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Digestive Symptoms in Oncology at The Time Of COVID-19: About Two Cases in An Oncology Department in Sub-Saharan Africa

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Abstract

Fever and respiratory symptoms have initially been described as the core symptoms in SARS-COV-2 or COVID-19 infection, but digestive manifestations such as anorexia, nausea, vomiting and diarrhea are becoming increasingly common in COVID-19 patients. These digestive symptoms can be falsely considered as side effects from the chemotherapy in oncology, thus delaying the diagnosis of COVID-19. Here, we report two cases of COVID-19 in patients undergoing chemotherapy for breast cancer. In case 1, SARS-COV-2 was diagnosed nine days after the onset of digestive disorders and the patient passed away before any COVID-19 treatment. In case 2, COVID-19 was suspected and diagnosed in the context of fever and vomiting within 24 hours. The patient has survived with adequate management. It emphasizes the importance to establish specific screening and treatment guidelines for SARS-COV-2 infection in Oncology.

Keywords: *Cancer, Chemotherapy, COVID-19, Immunosuppression, Digestive symptoms.*

Introduction

Cases of SARS-COV-2 infection or COVID-19 disease were initially defined by the combination of clinical symptoms like fever and respiratory symptoms. It was quickly realized that the infection could also be revealed by extra-pulmonary signs, especially digestive symptoms, such as diarrhea, vomiting and anorexia with or without respiratory signs (1-2). In medical oncology, these digestive disorders with or without fever are variably frequent in post-chemotherapy depending on the cytotoxic agent. When fever is present, the clinician's concern in a tropical environment is to eliminate above all, a bacterial infection and/or malaria. Thus, explorations are most often limited to medical imaging, thick blood smear and/or cultures of various biological specimens including blood, urine, pus etc... Even if viral infections are mentioned, the limited technical platform does not always allow to establish their diagnosis. SARS-COV-2 infection is a new emerging viral infection easily accessible at diagnosis. For its early diagnostic, the medical oncologist should suspect COVID-19 in front of digestive symptoms with or without fever. As compared to the general population, cancer patients are more likely to develop severe forms of COVID-19 (3) and have a poorer prognosis due to cancer and/or chemotherapy-induced immunosuppression (3-5). Thus, we emphasize the importance of the early diagnosis and management of COVID-19 in Medical Oncology through two cases of SARS-COV-2 infection in the context of cancer chemotherapy for breast cancer.

Case 1

Ms. O.D., a 40-year old woman was seen on 12/30/19 in the oncology department of the University Hospital Point G for a painful invasive ductal carcinoma (IDC) classified cT4bN0M1, grade II of Scarff-Bloom and Richardson (SBR), luminal B, with osteolytic vertebral metastasis (T_6-L_5). She received a palliative chemotherapy with Docetaxel (100 mg/m^2) and zoledronic acid (4 mg) once every three weeks (i.e. after 21 consecutive days). This chemotherapy was concomittant to Lamivudine (300 mg), Tenofovir (300 mg), and Efavirenz (600 mg). This antiretroviral treatment was initiated in August 2019 resulting in a normal CD4 count (555 cells/mm^3, N=500-1200) and undetectable viral load. The chemotherapy was relatively well-tolerated until the 3rd course of chemotherapy. The patient experienced asthenia, anorexia, alopecia and grade 2 vomiting (CTCAE v 5.0: Common Terminology Criteria for Adverse Events version 5.0). These vomiting were treated with Metoclopramide (10 mg per 8 hours) and were relieved in 48 hours. A complaint of lower back pain was relieved by slow release morphine (30 mg per 12 hours) and immediate-release morphine (10 mg per 4 hours) and by Gabapentin (300 mg per 8 hours). On 04/27/2020, the patient was hospitalized on day (D) 21 of her 4th course of chemotherapy for a week long non febrile diarrhea and vomiting grade 3 of CTCAE v5.0 persisting despite classic antiemetics and anti-diarrhea drug treatments. The clinical examination found a dehydrated patient with a WHO Performans Status (PS) at 3, with body temperature 37°C, oxygen saturation (O_2Sa) 93%, 136 heartbeats per minute, blood pressure 120/90 mm Hg and normal renal function, blood ionogram, and blood cell count. Symptomatic treatment corrected dehydration, but 48 hours later, she had a fever at 39°C with a significant desaturation (O_2Sa= 64%). Bacterial pneumonia or COVID-19, pulmonary embolism and carcinomatous lymphangitis were discussed as causative. Therefore, she received empirical antibiotic therapy {Ceftriaxone 2 g in 24 hours intravenously (IV)} and heparin therapy (Enoxaparin 6000 IU subcutaneously (SC) per 12 hours) before the availability of the results of additional examinations.

Thoracic-abdominopelvic CT angiography (Figures 1 and 2) shows a right basal segmental pulmonary embolism associated with sparse bilateral pulmonary parenchymal condensation, a liver segment IV metastasis and multiple osteolytic lesions (vertebral, iliac, bilateral femoral). Thick blood smear, blood, urine and stool cultures have not revealed any parasitic or bacterial infection. The oropharyngeal swab was tested SARS-COV-2 positive by RT-PCR (Reverse Transcriptase Polymerase Chain Reaction). Unfortunately, the patient had passed away by the time we received her COVID-19 test result. She therefore received no specific COVID-19 treatment.

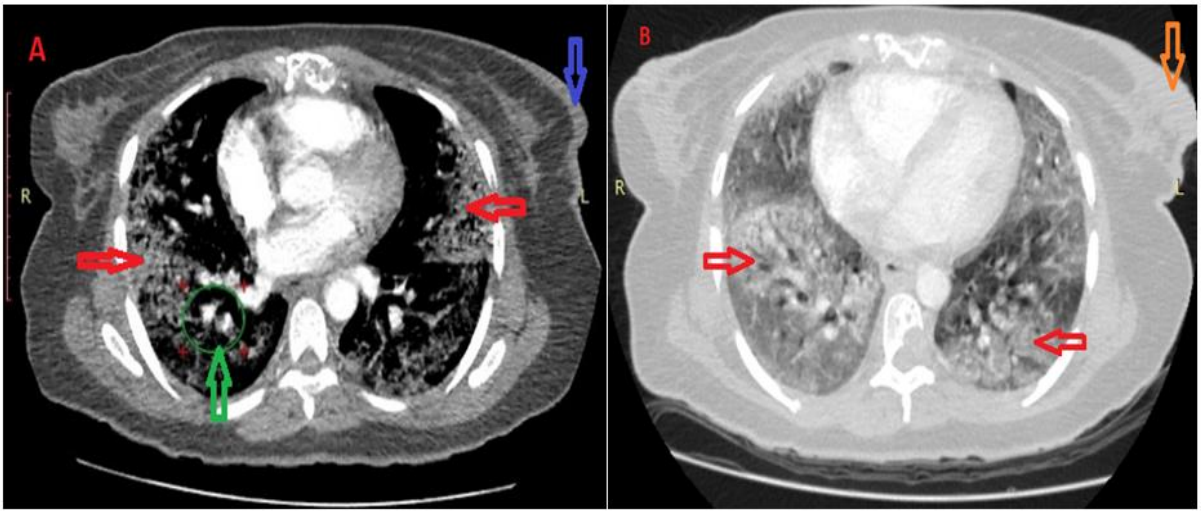

Figure 1: Thoracic sections in mediastinal (A) and parenchymal windows (B): mixed and sparse parenchymal condensations with air bronchogram (red arrows), endoluminal lacunar image in the right postero and mid-basal segment arteries (green arrow), thickening of the skin coating (blue arrow) and left breast tissue mass approximately 3 cm long (orange arrow).

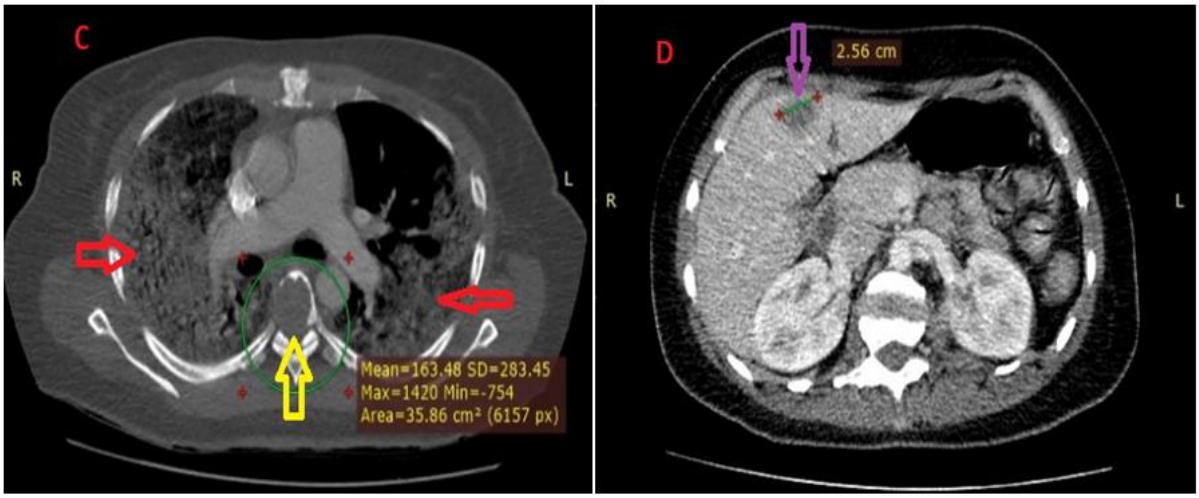

Figure 2: Thoracic and abdominal CT scan: axial section on the thoracic stage passing through the bifurcation of the pulmonary artery (C), showing diffuse bilateral pulmonary parenchymal lesions (red arrows) and T6 vertebral body osteolytic lesion (yellow arrow); axial section on the abdominal floor passing through the hilum of the kidneys (D), objectifying a hypodense nodular lesion of liver segment IV.

Case 2

Mrs. DT, a 35-year old woman with no personal medical history, has been followed in the oncology department of the University Hospital Point G since January 2020 for CCI of the right breast classified cT3N0M0, luminal A. We proposed a sequential neo-adjuvant chemotherapy with four cycles of AC60 (Adriamycin 60 mg/ m^2 plus Cyclophosphamide 600 mg/m^2) followed by four cycles Taxotere 100 mg/m^2 IV administration every three weeks (i.e after consecutive 21 days). Despite the premedication to prevent or minimize the side effects of chemotherapy, the patient was poorly tolerant since the onset of the first cycle of AC60 received on 01/27/2020. The following side effects occurred within 48 hours.

- Digestive toxicities: nausea, vomiting grade 3 of CTCAE vs 5.0 and abdominal pain for 72 hours relieved by IV injection of Ondansetron 8 mg/12 hours, Levosulpiride 25 mg/8 hours, Methylprednisolone 80 mg/24 hours and Phloroglucinol 80 mg/8 hours.
- Hematological toxicities: grade 3 neutropenia (620 neutrophils/mm^3, N: 2000-7000/mm^3) without fever on day 19 of the course of treatment, requiring the postponement of the 2nd course.
- Cutaneous toxicities: hyperpigmentation of the extremities, complete alopecia, grade 1 onycholysis relieved by simple antiseptic treatments and grade 1 oral mucositis treated with bicarbonate mouthwashes and a topical antifungal drug.
- Asthenia

The other AC60 cures were relatively better tolerated when we reinforced preventive treatments for the side effects of chemotherapy and the systematic administration of three doses of Filgrastim 30 MU, a Granulocyte Colony Stimulating Factor (GCSF) subcutaneously after each treatment.

The patient presented on 05/07/2020 -D4 of the 1st Taxotere treatment-, typical side effects of Taxanes i.e.- cutaneous toxicity grade 3 of CTCAE vs 5.0 (cutaneous detachment and diffuse itching), muscular pain and watery eyes. The concomitant appearance of CTCAE vs 5.0 grade 2 vomiting, fever at 40°C and chills led us to discuss febrile neutropenia, malaria, bacterial infection or COVID-19. The patient was a PS OMS 1, with blood pressure at 140/70 mm Hg, a O_2Sa at 98% and 90 heartbeats per minute. The somatic examination had no particularity apart from the cutaneous lesions. Noticeably, she had no respiratory symptoms.

The patient immediately received an empirical broad-spectrum antibiotic therapy with Tazocillin (Tazobactam 0.5 g / Piperacillin 4g) an IV injection every 8 hours and Filgrastim 30 MU subcutaneous daily.

The blood count confirmed a grade 4 neutropenia with 300 neutrophils/mm^3 and a grade 2 anemia (Hemoglobin at 9.6 g/dL). The blood smear, blood and urine cultures did not reveal any germ.

She tested COVID-19 positive. A thoracic-abdominopelvic CT-Scan carried out on 04/28/2020 as part of the therapeutic evaluation of her tumor pathology was strictly normal; no additional thoracic imaging was performed.in the absence of respiratory signs.

The patient was transferred to the COVID-19 management center at University Hospital Point G, Bamako, Mali on 05/08/2020. She was treated according to the national therapeutic protocol with Chloroquine Phosphate 200 mg/8 hours and Azithromycin 500 mg on D1 and 250 mg daily from the second to fourth day.

Apyrexia was obtained 24 hours and neutrophils count normalized 48 hours after her treatment started. Tazocillin and GCSF were then stopped within four days. Control COVID-19 tests were negative on D8 and D9 and she was discharged on 05/18/2020 at D10. Three weeks later, she was able to continue her well-tolerated neo-adjuvant chemotherapy with Paclitaxel 80 mg/ m^2 every week.

Discussion

The main clinical manifestations reported at the beginning of the Covid-19 pandemic caused by SARS-COV-2 infection were fever, cough, dyspnea and fatigue [1,2]. The gastrointestinal disorders initially described as rare, i.e. anorexia, diarrhea, nausea and vomiting have increasingly been reported by several authors [1,2,6]. In a multicenter study, Pan Lei *et al.* found digestive signs in 50.5% of patients including 6% without any respiratory symptoms. Anorexia was found in 78.6% of the patients, diarrhea in 34%, vomiting in 3.9% and abdominal pain in 1.9%. In this study, the delay between the onset of symptoms and the hospital admission was significantly longer in patients with digestive disorders than in those without a digestive sign, i.e. 9 versus 7.3 days on average [1]. This delay in the diagnostic was linked to the ignorance of a relationship between COVID-19 and these digestive symptoms. We observed a similar scenario in our patient Mrs. OD who presented digestive symptoms without fever, initially considered as side effects of chemotherapy with Docetaxel. COVID-19 was suspected when fever and dyspnea were present and confirmed within 48 hours after her hospital admission. We therefore wonder whether or not this case reflects the reality of SARS-COV-2 infection in our patients receiving chemotherapy. In contrast, febrile vomiting in our 2nd patient, Mrs. DT, made us suspect and diagnose the COVID-19 infection within 24 hours of symptom onset.

In addition to malignant cells, chemotherapy targets all rapidly renewing cell types, this is why its toxicity is felt in several such tissues in the body. This explains the high frequency of digestive and hematological complications with their corollary of immunosuppression [4,7]. Immunosuppression exposes patients not only to various viral, bacterial, fungal or parasitic infections with significant morbidity and mortality [3-4], but also to thromboembolic complications [8]. Thus, cancer patients have a higher risk of SARS-COV-2 infection, more severe complications and a poorer prognosis than the general population. Liang Wenhuan *et al.* reported 39% of severe complications of COVID-19 (admission to intensive care, intubation, ventilation and death) in cancer patients versus 8% in those without cancer. The median time to onset of these complications was shorter in cancer patients than in non-cancer patients (13 days versus 43 days) [3]. The risk of complications is even higher in patients who have received chemotherapy or surgery in the past month (75% versus 43%) than in those who had not received such treatments [3]. The presence of multimetastatic cancer associated with a heavy history of chemotherapy and immunodeficiency by HIV1 in our 1st patient allows us to classify her among patients at high risk of developing severe forms of SARS-COV-2 infection. This patient did indeed die in the context of pulmonary embolism, but it is difficult to relate this embolic complication to infection with SARS-COV-2 alone. She was immunosuppressed due to HIV-1 and had a metastatic cancer, two other risk factors for thromboembolic accidents [9,10]. The 2nd patient, younger, with no other poor prognostic factor apart from localized breast cancer and immunosuppression secondary to chemotherapy, was able to recover from COVID-19. This survival was probably due to an early diagnosis in the 24 hours of onset of symptoms and to a multidisciplinary and adequate management of SARS-COV-2 infection but also of febrile neutropenia (administration of GCSF and broad spectrum antibiotics). In the light of current data, our case reports clearly pose the fundamental question of recommendations for the SARS-COV-2 screening and management in oncology. It seems important to evaluate by multicentric research protocols, the efficiency of a systematic screening for SARS-COV-2 infection in patient undergoing chemotherapy and presenting any digestive disorder associated or not with fever and/or respiratory symptoms.

Conclusion

COVID-19 constitutes a health emergency, which requires specific preventive measures, early diagnosis and effective management of cancer patients similar to other people at high risk of COVID-19 infection. It is timely and urgent to develop standard recommendations for screening and specific management of this infection in oncology.

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