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Editorial

Learning hematology while surfing the waves of the COVID-19 pandemic

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We had heard of the Spanish flu pandemic during our days of learning Community Medicine but could not have imagined what a pandemic really is. I still remember that one of my colleagues assured me that it would be over by April 2020. The concept of quarantine was not new to us, courtesy of chickenpox in childhood, but a community lockdown was altogether a new experience teaching us the value of the contributions of so many persons in our daily lives. Looking at a fellow human suspiciously as a virus spreader and avoiding any sort of contact, went beyond our basic learning that man is a social animal.

CYTOKINE RELEASE SYNDROME AND STEROIDS

People were getting admitted with severe pneumonia and the health infrastructure was getting augmented with oxygen supply and ventilators. Why were the patients deteriorating so rapidly in spite of respiratory support? We hematologists had already learned about Cytokine Release Syndrome after CAR T-cell therapy and had been using steroids and tocilizumab to manage the symptoms. What was new was the fact that when the human immune central command failed to recognize the entry of the novel virus, in desperation, out of frustration, it could give rise to a similar syndrome which could be fatal, was really mind-boggling. Many of us were surprised with the findings of the controlled, open-label randomized evaluation of COVID-19 therapy (RECOVERY)[1] trial of dexamethasone in patients hospitalized with COVID-19. The trial randomly assigned patients to receive oral or intravenous dexamethasone (at a dose of 6 mg once daily) for up to 10 days or to receive usual care alone. The primary outcome was 28-day mortality. The authors concluded that "In patients hospitalized with COVID-19, the use of dexamethasone resulted in lower 28-day mortality among those who were receiving either invasive mechanical ventilation or oxygen alone at randomization but not among those receiving no respiratory support." There was a paradigm shift in the management of a viral infection when we were using steroids as an immunosuppressant to decrease mortality of COVID-19 pneumonia. The more expensive option tocilizumab was initially recommended in most of the guidelines and two recent meta-analyses[2,3] have shown that tocilizumab may have benefits in a selected population. Avni *et al.*[2] have concluded that "Tocilizumab reduces 28-day all-cause mortality in patients with moderate-to-severe COVID-19 vs. usual care. This mortality benefit was not demonstrated for critically ill patients and in trials that used corticosteroids for most of the included patients."

THROMBOSIS AND ANTICOAGULATION

COVID-19 has been associated not only with inflammation but also with a prothrombotic state, with increases in fibrin, fibrin degradation products, fibrinogen, and D-dimer levels.[4,5] In some

studies, elevations in these markers have been associated with worse clinical outcomes.[6,7] We had published our hypothesis linking the "happy hypoxia" and the prothrombotic state.[8]

Studies have reported varying incidences of venous thromboembolism (VTE) in patients with COVID-19. A meta-analysis of studies of hospitalized patients with COVID-19 treated with VTE prophylaxis found an overall VTE prevalence of 14.1% (95% CI, 11.6–16.9). The VTE prevalence was found to be higher in studies that used ultrasound screening (40.3%; 95% CI, 27.0–54.3) than in studies that did not (9.5%; 95% CI, 7.5–11.7). In randomized controlled trials conducted before the pandemic, the incidence of VTE in hospitalized patients without COVID-19 who received VTE prophylaxis ranged from 0.3% to 1% for symptomatic VTE and from 2.8% to 5.6% for VTE overall.

Guidelines about coagulopathy and the prevention and management of VTE in patients with COVID-19 had been released by multiple organizations, including the American College of Chest Physicians, American Society of Hematology, Anticoagulation Forum, International Society on Thrombosis and Haemostasis, Italian Society for Haemostasis and Thrombosis, National Institute for Health and Care Excellence (NICE), and Royal College of Physicians. All these guidelines agreed that hospitalized, non-pregnant patients with COVID-19 should receive, at a minimum, a prophylactic dose of anticoagulation to prevent VTE. The NICE guideline recommendation[9] states: "Consider a treatment dose of a low-molecular-weight heparin (LMWH) for young people and adults with COVID-19 who need low-flow oxygen and who do not have an increased bleeding risk." Results from clinical trials that assess the safety and efficacy of different anticoagulant doses and strategies have provided further information on antithrombotic strategies for patients with COVID-19. DOACs have been used more widely though a recent study has observed a lower risk of all outcomes associated with warfarin versus DOACs (testing positive for SARS-CoV-2, HR 0.73 [95% CI 0.68–0.79]; COVID-19-related hospital admission, HR 0.75 [95% CI 0.68–0.83]; and COVID-19-related deaths, HR 0.74 [95% CI 0.66–0.83]).[10]

We always wondered whether we can use antiplatelet agents to prevent COVID-19-related thrombosis. The ACTIV-4b placebo-controlled and randomized trial evaluated the efficacy of aspirin versus prophylactic (2.5 mg) or therapeutic (5 mg) doses of apixaban to prevent thromboembolic events, hospitalization, and mortality in outpatients >40 years with COVID-19. The trial was stopped in June 2021 due to a low event rate (one patient each in the placebo, aspirin, and apixaban 2.5 mg arms and two patients in the apixaban 5 mg arm) after randomization of 657 symptomatic outpatients.[11] An editorial in the heart journal[12] aptly sums up the current thinking: "The use of an antiplatelet agent, mainly aspirin, might improve clinical outcomes without increasing the risk of side effects such as bleeding. Aspirin is a safe, cheap, universally available, and well-tolerated medication. Using this drug in patients with COVID-19 should be encouraged unless contraindicated."

A VILLAIN CALLED D-DIMER

We had started getting referrals due to very high D-dimer levels post-COVID-19. Elevated D-dimer has been demonstrated as a predictor for the severity of SARS-CoV-2 infection. Increased D-dimer is associated with thromboembolic complications, but it could be also a direct consequence of the acute lung injury seen in COVID-19 pneumonia. CTPA studies have failed to document any pulmonary thromboembolism in most of these patients. Lehmannid *et al.*[13] have reported that in 15% of the patients recovered from COVID-19, persistent D-dimer elevation was observed after a median of 3 months following COVID-19. These patients had experienced a more severe COVID and still presented more frequently a lower mean pO2 and AaDO2. Increased D-dimer levels (>500 ng/ml) have been observed in 25.3% of patients up to 4 months post-SARS-CoV-2 infection in another cohort.[14] On univariate analysis, elevated convalescent D-dimers were more common in COVID-19 patients who had required hospital admission and in patients aged more than 50 years ($P < 0.001$) and there is a hypothesis that pulmonary microvascular immunothrombosis may be important in this context.

ANTIBODIES GALORE

Several studies have demonstrated that patients with COVID-19 exhibit marked increases in autoantibody reactivities as compared to uninfected individuals and show a high prevalence of autoantibodies against immunomodulatory proteins (including cytokines, chemokines, complement components, and cell-surface proteins).[15] These autoantibodies not only perturb immune function and impair virological control by inhibiting immunoreceptor signaling and by altering peripheral immune cell composition but also can lead to aggravation of or new-onset autoimmune diseases[16] such as ITP and autoimmune hemolytic anemia which have challenged the hematologists. These autoantibodies are possibly playing an important role in "Long COVID."

VACCINE EFFICACY IN PATIENTS WITH HEMATOLOGICAL MALIGNANCIES

Although all the available COVID vaccines have shown efficacy in preventing complications and hospitalization in the general population, there was a suspicion that they might not work in patients with active hematological malignancies. Patients with B-cell malignancies who are

distant from therapy or in remission appear to respond to vaccination, but those on B-cell-depleting agents or who have undergone cellular therapies are much less likely to be protected.[17] Since it has been documented[18] that many patients with hematologic malignancies are at risk of not producing antibodies after two doses of the mRNA SARS-CoV-2 vaccines, we should be aware that a substantial subset of vaccinated blood cancer patients may be at high risk of breakthrough COVID-19 infections.

POST-VACCINE THROMBOSIS AND THROMBOCYTOPENIA

On April 13, 2021, the U.S. Food and Drug Administration (FDA) and the Centers for Disease Control and Prevention (CDC) suggested pausing the administration of the AD26. COV2.S Johnson and Johnson vaccine to allow investigation of several cases of severe thrombosis with thrombocytopenia occurring post-vaccination. This announcement came on the heels of the initial reports of similar events in individuals receiving the CHaDOx1 nCov-19 AstraZeneca vaccine outside the United States. Comprehensive clinical and laboratory characteristics of VITT have been reported in retrospective series and a large prospective cohort. This syndrome has been termed "vaccine-induced prothrombotic immune thrombocytopenia (VIPIT)" or "vaccine-induced immune thrombotic thrombocytopenia (VITT)," and "thrombosis with thrombocytopenia syndrome (TTS)" in communications from the CDC and FDA. The risk appears far lower for the two mRNA vaccines. Estimates to date suggest that post-COVID vaccine ITP is rare (1 in 100,000–1 in 1,000,000) and may be related to vaccination or represent a coincidental event. Most patients respond to the combination of IVIG and/or steroids, with platelet transfusions if bleeding.[19]

ARE OUR PATIENTS GENERATING MORE SARS-COV-2 VARIANTS?

Patients with immunosuppression are at risk for prolonged infection with SARS-CoV-2. In several case reports, investigators have indicated that multimutational SARS-CoV-2 variants can arise during such persistent cases of COVID-19.[20,21] The findings that immunocompromised patients with persistent SARS-CoV-2 infection may generate more transmissible or more pathogenic SARS-CoV-2 variants have a number of medical and public health implications. Heightened precautions should be taken to avert nosocomial transmission of COVID-19 among our patients and they should be prioritized for anti-COVID-19 immunization not only to protect them from SARS-CoV-2 but also to mitigate persistent SARS-CoV-2 infections.[22] We should be vigilant and try to prevent the intermingling of patients with hematological malignancies.

MODELS OUT OF FASHION

Newer tools such as artificial intelligence and machine learning have made us dream about anticipating events and managing them in a better fashion. I was hoping that we could predict the events better using advancements in technology and data science. However, despite involving many excellent modelers, best intentions, and highly sophisticated tools, forecasting efforts have largely failed.[23] Each model made different assumptions about the properties of the novel coronavirus, such as how infectious it is and the rate at which people will die once infected. They also used different types of the mathematics behind the scenes to make their projections. And perhaps most importantly, they made different assumptions about the amount of contact we should expect between people in the near future.[24]

The pandemic should have made us humbler and inspired us to learn from each other to make the earth a better place to live in. Here's wishing you all the best as we try to improve ourselves.

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