acute tubular necrosis [1, 4, 12]	Pathology [1, 4, 12]
	Proteinuria	Acute kidney injury [2, 3, 5–7]	Laboratory analysis (increase in serum creatinine ± proteinuria) [2, 3, 5–7]
		Cell apoptosis [9]	In vitro, ex vivo, and in vivo molecular, genetic, and pathology studies [9]
Endocrine	Hypocortisolism	Increased serum lipids [13]	Lipid and metabolic profile, gas chromatography–mass spectrometry, and liquid chromatography–mass spectrometry [13]
	Hypothyroidism		
	Pancreatic islet cells injury		
	Pancreatitis		
		Binding of SARS Coronavirus-1 to its receptor damages islets cells [14]	Immunohistochemical staining of affected tissues from donors
		Decreased serum cortisol levels [15]	Laboratory analysis [15]
		Elevated serum lipase and amylase [16, 17]	Laboratory analysis [16, 17]
Liver	Increased transaminases	Increased viral load in parenchymal and endothelial cells	Pathology analysis [20]
	Portal inflammation	Eosinophilic bodies, balloon-like hepatocytes, apoptosis [20]	
	Hepatocyte apoptosis	Increased DPP-4 receptor facilitating viral infection [21]	Biopsy, immunohistochemical analysis [21]
Pancreas	Increased serum pancreatic enzymes	Edema and swelling of pancreas with peripancreatic stranding on CT and MRI (Fig. 1)	CT
Neuromuscular	Encephalopathy	White matter high signal intensity on FLAIR	MRI and CT
	Seizures	Low CT attenuation on corpus callosum and deep white matter	
	Cerebral ischemia	Microhemorrhages [49]	
	Myelitis	High signal intensity on cerebellum and diffusely in subcortical white matter, basal ganglia [45–51]	
	Peripheral neuropathy	Meningeal enhancement [50]	
	Myositis	Perfusion abnormalities [50]	
		Cranial nerve and spinal nerve root enhancement [51]	
Cardiovascular	Myocarditis	Arterial thrombosis and pulmonary thromboembolism	CT, MRI, PET, echocardiography
	Myocardial infarction	Myocarditis, pericarditis [53–69]	
	Pericarditis		
	Coagulopathy		
Perinatal	Miscarriage	Premature prelabor rupture of membranes	Clinical and Obstetric findings
	Preterm premature membrane rupture	Preterm birth	
	Growth Restriction	Preeclampsia	
	Preeclampsia	Fetal growth restriction [70]	

Patients with COVID-19 diagnosis have been reported to present with arrhythmia and myocarditis [60]. In a case series five had some type of cardiac injury [61]. Guo et al. [62] studied 187 patients with a diagnosis of COVID-19 in which 52 (27.8%) had a myocardial injury as indicated by elevated troponin levels, and the myocardial injury was significantly associated with fatal outcome. Tung-Chen [63] reported acute pericarditis in a patient diagnosed with COVID-19 that presented with pleuritic pain and pericardial effusion that was resolved after treatment with colchicine. The mechanism of cardiac involvement is not clear but hypotheses direct to possible direct viral injury and secondary to inflammatory process [64].

COVID-19 patients have increased coagulation abnormalities. Some studies have pointed out to the contribution of the inflammatory response and activation of coagulation cascade [65]. These hypotheses have been corroborated by some reported cases of patients with thromboembolic complications after cytokine storm, despite having no risk factors for thromboembolism [66].

Recent case reports have added to the knowledge of cardiac abnormalities, including deteriorating myocardial function, myocarditis, pancarditis, pericardial effusions, artery thrombosis, and coronary artery aneurisms [67]. Pulmonary thromboembolism is particularly prevalent in severely ill patients and involves mainly segmental and sub-segmental arteries of pulmonary segments affected by consolidation, raising concerns of inflammatory and hypercoagulability factors contributing to its pathogenesis [68].

Some patients may present cardiac involvement without symptoms or signs of interstitial pneumonia, as reported by Riccardo et al. on a patient later diagnosed with myopericarditis [69].

Gestational and perinatal abnormalities

Coronaviruses may be associated with perinatal complications. Recently a systematic review on pregnancy-related complications from SARS, MERS, and COVID-19 showed and increased prevalence of preterm birth and miscarriage, along with fetal distress and necessity for ICU treatment [70].

Discussion

Several studies have reported extra-pulmonary conditions in patients diagnosed with SARS, Influenza, MERS, and COVID-19, affecting the kidneys, pancreas, liver, peripheral nerves, muscles, the endocrine glandules, myocardium, and pericardium. Most of the studies are case reports or case series, and in some cases, it is not possible to be sure if there is direct invasion by the viruses (Table 1).

Conclusion

Patients with a diagnosis of SARS, MERS, influenza, and COVID-19 frequently present extra-pulmonary symptoms that may be caused by direct virus injury or secondary to the systemic inflammatory response [71–78]. Acute kidney injury and proteinuria, pancreatitis, hypocortisolism, hypothyroidism, myositis, encephalopathy, perinatal complications, and myocarditis can be associated with these viral infections. The progression from pulmonary disease to a systemic condition has a poor outcome and can result in multi-organ failure and death.

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Compliance with ethical standards

Conflicts of interest The authors of this study have no conflicts of interest to declare.

Ethical standards This article does not contain any studies with human participants or animals performed by any of the authors.

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