

COVID-19 in a patient receiving adjuvant breast cancer chemotherapy with granulocyte colony-stimulating factor (G-CSF) support: A case report

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Abstract. Patients receiving chemotherapy are at high risk for severe infections and complications such as acute respiratory syndrome. The most commonly used adjuvant chemotherapy protocols (docetaxel-cyclophosphamide every 3 weeks or the dose-dense regimen, doxorubicin-cyclophosphamide every 2 weeks followed by paclitaxel) incorporate granulocyte-colony stimulating factor (G-CSF). G-CSF is routinely administered to prevent chemotherapy-associated neutropenia but often results in significant neutrophilia. The present case describes a patient with breast cancer who was successfully treated for severe COVID-19 respiratory syndrome while under adjuvant chemotherapy (docetaxel-cyclophosphamide) treatment and long-term G-CSF support. In addition, the potential effect of G-CSF on the respiratory deterioration of the patient given its cardinal role in innate inflammation and, accordingly, the cytokine storm associated with COVID-19 was described. The case described in the present study indicated how solutions to the immunity challenges faced when treating a patient with chemotherapy may be the source of a larger problem within the coronavirus COVID-19 pandemic.

Introduction

Patients receiving chemotherapy are at high risk for severe infections and complications such as acute respiratory syndrome. The most commonly used adjuvant chemotherapy

protocols (docetaxel-cyclophosphamide every 3 weeks or the dose-dense regimen, doxorubicin-cyclophosphamide every 2 weeks followed by paclitaxel) incorporate granulocyte-colony stimulating factor (G-CSF) (1-3). G-CSF is routinely administered to prevent chemotherapy-associated neutropenia but often results in significant neutrophilia.

We describe a patient with breast cancer who was successfully treated for severe COVID-19 respiratory syndrome while under treatment with adjuvant chemotherapy (docetaxel-cyclophosphamide) and long-term G-CSF support. In addition, we discuss the potential effect of G-CSF on the respiratory deterioration of the patient given its cardinal role in innate inflammation and, accordingly, the cytokine storm associated with COVID-19. Our case shows how solutions to the immunity challenge faced when treating a patient with chemotherapy may be the source of a bigger problem in the coronavirus COVID-19 pandemic.

Case report

A 58-year-old woman with a history of obesity, hypertension, and dyslipidemia was diagnosed with grade 2 Estrogen/Progesteron-positive, HER2-negative invasive ductal breast carcinoma (7 mm) with axillary lymph node involvement (N=1/6) and extracapsular invasion. The patient underwent right lumpectomy and sentinel node biopsy. Systemic staging was negative for distant metastases. The 21-gene Recurrence Score (Oncotype-DX™) was 19. She was started on a regimen of intravenous (i.v.) docetaxel 75 mg/m² and i.v. cyclophosphamide 600 mg/m² every 3 weeks and subcutaneous (s.c.) pegfilgrastim (pegylated G-CSF) 6 mg on day 3 of each cycle. On day 7 of cycle 2, the patient presented with fever (38.2°C) and neutropenia [absolute neutrophil count (ANC) 700 cells/μl] and tested positive for COVID-19. Two tests were performed. The first in the emergency room, using geneXpert Xpress by Cepheid. The second test was Allplex™ 2019-nCoV assay by Seegene. The second test was performed while she was already in the department.

She reported a history of fatigue followed by fever of 4 days' duration. She was hemodynamically stable, with

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Abbreviations: G-CSF, granulocyte-colony stimulating factor; i.v., intravenous; s.c., subcutaneous; ANC, absolute neutrophil count; ALC, absolute leukocyte count

Key words: breast cancer, COVID-19, chemotherapy, granulocyte-colony stimulating factor, respiratory syndrome

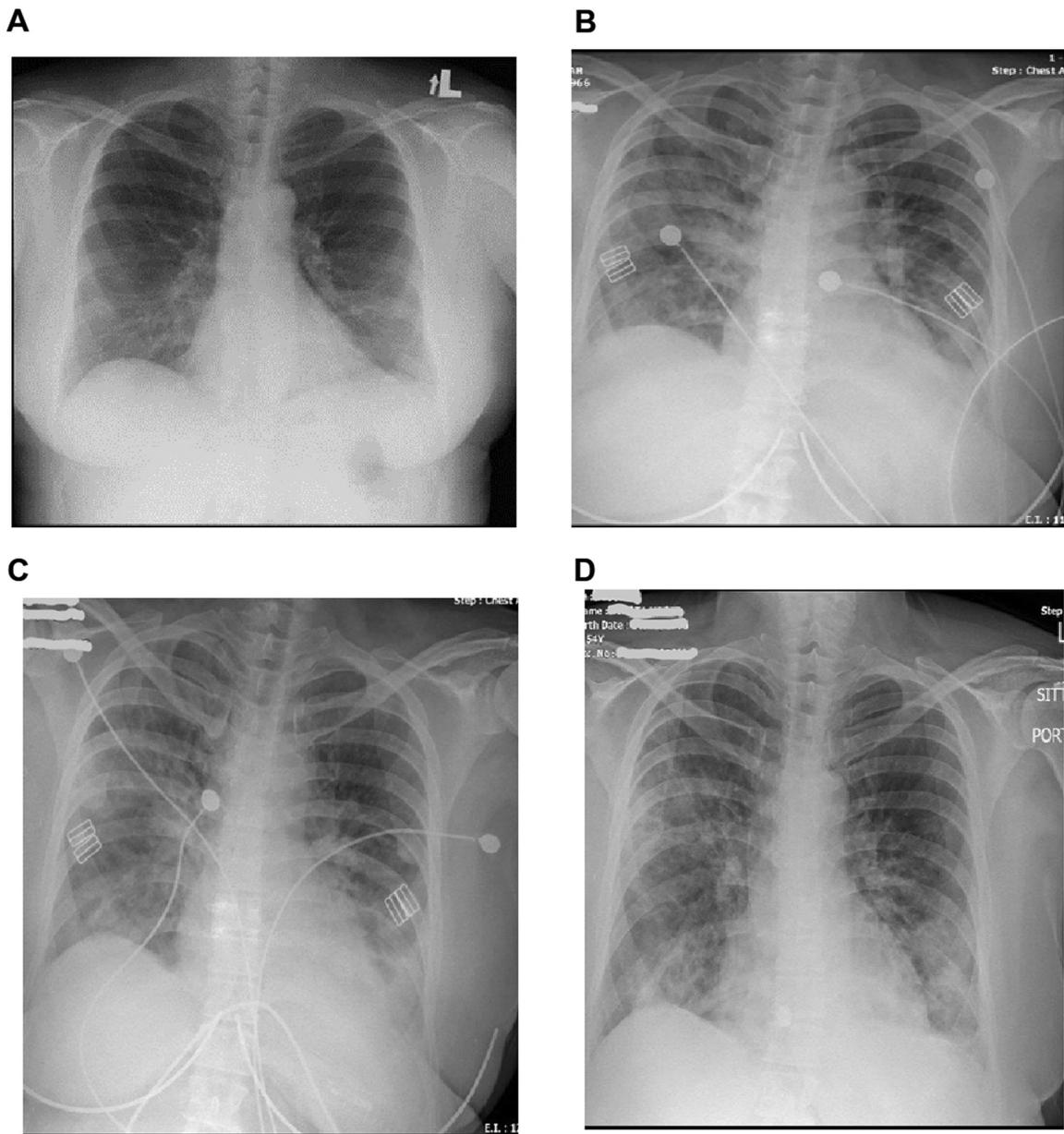


Figure 1. Chest X-ray findings during hospitalization course. (A) Day 1. Bilateral, mostly basilar, mild infiltrates. (B) Day 4. Bilateral diffuse infiltrates; worsening in line with the clinical deterioration. (C) Day 7. No significant change from day 4 despite clinical improvement on day 6. (D) Day 10. Mild improvement from day 7, with less opacity around left lower lung fields, in line with clinical improvement (high-flow nasal cannula no longer required).

oxygen saturation 95% in room air with mild tachypnea (20 breaths/min). There was no cough, chest pain, or shortness of breath. Chest X-ray showed mild bilateral infiltrates (Fig. 1). The patient also reported diarrhea grade 1.

After treatment with i.v. piperacillin/tazobactam (4.5 g every 8 h), the neutropenic fever resolved. However, the patient was increasingly tachypneic (respiratory rate 30 breaths/min, 88% desaturation) and was placed on 4L oxygen by nasal cannula. Blood and stool cultures were negative; *Clostridium* toxins were not detected. She also received s.c. enoxaparin sodium (1 mg/kg bid), i.v. dexamethasone (6 mg qd for 10 days), and i.v. remdesivir (loading dose 200 mg followed by 100 mg bid for 3 days).

The next day, the dyspnea and desaturation worsened. Work-up revealed ANC 4,700 cells/ μ l sterile blood cultures, and bilateral multifocal opacities on chest X-ray (Fig. 1). The

patient was placed on a high-flow nasal cannula (HFNC) therapy (flow 40 l/min, FiO_2 0.4%). On day 4, the ANC/absolute leukocyte count (ALC) ratio peaked at 18.5, and HFNC parameters were increased (flow 60 l/min, FiO_2 0.8%). Acute atrial fibrillation developed and was treated with amiodarone with conversion to sinus rhythm.

On day 6 of hospitalization (day 10 of COVID-19 symptoms), gradual clinical improvement was noted along with a decrease in ANC/ALC ratio. On day 14, the patient was discharged home with no significant respiratory symptoms (Fig. 1).

Discussion

During the COVID-19 epidemic, to minimize the risk of febrile neutropenia in patients receiving adjuvant

chemotherapy and to avoid overwhelming emergency rooms and hospitals, the NCCN extended the prophylactic use of G-CSF from high-risk-only patients (>20%) to intermediate-to-high-risk patients (10-20%). A cautionary note was added that cases of respiratory infection, respiratory symptoms, or confirmed or suspected COVID-19, G-CSF posed a risk of increased pulmonary inflammation or an increase in levels of inflammatory cytokines associated with an adverse outcome (4).

Our patient had pre-existing comorbidities known to be associated with respiratory and other systemic complications (5-7) in addition to two life-threatening conditions of febrile neutropenia and active COVID-19. Although per-protocol G-CSF administration may have prevented severe bacterial infection, it could also have caused further deterioration in her COVID-19-related lung status. Yang *et al* found that in patients with COVID-19, a high ratio of neutrophil count to lymphocyte count, high ratio was associated with a high rate of rapid development of severe disease (8).

Neutrophils are short-lived closely controlled cells that form an essential part of the host defense and inflammatory response. G-CSF regulates neutrophil production by inducing the proliferation and maturation of myeloid progenitors and promoting neutrophil release from bone marrow (9). Like G-CSF, granulocyte-macrophage CSF (GM-CSF) belongs to the hematopoietin/cytokine receptor superfamily and increases neutrophil chemotaxis and migration. However, its response kinetics differ and it is considered more pro-inflammatory (10). It also contributes to the development and maintenance of alveolar macrophages (11,12). Cumulative data suggest that both factors may play a cardinal role in innate inflammation and are potential mediators of the cytokine storm (13-15) as part of a positive feedback loop with inflammatory cytokines/chemokines, T-helper cells, and neighbouring cell populations (16).

Most of the reports on the involvement of stimulating factors in COVID-19 have focused on GM-CSF (13,14) and the incorporation of anti GM-CSF receptor to mitigate the COVID-19 cytokine storm (15,17,18). Using a prospective design, De Luca *et al* showed that administration of mavrilimumab, an anti-GSF monoclonal antibody, led to better clinical outcomes than standard treatment in mechanically ventilated patients with severe COVID-19 pneumonia, hypoxia, and systemic hyperinflammation (17).

There are no standardized treatments available for COVID-19. It is clear that one protocol does not fit all, and researchers are seeking accurate predictive markers to aid in the selection and manner of incorporation of the available drugs, including steroids (19). Dexamethasone is part of the standard of care for respiratory distress or severe pneumonia, and it seems that it may be of benefit in modulating G-CSF associated respiratory syndrome. In our patient, in view of the expected G-CSF-induced neutrophil activation the clinical course, and the developing cytokine storm, it was reasonable to add steroids.

We do not know which specific part(s) of the treatment (antivirals, steroids, supportive care, or their combination) had the greatest impact on the patient's outcome. Nevertheless, it is encouraging that an immune-suppressed patient with comorbidities and an apparently looming cytokine storm could

recover in a short time with current treatment protocols. Given the potential involvement of cytokines in exacerbation of COVID-19, the new risk/benefit balance of active treatments, especially those including G-CSF injections, needs to be carefully considered (20).

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Availability of data and materials

The datasets used and/or analyzed during the present study are available from the corresponding author on reasonable request.

Authors' contributions

RY is the primary care-giver in the Oncology institute, conceptualized and co-wrote the manuscript and performed the literature search. HG is part of the breast-unit multidisciplinary group in the oncology institute which advised regarding the patient's treatment, and in addition co-wrote to the manuscript. MS was the main care-giver during her hospitalization, in addition he co-wrote the manuscript. JD and RM treated the patient at her initial Covid-19 diagnosis. IK acted as medical supervisor during the patient's hospitalization with COVID-19 infection and co-wrote the manuscript. All authors had access to the data and a role in writing the manuscript. All authors read and approved the final manuscript.

Ethics approval and consent to participate

The Helsinki Committee of Rabin Medical Center provided exemption for this case report since it does not contain any studies with human participants performed by any of the authors.

Patient consent for publication

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Competing interests

The authors declare that they have no competing interests.

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