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Research Article

Lymphoma with skin localization and COVID 19 – a clinical case and review of literature

Maria Moneva-Sakelarieva[1,2], Yozlem Kobakova[1,2], Spiro Konstantinov[1], Georgi Momekov[1], Niya Emilova Semerdzhieva[2], Stefka Achkova Ivanova[3], Ventseslava Petrova Atanasova[4], Petar Yordanov Atanasov[2], Maria Stamova Vakrilova Becheva[5]

1 *Faculty of Pharmacy, Medical University – Sofia, Sofia, Bulgaria*
2 *Clinic of Internal Diseases UMHATEM "N. I. Pirogov", Sofia, Bulgaria*
3 *Bugarian Pharmaceutical Science Society, 2 Dunav Blvd., Sofia, Bulgaria*
4 *Bulgarian Pharmaceutical Union, Sofia, Bulgaria*
5 *Speciality „Rehabilitator", Medical College, Medical University – Plovdiv, 120 Bratya Buxton Str., Plovdiv 4004, Bulgaria*

Corresponding author: Stefka Achkova Ivanova (ivanovastefka_pharm@yahoo.com)

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Abstract

In this article, we present a clinical case of a 63-year-old patient who was treated in the COVID unit of the Clinic for Internal Diseases of UMBALSM (University General Hospital for Active Care and Emergency Medicine) "N. I. Pirogov" on the occasion of a proven coronavirus infection with a PCR positive test for SARS-CoV2-virus, clinical symptoms of severe coronavirus pneumonia, and with accompanying disease - lymphoma with skin localization, condition after lower right lobectomy, chemotherapy and checkpoint therapy for squamous cell carcinoma of the lung. We also examined the role of the transcription factor NF-kB in the course of the coronavirus infection in a patient with the indicated lymphoproliferative disease and a history of active smoking. We tried to clarify questions such as "Do severe forms of coronavirus infection and the relatively rare disease lymphoma with cutaneous localization have a common pathogenesis?" Is it possible to effectively pharmacotherapeutically influence two, at first glance, so heterogeneous diseases?" The conclusions drawn can help us to specify certain nosological units as "more vulnerable" to severe forms of COVID19 infection.

Keywords

COVID 19, cutaneous lymphoma, squamous cell carcinoma of the lung, transcription factor NF-kB, inflammation, carcinogenesis

Introduction

The 2019 novel coronavirus (2019-nCoV), currently known as SARS-CoV-2, is the cause of coronavirus disease 2019 (COVID-19). This virus was first discovered in Wuhan, China's Hubei province, and appears to have been a zoonotic infection that has now adapted to humans. SARS-CoV-2 is genetically similar to the 2003 severe acute respiratory syndrome (SARS) and shares many similarities with the disease characteristics of influenza virus infection (Rashid 2022). Like SARS-CoV-1, which emerged in 2002, both the novel SARS-CoV-2 infect host cells by binding their viral envelope spike-(S) proteins to the same receptor, angiotensin-converting enzyme 2 (ACE2) (Hoffmann et al. 2020). Although this mechanism is shared by SARS -CoV, a recent study using biophysical assays found that

the S protein of SARS-CoV-2 binds 10 to 20 times more strongly to the ACE2 receptor. The higher binding affinity to the ACE2 receptor has been suggested to be responsible for the greater viral spread and disease severity compared to SARS-CoV (Wrapp et al. 2020).

Many of the clinical manifestations of SARS-CoV-2 infection are related to virus-induced disruption of the immune system and resulting tissue damage. These changes in immunity include humoral immunodeficiency with B-cell defects, a hyperinflammatory state characterized by loss of T-cell subsets and high levels of cytokines driven by IL-6, IL-1β, TNF-α, and complement-mediated damage (Dupont et al. 2020).

Research has established that the inflammatory responses associated with COVID-19 are driven by nuclear factor (NF)-kappa B (NF-κB) (Hadjadj et al. 2020; Nilsson-Payant et al. 2021). As a result of immune system dysregulation after COVID-19, the unrestrained release of proinflammatory cytokines, elevated cytokine levels, and circulating chemokines cause hemorrhage, thrombocytopenia, and systemic inflammation (Attiq et al. 2021).

COVID-19 has been shown to cause more severe disease and increased mortality in patients with active cancer (Dai et al. 2020; Pinato et al. 2020; Tian et al. 2020; Grivas et al. 2021). The complex interplay of immune dysfunction, active malignancy, the effects of cancer treatment on the immune system, and additional comorbidities, significantly affect the course of the coronavirus disease. The effect of cancer on COVID-19 has also been shown to vary depending on the type of cancer (Bernard et al. 2021).

There is insufficient data in the literature on COVID-19 infection and cutaneous lymphomas. A diagnosis of cutaneous T-cell lymphoma (CTCL) does not predispose to viral infections, and most patients with CTCL have indolent disease. However, there should be an individualized approach in patients with aggressive primary cutaneous lymphomas and advanced CTCL. During the COVID-19 pandemic, different treatment strategies for cutaneous lymphomas should be considered (Elmasry et al. 2021). Cutaneous T-cell lymphomas (CTCLs) are a heterogeneous group of lymphoproliferative neoplasms that display a wide range of immune-phenotypic, clinical, and histopathological features. The biology of CTCL is complex and remains unclear. In recent years, the application of next-generation sequencing (NGS) has advanced our understanding of the pathogenetic mechanisms, including genetic aberrations and epigenetic abnormalities, which shape the mutational landscape of CTCL and represent one of the important pro-tumorigenic principles in CTCL initiation and disease progression (Patil et al. 2022). It has been suggested that antigen-driven T-cell proliferation induced by drug use, genetic predisposition, or somatic mutations in signaling pathways may contribute to the pathogenesis of CTCL. However, conflicting data have been obtained and the etiology of the disease remains unknown (Jahan-Tigh et al. 2013; Choi et al. 2015). Patients with CTCL are likely to develop various secondary malignancies such as other non-Hodgkin's lymphomas, melanomas, and lung or bladder cancer (Agar et al. 2010).

The majority of CTCL cases consist of mycosis fungoides (MF), which accounts for approximately 60% of CTCL cases, and CD30+ lymphoproliferative disorder (LPD), which accounts for approximately 25% of CTCL cases. Rare individual CTCLs have also been defined, such as Sézary syndrome (SS), accounting for about 5% of CTCL cases (Swerdlow et al. 2016; Geller 2018). The rarest subtypes, accounting for up to 2% of cases, include entities with an indolent clinical course and limited distribution, such as primary cutaneous CD4+ small/medium T-cell LPD (SMPTC-LPD), primary cutaneous acral CD8+ T-cell lymphoma (acral CD8+ TCL) and subcutaneous panniculitis-like TCL (SPTCL), as well as those with an aggressive course, such as primary cutaneous CD8+ aggressive epidermotropic cytotoxic T-cell lymphoma (CD8+ PCAETL) or primary cutaneous γδ T-cell lymphoma (PCGDTCL) (Damasco and Akilov 2019).

An independent analysis of genomic data published prior to 2017 covering 220 CTCL cases (186 SS; 25 MF; 9 CTCL NOS) highlighted at least 55 putative driver genes affecting multiple signaling pathways. Interestingly, there is significant overlap between MF and SS in the affected pathways. Commonly disrupted genes include those involved in TCR signaling pathways (PLCG1; CARD11; CD28; RLTPR) and those that selectively upregulate the NFkB pathway (Park J et al. 2017). Other disrupted pathways include DNA damage response (TP53; POT1; ATM; BRAC1-2), chromatin modification (ARID1A; TRRAP; DNMT3A; TET2), and JAK STAT signaling (STAT5B; JAK3). Critically, the aforementioned gene variants have been functionally validated, confirming their driver gene status (Choi et al. 2015; Prasad et al. 2016; Patel et al. 2020). Furthermore, CTLA4-CD28 and ICOS-CD28 gene fusions enhance CD28-dependent T-cell signaling, and RLTPR variants activate the NFκB pathway, thereby increasing downstream TCR signaling. The high prevalence of these NFkB pathway gene variants in CTCL, supported by functional data, indicates that there is a critical selection pressure for activation of the NFkB pathway in the transformation of mature T cells (Ungewickell et al. 2015; Park et al. 2017).

To date, increasing evidence supports a key role of endothelial dysfunction in the pathogenesis of COVID-19 and in determining its severity (Evans et al. 2020). Data from recent studies indicate that severe pulmonary manifestations in patients with COVID-19 are not solely due to ARDS, but also of macro- and microvascular involvement, with vascular endothelial damage and subsequent dysfunction (Fodor et al. 2021). Vascular damage is probably related to both the direct cytopathic effect of the virus on endothelial cells (EC) and the high levels of cytokines and other inflammatory markers, causing systemic endotheliitis, platelet activation, leukocyte adhesion, and reduced nitric oxide (NO) bioavailability (Fodor et al. 2020; Ambrosino et al. 2021). Smoking is also associated with endothelial dysfunction and increased free radical concentrations.

Cigarette smoking impairs pulmonary immune function and the upper respiratory tract and is a well-established risk factor for respiratory infectious diseases, morbidity, and mortality (Park et al. 2018; Strzelak et al. 2018;

Han et al. 2019). Cigarette smoke is an aerosol containing more than 4,700 components of reactive oxygen species (ROS) and carbon monoxide (CO) as important pathogenic constituents. Other well-known substances found in cigarette smoke are nicotine, polycyclic aromatic hydrocarbons and cadmium, as well as other metals and substances such as benzene, formaldehyde or tar (Pryor and Stone 1993; Smith and Fischer 2001; Ding et al. 2007; Csordas and Bernhard 2013).

Molecular mechanisms of endothelial dysfunction include oxidative stress, reduced NO availability, inflammation, increased monocyte adhesion, and cytotoxic effects of cigarette smoke and next-generation tobacco and nicotine products (Muller and Morawietz 2009; Hofmann et al. 2021; Evans et al. 2022; Amponsah-Offeh et al. 2023). Smoke disrupts cell-cell adhesions and damages the epithelial barrier through AJ proteins, including E-cad and p120 (Zhang et al. 2012). Adherent junctions (AJs) modulate cell-cell adhesion between epithelial cells through complexes that are composed of E-cadherin (E-cad), p120-catenin (p120), β-catenin (β-ctn), and α- catenin (α-ctn) (Reynolds and Roczniak-Ferguson 2004). Expression of p120 in endothelial cells modulates endotoxin-induced lung inflammation by interfering with NF-κB signaling (Wang et al. 2011).

Epithelial barrier function is the first line of defense against inhaled noxious agents. A sustained increase in airway epithelial permeability occurs in smokers and individuals exposed to secondhand smoke, where the epithelial barrier is disrupted and the subepithelial tissue is directly exposed to reactive chemicals and oxidants, free radicals.

In the largest US study to date on smoking and COVID-19, current and former smoking showed a lower risk of SARS-CoV-2 infection than never smoking, while a history of smoking was associated with a higher risk of severe form of COVID-19 (Young-Wolff et al. 2022).

An overall analysis was performed with 320 publications included. The pooled odds ratio for current versus never or never smokers was 1.08 (95% CI 0.98–1.19; 37 studies) for hospitalization, 1.34 (95% CI 1.22–1.48; 124 studies) for severity and 1.32 (95% CI 1.20–1.45; 119 studies) for mortality. Estimates for former versus never smokers were 1.16 (95% CI 1.03–1.31; 22 studies), 1.41 (95% CI: 1.25–1.59; 44 studies), and 1.46, respectively (95% CI 1.31–1.62; 44 studies). Estimates for ever versus never smokers were 1.16 (95% CI 1.05–1.27; 33 studies), 1.44 (95% CI 1.31–1.58; 110 studies), respectively) and 1.39 (95% CI 1.29–1.50; 109 studies). A 30–50% increased risk of progression to COVID-19 has been found for current and former smokers compared to never smokers (Gallus et al. 2023).

Inflammatory cytokines, oxidative stress, and infections can activate NF-κB (Attiq et al. 2018). Activated NF-κB is involved in various cell signaling pathways that affect cell differentiation, proliferation, survival, intercellular communication, and immunomodulation (Gerondakis et al. 1999; Mattson and Meffert 2006). Any disturbances in NF-κB function further lead to inflammatory and autoimmune conditions, metabolic disorders, and cancer (Courtois and Gilmore 2006; Baker 2011; Taniguchi and Karin 2018).

Patient and methods

In a retrospective analysis from April 2020 to May 2022, we made a finding of only one case of a patient with a positive RT-PCR test for SARS-CoV2 and lymphoma with cutaneous localization as hematological comorbidity. Here we present a case report of a 63-year-old patient with coronavirus pneumonia confirmed by a positive RT-PCR test for SARS-CoV2. Clinical-laboratory (hematological and biochemical), genetic (PCR) and imaging methods (conventional x-ray methods and highly specialized x-ray methods – CT) are used in the diagnosis, follow-up of patients and analysis of the clinical course of the disease.

Clinical case (Results)

The patient presents with complaints of cough, shortness of breath, chest pain, easy fatigue, high temperature up to 39 °C, severe headache. Complaints are 5–6 days old. He received symptomatic therapy – NSAIDs, antipyretics, vitamins and his main therapy for accompanying diseases. The patient reports the following past and co-morbidities: histological and IH data for Lymphomatoid papulosis type A (T cell lymphoma with phenotype CD3+, CD4+, CD30-/+), squamous cell carcinoma of the lung - status after right lower lobectomy, status after chemotherapy and therapy with checkpoint inhibitors. The patient denies family burden. With a history of smoking: about 40 pack-years. Denies allergies and drug intolerance.

From the patient's objective status, the following findings were established: A man of an apparent age corresponding to the actual one. Takes a forced sitting position in bed. Febrile at the time of examination (38.6 °C), contact, allo- and auto-oriented. Skin and visible mucous membranes were pale cyanotic, erythema-squamous plaques on the skin in places with ulcerations, mainly on the trunk. Slightly enlarged cervical lymph nodes were palpated. Thyroid gland remained not palpable and enlarged. Cardiovascular system presented by rhythmic heart activity, clear heart sounds, blood pressure (BP): 100/70 mmHg, heart rate (HR): 102 bpm. Physically the respiratory system showed asthenic symmetrical chest, preserved respiratory mobility, sonorous percussion tone, shortened bilaterally, weakened vesicular breathing bilaterally, O_2Sat. of atmospheric air – 84%, respiratory rate – 26/min. Abdominal observation showed soft painless abdominal wall, normal peristalsis. Liver size was estimated at 2 cm below the costal arch; Spleen was not palpable and enlarged. Goldflam's sign (Latin: succusio renalis) was bilaterally negative. Limbs were featureless.

Laboratory tests included a confirmed positive RT PCR- SARS-CoV-2 test. Complete blood count is shown in Table 1.

Biochemical studies show highly elevated markers of inflammation, slightly elevated transaminases and dyselectrolytemia.

Table 1. Hematological indicators.

Lab test	Result	Unit	Reference range
WBC	9.71	$\times 10^9$/L	4.1–11.0
LYM (no.)	0.44	$\times 10^9$/L	0.6–4.1
LYM %	4.5	%	20–40
HGB	104	g/L	140–180
PLT	112	$\times 10^9$/L	140–440

Table 2. Inflammatory markers.

Lab test	Result	Unit	Reference range
CRP	20.58	mg/dL	0.00–0.50
Fibrinogen	6.1	g/L	1.5–4.5
ERS (CYE)	45	mm/h	0–20
Ferritin	708.5	ng/mL	20–250

The patient was examined for arterial acid–base balance – with evidence of hypoxemia – Sat. O2– 89.2%, without hypercapnia and with compensated acidosis.

The coagulation status of the patient was also disturbed – data on increased D-Dimer – 955.0 ng FEU/ml (0–500).

We present a chest CT at the patient's admission to the clinic.

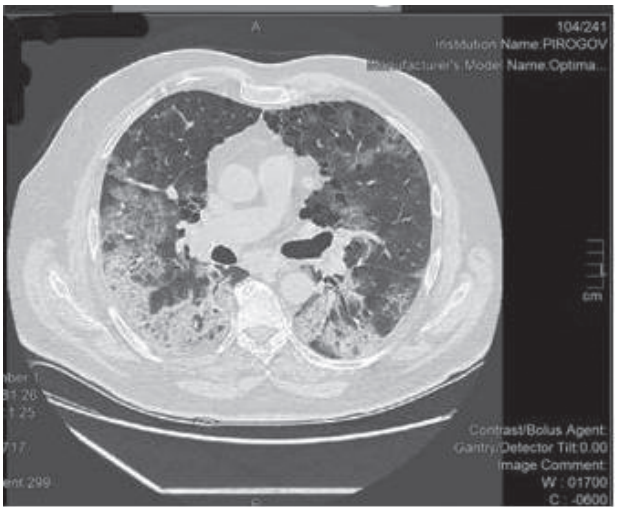


Figure 1. CT-data on changes in the lung parenchyma according to the type of atypical pneumonia with viral genesis, severe degree (50–75% involvement). Emphysematous bullae.

After the diagnostic procedures, complex therapy was started for the patient in view of the deteriorated general condition and the developed COVID19 infection:

1. Oxygen therapy – the patient went through the following modes of oxygen therapy, dynamically tailored to his needs: 1) non-invasive oxygen therapy with 14 l/min with a mask with a tank; 2) non-invasive ventilation – oxygen therapy with a high-flow nasal cannula, with a volume of supplied oxygen reaching up to 60 l/min; 3) facial oxygen mask with a gradually decreasing volume of supplied oxygen. 4) the last three days of the stay in the clinic without the need for oxygen therapy
2. Control of inflammation – NSAIDs (Nimesulide 100mg as needed for the first 5 days to control the severe headache; glucocorticoids (Methylprednisolone 40mg with the following scheme 80-40-0 for 5 days; 80-0-0 for 5 days; 40-0-0 for 3 days; 20-0-0 for 3 days
3. Antipyretics – Paracetamol 10mg/100ml twice a day for five days plus additional Metamizole if needed.
4. Anticoagulant – Enoxaparin sodium 6000 IU twice a day for 14 days and another 4 days once a day.
5. Antibacterials – Levofloxacin 500 mg once daily i.v. (10 days)
6. Ensuring water-electrolyte and energy balance (Sodium Chlorid 0.9%; Ringer; Serum glucose.) – the infusions are tailored to the reported diuresis, the ionogram, the patient's diet in order to ensure an optimal caloric balance.
7. Stress ulcer therapy – Famotidine 20mg twice a day for 14 days and another 4 days at 20mg/day
8. Immunomodulators (Serrazimes, Bromelain, Quercetin); essential oils – (Distillate of a mixture of rectified essential oils of eucalyptus, sweet orange, myrtle and lemon) - the therapy with these medications was started on the last 5 days of hospital stay and continued until the control examination on the 6th month.
9. Therapy for accompanying diseases

The patient has severe lung involvement from coronavirus pneumonia. Length of hospital stay – was 18 days.

The patient was discharged after a negative PCR test for SARS-CoV2, without need of oxygen therapy, with reduced complaints of shortness of breath, cough. He was afebrile for more than three days, with improved physical capacity. Reverse resorption of the inflammatory changes on the lung parenchyma was established. Since before the discharge of the patients, an imaging study – radiography was done, we present the CT study of the control examination after 6 months for an easier comparison.

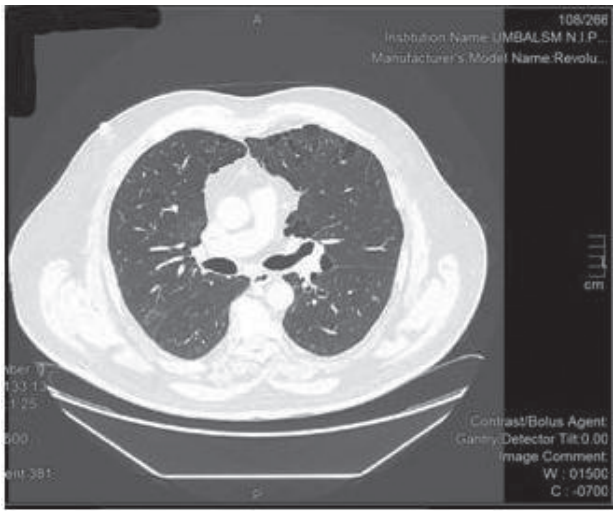
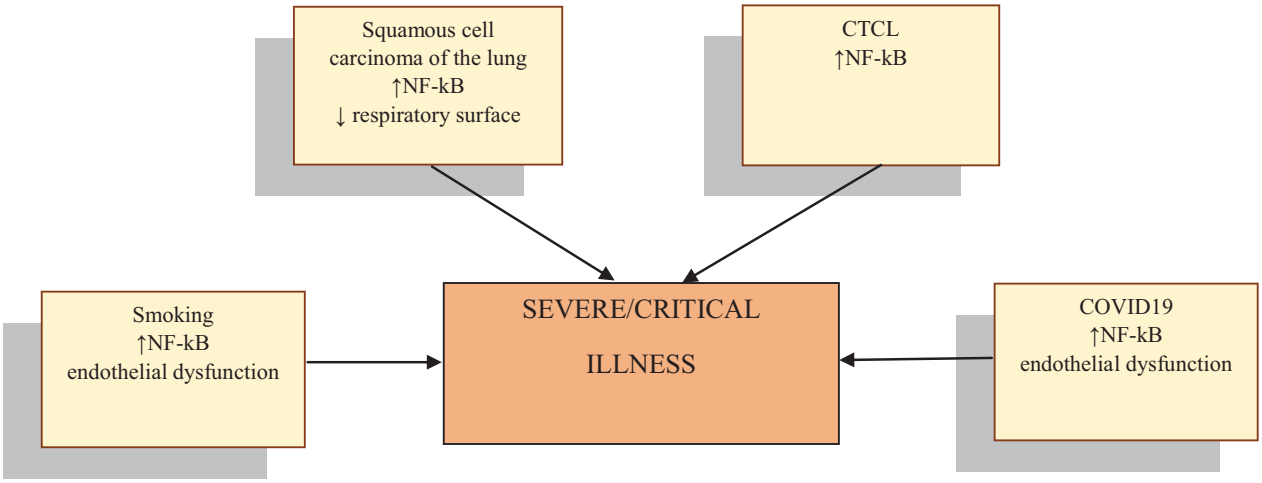


Figure 2. Without CT data on changes in the lung parenchyma according to the type of atypical pneumonia with viral genesis in the stage of advanced resorption. The described emphysematous bullae persist.

Discussion



Scheme 1.

Cutaneous T cell lymphoma (CTCL) is a spectrum of lymphoproliferative disorders caused by the infiltration of malignant T cells into the skin. Despite recent advances, CTCL remains challenging to diagnose. The mechanism of CTCL carcinogenesis still remains to be fully elucidated. Hence, experiments in patient-derived cell lines and xenografts/genetically engineered mouse models (GEMMs) are critical to advance our understanding of disease pathogenesis (Gill et al. 2022). Genomic profiling data for HUT-78 detailed a deletion at 10q25 underlying reported NFKB2 activation. Moreover, amplifications of ID1 (20q11) and IKZF2 (2q34) in this cell line drove overexpression of these NK cell differentiation factors and possibly thus formed corresponding lineage characteristics. Fusion Gene FOXK2::TP63 analysis for NFKB1 via siRNA-mediated knockdown in HH revealed activation of TP63, MIR155, and NOTCH pathway component RBPJ. Finally, treatment of HH with NFkB inhibitor demonstrated a role for NFkB in supporting proliferation, while usage of inhibitor DAPT showed significant survival effects via the NOTCH pathway. The analysis by Nagel St. et al. suggest that NFkB and/or NOTCH inhibitors may represent reasonable treatment options for subsets of CTCL patients (Nagel et al. 2022). For example, vorinostat increased IFN-γ and IL-23 signaling, while it suppressed IL-6, IL-7, IL-15, and IL-17 signaling pathways in Myla but not HH cells. IL-17 family cytokines are produced by many cells, including mast cells, neutrophils, and Th17 cells, and promote an immune response to extracellular pathogens. IL-17 is thought to contribute to CTCL by activating pathways such as NF-kB and MAPK as well as by promoting angiogenesis (Lauenborg et al. 2017; Bordeaux et al. 2023). Suppressed activation of NF-kB pathway may provide new therapeutic options for the treatment of CTCL.

The overactivation of the transcription factor NF-kB during SARS-CoV-2-virus infection leads to the uncontrolled release of inflammatory mediators, which mediates the development of a cytokine storm and is clinically manifested by the development of an acute respiratory distress syndrome with a very poor prognosis. Taking into account the oncological disease, where the activity of the transcription factor NF-kB is presumably higher, the more severe course of infection with SARS-CoV2 is absolutely expected, as it turns out in our clinical case. Also, additional facts complicating the course of the disease are active long-term smoking with accompanying endothelial dysfunction. The total respiratory surface is smaller, due to a surgical intervention – right lower lobectomy as part of the therapy of squamous cell carcinoma of the lung.

For the favorable outcome of our patient, namely his discharge in a significantly improved general condition, the lack of need for oxygen and the initial reverse resorption of the inflammatory changes, it is important to apply complex therapy with anti-inflammatory drugs such as NSAIDs and glucocorticoids, immunomodulators which are simultaneously and inhibitors of the transcription factor NF-kB.

Conclusion

The described clinical case is an interesting example of the "nuances" in the clinical course of the coronavirus infection in neoplastic comorbidity and the possibility to predict the clinical course of Covid19 in CTLC. This, in turn, facilitates the replication of such patients given the immunological terrain, the expected more severe course of the disease – early hospitalization, optimal prevention of the development of a "cytokine storm" and intensive monitoring and follow-up of such groups of patients is an imperative strategy for a better outcome of the disease.

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