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Case Report

COVID-19 outbreak in Italy: Clinical-radiological presentation and outcome in three oncologic patients[☆]



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ABSTRACT

We present three patients affected by pulmonary squamous cell carcinoma, metastatic esophageal cancer and advanced non-Hodgkin lymphoma, who incurred in coronavirus 2019 (COVID-19) infection during the early phase of epidemic wave in Italy. All patients presented with fever. Social contact with subject positive for COVID-19 was declared in only one of the three cases. In all cases, laboratory findings showed lymphopenia and elevated C-reactive protein (CRP). Chest x-ray and computed tomography showed bilateral ground-glass opacities, shadowing, interstitial abnormalities, and "crazy paving" pattern which evolved with superimposition of consolidations in one patient. All patients received antiviral therapy based on ritonavir and lopinavir, associated with hydroxychloroquine. Despite treatment, two patients with advanced cancers died after 39 and 17 days of hospitalization, while the patient with lung cancer was dismissed at home, in good conditions.

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1. Introduction

In December 2019, a new pathogen enveloped RNA betacoronavirus has been identified and named severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) which was linked to severe pulmonary disease in 14% of the cases [1,2]. The diffusion of this pathogen started as epidemic in Chinese region, and thereafter spread throughout several countries in the world. The World Health Organization (WHO) has recently declared pandemic the coronavirus disease 2019 (COVID-19) [3]. In Italy were declared 294,932 cases with 35,668 deaths, at September 19, 2020 [4].

Oncologic patients are more susceptible to infection than healthy individuals due to systemic immunosuppression and

anticancer treatments. Furthermore, patients who suffer from cancer carry poorer prognosis in case of infection. During Covid-19 outbreak is fundamental to differentiate oncologic patients with fever and respiratory symptoms due to COVID-19 from other causes, in order to administer appropriate treatment in positive cases and to protect negative patients from this infection. The recent multinational consensus proposed by the Fleischner Society guide medical practitioners in the use of chest x-ray (CXR) and computed tomography (CT) for the management of COVID-19 [5]. We present radiologic presentation, treatment, and outcome of 3 patients affected by esophageal cancer, pulmonary squamous cell carcinoma, and non-Hodgkin lymphoma (NHL) with diagnosis of COVID-19 during recent Italian outbreak.

2. Case report

The first patient was a 70 years old male with diagnosis of esophageal cancer in July 2019, treated surgically with esophago-gastric resection followed by intrathoracic esophago-gastroplasty through both abdominal laparoscopic and right thoracotomy approach. Local, hepatic, and osseous relapse occurred in January 2020. In January 2020, the patient underwent the first cycle of

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combined folinic acid, 5-fluorouracil, and irinotecan (FOLFIRI). The patient lived in the Lombardy region, the first epidemic site in Italy, and he was admitted at the Emergency department on February 24, 2020 showing fever (body temperature, BT: 37.9 °C), asthenia, anorexia, and dysphagia since 3 days. At physical examination he manifested scattered bilateral inspiratory rhonchi. The breath rate was 18 acts/minute and the blood oxygen saturation (SaO₂) was 96%. Laboratory findings showed leucopenia (white blood count, WBC: $3.37 \times 10^3/\mu\text{l}$; normal values, VN: $4\text{--}10 \times 10^3/\mu\text{l}$), lymphopenia (lymphocytes count, LC: $0.28 \times 10^3/\mu\text{l}$; VN: $1.5\text{--}4 \times 10^3/\mu\text{l}$) and elevated C-reactive protein, (CRP, 11.55 mg/dl; VN: 0–0.5 mg/dl). CXR showed the gastric tubulization that occupies the inner third of the right hemithorax, diffuse interstitial thickening in medium and lower pulmonary fields, and reticulo-nodular opacities in the left lower field (Fig. 1). The real-time reverse-transcriptase-polymerase-chain-reaction (RT-PCR) assay of nasal-pharyngeal swab specimen was positive for SARS-CoV-2 on February, 26. He received antiviral therapy based on oral lopinavir 400 mg plus ritonavir 100 mg, associated with oral hydroxychloroquine 200 mg administered twice a day for 10 days. Antibiotic therapy with intravenous (iv) ceftriaxone 1g daily was given for 10 days. Oxygen supportive therapy was administered with nasal cannula. Due to the onset of nausea and vomiting associated with the development of cachexia, antiemetic therapy (iv metoclopramide 10 mg) and sedoanalgesia (intradermal fentanyl 25mcg/hour or iv tramadol 100 mg) were introduced, as needed. A second RT-PCR assay of nasal-pharyngeal swab was still positive 20 days later. The patient died at day 39 of hospital stay, due to worsening of the general conditions.

The second patient was a 64 years old male affected by lung squamous cell carcinoma treated by neoadjuvant immunotherapy with pembrolizumab (from January 2019) followed by left upper lobe lobectomy and mediastinal lymphadenectomy (September 2019). He was then treated with pembrolizumab as post-surgical treatment until January 2020. The patient was exposed to a subject positive for SARS-CoV-2 on February 14, 2020. On February 28, he was admitted at the Emergency department with fever (BT: 38.5 °C) and dyspnea since 5 days. The physical examination was normal. The

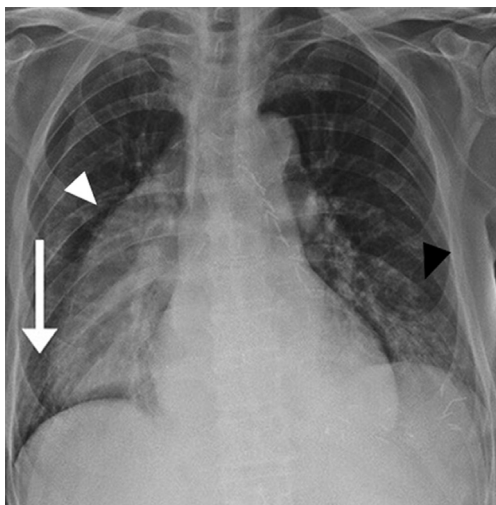


Fig. 1. A 70 years-old male affected by advanced esophageal cancer receiving combined folinic acid, 5-fluorouracil, and irinotecan (FOLFIRI) chemotherapy, with positivity for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) at real-time reverse-transcriptase-polymerase-chain-reaction (RT-PCR) nasal-pharyngeal swab; the chest x-ray of showed the gastric tubulization that occupied the inner-third of the right hemithorax (white arrowhead), the presence of bilateral interstitial thickening at the middle and lower pulmonary fields, particularly on the right side (white arrow), and reticulo-nodular opacities in the left lower field (black arrowhead).

breath rate was 22 acts/minute and the SaO₂ was 98%. At the laboratory findings lymphopenia (LC: $0.57 \times 10^3/\mu\text{l}$) and elevated CRP (1.73 mg/dl) were observed. Nevertheless, no alteration of the WBC count was registered ($4.13 \times 10^3/\mu\text{l}$). In comparison with a chest contrast-enhanced CT done 14 days before, the CT scan performed on the admission day showed the appearance of patchy peripheral ground-glass round opacities associated with focal opacities with “crazy-paving” aspect which is characterized by ground-glass superimposed by thickening of the interlobular septa in both lower lobes (Fig. 2) [6]. The RT-PCR of nasal-pharyngeal swab was positive for SARS-CoV-2 on March 4. The patient was treated twice a day with oral lopinavir 400 mg plus ritonavir 100 mg, associated with oral hydroxychloroquine 200 mg both for 10 days. Additionally, he received antibiotic therapy, namely oral azithromycin 500 mg daily for 7 days and intravenous ceftriaxone 2 g daily for 8 days. Supportive oxygen therapy was given through nasal cannula. After resolution of both fever and dyspnea, he was discharged at day 12 of hospital stay, with supportive oxygen therapy, in home isolation. Two RT-PCR of nasal-pharyngeal swab performed respectively 21 days and 38 days after hospital admission, were still positive for SARS-CoV-2; nevertheless the patient was in good conditions at home isolation until two nasal-pharyngeal swabs negative for SARS-CoV-2 performed 53 and 55 days after hospital admission.

The third patient was a 79 years old male suffering from lymphoplasmacytic NHL discovered in December 2019. The patient was administered with the first cycle of rituximab combined with bendamustine at the end of January 2020. On March 5, 2020 he was admitted at the Emergency department with fever (BT: 38.4 °C) from 4 days, denying any contact with COVID-19 positive subjects. No significant findings were observed at the physical examination. The breath rate was 20 acts/minute and the SaO₂ was 94%. Lymphopenia (LC: $0.39 \times 10^3/\mu\text{l}$) and elevated CRP (9.69 mg/dl) were recorded from the laboratory testing; the WBC count was normal ($7.69 \times 10^3/\mu\text{l}$). As compared with chest contrast-enhanced CT done in December 2019, CT performed on the admission day, documented the appearance of bilateral peribronchial and peripheral “crazy-paving” opacities, extended for 30–35% of all the lung volume, based on visual score [7]. The patient refused the hospitalization, nevertheless he presented further at the Emergency department 4 days later for persisting fever and for new onset of dyspnea, after receiving the positivity for SARS-CoV-2 of the RT-PCR nasal-pharyngeal swab, on March 8. At this time respiratory acts were 24/minute and the SaO₂ was 89%; the lymphopenia (LC: $0.34 \times 10^3/\mu\text{l}$) and WBC ($8.79 \times 10^3/\mu\text{l}$) were substantially unchanged while CRP level increased (14.48 mg/dl). CT revealed the impairment of the infiltrates extension (40–45% vs 30–35%) and the appearance of band-like peripheral consolidation in both inferior lobes superimposed on a prevalent crazy paving pattern (Fig. 3) [7]. He was administered antiviral therapy; first, he received oral lopinavir 400 mg plus ritonavir 100 mg, twice a day for 2 days, suspended for diarrhea onset. Then, he received oral darunavir 800 mg and cobicistat 150 mg daily for 5 days. In addition, oral hydroxychloroquine 200 mg was given in two daily administrations for 14 days. Two antibiotics were also administered: 2 g of intravenous ceftriaxone for 8 days and oral 160/800 mg of trimethoprim/sulfamethoxazole for 7 days. During the hospitalization, the patient received high flow oxygen therapy with either nasal cannula and reservoir facemask. Despite supportive oxygen and administration of both antiviral and antibiotic therapy the patient died from respiratory failure, after 17 days of hospital stay.

3. Discussion

Several recent reports have described radiologic abnormalities observed in patients affected by COVID-19 pneumonia [8–10]. CXR

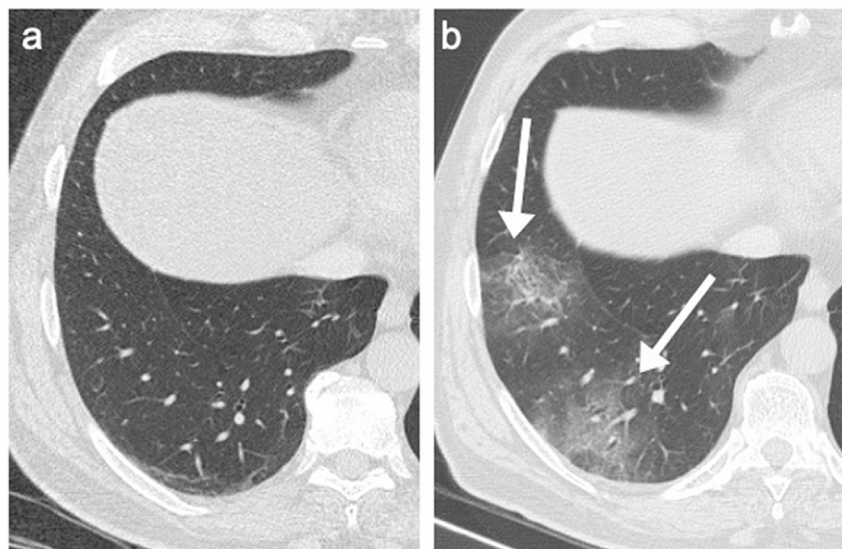


Fig. 2. A 64 years-old male suffering from lung squamous cell carcinoma treated by surgery and pembrolizumab with positivity for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) at real-time reverse-transcriptase-polymerase-chain-reaction (RT-PCR) nasal-pharyngeal swab; (a) unenhanced chest computed tomography (CT) performed 14 days before symptoms onset showed no infiltrates in the right lower lobe, while (b) CT at hospital admission day revealed the appearance of bilateral ground-glass rounded opacities, more extended in the right lower lobe (white arrows).

findings are supposed to be bilateral or local patchy shadowing, ground-glass opacity, and interstitial abnormalities [9]. The chest CT scan shows the presence of bilateral ground-glass opacities and consolidation in the majority of the cases, with a “crazy paving” pattern observed after 3 days of symptoms onset [8]. In addition, during the first and second week after the disease manifestations is reported an increase of abnormalities extent at CT with a transition from prevalent ground-glass pattern to consolidation or a mixed type [10].

We presented three cases of oncologic patients with diagnosis of COVID-19 based on RT-PCR nasal-pharyngeal swab positivity, at the beginning of the Italian outbreak. According with the current literature, the manifestations of the disease were the appearance of interstitial abnormalities at CXR, while of ground-glass and concomitant consolidations or “crazy paving” pattern at CT, with

impairment of disease extension in few days [8–10]. However, in patients affected by cancer, particularly with ongoing chemotherapy, these radiological findings associated with fever or dyspnea should be differentiated with further disease, particularly drug-related lung toxicity and other infections than COVID-19, requiring specific therapy, respectively with steroids and antibiotics. Lee YJ et al. described a case of organizing pneumonia during FOLFIRI chemotherapy, manifesting with multifocal patchy ground glass opacities and consolidation on both lungs at CT, requiring steroid therapy [11]. Although rare (2.7% of the cases), pneumonitis related with pembrolizumab should be considered, particularly in non-small cell lung cancer (NSCLC), that manifested higher incidence (4.1%) in comparison to other cancer treated with the same therapy [12]. Furthermore several cases of interstitial lung toxicity manifesting with extensive bilateral ground-glass opacity were

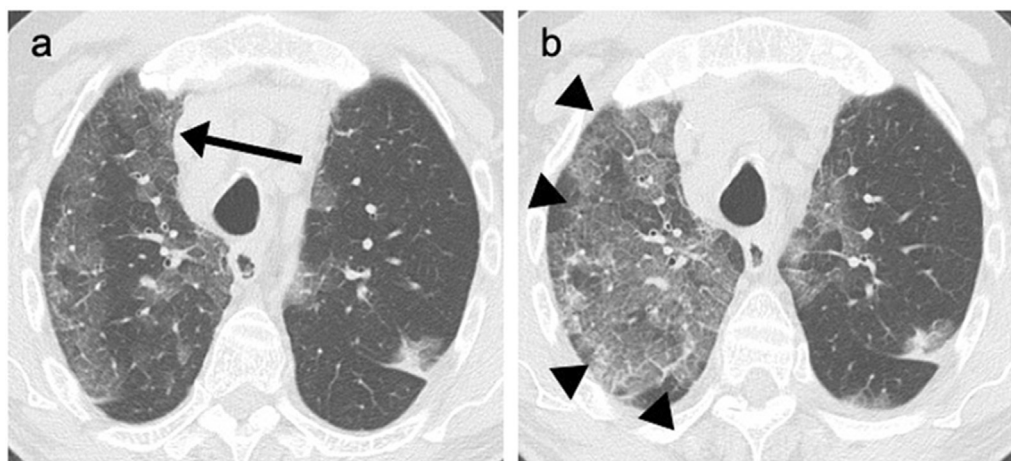


Fig. 3. A 79 years old male with lymphoplasmacytic non-Hodgkin lymphoma (NHL) under R-bendamustine scheme therapy with positivity for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) at real-time reverse-transcriptase-polymerase-chain-reaction (RT-PCR) nasal-pharyngeal swab; (a) unenhanced chest computed tomography (CT) performed 4 days after symptoms onset documented the presence of ground-glass opacities in both upper lobes, with superimposed smooth interlobular septal thickening known as “crazy paving” pattern (black arrow); the CT (b) performed 8 days later after symptoms onset requested for occurrence of mild respiratory failure depicted the increase of lung parenchymal extent, in particular in the right upper lobe (black arrowheads).

described after rituximab therapy for NHL [13]. Infection other than COVID-19 should also be considered as differential diagnosis, particularly opportunistic pathogens such as *Pneumocystis jirovecii*, which usually require bronchoalveolar lavage (BAL) using bronchoscopy. Nevertheless, in our patients the combination of epidemiologic and clinical findings in association with radiologic abnormalities guided to the diagnosis of COVID-19, confirmed by nasal-pharyngeal swab positivity for SARS-CoV-2.

All the patients received the association of lopinavir and ritonavir; the use of this association during the early phase of COVID-19 epidemic was based on the results obtained by Chu et al., demonstrating a significant reduction of acute respiratory distress syndrome (ARDS) and death in patients affected by SARS-CoV-1 [14]. Hydroxychloroquine was administered in all patients, considering the encouraging reports deriving from China in the management of COVID-19 [15]. In one patient was used the combination of darunavir and cobicistat, as previously described, after suspension of lopinavir/ritonavir for sudden onset of diarrhea [16]. The current fatality rate of patients with cancer and COVID-19, is higher as compared to overall mortality (5.6% vs 2.3%) [2].

In conclusion, during COVID-19 outbreak in patients affected by cancer, even during chemotherapy, the new onset of fever or dyspnea in association with radiologic appearance of diffuse interstitial abnormalities or multiple infiltrates at CXR or ground-glass opacities, consolidation, and crazy-paving pattern at CT should be considered as a sign of this potentially fatal infection. COVID-19 lead to death two out of three patients with advanced cancers, despite the use of the current widely used pharmacological treatment.

Declaration of competing interest

The Authors declared no conflict of interest.

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