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Manifestation of COVID-19 Mimicking Rheumatic Diseases

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ABSTRACT

Background Diagnosing the newfound disease has been always the vital strategy of controlling and managing Corona Virus Disease (COVID)-19. Interestingly, patients with COVID-19 may also have features mimicking rheumatic diseases due to immunology responses and viral properties. **Methods** We systematically searched both from MEDLINE (accessed from PubMed) and Google scholar from late of 2019 to June 2020 for related published articles. In both electronic databases, the used key words were "COVID-19" or "Corona virus", "rheumatic diseases" and "clinical characteristics" **Results** Through the search, we were able to conclude some characteristics that could be manifested both in COVID-19 infection and rheumatic diseases, including but not limited to constitutional manifestation, arthralgia and/or myalgia, myositis, hematologic manifestation, skin manifestation, acute interstitial pneumonia, myocarditis and gastrointestinal manifestation. Most studies were able to explain the possibility of immune dysregulation similar to what rheumatic diseases exhibit, include post mortem biopsy of a tissue damage similar to rheumatic complication in COVID-19 infection. **Conclusion** Since the possibility of overlap symptoms between COVID-19 infection and rheumatic diseases was able to be enucleated through our review, we believe that in the future clinical awareness to differentiate between autoimmune and infection origin of many rheumatic manifestations will hold pivotal role in prohibiting reemergence disease. Future study to assist clinicians to swiftly diagnose autoimmune diseases in the era of pandemic is essential.

1.Introduction

Since its discovery in December 2019, the new Corona virus, later identified as Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV2), has been known as the etiologic agent of new pneumonia cluster in Wuhan, China.[1] Since March 2020, more than 110 countries have been exposed and about 600.000 cases have been identified, therefore marked the COVID-19 infection The main pathogenesis of COVID-19 thought to be related to activated body's humoral and cellular immunity, mediated by virus-specific B and T cells.[5] Humoral immune response, which is marked by the presence of IgM and IgG antibody to SARS-CoV2, similar to what has been studied in SARS-CoV mechanism, as well as cellular immunity response pictured by reduced CD^{4+} and CD^{8+} T cells in peripheral blood following its excessive activation status.

From clinical perspective, manifestation of COVID-19 can be divided into three phases: (1) asymptomatic state in 1-2 days initial of infection, marked by binding of viruses to epithelial cells in nasal cavity, which can be detected by nasal swabs after activation of limited innate immune response, (2) respiratory tract response, which last the next few days, when virus multiplication and local inflammation in the lungs present, followed by (3), the severe phase of COVID-19, featured by hypoxia, ground glass infiltrates, and possible progression of ARDS. The latter phase was marked by high inflammation response, with increasing level of inflammatory markers such as Interleukin (IL)-2, IL-6, IL-7, granulocyte-colony stimulating factor, macrophage inflammatory protein 1-α, tumor necrosis factor-α, C-reactive protein, ferritin, and D-dimer.[5-7]

Interestingly, patients with COVID-19 may also have features mimicking rheumatic diseases due to immunology responses and viral properties.

as pandemic.[2]

This RNA virus, single-stranded and enveloped SARS-CoV2 belongs to Orthocoronavirinae subfamily, and part of Sarbecovirus subgroup, [3, 4] has been known to transmit from one person to another and in some cases could cause severe complications such as respiratory distress and ARDS.[4]

In this systematic review, we aim to highlight features of COVID-19 that mimic those of rheumatic diseases, in hope to raise clinical awareness and prevention

2.Methods

We systematically searched both from MEDLINE (accessed from PubMed) and Google scholar from late of 2019 to June 2020 for related English-language published articles. In both electronic databases, the used key words were "COVID-19" or "Corona virus", "SARS-COV2", "autoimmune diseases", "rheumatic diseases" and "clinical characteristics". Authors included case reports, case series and the observational studies done in COVID patients. Additional relevant articles were identified from the citations referenced.

3.Results

The clinical signs and symptoms of COVID patients are considered atypical, ranging from constitutional symptoms such as fever to respiratory symptoms and pneumonia.[5] Patients with COVID-19 may also have

features mimicking rheumatic diseases, such as arthralgia, acute interstitial pneumonia, leucopenia, lymphopenia, thrombocytopenia, myocarditis, and cytokine storm with features indistinguishable to secondary hemophagocytic lymphohistiocytosis.[8] Diagnosis of COVID-19 and rheumatic diseases is especially challenging, due to range of both of diseases in term of variations of symptoms. Clinical suspicion needs to be refined, and clinicians should aware of how diverse the signs and symptoms are. The decision to determine COVID-19 infection or flare state of the rheumatic autoimmune disease warrants the holistic reviews by clinicians.

Differentiate infection and autoimmune flare up could be notoriously difficult, since infection itself can imitate, trigger and/or coexist with autoimmune diseases such as Systemic Lupus Erythematosus (SLE).[9, 10] Infection itself could worsen autoimmune diseases, since patients are often on long-term immunosuppressive therapies. Therefore clinicians should always consider other options regarding to episodes of autoimmune disease flares. It is imperative for clinicians to promptly place COVID-19 possibility as one of differential diagnosis, since delayed diagnosis could contribute to more transmission and spread of COVID-19.[11]

Constitutional manifestation

Study conducted to 1099 patients in China reveal fever as the most common symptoms of COVID19, making it more difficult for clinicians to differentiate between infection and autoimmune disease flares since most of rheumatic diseases especially lupus tend to have fever during disease flare.[10, 12] The situation is even harder when non specific syndromes such as fever, dry cough and fatigue manifested in the beginning of incubation period.[13] Fever and fatigue were among the most common clinical manifestations in COVID-19, a meta-analysis conducted on 3062 patients exhibiting fever in 80.4% patients (95%CI 73.0%-86.9%) and fatigue in 46% patients (46%, 95%CI 38.2%-54%).[12, 14, 15] Further investigation on biomarkers and additional examinations are in demand to assist clinicians differentiating whether it is autoimmune or infection origin.

Arthralgia and/or Myalgia

Arthralgia is in among the typical symptoms of COVID-19. According to report from World Health Organization (WHO), arthralgia and myalgia constitute 14.8% of 55.924 confirmed cases, demonstrating its common property among COVID-19 patients.[14] Meta-analysis study concluded that since the earliest stage of infection, arthralgia and/or myalgia were already present. Some of the patients who were in need of intensive care were also reported to have arthralgia and/or myalgia at one point of disease progression.[16] The present of acute arthralgia in patients should involve virus as possible agent, considering it is proven that many virus infection could present as acute arthralgia and arthritis. Study mainly postulate that the cause of arthralgia among virus infection is due to indirect effect of immune and/or inflammatory responses, however other hypothesizes such as direct damage by the virus on peripheral nerves or endothelium may arise.[16, 17]

Myositis

Though rare, a study reported that one patient developed myositis as a manifestation of COVID-19. Even though myalgia has been widely reported as one of typical symptoms of COVID-19, myositis could occur as a manifestation as well. The symptoms include diffuse myalgias and proximal lower limb muscle weakness that cause instability to walk. Elevated creatinine kinase was also reported from the same study.[18] Other study reported a patient who developed rhabdomyolisis without presenting fever, although the comorbidities and previous drugs history should be taken into account regarding this study.[19] The presence of myositis during viral infection itself was mainly studied in children and influenza patients. Another study on the other hand pointed out that myositis in COVID-19 patients is similar to that of influenza patients, followed by elevation of aminotransferase enzymes.[20, 21] Patients often experience diffuse muscle pain and lower-limb weakness, mainly in calves and thighs.[20, 21] Literature of arthritis in COVID-19 patients is scarce compared to reported joint and muscle pain. One study reported 4 cases of acute arthritis in COVID-19 patients. The tested synovial fluid studies revealed no SARS-CoV2 to date. More study about arthritis in COVID-19 patients are encouraged, with possibility of it emerge in patient is possible according to current report.[22]

Hematologic manifestation

Hematologic manifestations have been reported linked with SARS-CoV2 infection. Some of the manifestations are even related to severity of disease. Thrombocytopenia has been reported among patients with severe condition and in need of intensive care.[23] Severe course of disease is also associated with dynamic changes of leucocyte and lymphocyte.[24] Clinicians should aware whether such developments come from infection or autoimmune.

Recent meta analysis concluded that low platelet count was associated with greater odds of fivefold risk of COVID-19 (OR, 5.1; 95% CI, 1.8–14.6).[24] Thrombocytopenia in patients with COVID-19 was thought to be multifactorial origin. Based on previous study on coronaviruses, SARS-CoV2 is thought to be able to directly infect bone marrow cells, thus reduce platelet production and resulting in abnormal hematopoiesis.[25] Second mechanism includes alteration of lung morphology that caused reduction of platelet due to its property of megakaryocytes maturation organ. This way, any alteration of pulmonary capillary bed may impair platelet defragmentation. Third mechanism includes the elevated levels of autoantibodies and autoimmune complexes that in turn will promote platelet destruction and consumption.[23, 25]

Consistent with respiratory virus infection, patients with COVID-19 presented with lymphocytopenia and leukocytopenia.[26] Other study in China showed that both are commonly present in COVID-19 patients, suggesting virus ability on depleting CD4 and CD8 cells. Other changes of peripheral white blood cells are also due to cytokine storm and generations of several immune responses.[27] Other study in Singapore presented significantly lower patients with lymphopenia compared to study in China, notably due to disparity of numbers. However, it may be taken into account that COVID-19 patients in need of ICU have relatively lower level of absolute lymphocyte

count compared to non-ICU patients.[28]

Being one of the system that heavily affected by chronic inflammation through immune- and non-immune-mediated mechanisms via overproduction of autoantibodies, inflammatory cytokine release, and deposition of immune complex, hematopoietic system has been showed to experience one or more changes in its cellular lineage.[29] One example is neutrophil-lymphocyte (NLR) ratio, which was proven to be elevated in some rheumatic diseases such as rheumatoid arthritis (RA), ankylosing spondylitis (AS), and Behcet disease (BD), that has pivotal role in COVID-19 infection.[8, 30] As explained before, one mechanism thought to be elicited by SARS-CoV2 is through reduced CD^{4+} and CD^{8+} T cells in peripheral blood following its excessive activation status, further triggering increased NLR.[5-7, 31] Cohort study in China suggested that each unit increase of NLR was followed by 8% higher risk of in-hospital mortality (OR=1.08), with other study suggested that patients with age ≥ 50 years and NLR ≥ 3.13 should be transferred to intensive care units (ICU) while who are ≥ 50 years old and NLR < 3.13 can be admitted to isolation ward with monitoring and supportive care, exhibit the properties of risk stratification and management using NLR evaluation.[32, 33]

Thromboembolism manifestations that could occur in patients with anti phospholipid syndrome (APS) and SLE could also manifest in patients with COVID-19.[8, 34] Comparison among survivals reveal elevated levels of D-dimer and fibrin degradation products (FDPs) (3,5 and 1,9-fold, respectively) as well as PT prolongation among non survivals.[35] Post mortem study conducted in patients with COVID-19 revealed thromboembolism evidence in 7 out of 12 patients, which was not suspected before death, with pulmonary embolism as a direct cause of death in 4 patients.[36]

Skin manifestation

Skin manifestations among COVID-19 patients are considered to be rare, with very limited cases and reports could be found on literatures. However, clinicians should aware of the possibilities due to variations of rheumatic diseases that manifest on skin. The most common cutaneous manifestation of COVID-19 is generalized macular or maculopapular exanthem (morbilliform). Other manifestations include papulovesicular rash (vesicles), urticaria, painful acral red purple papules, livido reticularis and petechiae.[37] Experts furthermore speculate that cutaneous involvements are very similar to common viral infections.[38] Other notable condition is called Chilblain-like eruptions, which commonly appear in youngster and young adults, and disappear after the infection. Cutaneous manifestation in COVID-19 patients is considered to be unique, since it may be the only manifestation occurred in youngster patients without any typical symptoms.[39]

Acute interstitial pneumonia

Proven to be the major cause of morbidity and mortality in COVID-19, acute bilateral interstitial pneumonia also appeared in COVID-19 patients. Most notably in patients with SLE and Sjogren's syndrome, patients with acute interstitial pneumonia should be questioned whether it is infective or autoimmune in origin.[8] According to

study conducted with 81 COVID-19 patients in China, interstitial pneumonia developed in second week after symptoms occurred, pictured by the appearance of bronchiolectasis and irregular interlobular or septal thickening.[40] As one of the most predominant radiologic finding in COVID-19, ground glass opacity could also occur on patients with systemic sclerosis, which could occur in early stage for the latter, making it also a challenge for clinicians and radiologists to differentiate between autoimmune and infection origin based on radiologic findings.[40-42]

Myocarditis

Viral myocarditis has a very set wide of clinical pictures, with influenza virus infection and corona virus have been reported as etiologic agents. Myocarditis can also be found in patients with rheumatic diseases such as RA and SLE. Similarly enough, cardiac manifestations of autoimmune rheumatic diseases range widely, since rheumatological disorders can affect myocardium, valves, pericardium, conduction system and the vasculature.[43] The present of focal or global myocardial inflammation, necrosis, and ventricular dysfunction suggest myocarditis. One case report of COVID-19 patient presented a woman with fatigue and low voltage in the limb leads, diffuse ST-segment elevation (notably in inferior and lateral leads), and ST-segment depression with T-wave inversion in leads V1 and aVR. The patient experienced echocardiography changes, regional wall motion abnormalities, and elevated markers of myocardial necrosis with no signs of obstructive coronary disease, suggesting myocarditis.[44]

It may be noticed that biopsy performed in COVID-19 patients with myocarditis showed no presence of SARS-CoV2 within myocardial tissue. The autopsies reveal inflammatory infiltrates composed of macrophages and CD^{4+} T cells instead, which further suggest indirect involvement of virus to myocardial damage.[45] The presence of inflammatory infiltrate suggest similarity of process compared to autoimmune origin of myocarditis via leukocyte activation, hence the possible mimicking condition may up to further discussions.[43]

Gastrointestinal manifestation

Although rare, some gastrointestinal manifestations could occur in COVID-19 patients, which show increasing in trends among patients in later stage of epidemic in China. Study suggested that diarrhea was the common manifestation in adult and children, while nausea and vomiting were more commonly found in children.[12, 46] A case report in Indonesia describe a patient with epigastric pain, nausea and vomiting.[47] One study postulated that ACE2 receptors were also found in gastrointestinal tracts, making the entry via gastrointestinal tracts possible. Enteric symptoms like diarrhea was also made possible by the increasing gastrointestinal wall permeability to foreign pathogens.[48]

Conclusion

The world has been challenged with a new pandemic, causing health problems to be especially scrutinized, and in need of massive collaboration involving all branch of health science, including rheumatology. The rheumatologist as one of the front liners should always consider other options

whenever a patient comes with common rheumatic manifestations, since the evidences of clinical manifestations mimicry and overlap are present as well as to prevent more transmissions. In the future, clinical awareness to differentiate between autoimmune and infection origin of many rheumatic manifestations will hold pivotal role in prohibiting re-emergence of disease. Meanwhile, more cases and further studies are expected to swiftly diagnose COVID-19.

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