Int J Clin Exp Pathol 2023;16(1):1-7
www.ijcep.com /ISSN:1936-2625/IJCEP0143431

Original Article

Coexistence of malignancy and tuberculosis: is it double disease or double hit related to COVID-19? - Experience from a tertiary care center

Subhashini Ramamoorthy, Bheemanathi Hanuman Srinivas, Bhawana Ashok Badhe, Sreerekha Jinkala, Rajesh Nachiappa Ganesh

Department of Pathology, Jawaharlal Institute of Postgraduate Medical Education and Research (JIPMER), Puducherry-605006, India

Received April 9, 2022; Accepted June 22, 2022; Epub January 15, 2023; Published January 30, 2023

Abstract: Background: Coexistent malignancy and tuberculosis (TB) are rarely encountered. Cancer patients are a highly vulnerable subgroup during this Covid crisis. Delayed treatment for malignancy because of COVID-19 pandemic leads to higher chances to get infections. Purpose: The present study aimed to present the clinicopathologic profile of the patients with coexistent carcinoma and TB during the COVID-19 pandemic in a tertiary care center. Materials and methods: This was a retrospective study conducted during the COVID-19 pandemic between April 2020 to May 2021 in the Department of Pathology of our Institute. 11 patients with coexistent malignancy and caseous necrotizing granulomatous inflammation with Langhans giant cells and or acid-fast bacilli (AFB) positivity were included in the study. Cases of ill-defined granulomas coexistent malignancy were excluded. We studied varied clinical and histopathologic features of these cases. Results: Eleven cases were reported with coexistent malignancy and tuberculosis, of which 8 were reported in 2021 and 3 cases were reported in 2020. Adenocarcinoma comprised 9 cases (81.8%) and the remaining 2 were squamous cell carcinoma (18.1%). Out of 11, 10 (90.9%) were new TB cases. Of these, 10 were extrapulmonary TB and one pulmonary TB case with cancer. Regarding chemotherapy, four patients accepted that chemotherapy was delayed because of the COVID-19 crisis. Conclusion: In this covid pandemic, India being the 2nd most populous country and endemic for TB, there is a higher chance of latent and active TB. The coexistence of two different pathologies is rare, even in a region with a high incidence of TB. Delayed chemotherapy in a pandemic situation leads to an increased incidence of infectious diseases such as TB.

Keywords: Malignancy, tuberculosis, COVID-19, pandemic

Introduction

Tuberculosis (TB) is a global threat to mainly developing and developed countries, and the estimated global incidence is ten million, according to World Health Organization (WHO). There were 1.2 million deaths due to TB in 2019. India being an endemic location for TB, constitutes around 26% of global TB, which is the highest of all countries [1]. Cancer is the second leading cause of death after coronary artery disease [2]. The association of TB with carcinoma was initially described 200 years ago by Bayle, who considered 'cavitation cancereuse' as one of the various types of TB [3]. The coexistence of carcinoma and tuberculosis has been reported in many sites, more commonly seen in the lungs, skin & larynx [4]. Simultaneous carcinoma and tuberculosis cases are rarely encountered in other sites such as colon, stomach, peripancreatic node, breast, and buccal mucosa. Cancer patients are a highly vulnerable sub-group in this COVID-19 crisis, prone to get varied types of infectious diseases during this pandemic. The current coronavirus pandemic has severely impacted India's health care system and also all around globally. Among the general population, the severely affected are those with cancer, who are at risk of disease progression and or increased chance of getting an infection. Cancer patients are more susceptible to infections due to their immunocompromised states, either due to the disease or treatment-related toxicity. This may result in

a dismal prognosis for cancer patients [5]. The present study aimed to present a clinicopathologic profile of patients with coexistent carcinoma and tuberculosis during the COVID-19 pandemic in a tertiary care center.

Materials and methods

A retrospective study was conducted on the coexistence of malignancy (any type) and tuberculosis reported during the COVID-19 pandemic from April 2020 to May 2021 in our Institute. Institute Ethics Committee approval was obtained IEC/2021/221.

Data collection procedure

For this study, we reviewed the cases reported as malignancy with tuberculosis during the study period, which includes 11 patients. Patient clinical and demographic details were collected from Medical Records Department (MRD). The patient's age, gender, chief complaints, co-morbid conditions, history, and family history of tuberculosis and lab results (for HIV status, covid status, tumor markers) were collected. Histopathologic findings, including the site & type of malignancy and site of tuberculosis, and tissue reaction were studied using Hematoxylin and Eosin (H & E), Acid Fast Stain (AFS) and Periodic Acid Schiff (PAS) stained slides. The characteristic histopathology finding of caseating granuloma and Langhans type of giant cell and/or identification of acid-fast bacilli were used as criteria for diagnosis of TB. Cases of ill-defined granulomas coexisting with malignancy were excluded.

Data analysis

Data analysis was done using SPSS software (version 20). Categorical variables were expressed using frequency and percentages. Quantitative variables were expressed using the mean. The demographic data such as age, sex, etc were expressed in percentage and ratio.

Results

We found 11 cases totally that had coexisting carcinoma and tuberculosis from various sites during this study period. Out of 11 patients, three patients were seen in 2020 (for 9 months), and the remaining 8 patients were reported in 2021 (over five months).

Male:female ratio was of 1:2.3 with female predominance. The age group ranges from 39 to 70 years, with a mean age of 55.3 years. Three patients had comorbidities with diabetes being the most common, (n=3) and in addition, one had ischemic heart disease (IHD). Among the malignancies, the majority were adenocarcinoma which constituted 9 (81.8%); the remaining 2 (18.1%) cases were squamous cell carcinoma. All 11 patients were HIV-negative. Out of 11, 10 (90.9%) cases of TB were new cases and one patient had a history of TB. There were 10 extrapulmonary TB and one pulmonary TB case with cancer. The extrapulmonary TB cases include 5 peripheral TB lymphadenopathy and 5 abdominal TB lymphadenopathy. Among those five abdominal TB lymphadenopathies, two cases showed caseating granuloma in the colonic wall along with malignancy. Five peripheral TB lymphadenopathy cases included three breast carcinoma, one lung cancer, one carcinoma of tongue, and one carcinoma of buccal mucosa (**Table 1**). All 11 cases showed caseating granuloma, and only one showed AFS positivity.

COVID-19 test was done in all patients (before surgery) and was negative. Anti-Tuberculous treatment (ATT) was started in 3 patients, 2 patients had completed ATT, 3 cases yet to start the treatment for TB & 2 patients succumbed to the disease. One patient expired because of postoperative sepsis and another patient died of advanced disease. Regarding chemotherapy to the remaining alive 9 patients, 3 patients completed chemotherapy, five patients are currently on chemotherapy treatment & one patient is yet to start chemotherapy [as of this writing]. Among the five patients who were on chemotherapy treatment, chemotherapy was delayed in four patients due to the COVID-19 pandemic (**Table 2**). This was significant in our study as the treatment got delayed in four out of five patients due to the COVID-19 pandemic.

Discussion

With the ongoing COVID-19 pandemic, there has been a sudden surge of cases with coexisting malignancy with tuberculosis. In our study, out of 11 cases in total, of which 8 cases were reported in 2021 up to May (i.e., for 5 months duration). The remaining 3 cases were in 2020 from April to December 2020 over 9 months.

Table 1. Clinical characteristics, site of malignancy, and TB

S. No.	Age (In years)	Sex*	Chief complaints	Site of carcinoma	Site of TB (n*)
1	39	F	Ulcerated lump in the left breast	Left breast	Left supraclavicular lymph node(1)
2	67	F	Abdominal pain, jaundice & fever	Periampullary region	Celiac, common hepatic & cystic nodes (11)
3	47	F	Lower abdominal pain	Ileocaecal junction	Colonic wall & lymph nodes (5)
4	66	F	Colicky abdominal pain with bilious vomiting & diarrhea	Caecum	Colonic wall & lymph nodes (20)
5	49	F	Colicky abdominal pain with fever, vomiting & diarrhea	Ileocaecal junction	Pericolic lymph node (1)
6	62	M	Fever with abdominal pain & right neck swelling	Metastatic deposit in right cervical node	Right Cervical Lymph node (1)
7	55	M	Recurrence Left ca tongue, with right neck swelling	Left ca tongue	Right cervical node (1)
8	62	F	Breathlessness	Right lung	Right lung
9	42	F	Left buccal mucosal growth with flap necrosis	Left buccal mucosa	Left cervical Lymph nodes (2)
10	50	F	Right breast lump with loss of weight	Right breast	Right supraclavicular lymph nodes (10)
11	70	M	Intolerant to solid and liquid Food	Antro-pyloric region	Lymph nodes from all station D2,8B & 9 (3)

*M, Male; F, Female; *n, Number of nodes involved.

Table 2. Histopathologic features, treatment & complications

S.No	Histopathology final diagnosis	Tissue reaction	AFB*	Chemotherapy	Delayed treatment
1	Invasive ductal carcinoma	Caseating granuloma	Negative	On chemotherapy	Yes, because of COVID-19
2	Periampullary adenocarcinoma	Caseating granuloma	Negative	Planned for chemotherapy	Yet to start chemo
3	Mucinous adenocarcinoma	Caseating granuloma	Negative	On chemotherapy	Yes, because of COVID-19
4	Well differentiated adenocarcinoma	Caseating granuloma	Negative	-	Expired
5	Well differentiated adenocarcinoma	Caseating granuloma	Negative	On chemotherapy	Yes, because of COVID-19
6	Metastatic adenocarcinoma	Caseating granuloma	Positive	On chemotherapy	Yes, because of COVID-19
7	Metastatic squamous cell carcinoma	Caseating granuloma	Negative	On chemotherapy	On treatment timely
8	Lung adenocarcinoma	Caseating granuloma	Negative	-	Expired
9	Residual squamous cell carcinoma	Caseating granuloma	Negative	Completed chemotherapy	Completed chemotherapy
10	Residual invasive breast carcinoma	Castrating granuloma	Negative	Completed chemotherapy	Completed chemotherapy
11	Residual adenocarcinoma	Caseating granuloma	Positive	Completed chemotherapy	Completed chemotherapy

*AFB, Acid fast bacilli.

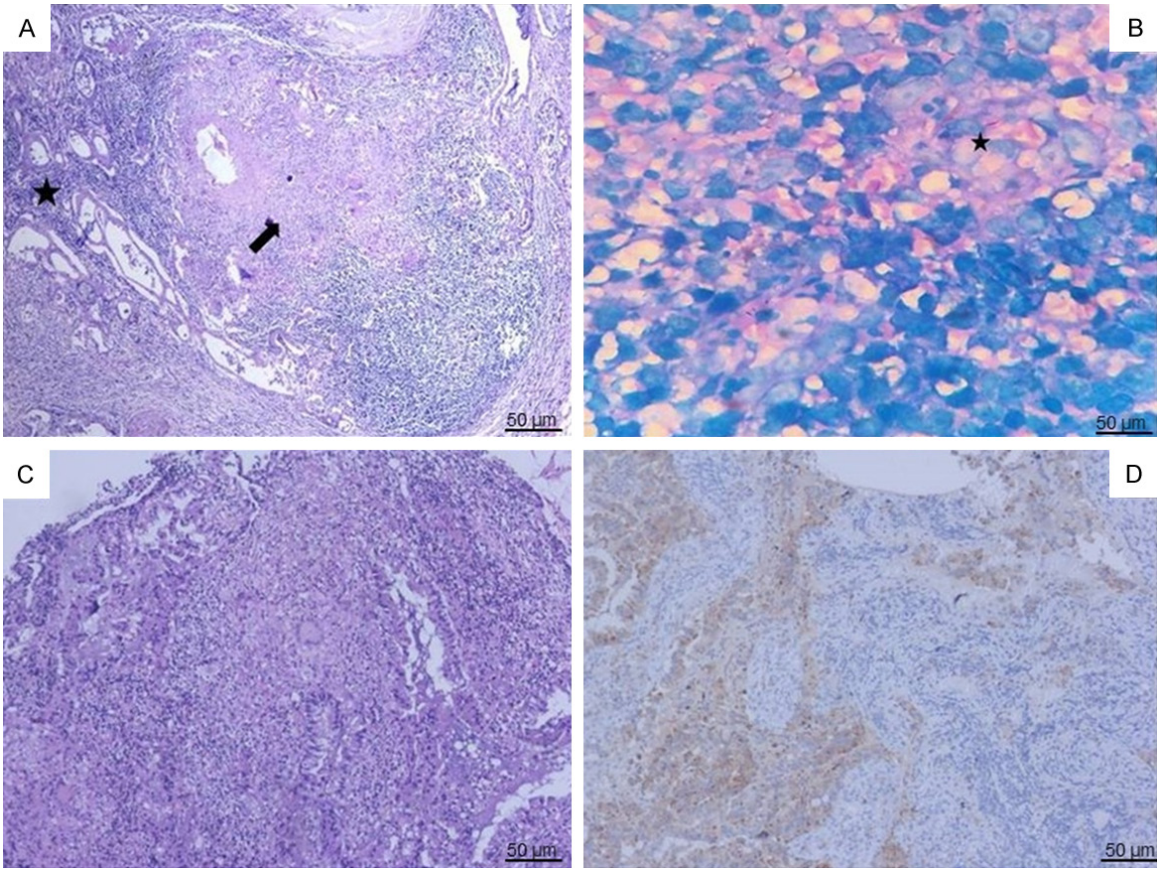

Figure 1. Coexistence of adenocarcinoma and caseating granuloma. A. Lymph node metastasis by colonic adenocarcinoma (*) with coexisting caseating granuloma (indicated by ↑) in colectomy and mesocolon resection specimen (H & E X 100). B. AFS stain: Positive for acid-fast bacilli in lymph node metastasis (indicated by *) by adenocarcinoma (AFS X 200). C. Lung biopsy shows malignant glands suggestive of adenocarcinoma (*) with coexisting caseating granuloma (H & E X 200). D. Immunohistochemistry (IHC) of lung adenocarcinoma highlighted by cytoplasmic positivity of Napsin-A IHC (DAB X 200).

The synchronous association of malignancy and tuberculosis can occur by several pathways. The possible association includes: i) Coincidence without any apparent relationship, ii) Secondary infection of cancer because of immunosuppression or secondary to chemotherapy or any delayed treatment, iii) Carcinoma develops in old TB foci, iv) Simultaneous development of both cancer and tuberculosis [6].

Generally, the chronic inflammatory condition has been an appropriate site of a microenvironment for carcinoma development through a possible mechanism. One such is an increased cell turnover rate, which provokes the chances of genetic errors [7].

A few chronic inflammatory diseases like Crohn's disease, ulcerative colitis, and schistosomiasis lead to changes from metaplasia to dysplasia progressing to malignancy. Pulmonary scarring in the periphery of the lung leads to lung carcinoma particularly adenocarcinoma also suggested by the same evidence as described above [8].

The simultaneous or sequential TB and lung cancer occurrence in the same patient have been reported in the case series and case-control studies [9]. In our study, only one case was reported as simultaneous lung cancer & TB (**Figure 1C**). In this current study, the most common association of malignancy with TB was gastrointestinal adenocarcinoma (n=5) (**Figure 1A**), followed by breast (n=2), one case each of carcinoma of the tongue, metastatic carcinoma of lung to cervical node highlighted by immunohistochemistry with Napsin A (**Figure 1D**), and

buccal mucosa. Abdominal TB is one of the commonest sites of extrapulmonary TB & typically occurs in the ileocaecal region, because of abundant lymphoid tissue and prolonged stasis. It can manifest in many ways and can affect the wall of the intestine, lymph nodes, solid organs, or peritoneum [10]. Peripancreatic tuberculous lymphadenitis is rare and sometimes mimics pancreatic pseudotumor & occasional case reports were reported in the literature. Desai et al have reported one similar case report [11]. Gastric tuberculosis is a rare entity even in endemic areas of TB. Gastric TB can be due to primary or secondary infection [12]. In our study, there was no such history of tuberculosis in the patient with stomach adenocarcinoma. The co-existence of breast and tuberculous axillary lymphadenitis is also rare and it was first described in 1899 by Warthin [13]. In a study by Kalpan et al, among 14,782 cases of breast cancer, 28 cases had coexisting tuberculosis with breast cancer [14].

Clinical diagnosis of coexisting malignancy with TB is difficult because of similar clinical and non-specific features of TB. The definitive diagnosis is based on histologic and bacteriologic evidence of TB. Histopathologically, TB is diagnosed by the presence of caseating granuloma with Langhans type of giant cells. However, the presence of granuloma can be confused with sarcoid-like granuloma, which is due to tumor antigens [15]. In our study, all 11 cases showed caseating granuloma, in addition, one case showed AFS positivity (**Figure 1B**) in gastric nodes.

According to the researchers, any connection between TB and malignancy will lead to reactivation of infection in immunocompromised patients who have cancer rather than the cause-effect relationship between infection and malignancy [16]. A study by Chaudhary et al [17] stated that malignant features can be dominant and there is a likelihood of missing tuberculous lesions. The coexistence of two pathologies can be considered in the following scenarios such as i) when TB colon does not show expected improvement or still progressive worsening ii) in patients with equivocal symptoms. Undiagnosed cancer or misdiagnosis is deleterious especially if the patient has a coexistent underlying TB infection because the initiation of chemotherapy will lead to dissemination and often fatal infections [2].

In the current scenario of the COVID era, COVID-19 RT-PCR and Rapid Antigen Detection (RAD) tests were done on all our patients. Fortuitously, all our 11 patients were negative. These tests were done preoperatively and also before starting chemotherapy. Being a vulnerable subgroup in this crisis, the mortality rate is two times higher in cancer patients than general population respectively, 5.6% versus 2.3% [18]. Among cancer patients, the mortality rate is higher with hematologic malignancies such as leukemia and lymphoma (37%) than with solid malignancies (25%) [19]. However, we did not find in such cases even a thorough checkup during this period. The continuous health care for cancer patients has been dramatically disrupted by the ongoing COVID-19 pandemic, both therapeutically and also in performing diagnostic procedures [20]. Most of the elective surgeries have been postponed as excessive strain on healthcare systems due to COVID-19 has led to a decline in the quality of care provided to cancer patients [21]. This can be one of the reasons that supports our study that delayed treatment may lead to secondary infections such as TB. In our current study, 4 patients are affected by delayed chemotherapy treatment. Though the COVID-19 has detrimental effects, the beneficial context was explained by a study by Spezzani et al stated that a stage 4 breast cancer patient, affected by COVID-19 infection, who is receiving immunosuppressive chemotherapy with leukopenia might have contributed to the rapid recovery and prevention of a cytokine storm and other COVID-19 complications [22]. A recent study reported that patients with metastatic cancer have the highest mortality rate [23].

There was a limitation in continuing the hospital services including the laboratory and radiology services for these patients, as the above was being diverted for COVID-19 management [24]. Along with these, patients were already old aged and also afraid of coming to the hospital, as they may get the infection [25]. Imposition of lockdown and travel restrictions are also a few reasons for cancer treatment interruption, especially in developing countries like India. For cancer patients, efforts are made to reduce the number of hospital visits and the extent of immunosuppression. Telemedicine is one such area that helps us to overcome this problem, even though it has its limitations. This Teleconsultation is best works for cancer

patients who are on follow-up [26]. In our study, three patients have completed the course of chemotherapy; telemedicine is useful for the follow-up of these patients.

Conclusion

In this COVID-19 pandemic, India, being the 2nd most populous country and endemic for TB, there is a higher chance of latent and active TB. Further immunocompromised states with cancer will just add the risk of a flare-up. The coexistence of two different pathologies is rare, even in a region with a high incidence of TB. But COVID-19 had suddenly increased the number of cases of double diseases. Delayed chemotherapy in a pandemic situation leads to an increased incidence of infectious diseases such as TB. Teleconsultation is one of the salvage options to reduce the double disease by giving the optimum treatment at an appropriate time. This pandemic has highlighted the shortcomings of our system and gave us an insight to positively improve our health care system to provide better cancer care.

Acknowledgements

We would like to acknowledge the patients and their families for allowing us to use their medical records in our study and allowing them to be published.

Disclosure of conflict of interest

None.

Abbreviations

TB, Tuberculosis; WHO, World Health Organization; H & E, Hematoxylin and eosin; AFB, Acid fast bacilli; PAS, Periodic acid schiff; MRD, Medical records department; ATT, Anti tuberculous treatment; RAD, Rapid antigen detection.

Address correspondence to: Dr. Bheemanathi Hanuman Srinivas, Department of Pathology, Jawaharlal Institute of Postgraduate Medical Education and Research (JIPMER), Puducherry-605006, India. Tel: 9443968232; E-mail: srinivas.bh08@gmail.com

References

[1] Global tuberculosis report 2020. Geneva: World Health Organization; 2020. Licence: CC BY-NC-SA 3.0 IGO.

[2] Falagas ME, Kouranos VD, Athanassa Z and Kopterides P. Tuberculosis and malignancy. QJM 2010; 103: 461-487.

[3] Pandey M, Abraham EK, K C and Rajan B. Tuberculosis and metastatic carcinoma coexistence in axillary lymph node: a case report. World J Surg Oncol 2003; 1: 3.

[4] Gopal SV, Panda S, Kadambari D and Srinivas K. Carcinoma colon associated with tuberculosis: an unusual presentation. Int J Colorectal Dis 2007; 22: 843-844.

[5] Shankar A, Saini D, Bhandari R, Bharati SJ, Kumar S, Yadav G, Durga T and Goyal N. Lung cancer management challenges amidst COVID-19 pandemic: hope lives here. Lung Cancer Manag 2020; 9; LMT33.

[6] Harikrishna J, Sukaveni V, Kumar DP and Mohan A. Cancer and tuberculosis. J Ind Acad Clin Med 2012; 13: 142-144.

[7] Schottenfeld D and Beebe-Dimmer J. Chronic inflammation: a common and important factor in the pathogenesis of neoplasia. CA Cancer J Clin 2006; 56: 69-83.

[8] Gandhi V. Abdominal tuberculosis with synchronous colon carcinoma- a case report. Univ J of Surg and Surgical Specialities 2020; 6: 1-2.

[9] Silva DR, Valentini Junior DF, Müller AM, de Almeida CP and Dalcin Pde T. Pulmonary tuberculosis and lung cancer: simultaneous and sequential occurrence. J Bras Pneumol 2013; 39: 484-489.

[10] Sharma MP and Bhatia V. Abdominal tuberculosis. Indian J Med Res 2004; 120: 305-315.

[11] Desai CS, Lala M, Joshi A, Abraham P, Desai D, Deshpande RB and Shah SR. Co-existence of periampullary carcinoma with peripancreatic tuberculous lymphadenopathy. JOP 2004; 5: 145-147.

[12] Kang HJ, Lee YS, Jang YJ and Mok YJ. Gastric cancer and concomitant gastric tuberculosis: a case report. J Gastric Cancer 2012; 12: 254-257.

[13] Warthin AS. The coexistence of tuberculosis and carcinoma of the mammary gland. Am J Med Sci 1899; 118: 25.

[14] Kalpan MH, Armstrong D and Rosen P. Tuberculosis complicating neoplastic disease: a review of 201 cases. Cancer 1974; 33: 850-858.

[15] Sharma S, Vijay Kumar AK, Kakkar N and Gupta V. Coexisting tuberculosis and adenocarcinoma of colon. Indian J Pathol Microbiol 2016; 59: 560-561.

[16] Browne M and Healy TM. Coexisting carcinoma and active tuberculosis of the lung: 24 patients. Ir J Med Sci 1982; 151: 75-78.

[17] Chaudhary P, Bhadana U and Lal R. A Retrospective cohort study of coexistence of carci-

noma and tuberculosis of colon: 12-year experience. Indian J Surg Oncol 2021; 12: 61-66.
[18] Zhang L, Zhu F, Xie L, Wang C, Wang J, Chen R, Jia P, Guan HQ, Peng L, Chen Y, Peng P, Zhang P, Chu Q, Shen Q, Wang Y, Xu SY, Zhao JP and Zhou M. Clinical characteristics of COVID-19-infected cancer patients: a retrospective case study in three hospitals within Wuhan, China. Ann Oncol 2020; 31: 894-901.
[19] Mehta V, Goel S, Kabarriti R, Cole D, Goldfinger M, Acuna-Villaorduna A, Pradhan K, Thota R, Reissman S, Sparano JA Gartrell BA, Smith RV, Ohri N, Garg M, Racine AD, Kalnicki S, Perez-Soler R, Halmos B and Verma A. Case fatality rate of cancer patients with COVID-19 in a New york hospital system. Cancer Discov 2020; 10: 935-941.
[20] Serraino D. COVID-19 and cancer: looking for evidence. Eur J Surg Oncol 2020; 46: 929-930.
[21] Li R, Rivers C, Tan Q, Murray MB, Toner E and Lipsitch M. Estimated demand for US hospital inpatient and intensive care unit beds for patients with COVID-19 based on comparisons with Wuhan and Guangzhou, China. JAMA Netw Open 2020; 3: e208297.
[22] Spezzani V, Piunno A and Iselin HU. Benign COVID-19 in an immunocompromised cancer patient - the case of a married couple. Swiss Med Wkly 2020; 150: w20246.
[23] Lee LY, Cazier JB, Angelis V, Arnold R, Bisht V, Campton NA, Chackathayil J, Cheng VW, Curley HM, Fittall MW, Freeman-Mills L, Gennatas S, Goel A, Hartley S, Hughes DJ, Kerr D, Lee AJ, Lee RJ, McGrath SE, Middleton CP, Murugaesu N, Newsom-Davis T, Okines AF, Olsson-Brown AC, Palles C, Pan Y, Pettengell R, Powles T, Protheroe EA, Purshouse K, Sharma-Oates A, Sivakumar S, Smith AJ, Starkey T, Turnbull CD, Várnai C, Yousaf N; UK Coronavirus Monitoring Project Team, Kerr R and Middleton G. COVID-19 mortality in patients with cancer on chemotherapy or other anticancer treatments: a prospective cohort study. Lancet 2020; 395: 1919-1926.
[24] Waterhouse DM, Harvey RD, Hurley P, Levit LA, Kim ES, Klepin HD, Mileham KF, Nowakowski G, Schenkel C, Davis C, Bruinooge SS and Schilsky RL. Early impact of COVID-19 on the conduct of oncology clinical trials and long-term opportunities for transformation: findings from an American Society of Clinical Oncology survey. JCO J Oncol Pract 2020; 7: 417-421.
[25] Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z, Xiang J, Wang Y, Song B, Gu X, Guan L, Wei Y, Li H, Wu X, Xu J, Tu S, Zhang Y, Chen H and Cao B. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet 2020; 395: 1054-1062.
[26] Goyal N, Saini D, Angural H, Richa, Kaushal V and Shankar A. COVID-19 and its impact on cancer patient's outcome and cancer research. Asian Pac J Cancer Care 2020; 5: 199-201.