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Short Communication

Egypt's groundwork blessing during the COVID-19 pandemic curse: Rheumatologic experience

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On the 25th of March 2020, the WHO team of experts concluded that Egypt's strong disease surveillance system and contact tracing efforts have proven effective in controlling and managing sporadic and clusters of cases before they can spread and that Egypt made substantial efforts to control the corona virus disease 2019 (COVID-19) outbreak (1). In line with many other countries unable to perform laboratory tests on a nationwide scale, the reliability of the reported number of infected cases is questionable. Nevertheless, the minimal mortality because of COVID-19 in Egypt is remarkable and deserves further research. In fact, the mortality rate has not changed even after the pandemic outbreak in December 2019 when compared with rates over the last decade (2). In an attempt to understand the mysterious, promising detention of the COVID-19 spread in Egypt, the WHO clearly pointed to the considerable efforts made by the Egyptian government in potentially and effectively allocating human and financial resources needed to contain the outbreak (1). Few countries have systematically tested and treated their people for the most threatening diseases. Egypt's hepatitis-C virus program provides an example of how routine testing and treatment for infectious diseases for an entire country can be achieved (3).

However, there are arguments that the slowly increasing herd immunity was concurrently building up and adding to the community's development of subclinical overlooked COVID-19 cases. Other reasons to the relatively reduced mortalities in Egypt because of COVID-19 included the possible overall enhanced immune system of population because of obligatory previous national vaccinations provided for decades against other microbes and the potentially well-built memory of the immune response (4).

As reported by the International Association for Medical Assistance to Travelers, tuberculosis is endemic in Egypt, and according to the Global Alliance for Vaccines and Immunization alliance on the 26th of March 2020, a Dutch team of researchers have been trying to use the tuberculosis vaccine to protect health workers against COVID-19. The Bacillus Calmette-Guérin (BCG) vaccine already seems to boost immune systems to protect people against the flu (5). Recently, it was described that BCG augmented the memory of the innate immune system, "trained immunity," thus conferring nonspecific fundamental protection against a wide variety of infections (6), and it possibly serves as a promising ally in the war against COVID-19. Early BCG vaccination was associated with a reduced risk of leukemia because of its ability to trigger the naive immune response and to raise the plasma cortisol concentration. There is some evidence of a BCG vaccine shielding from all-cause mortality and endorsement of protection beyond the intended target pathogen via activation of innate immune memory, regulation of natural killer cells, macrophages, or cytotoxic T-lymphocytes (4).

The correspondence (7) published on the 26th of March 2020, astonishingly proposed that Egypt has a large burden of unreported COVID-19 cases and might be a source of exportation that is not yet accounted for. In the short Canadian letter, several inquiries and critics are held doubtful and misleading because of overusing words of uncertainty, such as "probably, might have, assumed, we estimate…," presenting assumptions and scenarios based on case reports, the lack of a reliable study design while conducting the predictive statistical models based on a few cases, as well as the conspicuous conflict of interest, because one of the coauthors is the founder and CEO of the artificial intelligence division of the Canadian company responsible for tracing COVID-19 across various countries and the corresponding author is a consultant at the same organization. Certainly, their method of estimation of more than 50,000 positive COVID-19 cases in Egypt is unclear (7) and attests the importance of obtaining results on the basis of future higher numbers of reported real-time infected patients. However, the other mentioned conservative estimate of 6,000 cases is more appealing (7). Lack of information about the incidence of infection and basic reproduction number are among the limitations to that report.

The clinical signs, radiological and laboratory findings that raise suspicion toward COVID-19, are well known. Nasopharyngeal and oropharyngeal swabs allowing viral isolation would confirm the diagnosis.

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The rheumatic manifestations of COVID-19 patients are not reported yet. However, in Italy, because of shortage of medical professionals, dermatologists joined the first lines in triage stations and medical wards with positive cases. Skin manifestations in COVID-19 were reported for the first time after excluding those with a recent history of drug reaction. A total of 20% of cases had cutaneous lesions: erythematous rash in 70%, widespread urticaria in 15%, and chicken pox–like vesicles in 5%. Lesions were not related to the disease severity (8). In view of the reported cytokine imbalance, it could be interesting to determine whether the associated skin lesions are related to an underlying rheumatic/autoimmune disease or vasculitis syndrome. Three hospitalized patients with laboratory-confirmed COVID-19 had clinically significant coagulopathy, antiphospholipid (APL) antibodies, and multiple infarcts. Besides their importance in the diagnosis of antiphospholipid syndrome, APL antibodies can also arise transiently in patients with serious illness and various infections. These antibodies may rarely lead to thrombotic events that are difficult to differentiate from other causes of multifocal thrombosis in critically ill patients (9). Hopefully, those with seronegative spondyloarthritis are protected from COVID-19, as reported about patients with HIV and hepatitis C (10). Interestingly, the rheumatologic spectrum of COVID-19 is on its way through the recently announced COVID-19 Global Rheumatology Alliance (11), EULAR COVID-19 database (12), and CARRA COVID-19 Global Pediatric Rheumatology Database (13) registries.

The different approaches taken by Egypt toward COVID-19 outbreak include the following. Close monitoring of the newly diagnosed cases and increasing awareness via focused media, with special emphasis on self-hygienic measures. The country adopted a partial shutdown early in the course of the outbreak with lockdown of its international borders. Nighttime curfew measures were enforced to prevent the spread of the virus. Social distancing and mandating people to stay at home with fully paid wages was implemented, schools and universities were shut down and online learning was endorsed. Using masks and gloves as well as personal protection equipment was considered for all the involved health professionals. Nationwide specialized isolation hospitals were allocated to quarantine and treat all cases with positive COVID-19. Medical professionals including physicians from various specialties, pharmacists, dentists, and other volunteer healthcare professionals were trained in handling intensive care units and on dealing with respiratory ventilators.

The COVID-19 pandemic also affected patients with rheumatic diseases. The global COVID-19 crisis is swiftly boosting pressure on health systems, especially in the high-income countries that make up most current hotspots. The everyday management of rheumatic diseases is beginning to feel the strain. Accordingly, rheumatologists had to come back hastily toward virtual patient care (telemedicine) to adjust patients' medications and offer advice. Throughout the pandemic, in a hospital in New York City, none of the patients with rheumatic diseases infected with COVID-19 needed hospital care and time may ascertain if the course of the disease is more serious in these patients (14). Rheumatic diseases and immune suppression may lead to active viral replication. Yet, the initial risk of COVID-19 infection is unknown. During an influenza season in Italy, patients with rheumatoid arthritis who were on biologic drugs had a high infection rate but no increased complications or hospitalizations (15). Those at the highest risk of dying from COVID-19 are the elderly and those with immunodeficiencies or underlying chronic medical conditions. In critically ill COVID-19 patients, there are clinical signs and symptoms, as well as laboratory abnormalities, that suggest a cytokine storm syndrome (CSS) (16).

Rheumatologists in Egypt are enormously expanding and mastering the tools that aid them in enhancing the management of the diseases (17). Egypt has a high number of registered (2) and qualified physicians. However, many are working abroad in Western and gulf-region countries. Consequently, as in many other countries, in Egypt there is an increasing shortage of rheumatologists per population (17). Moreover, as rheumatologists are aware of CSS/macrophage activation syndrome among their patients, they can help to champion the screening for, and diagnosis of, CSS among hospitalized COVID-19 patients (16).

The Egyptian Society of Rheumatic Diseases, the Egyptian Rheumatologist Journal (hosted and produced by Elsevier) and the Egyptian College of Rheumatology study groups officially signed up in support of the COVID-19 Global Rheumatology Alliance and registry initiative (11).

The views of the impact of the pandemic on rheumatology treatments are in harmony with those in other countries globally. It is reported that biologics and corticosteroids may promote secondary bacterial infection after any viral infection (18). Those taking biologics had less sepsis or fatal outcome after a serious infection. Methotrexate has a minimal risk of increased infections and there is no evidence that hydroxychloroquine or sulfasalazine increases the risk (19). Despite the concern that immunosuppressive drugs may increase complications for infected patients at risk, there is some hope that they can blunt lung injury in COVID-19. The clinical trials in progress on biologic anticytokine agents to treat COVID-19 and the CSS pave way for a rising key role of the rheumatologists in the managing team of the crisis (16).

Although there are reports that COVID-19 infection may result in a CSS that is similar to macrophage activation syndrome with a massive release of various cytokines, particularly interleukins (ILs), biologics used by rheumatologists may be potentially effective in treating severe COVID-19 infections. IL-1 and IL-6 blockers have been effective in adult respiratory distress syndrome and the IL-6 blocker, tocilizumab, is being used in COVID-19 clinical trials in China and Italy (18). The anti-tumor necrosis factor adalimumab may also be effective for COVID-19 infection and a double-blind US trial was launched on the IL-6 inhibitor sarilumab in patients with severe COVID-19 infection (20, 21).

How the rheumatology patients were managed during this period was similar to outlines considered in many areas of the world, as patients' visits were spaced and were instructed to remain on their latest regimens and doses unless there is evidence of an active infection and follow-up by phone. Patients with a stable disease status or in a remission, a slow taper of immune suppressant medications was carefully considered on a case-by-case basis. Priority was for urgent and infection-related visits over routine appointments. During an infection, particularly in a hospitalized patient, immunosuppressive therapy was paused, and the exact time frame varied on an individual patient basis. In addition to their effective disease-modifying antirheumatic drug effect, antimalarials have been shown to be potentially useful in the treatment of COVID-19 (18). However, following the US president's announcement that antimalarials may be effective and safe as well as being relatively cheap, a worldwide shortage has developed. In Egypt, similar to many countries, there was an obvious shortage of chloroquine and hydroxychloroquine mandating adjustments of their treatment regimens. The conflicting data regarding the safety of nonsteroidal anti-inflammatory drugs (NSAIDs), such as ibuprofen during COVID-19 infection as recommended by the WHO, led to a cautious use nationwide, even though a few days later the WHO reversed its decision. The use of NSAIDs and acetaminophen was in

the main not encouraged as they could mask fever potentially leading to a subsequent delay in a diagnosis. So far there is no evidence that NSAIDs are unsafe to use during COVID-19 infection (22).

Interaction was amplified via specialized social media channels such as the largest Facebook "Rheumatology" group, initially founded in Egypt, serving 20,000 members from more than 100 countries and carefully guiding cases. In university hospitals, inpatients, not in condition to be discharged, were carefully managed in view of the national medical policies in dealing with the COVID-19 outbreak.

Patients with rheumatic/immune diseases were categorized as high-risk and encouraged to alert the treating physician if a question of COVID-19 infection is considered.

Those requiring rehabilitative care and physical therapy were instructed by telephone or guided with virtual technology. Measures were taken based on the Centers for Disease Control and Prevention guidelines in regard to protecting patients and medical personnel during all office and hospital visits.

The minute-by-minute changes worldwide could easily make this response not up to date at a certain stage yet hopefully soon once the COVID-19 global crisis is halted, the true numbers released from Egypt will provide exact values on how the outbreak was effectively suppressed, rather than the imaginary expectations.

Egypt continues to amaze the world in the setting of a hidden force by the extraordinary effort of the healthcare professionals in containing the fatality and spread of the virus and is among the most controlling countries in spite of the limitation that the assessed and detected cases are less than expected.

As this corona virus pandemic broadens, rheumatologists having a strong background in understanding the immune system and well trained with utilizing biologics are well positioned to assist in management. Such cooperative effort should help reduce mortality during these trying times.

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