Review Article

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Uncommon Atypical Presentations of COVID-19: Important and Should Not be Under Recognized!

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Abstract:

Coronavirus disease 2019 (COVID-19) is a new viral disease that has become a global public health concern in 2020. This disease is caused by a novel coronavirus firstly detected in the People's Republic of China. This viral infection can cause febrile illness and respiratory problems. There are other uncommon clinical presentations of COVID-19 such as afebrile illness, diarrhea, non-coughing and confusion. These atypical presentations can result in difficulty in diagnosing the disease. In this short review, the authors specifically discuss the important uncommon atypical presentations of COVID-19.

Keywords: atypical, COVID-19, manifestation

Introduction

The novel coronavirus disease 2019 (COVID-19) infection is a new emerging respiratory disease. This disease started in the People's Republic of China (PRC) in December 2019 and presently has become a global public health threat. This new disease is caused by a novel coronavirus firstly isolated and reported in Hubei, PRC[1], and has now to many countries.[2] The countries with a secondary outbreak, with phase 3 transmission, are Japan, South Korea, Iran and Italy. The incubation period of this coronavirus infection is between 2 and 11 days.[3] Death is a possible outcome if infection occurs in an old person with an underlying personal illness.[1,3] The gold standard diagnosis for COVID-19 is reverse transcription polymerase chain reaction molecular diagnosis.[3]

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This new coronavirus infection can cause febrile illness and respiratory clinical presentations.[1] There are also uncommon atypical presentations of COVID-19. A COVID-19 patient might have no fever, no coughing, diarrhea and confusion. Although COVID-19 is a new emerging disease which has spread from he polymerase chain reaction (PCR) to other countries and there are only a small number of data/reviews to date of the characteristics and common presentation of this disease, a summary on atypical presentations at this time can provide useful basic data for further research on the clinical aspects of the disease.

In this minireview, we summarize and discuss the atypical presentations as suggested of COVID-19 which the practitioner must be aware of to properly deal with his or her patients.

Atypical and uncommon clinical presentations of COVID-19

A. No fever

While it is generally accepted the fever [body temperature over 100.4 F (38 °C)] is the main criterion for screening for COVID-19, it is apparent that many patients might manifest no fever and this can result in underdiagnosis of the infection.[4-6] According to a recent report, 2.0% of the included patients were afebrile at presentation.[4] These patients developed fever within 2-3 days after the initial diagnosis.[4] A recent report also confirmed that temperature monitoring can result in both false negatives and false positives regarding disease detection.[7] There are many potential confounding factors interfering with reliable temperature measurement, for example body temperature measurement technique, the quality of the temperature measurement tool and the use of self prescribed antipyretic drugs (such as acetaminophen) can alter body temperature. Self-reporting of fever or self-measurement of body temperature by the patient might not reliable. In clinical practice, it is necessary to decimate between self-reported temperature and accessed temperature as assessed by qualified health workers at the clinic. The verification of a patient complaint of fever or no fever has to be done by standard body temperature measurement.

B. Thrombocytopenia and bleeding tendency

In general lymphopenia (average lymphocytes $0.8x10^9$/L) is a common finding from a complete blood count in COVID-19 patients (frequency about 63.0%).[4,5] The clinical importance of lymphopenia in COVID-19 patients is still not known. In addition to lymphopenia, another common finding in COVID-19 patients is thrombocytopenia.[4-6] In general, the average platelet count of the patient is about $164.5x10^9$/L and thrombocytopenia is observed in 5.0% of cases.[4,5] In addition, an abnormal coagulation profile (prolonged prothrombin time (PT) and activated partial thromboplastin time (aPTT) about 1.5 to 25 times normal) might be detectable (frequency about 5.0%).[4,5] With thrombocytopenia and a coagulation system defect, it is possible that the patient might have bleeding as an initial clinical presentation. Some patients (less than 1.0%) might have petechiae but there is still no report on massive bleeding in patients with COVID-19.[4-6]

C. Diarrhea

Another possible atypical presentations of COVID-19 is diarrhea.[4-6] In fact, diarrhea is a common gastrointestinal manifestation in many viral infections. While COVID-19 is a respiratory disease, it can also have voluminous watery diarrheal presentation (frequency–3.0%).[4] The exact pathogenesis of diarrhea in COVID-19 is not known, and it is difficult to use the presence of diarrhea to distinguish COVID-19 from other respiratory infections such as influenza.

D. Confusion

Although there is no clear evidence that COVID-19 can cause neurological alteration, confusion has been reported in patients with COVID-19.[4-6] In one recent report,

9.0% of the COVID-19 patients had confusion and these patients usually had severe infection terminating in death in the worst cases.[8] To date there have been no reports on an association between COVID-19 and encephalopathy or encephalitis. Brain stem involvement has been reported in patients and animal models of severe acute respiratory syndrome coronavirus (SARS CoV) infection.[9]

E. Renal dysfunction

Renal disease is a possible complication in COVID-19. This is similar to other emerging coronavirus infections.[10,11] Renal dysfunctions in COVID-19 include decreased urine output, uncorrectable acidosis or electrolyte disturbances.[4–6,12] Acute renal injury or acute renal failure have been observed in some patients with COVID-19.[4–6,12] Patients with acute renal failure usually have a poor clinical outcome.[4–6,12] The exact renal pathophysiological process leading to renal failure in COVID-19 patients will be an interesting issue for further study.

F. No coughing

As a respiratory illness, coughing is usually expected in COVID-19 patients. However, some COVID-19 patients have presented with no coughing.[4–6] According to a recent report, the percentage of COVID-19 patients who did not have a cough at presentation was 24.0%.[4] These patients developed fever within 2–3 days after their initial diagnosis.[4] This can lead to missed or delayed diagnosis of COVID-19. It might be questionable to refer to no cough as an atypical manifestation, nevertheless, it should be specifically mentioned to highlight the possibility.

Possible uncommon laboratory presentations of COVID-19

A. Eosinophilia

The main clinical findings on a complete blood count in COVID-19 are leukopenia and lymphopenia.[4–6] About 68.8% of the patients have lymphocytopenia.[4–6] However, the patients might also have atypical complete blood count results from standard automated hematology analysis.[13] Eosinophilia might be observed with no related background allergic disorder of the patient.[13] The prevalence of eosinophilia (absolute eosinophil count more than 500 μL) in a recent report was about 89.6%.[13]

B. Abnormal coagulation test

An abnormal coagulation test might be found in a COVID-19 patient. Abnormal PT and aPTT tests are possible laboratory findings.[4–6] In fact, the coagulation abnormality might result in a hemorrhagic episode and might lead to a misdiagnosis of COVID-19 as another common endemic disease such as dengue.[14] There are many potential causes of abnormal coagulation cascade evaluation in COVID-19. The presence of disseminated intravascular coagulation[4–6] or a liver complication[15] causing synthesis dysfunction might cause abnormalities in the coagulation cascade. According to a recent report, elevation of d-dimer is a predictor for mortality in COVID-19.[12]

C. Abnormal liver function test

An abnormal liver funding test is another possible laboratory finding in patients with COVID-19. The main clinical finding in an abnormal liver function test is hepatocellular injury.[15] Hepatitis is also possible. The potential causes of an abnormal liver function test include shock and drug-induced hepatitis. However, there is still no known pathogenesis of hepatitis in a COVID-19 patient.[15] Studies on a previous coronavirus infection, SARS CoV, found that an abnormal liver function test was usually temporary.[16] The higher aspartate transaminase and alanine transaminase levels were observed in deceased cases and the liver histopathology is usually non-specific hepatitis.[17] Regarding the Middle East respiratory syndrome coronavirus (MERS CoV) infection, there were no significant changes in liver function tests.[18]

D. Abnormal renal function test

As already mentioned, renal problems are possible in COVID-19. Some patients (about 10.0%) might have increased blood urea nitrogen (BUN) and creatinine

(reported average BUN and creatinine levels were 16.5 mg/dL and 1.50 mg/dL, respectively, but there are to date no specific reports on alteration of creatinine clearance of COVID-19 patients).[4-6] An elevation of creatinine is a predictor for mortality.[12] As with hepatitis, the exact underlying pathophysiology of in is as yet unknown. The potential causes of an abnormal renal function test include shock and drug-induced renal toxicity. Regarding previous similar coronavirus diseases, there have been some reports on acute renal failure in patients with SARS CoV and MERS CoV infections.[19,20]

E. PCR negative case of COVID-19

The PCR negative case of COVID-19 is an actual challenge in laboratory test for COVID-19. In a recent report from the PRC, the diagnosis rate for cases with pneumonia by PCR is less than chest computer tomography (71.0% versus 98.0%).[21] In fact, the PCR test might result in a false negative for various reasons such as inappropriate specimen collection or a poor quality PCR test. Adequate quality control of laboratory test is required. The variations in reliable results of different PCR tests might be due to the probe and region detecting this virus, the technique of each test, the stage of disease and type of clinical specimen (nasopharyngeal swab, throat swab, sputum or blood). In some cases a PCR might be negative from a simple nasopharyngeal specimen sample test but positive from a bronchoalveolar lavage specimen test. The exact frequency of false negatives is still unknown and this is an interesting topic for further studies.

Discussion

COVID-19 is a new emerging virus infection that has become a global public health problem with a number of possible clinical presentations[4,5,13,22,23] (Table 1). The common respiratory presentations in this new disease include cough, rhinorrhea, chest pain and respiratory difficulty. After contact and the incubation period, the patient usually presents with fever usually accompanied by respiratory symptoms. Of the several possible respiratory symptoms, cough is the most common symptom, seen in 75.0% of patients.[13] In the present situation of worldwide pandemic, the knowledge of common or usual manifestations of COVID-19 might not be sufficient for clinical practice. Some less common clinical features of COVID-19 might be present in only a small number of patients. Some might have non-respiratory clinical presentations. Those clinical presentations are called atypical presentations, in the same way atypical presentations were observed in earlier coronavirus infections such as SARS CoV and MERS CoV. The practitioner might not recognize these atypical presentations resulting in missed or delayed diagnoses.

Table 1 Frequency of common clinical presentations of COVID-19 reported from different countries

Clinical presentation	Frequency in different countries (%)		
	People's Republic of China[4,5,13]	Singapore[22]	South Korea[23]
Fever	91.7-98.0	72.0	32.1
Cough	48.2-76.0	83.0	17.9
Myalgia/fatigue	32.1-75.0	N/A	14.3

N/A=data not available

Due to the nature of a new infectious disease such as COVID-19, it is difficult to discriminate with certainty at this early period between common and atypical presentations of this disease. The aim of this work was to summarize "uncommon atypical presentations", which have not received enough attention in descriptions of the disease presentation to date. There are some clinical presentations and laboratory findings that are seen in only a small number COVID-19 patients such as non-respiratory clinical presentations such as diarrhea and confusion. Those possible clinical presentations should be recognized. It is necessary to recognize that COVID-19 might result in abnormal atypical presentations. Nevertheless, there are potential confounding factors which can interfere with the clinical manifestations such as the previous use of anti-pyretic agents, receiving anti-viral agents or constitutionalsymptoms causing dehydration.

The clinical impact of those atypical manifestations is very important. The differences from the criteria of patient under investigation (PUI) might result in under diagnosis. If the practitioner does not update their knowledge on uncommon atypical presentations of COVID-19, some COVID-19 patients are likely to be misdiagnosed, possibly leading to further transmission.[11] The delayed diagnosis is possible and the poor outcome of treatment following such delays is expected.

Finally, we recommend diagnosing COVID-19 infections using the PUI criteria. Additional investigations should be performed in specific cases that might fulfill some criteria or have extra clinical presentation adding to basic criteria. It is also necessary to update the criteria to match the changing situation of the outbreak. A good example of PUI criteria that easily becomes outdated is the list of names of the COVID-19 risk territories.

Conclusion

There are many possible atypical clinical presentations in COVID-19. Since those clinical presentations might be initial presentations and the practitioner might under-recognize true cases, it is necessary to emphasize the importance of those atypical clinical manifestations.

Conflicts of interest

None

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