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COVID-19 INFECTION IN PATIENTS WITH HEMATOLOGIC DISORDERS IN THE REPUBLIC OF ARMENIA: FOUR CASES STUDIES FROM THE NORK NATIONAL CENTER OF INFECTIOUS DISEASES

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Abstract

The COVID-19 pandemic presents unique challenges for immunocompromised patients. These patients include those with hematological malignancy such as acute and chronic leukemias, lymphomas, myelodysplastic syndromes, and multiple myeloma. Patients with malignancy disproportionately suffer from severe complications and fatality from COVID-19. These patients are at high risk of developing secondary bacterial and/or fungal infections.

Theoretically if treated with steroids during the first week of COVID-19 disease, worse clinical outcomes might be expected in immunocompromised patients. If so, the start of aggressive steroid treatment in the early stages of COVID-19 can prolong the course of disease and cause complications thus increasing the mortality rate.

We conducted a prospective observational study in all patients with COVID-19 diagnosis from the Nork National Center of Infectious Disease hospital between August 1st and November 30th, 2020. Four unique cases of SARS CoV-2 infection with hematological malignancies are described.

Based on analysis of the clinical course in these four patients we conclude that steroid therapy should not be casually administered in late stages of COVID-19. The choice of steroid, including dosage, duration, the initiation time and supportive therapy should be determined individually for each patient taking into account the course of the disease and the treatment received up to that point. In patients with immunosuppressed status, the risk of developing serious secondary infection is high. Receiving chemotherapy within the previous six months can significantly impact disease severity and outcomes. Further expanded investigations are needed to assess multiple factors impacting outcomes for patients with malignancy.

Keywords: *Severe COVID-19; myelodysplastic syndrome; lymphoma; leukemia; steroid therapy; secondary infections*

Introduction

The global pandemic of the novel coronavirus SARS-CoV-2 represents one of the greatest infectious challenges to human health in recent history. [*Zhu N et al.*, 2020] The pandemic has affected millions globally. [*Abid H, Mohd J, 2020*] In Armenia the first case of COVID-19 was reported on March 1st 2020. [*Wikipedia 2021*] The disease has since spread to all of the regions (marz) of Armenia with over 160,000 people infected, and 3000 fatalities in a population of 3 million. Identification of risk factors that contribute to the development of severe disease is important to enable risk stratification, optimize hospital resource allocation, and guide public health recommendations and interventions. *[Hariyanto TI, 2020]*

The COVID-19 pandemic presents unique challenges for immunocompromised patients such as those with blood dyscrasia and hematological ma-

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lignancies such as acute and chronic leukemias, lymphomas, myelodysplastic syndromes, multiple myeloma. [*Vijenthira A et al., 2020*] Patients with malignancy disproportionately suffer from severe complications and fatality from COVID-19. These patients are more likely to develop nosocomial infections, respiratory distress, and to be admitted to the intensive care unit. [*Cornejo-Juarez P. et al., 2016*] Data are limited, but the outcomes of patients with cancer, including patients with hematologic malignancies, who are COVID-19-positive at this time appear to be worse than for COVID-negative patients. [*Liang W et al.,2020*]

In the initial period of the COVID-19 pandemic, the recommendation of American Society of Hematology was to delay chemotherapy in those in whom it was not of urgent necessity and to avoid clinic visits. This was true for patients with chronic lymphocytic leukemia (CLL). For patients who required immediate therapy, the best treatment option was offered considering disease and patient-specific factors. When the COVID-19 pandemic is under control per local authorities, we follow standard treatment guidelines for CLL treatment. [*Shadman M et al., 2021*] In general, patients with CLL are considered high-risk for infections, due to immunodeficiency and inadequate immune response to infections. Patients with CLL have many risk factors that predispose them to a more severe course of COVID-19 related illness, including older age, higher prevalence of comorbidities, immunodeficiency from leukemia, and, possibly, immunosuppression from CLL treatments. [*Monteserrat E, 2020*] This patient population is of particular concern. [*Loguidice CT, 2021*] At this time, there is no evidence indicating a disproportionately higher incidence of severe COVID-19 in patients with CLL compared to patients with other malignancies. [*Shadman M et al., 2020*] However, two large multicenter studies have shown a high mortality rate in patients with CLL and severe COVID-19 in the range of 30%. This high-mortality rate was reported in patients with severe COVID-19 in both 'watch and wait' and treated groups. There is also an indication that severity of COVID-19 in patients with CLL increases with age, as in the general population. [*Shadman M et al., 2021*]

To overcome it is possible, due to the uniting the knowledge and will of all doctors in the world

While most studies have not assessed COVID-19 disease severity or death in patients with myelodysplastic syndrome (MDS) independently, multiple studies have now indicated that related conditions such as acute myeloid leukemia are associated with higher death rates due to COVID-19. We consider patients with MDS to be a high-risk group. MDS patients with febrile neutropenia are especially at risk. [*Sekeres MA et al., 2021*]

The topic of steroid administration in these already immunocompromised patients is important. We hypothesize that all patients with hematological dyscrasias and malignancies should be considered a high-risk group for serious complications and high mortality if treated with steroids during the first week of COVID-19 disease. The start of aggressive treatment in early stages of COVID-19 can prolong the course of chemotherapy treatment, cause complications and thus theoretically increase the mortality rate. In addition, these patients are at high risk of developing secondary bacterial and/or fungal infections. [*Busca A, 2012*] In this study we report the clinical characteristics, treatment in patients with hematological malignancies in four illustrative acase studies.

MATERIALS AND METHODS

We conducted a prospective observational study in all patients with COVID-19 diagnosis from Nork National Center of Infectious Disease between August 1st and November 30th, 2020. A confirmed case of COVID-19 was defined by a positive result on a reverse-transcriptase polymerase chain reaction assay of a specimen collected by nasopharyngeal swab and/or by fulfilling clinical and epidemiological diagnostic criteria and detectable COVID-19 antibodies. Four unique cases of

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SARS-CoV-2 infection in patients with hematological disorders are described.

Clinical laboratory investigation included studies of complete blood count (CBC), coagulation profile, serum biochemical tests (including renal and liver function, electrolytes and lactate dehydrogenase). The plasma samples of patients were analyzed with chemiluminescent immunoassay (CLIA) based on the ACCENT 200 Automatic ClinicalBiochemistry Analyser.

Ferritin, procalcitonin (PCT), C reactive protein (CRP), D-dimer quantitated in serum of patients.

D-dimer, ferritin, and PCT levels were tested using microsphere flow immunofluorescence, according to the instructions of the manufacturer of the commercial kit supplied by MAGLUMI 600, Shenzhen New Industries Biochemical Engineerig Co., Ltd, China. The normal range of ferritin levels is between 13-350 *ng/ml*, D-dimer is normal if <0.55 *FEU/ml. A PCT level* of >0.05 *ng/ml* was considered abnormal. CRP levels were measured by nephelometric method. The normal range of CRP levels is between 0-5 *mg/L.*

A complete blood count test was done for each patient using a Yumizen H500, HORIBA ABX SAS hematology analyzer. CBC included red blood cells (RBC- N3.9-5.6x10^{12}/µL), Hemoglobin (HGB- N110-170 *g/l*), Hematocrit (HCT-N39-52*%*), Erythrocyte sedimentation rate (ESR N-5-15*sec*), Platelets (PLT- N150-400x10^9/ µL), White blood cells (WBC- N4-10x10^9/µL), Lymphocytes (LYM-N 1.00-3.00x10^9/µL /19.3-51.7%), Neutrophils (NEU-N 1.60-7.00x10^9/µL /34-71%), Monocytes (MON-N 0.10-0.80x10^9/µL /4.7-12.5%), Eosinophils (EO-N 0.7-5.8%), Basophils (BASO-N 0.1-1.2%).

Ethical Considerations:

This study was approved by the Internal Review Board of the Nork National Center of Infectious Disease. Records were anonymized to protect identifying patient information.

Results

More than 60 patients with a broad range of hematological disorders of different etiologies, CLL, MDS, lymphoma etc. were recorded in our study cohort. The median age was 65 (36-81) and proportion of females was 86.9%. The fatality rate was 9.8%.

The median hemoglobin level in this cohort was 85 *g/l* (61-108 *g/l)*, ferritin level fluctuated between 7.1-1978*ng/ml*, in 8 cases reported thrombocytopenia-PLT-54-101 x109/ µL. In 13 cases thrombocytosis with a platelet range from 512-1413 x109/ µL was detected. Leukocytosis was detected in 6 cases with WBC levels of 18.4-154.3 x109/µL, and leukopenia in 4 cases-WBC 1.86-2.89 x109/µL. Neutropenia was found in 7 cases and neutrophilia in 8 cases, the range of neutrophils was 0.48-18.3x109/µL. Lymphocytosis was detected in 5 cases LYM-17.34-102.7 x109/µL, and lymphopenia was recorded in 21cases (LYM 0.15-0.91 x109/µL*)*. Lymphopenia was seen in non survivors (LYM-0.15-0.48 x109/µL*)*.

Below we describe four illustrative cases of COVID-19 infection in patients with hematological malignancies.

Case One

A 72-year-old woman with myelodysplastic syndrome (MDS) was admitted to hospital on the 5th day of COVID-19 disease with complaint of fever, weakness, nausea, vomiting, and cough. Chest CT progressive bilateral interstitial pneumonia covering 15% of lungs and pericardial effusion was detected. In objective examination there was pallor and crackles were auscultated in the lungs. Vital signs were as follows: temperature (T) 37.2C, oxygen saturation (SpO2) 93% in room air, heart rate (HR) 88/min, respiratory rate (RR) 22/min, Blood pressure (BP) 130/80mmHg. In addition to MDS, the patient had ischemic cardiac disease, hypertension, hypothyroidism, and a body mass index (BMI) of 33. MDS was diagnosed abroad, 3 years prior to presentation with bone morrow biopsy and was being treated with Revlimid. Additionally, antihypertensive drugs and L-thyroxine were being used daily. Revlimid treatment was stopped during COVID-19 infection on advice of the hematologist. Before hospitalization vitamins C and D, aspirin, and paracetamol intake was recorded. During hospitalization the fever continued for 8 days, maximum temperature of 38C was only

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for 2 days. Cough and weakness continued with a minimum SpO2 of 91%. Biochemical profile, ferritin, procalcitonin and coagulation studies were within the normal limits. A high level of fibrinogen 489mg/dl (N200-400mg/dl) and D-dimer 1.04 FEU/ml (N 0.55 FEU/ml) were detected. In serial blood studies, the level of thrombocytes normalized, but neutropenia developed. The complete blood count (CBC) analysis is presented in table 1.

Treatment in hospital consisted of saline infusion, vitamin infusion, and anticoagulation with control of coagulation studies and D-dimer. A Proton pump inhibitor (PPI), and acetylcysteine were added. When the neutropenia worsened on the 5th day of hospitalization antibacterial and antifungal prophylaxis was started (levofloxacin 500*mg/day* p/o, fluconazole 150*mg/day* 5 days).

The patient was discharged after 9 days of hospitalization with full recovery. On the 20th day after the onset of symptoms CBC and other laboratory results normalized, and chest CT showed no abnormalities in the lungs.

Case Two

A 60-year-old female was admitted to Nork National Center of Infectious diseases on the 15th day after appearance of symptoms. She had history of transitional cell carcinoma of the bladder, and small lymphocytic lymphoma (SLL). One month before the hospitalization the patient had successfully completed SLL treatment with 6 courses of chemotherapy with Fludarabine-Cyclophosphamide plus Rituximab). She also had a history of hypertension. The initial CT performed outpatient on the 5th day after the symptoms onset showed bilateral interstitial pneumonia covering 35% of the lungs described as ground glass opacities (GGO). Before hospitalization a treatment course was followed at home of IV dexamethasone (cumulative dose was 116mg) and IV Ceftriaxone for 10 days. Dyspnea developed a week after in home treatment.

On admission patient complained of fever, weakness, nausea, dizziness and shortness of breath. Physical examination: T 36.5, Bp 160/80*mmHg*, Respiratory Rate 20/*min*, Heart Rate 110/*min*. The oxygen saturation was 83% on room air and 90-91% with oxygenation.

Laboratory results on hospital day one reflected pancytopenia (WBC count: $3.2\times10^9/\mu L$, LYM $0.16\times10^9/\mu L$, NEU-$2.93\times10^9/\mu L$, PLT 54×10^9/μL, RBC-$2.85x10^{12}/\mu L$, HGB-70*g/l*, CRP-256 *mg/l* , D-dimer-2.54 *FEU/ml*, and normal levels of liver enzymes. The second CT done in the 1st day of hospitalization showed progressed

TABLE 1.

The complete blood count analysis patients with COVID-19 diagnosis

Parametrs	Day of disease				
	5th	7th	9th	11th	17th
White blood cell ($x10^9/\mu L$)	2.67	1.88	1.86	2.23	3.16
Red blood cell ($x10^{12}/\mu L$)	4.77	4.76	4.59	5.24	4.93
Platelets ($x10^9/\mu L$)	84	100	108	148	189
Hemoglobin (*g/l*)	144	144	138	155	148
Hematocrit (*%*)	43	42.5	41.3	45.8	44.5
Erythrocyte sedimentation rate (*sec*)	25	31	37	43	20
Lymphocytes ($x10^9/\mu L$ *(%)*)	1.19 (44.6%)	0.84 (44.7%)	1.05 (56.5%)	1.01 (45.3%)	1.51 (47.8%)
Monocytes ($x10^9/\mu L$ *(%)*)	0.39 (14.6%)	0.35 (18.6%)	0.26 (14%)	0.27 (12.1%)	0.22 (47.8%)
Neutrophils ($x10^9/\mu L$ *(%)*)	1.06 (39.7%)	0.68 (36.2%)	0.55 (29.5%)	0.93 (41.8%)	1.39 (44%)
Eosinophil (*%*)	0.7	0.0	0.0	0.4	0.9
Basophil (*%*)	0.4	0.5	0.0	0.4	0.3

NOTES: WBC - White blood cells, RBC - Red blood cell, PLT- Platelets, HGB- Hemoglobin, HCT- Hematocrit, ESR- Erythrocyte sedimentation rate, LYM- lymphocytes, MON- Monocytes, NEU- Neutrophils, EO- Eosinophil, BASO- Basophil,

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bilateral involvement of 75% of lungs, with GGO, reticulation, patchy consolidation and subpleural sparing, in accordance with an organizing pneumonia mixed with nonspecific interstitial pneumonia (NSIP) pattern.

In the hospital the patient was treated with dexamethasone 8mg/day, and treatment doses of anticoagulation, as well as oxygen and symptomatic treatment. Washed red blood cell transfusion was performed twice, and platelets transfusion once. Within first three days of hospitalization the patient reported feeling better. Vitals were reported as SpO2-95% in 15l oxygenation. Laboratory studies showed elevation in hemoglobin and platelet levels (HGB-70→97 *g/l*, PLT 54→82×10^9/*μL*), lymphopenia preserved (LYM-0.19×10^9/μL), but neutrophilia developed (NEU-2.93→7.2×10^9/μL), and C-reactive protein 196*mg/L*, PCT-0.298 *ng/ml*, D-dimer-1.2 *FEU/ml*.

There was concern over the activation of inflammatory biomarkers, which could be associated with bacterial co-infection. Antibacterial treatment was started with levofloxacin, and bacteriological examination of sputum conducted. On the 5th day of hospitalization, unexpected deterioration of condition was observed. Severe ARDS developed, SpO2 reduced to 75% in 15*l/min* oxygenation, and patient was admitted to the intensive care unit (ICU) department. Chest CT showed progressing pneumonia with 95% involvement of lung tissue. Continuous positive airway pressure (CPAP) therapy and high doses of corticosteroids were started. Strep pneumoniae 10^7 was isolated in sputum culture (sensitive to levofloxacin), as well as candida 10^6. Antifungal therapy was administered, respectively. On the 5th day of hospitalization, the patient died due to progressive ARDS and heart failure.

Case Three

There were two critically severe COVID-19 cases with CLL reported in our cohort: 71-year-old and 58-year-old females. The 71 years old patient with CLL and hypertension was admitted to Nork Hospital on the 4th day of disease with no prior treatment. She was in complete remission from her leukemia. Her main complaint was dyspnea and SpO2-80% in room air. CT showed bilateral nonspecific interstitial pneumonia. Treatment with 12mg/day IV dexamethasone, fraxiparine 0.4ml/12hour subcutaneously, as well as oxygen and supportive therapy was started.

Within the first 6 days of hospitalization the disease was progressing each day. Activation of inflammatory markers was noted (CRP- 87→145 *mg/L*, PCT-0.12→0.792 *ng/ml*, ferritin-876→1136 *ng/ml*, IL6-78 *pg/ml*), and CBC (WBC-45.73→101.9 x10^9/μL, LYM-40.1→86.9 x10^9/μL, MON 0.86→5.14 x10^9/μL, NEU-3.71-9.03 x10^9/μL). The patient's clinical status worsened with SpO2-58-60% on room air and 86-88% with oxygenation through oxygen mask. A CT scan showed progress of pneumonia to 70-75% of the lungs. A decision was made to do pulse therapy with methylprednisolone with dosage of 500mg/day. Anticoagulation was continued with therapeutic dosages. Sputum culture results showed no pathogen isolated. Sputum microbiological examination was repeated and empiric treatment with levofloxacin started. Candida 10^8 was subsequently isolated. Antifungal treatment with nystatin administered, respectively. The improvement was observed starting the 3rd day treatment with methylprednisolone.

The patient was discharged after 19 days with 92% of SpO2 on room air, and normal inflammatory and other biomarkers' results: WBC-94.96 x10^9/*μL*, LYM-80.49 x10^9/*μL*, MON 4.21 x10^9/*μL*, NEU-9.47 x10^9/*μL*). The patient followed up with a hematologist.

Case Four

The second severe case was a 58-year-old female admitted to the ICU with progressive ARDS on the 10th day after the appearance of symptoms. Home treatment prior to hospitalization included ceftriaxone for 8 days and dexamethasone for 3 days. The patient had been using chlorambucil (Leukera) and allopurinol for the last 4 years, as well as antihypertensive medication. Relapse of CLL was recorded during the hospitalization. Treatment was not paused during COVID-19. During the hospitalization the patient was treated with high doses of dexamethasone (maximum 36mg/day), anticoagulation, antibiotics and antifungal drugs. The disease alternated with improvement

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and worsening in both clinical manifestations and bio-parameters.

The most critical lab results were as follows : WBC- 127.9x10^9/*μL*, LYM-104.6x10^9/*μL*, MON-3.7 x10^9/*μL*, NEU-17.9 x10^9/μL, HGB-123*g/l*, CRP-108*mg/l,* PCT-0.245*ng/ml*, PLT-1424 x10^9/*μL*, ferritin-34 *ng/ml*, D-dimer 0.453 *FEU/ml*, IL6-49 *pg/ml.* High temperatures continued for 14 days after the start of the disease. On hospital day 15 secondary infection was reported with Streptococcus pneumonia isolated from the sputum culture. After successfully treatment of the bacterial infection, candidiasis developed. CBC results on the day of discharge were normalized: CBC (WBC-10.68 x10^9/μ*L*, LYM-6.9 x10^9/μ*L*, MON-0.3 x10^9/μ*L*, NEU-3.24 x10^9/μ*L*, HGB-107 *g/l).* PLT-148 x10^9/μL. After 58 days of prolonged hospitalization, the patient was discharged home for follow up by family doctor and a hematologist. She continued oxygen therapy and chlorambucil (Leukera) and allopurinol at home.

DISCUSSION

In this report we discuss the clinical outcomes of four patients with hematologic dyscrasias and malignancies following infection with the novel coronavirus. The patient with MDS had a severe course of COVID-19 disease but didn't develop life threatening conditions. Due to the assessment of secondary infection risk, short-term prophylaxis was performed, and the onset of the secondary infection was successfully prevented. No steroid therapy administered to that patient.

With patient two, the early start of high dosage steroid therapy is one possible causes of disease complications. The treatment with steroids increases the risk of thrombosis and secondary infections, including invasive fungal infections. On the other hand, this patient has received chemotherapy during last 6 months, which is also immune-suppressive factor, and which increased the risk of developing severe complications. The risk of co-infections can be increased by the administration of broad-spectrum antibiotics. Despite the administered treatment, the disease progressed. Within the first 2 weeks, a patient was administered a steroid therapy and no anticoagulation, and on admission had many micro-thromboses (D-dimer was about 5 times higher normal).

Comparing the last two patients, who had the same co-existing chronic diseases, but the first one was in risk group because of the advanced age, we see that in first case the patient didn't receive aggressive treatment early on. Both patients had recurrence of CLL. The second patient continued her regular therapy, adjusting the dosage under the supervision of a hematologist. She was admitted to the hospital in critical condition, a combined treatment was administered. By the end of 2nd week, a combined therapy with methylprednisolone starting with 500 *mg* for 3- day duration and improvement was recorded when the cumulative dosage reached 2000 *mg*. In the fourth case, the early start of antibacterial and steroid therapy in a patient receiving immunosuppressive treatment led to the deepening of immunosuppression and the disease progression. The recovery process started late in the fourth week of disease. Full recovery was not recorded because of post COVID-19 pulmonary fibrosis developed. A patient received three courses of antibacterial and antifungal treatment during the two-month hospitalization period.

In both patients, CLL relapses with worsened CBC results were recorded. A striking feature was the clinical severity of infection with fatal outcome in one patient, critically severe disease developed in two, and severe in one patient, respectively. In addition, these patients had underlying health conditions, including hypertension, arrythmia or other heart disease, hypothyroidism and obesity.

CONCLUSION

COVID-19 is a newly emerging disease that is not yet fully understood. [Yi Y et al., 2020] We have faced with the challenge of making complex treatment decisions in SARS-CoV-2 patients with aggressive but potentially curable blood cancers. The questions of when to treat, how to treat, when to wait, how long to wait, how to predict and manage toxicities, and how to avoid compromising cure rates remain unknown. [*Isidori A et al., 2020*]

Based on analysis of the clinical course in four

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patients with confirmed diagnosis of COVID-19 who had hematological dyscrasias and malignancies, we conclude that steroid therapy should not be administered casually in late stages of COVID-19. The choice of steroid, including dosage, duration, the initiation time and supportive therapy should be determined individually for each patient consulting the period of the disease and received treatment, to increase the survival rate. On the other hand, chemotherapy prolongs the course of disease, delays recovery due to delayed viral clearance as of existing immunosuppression. In patients with immunosuppressed status, the risk of developing serious secondary infection is high. Surveillance for superinfection must be rigorous. Clinicians must focus attention on the risk assessment in terms of co-existence of bacterial or fungal origin infections in immunosuppressed patients. Those who had received unregulated antimicrobial and steroid therapy before hospitalization are at the highest risk. Individual case-by-case clinical management has to be approached considering the stage of the disease and treatment received prior to hospitalization. Consensus guidelines for CLL and indolent lymphomas have long routinely supported watchful waiting and initiation of therapy only when there is a clear indication. These criteria remain valid and should be followed even more strictly during the pandemic. Decisions should be made on a case by case basis and according to best clinical judgement, but if the indication for therapy is questionable, treatment deferral with repeat imaging and close monitoring should be offered to the patient. [*Isidori A et al., 2020*]

Study limitations included the small number of patients with immunosuppressed conditions of CLL on admission or complications developed during the hospitalization stage as of viral load or virus strain, specific genetic specifics of the patient or specifics of combined or recently received treatment. Receiving chemotherapy within the previous six months significantly impacted the disease severity and outcomes.

Further investigations will be needed to assess multiple factors affecting clinical outcomes patients with hematologic conditions.

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