The COVID-19 pandemic and immunological phenomena

Risk assessment for patients on immunosuppressive and immunomodulating medication

Penninga, L; Arvesen, K B; Bjerring, P; Mikkelsen, C S

Published in:
Forum for Nordic Dermato-Venerology

Publication date:
2020

Document Version
Publisher's PDF, also known as Version of record

The COVID-19 Pandemic and Immunological Phenomena: Risk Assessment for Patients on Immunosuppressive and Immunomodulating Medication

Luit Penninga[1], Kristian Bakke Arvesen[2], Peter Bjerring[2] and Carsten Sauer Mikkelsen[3]

[1]Specialist in Surgery, Ilulissat Hospital, Avannaa Region, Ilulissat, Greenland, [2]Specialist in Dermato-venereology, Department of Dermato-Venereology, Aalborg University Hospital, Denmark, and [3]Specialist in Dermato-venereology, Private Practice in Dermato-Venereology, Brønderslev, Denmark, and Research Lab., Department of Dermato-venereology, Aalborg University Hospital, Denmark

Background

As the COVID-19 pandemic evolves, more evidence becomes available on the nature of this novel disease and how it affects individuals in different ways. From the beginning COVID-19 was thought to be a 'viral pneumonia' (1). Gradually, it turns out to be a disease that affects many different organs and presents with a variety of different symptoms and diseases (2). It has been stated that COVID-19 somehow is more of an immunological disease than an infectious disease. Recently, hypercoagulability, thromboembolic events, and vascular characteristics associated with COVID-19 have been highlighted (2). There is increasing evidence that the viral infection in certain patients causes a severe immunological reaction which actually is responsible for the severe mortality and morbidity seen with COVID-19 (1).

Immunological phenomena of COVID-19

The immune response of patients affected by COVID-19 appears to be the main cause of organ damage, including severe lung tissue damage (1). The primary immune response leads to viral clearance in the vast majority of those getting ill with COVID-19. A minority of patients develops a severe secondary immune response. The severe reaction of the immune system probably occurs as this novel coronavirus is unknown to the human body (3). The immune system reacts by producing high levels of cytokines including interleukin 6, interleukin 1, anti-tumour necrosis factor, and macrophages. This cytokine storm and systemic hyperinflammatory response is associated with adverse outcome leading to severe inflammatory-induced lung injury and other complications including pneumonitis, acute respiratory distress syndrome, respiratory failure, shock, organ failure, and death (1,4). It is still unclear which component of the cytokine storm causes most damage (5).

Aside of lung injury, major vascular complications have been described with COVID-19. This includes patients with severe stroke, cardiac problems, mesenterial ischaemia and dark colouring of the toes (2). Patients with COVID-19 are at high risk of developing thromboembolic events, both in major blood vessels, but micro thromboembolism also occurs in small blood vessels. These vascular complications can occur in all organs of the body, and appear to be the result of a reaction of the endothelial cell function of blood vessels. Endothelial cell infection, endotheliitis and thromboembolism are pathological findings in these patients (2). Recently, it has become clear that pulmonary thromboembolism also plays a role in respiratory failure. Blood vessels especially in the lower regions of the lungs are affected. Recognition of the frequent incidence of thromboembolic events with COVID-19 means that patients with moderate–severe disease now are treated with double dose low molecular weight heparin.

Recently, another immunological phenomenon associated with COVID-19 has been reported in children in different countries (6). This concerns children presenting with Kawasaki-like symptoms, and has been called the 'paediatric inflammatory multisystem syndrome'. These children get severely ill several weeks after infection with COVID-19, and even mortality has been reported (7). The classic Kawasaki disease we know is primarily a vasculitis of medium-sized arteries. Kawasaki disease typically occurs in children below 5 years of age. Children with Kawasaki disease present with fever, erythema of the lips and oral mucosa, rash, and changes in the extremities including erythema of the palms and soles, bilateral non-exudative conjunctivitis and cervical lymphadenopathy (8). These features normally develop after a short course of respiratory or gastrointestinal symptoms (8). The aetiology of classic Kawasaki disease is unknown (9). It is thought to be caused by an overreaction of the immune system following a mild infection (8). Earlier an association of Kawasaki disease with another coronavirus, the Coronavirus NL63, was suggested, but could not be confirmed (10). Children affected by the COVID-19-associated paediatric inflammatory multisystem syndrome are often older (mean age 7.5 years) than those affected with classic Kawasaki disease (< 5 years of age) (6, 7).

Occurrence of this COVID-19 associated paediatric inflammatory multisystem syndrome is worrisome, especially as it was previously thought that children only get mild symptoms when infected with COVID-19. This might be true for the majority, but Kawasaki-like symptoms occurring after the initial infection may be the exception to the rule. Classic Kawasaki disease is treated with immunoglobulins to reduce the risk of aneurysms of the coronary arteries (8). Whether patients with the paediatric inflammatory multisystem syndrome also are at risk of developing coronary artery aneurysms remains to be determined. Immunoglobulin treatment is beneficial in classic Kawasaki disease, but we do not know whether this should also be applied in children with the COVID-19 associated paediatric inflammatory multisystem syndrome.

Immunological phenomena and Immunosuppression

Considering these immunological phenomena of COVID-19, the question arises how we should estimate the risk of a severe course of COVID-19 in patients on immunomodulating and immunosuppressive medication (11,12).

It was assumed that patients with a suppressed immune system would have a higher risk of an adverse outcome with COVID-19 because they are at increased risk when affected by common viral infections with adenovirus, rhinovirus, norovirus, and influenza (11). Based on this assumption, immunosuppressed patients were advised to be extremely careful regarding COVID-19 (12, 13).

Many patients on immunomodulating and immunosuppressive agents have avoided any risk of getting infected with COVID-19. These patients have isolated themselves in their homes and taken other preventive measures (12). Now, as the pandemic continues and countries are beginning to lift lockdown measures, it is important to know how these patients should act.

Patients on immunomodulating and immunosuppressive medication include patients with dermatological, gastrointestinal, and rheumatological diseases but also bone marrow and solid organ transplant recipients. Alongside these groups there are other groups with weak immune systems, and lower immune capacities to fight infections and cancer. This group of immunocompromised includes those with an inherited immunodeficiency, people with HIV, patients with bad nutritional status and cancer patients (especially those in active chemotherapy). Also, their risk when infected with COVID-19 has been questioned and remains to be determined.

Interestingly, immunosuppressive drugs are part of the treatment strategies currently tested for COVID-19 (14). These immunosuppressive drugs aim at reducing this cytokine storm and hyperinflammation (1,4,5,). These immunosuppressive drugs include treatment with low-dose corticosteroids, interleukin-1 receptor antagonists, interleukin-6 receptor antagonists, mammalian target of rapamycin inhibitors, IFN-γ, intravenous immunoglobulin and anti-tumour necrosis factor (1, 4, 15). These treatments should be balanced in order to reduce the hyperinflammation, but the immune system should still be able to respond to the infection and bacterial infections (3)

Dermatological patients on immunomodulating treatment

Whether patients on immunomodulating treatment for dermatological, gastrointestinal and rheumatological diseases are at increased risk for adverse outcomes when infected by COVID-19 is still unclear (16–18). There is no evidence that psoriasis patients treated with biologics have a high risk of being infected, or a higher risk of a severe course of the disease (19). It has been pointed out that evidence is lacking to stop treatment with biologicals as a preventive measure (19, 20). Hence, most do not advice to discontinue medication. Of course, this must be considered on an individual basis, and like the rest of the population, elderly patients with pulmonary and cardiovascular comorbidities are at increased risk (17, 19).

Careful consideration of whether the skin disease justifies immunosuppressive treatment should always be considered, especially when starting new patients on immunomodulating drugs (21). Furthermore, age, comorbidity, and obesity should be taken into consideration when advising these patients.

In patients with active infectious disease, discontinuation of biologics has been the rule, and this has also been advised for COVID-19 infection (16). A report from Italy describes continuing biological treatment in asymptomatic patients or patients with mild symptoms without fever and without contact to COVID-19 patients (22). Treatment was discontinued in patients with moderate or severe respiratory symptoms (fever, cough and/or difficulty breathing) and without COVID-19 contacts. In this group treatment was restarted when complete remission of symptoms was reached and after at least 72 h without fever. Treatment was discontinued in patients with mild respiratory problems and contact to COVID-19 confirmed cases until the patient had a laboratory-confirmed negative test for COVID-19. In patients with moderate to severe respiratory symptoms and contact to COVID-19 patients or clinical/radiological COVID-19, treatment was interrupted, and patients were admitted to a COVID-19 hospital (22). More data is urgently needed to identify specific patients at high-risk of an adverse outcome. The international league of dermatological societies has launched an app titled 'PSOprotect' to register how psoriasis patients taking immunomodulating

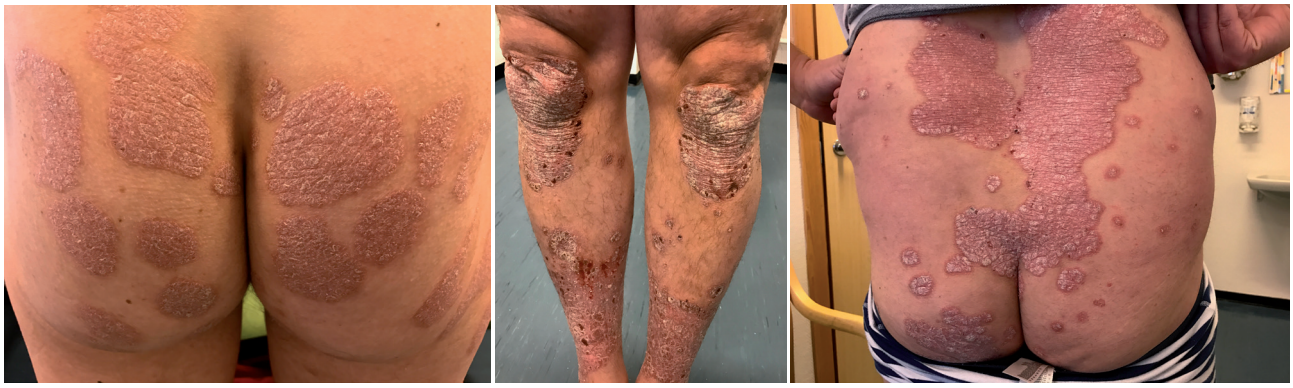

Fig. 1. Patients with severe psoriasis on immunomodulating medication.

medication are affected by COVID-19 infections (PSO-Protect)(23). Furthermore, an online registry for patients with atopic dermatitis on immunomodulating medication, the SECURE-AD registry, has been launched (SECURE-AD) (24). Similar registries exist for rheumatological (Rheum-covid) and gastrointestinal patients (Covidibd) (25, 26). The NICE Institute in the UK has prepared guidelines for dermatological patients on immunomodulating medication which are in line with recommendations from the British Dermatological Society (NICE) (27). They advise to avoid unnecessary hospital visits, to carefully consider when starting new patients on immunomodulating medication, and to advise on an individual basis whether patients should continue treatment (NICE) (27).

Immunosuppressed organ transplant recipients

Early reports from China and Italy suggested that immunosuppressed organ transplant recipients did not have a more severe course of COVID-19 infection than the general population (11, 13, 28–32). Later reports have confirmed these early findings and currently it is assumed that high age and presence of cardiopulmonary co-morbidities, just as in the general population increase the risk of a severe outcome (33). Whether immunosuppressed organ transplant recipients more often experience a mild form of the disease due to lack of an extreme immune response against the virus remains to be determined. Also, evidence lacks whether immunosuppressed treatment should be reduced when an active COVID-19 infection occurs.

Risk of infection

A study from Italy including 160 kidney transplant recipients who were either children or young adults, did not report any occurrence of COVID-19. Based on this, they advised not to change chronic immunosuppression in this group (34). In addition, a case series from Italy showed that paediatric liver transplant recipients, despite being immunosuppressed, were not at increased risk of severe pulmonary disease compared with the general population (11). A Chinese study on 87 heart transplant recipients from the Hubei province reported that 4 patients developed upper airway symptoms, but none of them was tested positive (32).

Course of disease

Early reports from Italy initially described that no COVID-19 fatalities had occurred among transplanted patients (11). Though, more recent studies reported on 3 long-term liver transplant survivors who died due to COVID-19 out of a total of 111 long-term transplant survivors (33). Characteristic for all of them was that they received very low doses of immunosuppression as they had been transplanted long ago. Furthermore, all 3 were males, older than 65 years, overweight, and all had severe co-morbidity with diabetes, hypertension and hyperlipidaemia (33). Cases from China on COVID-19 in heart, kidney and liver transplant recipients report successful recovery (28–32). Reports from Spain and the US agree that immunosuppressed transplanted patients do not experience a more severe course of the disease (35, 36). A study from Spain reports on 33 kidney transplant recipients infected with COVID-19: 2 patients of high age (87 and 72 years) died, 1 patient with chronic graft dysfunction lost a graft, 21 patients recovered and were discharged, 2 patients were at the time of the report in intensive care unit (ICU) with non-invasive ventilation (35). A study from New York reported on 41 renal transplant recipients with confirmed or suspected COVID-19 disease, one third required hospitalization, and at the end of the follow-up no mortality had occurred (36). Another report describes 12 renal transplant recipients with a severe disease course, of which 4 patients recovered and 8 patients died (37).

A hospital in South-eastern Michigan, US, admitted 13 heart transplant recipients with COVID-19. Six of these required admission at the ICU, and 2 eventually died. All 13 patients were black males (38). A Chinese case report describes a renal transplant patient and a bone marrow transplant, both

infected with COVID-19. Maintenance immunosuppression was withdrawn in these two patients, and treatment with low-dose corticosteroids was initiated, unfortunately with fatal outcome (39).

An Italian transplant centre reports on two lung transplant recipients infected with COVID-19 (40). In both patients mycophenolate mofetil was stopped when patients were tested positive. In the first patient calcineurin inhibitor administration was continued, while in the second patient this was stopped. The first patient had a favourable course and was discharged, while the second patient died (40). Two lung transplant recipients from a German transplant centre were tested positive for COVID-19. One was without symptoms and the other only had mild symptoms. Both had a favourable course (41).

Cancer patients

A Chinese study from 3 hospitals in Wuhan reported on 28 cancer patients infected with COVID-19 (42). The most common type of cancer in this group was lung cancer (25%). Serious adverse events in these patients were very common, and mortality was high (29%). Especially patients who had received active therapy within the last 14 days were at high risk for serious adverse events (42). Reviews and guidelines regarding care of cancer patients during the COVID-19 pandemic have been launched (43). Patients on active treatment have increased risk of an unfavourable course of disease (43). This means that preventive measures to avoid infection should be taken, unnecessary hospital visits should be avoided, and cancer treatment should be well-planned. It is also important to acknowledge that postponed or cancelled cancer treatment affects survival in these patients. A randomised trial specifically looking at treatment of COVID-19 in cancer patients is currently being performed (43).

Discussion

Risk assessment related to COVID-19 appears to be very complicated. We have seen healthy people between 15 and 35 years old who died of COVID-19, while a 102-year-old person recovered.

From start we feared that patients on immunosuppression were at higher risk of having a severe courses of COVID-19 (11). As the pandemic evolves, our understanding of the disease increases and data on presentation and course of the disease in different patient populations become available. More data and evidence is needed, as present knowledge is scarce and often based on small case studies.

At present, it is not possible to draw firm conclusions on whether immunosuppressed patients have a higher risk of adverse outcome when infected by COVID-19. Studies on immunosuppressed transplanted patients suggest that major risk factors for adverse outcome are age and cardiovascular comorbidity rather than immunosuppression (33). Available reports suggest an increased risk for cancer patients in active therapy (42, 43).

Whether immunosuppression helps to prevent a cytokine storm in immunosuppressed patients remains to be elucidated (14). We also do not know whether immunosuppressive medication can play a role in the treatment of COVID-19 (1, 14). More research is necessary to characterize the full spectrum of clinical illnesses, transmission efficiency, and the duration of viral shedding for immunocompromised patients with COVID-19 (44, 45).

Currently, there is no clear evidence to support an interruption of immunomodulating medication in our dermatological patients, but more epidemiological data is necessary to assess the risk of adverse outcomes with COVID-19.

References

1. Mehta P, McAuley DF, Brown M, Sanchez E, Tattersall RS, Manson JJ; HLH Across Specialty Collaboration, UK. COVID-19: Consider Cytokine Storm Syndromes and Immunosuppression Lancet 2020; 395: 1033–1034.
2. Varga Z, Flammer A, Steiger P, Haberecker M, Andermatt R, Zinkernagel AS, et al. Endothelial cell infection and endotheliitis in COVID-19. Lancet 2020; 395: 1417–1418.
3. Ritchie AI, Singanayagam A. Immunosuppression for hyperinflammation in COVID-19: a double-edged sword? Lancet. 2020; 395: 1111.
4. Sarzi-Puttini P, Giorgi V, Sirotti S, Marotto D, Ardizzone S, Rizzardini G, Antinori S, Galli M. COVID-19, cytokines and immunosuppression: what can we learn from severe acute respiratory syndrome? Clin Exp Rheumatol 2020; 38: 337–342.
5. Ye Q, Wang B, Mao J. The pathogenesis and treatment of the `Cytokine Storm' in COVID-19. J Infect 2020; 80: 607–613.
6. Mahase E. Covid-19: concerns grow over inflammatory syndrome emerging in children. BMJ 2020; 369: m1710.
7. Verdoni L, Mazza A, Gervasoni A, Martelli L, Ruggeri M, Ciuffreda M, et al. An outbreak of severe Kawasaki-like disease at the Italian epicentre of the SARS-CoV-2 epidemic: an observational cohort study. Lancet 2020; 395: 1771–1778.
8. Penninga L, Lorentzen AK, Sauer Mikkelsen C. Kawasaki disease: Two episodes of recurrent disease in a Greenlandic Inuit boy. J Forum Nord Derm Ven 2019; 24; 26–27.
9. Rowley AH, Finding the Cause of Kawasaki Disease: A Pediatric Infectious Diseases Research Priority, J Infect Dis 2006; 194: 1635–1637.
10. Esper F, Shapiro ED, Weibel C, Ferguson D, Landry ML, Kahn JS. Association between a novel human coronavirus and Kawasaki disease. J Infect Dis 2005;191: 499–502 .
11. D'Antiga L. Coronaviruses and immunosuppressed patients. The

facts during the third epidemic. Liver Transplant 2020; 26: 832–834.
12. Gori A, Dondossola D, Antonelli B, et al. Coronavirus disease 2019 and transplantation: A view from the inside. Am J Transplant 2020; 20: 1939–940.
13. Ju CR, Lian QY, Zhang JH, Qiu T, Cai ZT, Jiang WY, et al. Recommended prophylactic and management strategies for severe acute respiratory syndrome coronavirus 2 infection in transplant recipients. Chron Dis Translat Med 2020; 6: 87–97.
14. Romanelli A, Mascolo S. Immunosuppression drug-related and clinical manifestation of Coronavirus disease 2019: a therapeutical hypothesis. Am J Transplant 2020; 20: 1947–1948.
15. Feldmann M, Maini RN, Woody JN, Holgate ST, Winter G, Rowland M, Richards D, Hussell T. Trials of anti-tumour necrosis factor therapy for COVID-19 are urgently needed. Lancet 2020; 395: 1407–1409.
16. Torres T, Puig L. Managing Cutaneous Immune-Mediated Diseases During the COVID-19 Pandemic. Am J Clin Dermatol 2020; 21: 307–311.
17. Lebwohl M, Rivera-Oyola R, Murrell DF. Should biologics for psoriasis be interrupted in the era of COVID-19? J Am Acad Dermatology 2020; 82: 1217–1218.
18. Price KN, Frew JW, Hsiao JL, Shi VY. COVID-19 and immunomodulator/immunosuppressant use in dermatology. J Am Acad Dermatol 2020;82: e173–e175.
19. Bashyam AM, Feldman SR. Should patients stop their biologic treatment during the COVID-19 pandemic? J Dermatolog Treat 2020; 31: 317–318.
20. Amerio P, Prignano F, Giuliani F, Gualdi G. COVID-19 and psoriasis: Should we fear for patients treated with biologics? Dermatol Ther 2020; Apr 20: e13434.
21. Conforti C, Giuffrida R, Dianzani C, Di Meo N, Zalaudek I. COVID-19 and psoriasis: Is it time to limit treatment with immunosuppressants? A call for action. Dermatol Ther 2020; Mar 11: e13298.
22. Di Lernia V. Reply: Biologics for psoriasis during COVID-19 outbreak, J Am Acad Derm 2020; 82: e217–e218.
23. PSOprotect: Psoriasis patient registry for outcomes, therapy and epidemiology of Covid-19 infection. Available at: https://psoprotect.org/.
24. SECURE-AD: Atopic Dermatitis Registry for outcomes, therapy and epidemiology of Covid-19 infection. Available at: www.covidderm.org.
25. Rheum-covid: Rheumatology case registry for outcomes, therapy and epidemiology of Covid-19 infection. Available at: https://rheum-covid.org/.
26. COVIDIBD: Inflammatory bowel disease case registry for outcomes, therapy and epidemiology of Covid-19 infection. Available at: www.covidibd.org/.
27. NICE guideline [NG169]. COVID-19 rapid guideline: dermatological conditions treated with drugs affecting the immune response. Available at: https://www.nice.org.uk/guidance/ng169.
28. Li F, Cai J, Dong N. First cases of COVID-19 in heart transplantation from China. J Heart Lung Transplant 2020; 39: 496–497.
29. Liu B, Wang Y, Zhao Y, Shi H, Zeng F, Chen Z. Successful treatment of severe COVID-19 pneumonia in a liver transplant recipient. Am J Transplant 2020; 20: 1891–1895.
30. Chen S, Yin Q, Shi H, Du D, Chang S, Ni L, et al. A familial cluster, including a kidney transplant recipient, of coronavirus disease 2019 (COVID-19) in Wuhan, China. Am J Transplant 2020; 20: 1869–1874.
31. Qin J, Wang H, Qin X, Zhang P, Zhu L, Cai J, Yuan Y. Perioperative presentation of COVID-19 disease in a liver transplant. Hepatology 2020 Mar 27. [Online ahead of print.]
32. Ren ZL, Hu R, Wang ZW, Zhang M, Ruan YL, Wu ZY, et al. Epidemiological and clinical characteristics of heart transplant recipients during the 2019 coronavirus outbreak in Wuhan, China: a descriptive survey report. J Heart Lung Transpl 2020; 39: 412–417.
33. Bhoori S, Rossi RE, Citterio D, Mazzaferro V. COVID-19 in long-term liver transplant patients: preliminary experience from an Italian transplant centre in Lombardy. Lancet Gastroenterol Hepatol 2020; 5: 532–533.
34. Angeletti A, Trivelli A, Magnasco A, Drovandi S, Sanguineri F, Santaniello M, et al. Risk of COVID-19 in young kidney transplant recipients. Results from a single-center observational study. Clin Transplant 2020 May 12. [Epub ahead of print].
35. Montagud-Marrahi E, Cofan F, Torregrosa JV, Cucchiari D, Ventura-Aguiar P, Revuelta I, et al. Preliminary data on outcomes of SARS-CoV-2 infection in a Spanish single center cohort of kidney recipients. Am J Transplant 2020 May 5. [Epub ahead of print].
36. Husain SA, Dube G, Morris H, Fernandez H, Chang JH, Paget K, et al. Early outcomes of outpatient management of kidney transplant recipients with coronavirus disease 2019. Clin J Am Soc Nephrol 2020; 15: 1174–1178.
37. Abrishami A, Samavat S, Behnam B, Arab-Ahmadi M, Nafar M, Sanei Taheri M. Clinical course, imaging features, and outcomes of COVID-19 in kidney transplant recipients. Eur Urol 2020; 78: 281–286.
38. Ketcham SW, Adie SK, Malliett A, Abdul-Aziz AA, Bitar A, Grafton G, et al. Coronavirus disease-2019 in heart transplant recipients in Southeastern Michigan: A Ccase series. J Card Fail. 2020; 26: 457–461.
39. Huang J, Lin H, Wu Y, Fang Y, Kumar R, Chen G, Lin S. COVID-19 in post-transplantation patients-report of two cases. Am J Transplant 2020; 20: 1879–1881.
40. Cozzi E, Faccioli E, Marinello S, Loy M, Congedi S, Calabrese F, et al. COVID-19 pneumonia in lung transplant recipients: report of two cases. Am J Transplant 2020 May 12. [Epub ahead of print].
41. Koczulla RA, Sczepanski B, Koteczki A, Kuhnert S, Hecker M, Askevold I, et al. SARS-CoV-2 infection in two patients following recent lung transplantation. Am J Transplant 2020 May 12. [Epub ahead of print].
42. Zhang L, Zhu F, Xie L, Wang C, Wang J, Chen R, et al. Clinical characteristics of COVID-19-infected cancer patients: A retrospective case study in three hospitals within Wuhan, China. Ann Oncol 2020; 31:894–901.
43. Gosain R, Abdou Y, Singh A, Rana N, Puzanov I, Ernstoff MS. COVID-19 and cancer: a comprehensive review. Curr Oncol Rep 2020; 22: 53.
44. Guillen E, Pineiro GJ, Revuelta I, Rodriquez D, Bodro M, Moreno A, et al. Case report of COVID-19 in a kidney transplant recipient: Does immunosuppression alter the clinical presentation? Am J Transplant. 2020; 20: 1875–1878.
45. Man Z, Jing Z, Huibo S, Bin L, Fanjun Z. Viral shedding prolongation in a kidney transplant patient with COVID-19 pneumonia. Am J Transplant 2020; 20: 2626–2627.