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Case Report

Is COVID-19 Infection a Death Sentence in Patients Living with Haematological Malignancies? A Case Series

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ABSTRACT

The year 2020 saw the rise of an influenza-like illness from SARS-nCoV2 (Severe Acute Respiratory Illness by novel Coronavirus 2), which causes myriad of symptoms in patients, ranging from mild upper respiratory symptoms to severe ARDS (Acute Respiratory Distress Syndrome). It is, however, known to cause high morbidity and mortality in patients with underlying comorbidities like diabetes, hypertension, kidney disease, obesity and malignancies. Amongst these, the subset with haematological malignancies has an especially poor prognosis possibly as a result of immune suppression, due to underlying bone marrow depression as well as effects of chemotherapeutic agents. These patients need frequent visits and admissions to the hospital for treatment, thus exposing them to the risk of acquiring the infection. Also, a high index of suspicion, with low threshold for testing is needed in view of possible atypical presentation and symptoms. These patients may also warrant an early ICU admission, as they tend to develop severe disease with ARDS more frequently, with an overall poor prognosis and high mortality rate.

We hereby present a series of six patients with underlying haematological malignancies who were admitted in our ICU with a serious COVID-19 illness and a grave outcome.

Since COVID-19 (Coronavirus disease 2019) has been declared a pandemic in March 2020, much research has been done on its presentation as well as its association with various other comorbidities. The infection may be asymptomatic or may present with minor symptoms like cough, fever, sore throat, headache, myalgia and weakness. The percentage of patients with severe pneumonia-like features or critical disease with ARDS are 15% and 5% respectively [1]. Amongst various comorbidities which result in poor prognosis, haematological malignancies form a sub-group which has shown the highest mortality associated with COVID-19 (35% - 40%) [2-3]. This group is at higher risk probably due to low immunity as a part of the disease process [4-6], effect of chemotherapeutic agents on the body [7], or the high interaction with medical staff leading to an increased exposure. Identification of the infection in such patients in also not easy as they are more prone to neutropenic lower respiratory tract infections (LRTIs), as well as their atypical symptomatology [8]. It becomes imperative that a high index of suspicion for COVID-19 be maintained in this subset of patients especially during the pandemic and early admission to COVID Intensive Care Unit (ICU) be considered. Unfortunately, patients also develop severe/critical disease most of the time, with high case fatality.

Case Discussion

We report a series of six RT-PCR confirmed cases admitted in the COVID ICU of our hospital, who were suffering from various haematological malignancies. The

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particulars are explained in (Table 1). Written consent for publication was taken from patients themselves or next of kin of deceased patients.

Out of the 6 patients in the series, 5 were adults (all males) and 1 belonged to paediatric age group (13-year-old female). Majority of them had underlying high-risk haematological malignancies, i.e., Myelodysplastic Syndrome (MDS), Acute Lymphocytic Leukaemia (ALL), Acute Myeloid Leukaemia (AML) and Chronic Myeloid Leukaemia (CML), and developed severe COVID infection. The only patient who had mild-moderate infection and survived, was incidentally detected as having Follicular Lymphoma with super-imposed COVID-19. The mortality rate was very high, with 5 out of 6 succumbing to the disease.

Blood count picture of all the cases can be seen in (Table 2). Anaemia was seen in most of the patients, and haemoglobin was less than 8 g/dl in three out of six, requiring packed cell transfusion. At the time of admission, the total leucocyte count (TLC) of all except one was less than 4000/mm3. The TLC count of the second case (62-year-old male) was over 6000/mm3 on admission, but reduced during the course of the disease to reach a minimum of around 2100/mm3. Four patients were administered Filgastrim, Granulocyte-Colony Stimulating Factor (G-CSF) to increase TLC, all showing a positive response, and the counts of one patient (first case) reached the normal range. This implies that all the patients were immunocompromised at time of ICU admission, which might be the reason behind the severity of the COVID-19 infection. Only 2 patients had TLC within normal range during ICU stay, one of whom survived. Filgastrim had to be stopped for the third case, 48-year-old male, when his platelet count decreased to 4000. Platelet count had a similar profile like TLC. All patients, except the one with follicular lymphoma had low platelet count, probably due to disease spectrum and chemotherapy effects. Among the expired patients, almost all showed sudden deterioration after admission to COVID ICU, and expired within 5 days of ICU stay, with the last case succumbing to the infection on the same day as ICU admission. The only patient to have a long ICU stay was the one with AML who had a total stay of 13 days in the ICU.

Table 1- Clinical Description of patients with Haematological Malignancies

No.	Age/ sex	Clinical Presentation	COVID-19 symptoms	Co-morbidities	Final Diagnosis	Treatment	Outcome
1	58y/M	Haemoptysis, jaundice, tongue ulcers, AKI	Fever, cough – 2 days	MDS, hypothyroidism	MDS with treatment related myelosuppression, COVID-19 infection with ARDS and sepsis, hypothyroidism	MV Meropenem Teicoplanin Amphotericin B Filgastrim Dexamethasone Eltroxin	Expired after 5 days of ICU admission
2	62y/M	Admitted for chemotherapy for atypical CLL, Haemoptysis after admission	Fever, cough	Atypical CLL, Hypertension, P.vivax malaria	Atypical CLL with PRCA, COVID-19, P Vivax Malaria, Hypertension	MV Filgastrim Meropenem Teicoplanin Artemether Dexamethasone Remdesivir	Expired after 4 days
3	48y/M	Admitted for chemotherapy, Developed diarrhoea	Fever, possibly diarrhoea	AML, chronic AF	AML (Inversion 16), COVID-19, treatment related myelosuppression, Cardiogenic shock, ARDS	MV Meropenem Colistin Linezolid Amphotericin B Filgastrim Amiodarone Dexamethasone	Expired after 13 days

4	48y/M	Cough with expectoration, fever, dyspnoea – 5 days	Cough, fever, dyspnoea	None (detected with follicular lymphoma incidentally after admission)	Mild to Moderate COVID-19	Oxygen therapy Remdesivir Meropenem Teicoplanin Fluconazole Dexamethasone	Recovered, shifted toward after weaning off from oxygen
5	13y/F	Admitted for chemotherapy Chest pain x 1 days Weakness -1 day Dyspnoea – 1 day	Chest pain, weakness, dyspnoea	B-ALL	B/L Pneumonitis, COVID-19, MODS with B-ALL	MV Filgastrim Meropenem Teicoplanin Colistin Voriconazole Acyclovir MPS	Expired after 4 days
6	30y/M	Admitted for chemotherapy Fever – 5 days Dyspnoea – 3 days	Fever, dyspnoea	CML	Septic shock, COVID-19, Severe ARDS, CML	MV Colistin Meropenem Teicoplanin Metronidazole Amphotericin B Dexamethasone	Expired same day of ICU admission

Abbreviations: AKI (Acute kidney injury), MV (Mechanical Ventilation), MPS (Methylprednisolone), MDS (Myelodysplastic syndrome), ALL (Acute Lymphocytic Leukaemia), CML (Chronic Myeloid Leukaemia), MODS (Multiple Organ Dysfunction Syndrome)

Table 2- Laboratory findings of cases with Haematological Malignancies

S.No	Age	RTPCR	Initial CBC	Progression
1	58y/M	Positive-14/5/20	9/5/20 – Hb – 9 g/dl TLC – 1100/mm3 Platelets – 13000/ mm3	- TLC increased to a maximum of 8300 (14/5). - Hb initially increased, to a low of 5.1 (11/5) – 1unit PC given; increased to 9.5 (15/5) - Platelet decreased to less than 1000 on 11/5 – PRP given. Later increased to a maximum of 21000 on 15/5. - Deranged INR = 3.2 (15/5/20). - Deranged KFT, remdesivir not given.
2	62y/ M	Positive-23/7/20	19/7/20 – Hb 6.5 g/dl TLC – 6610/mm3 Platelets – 17000/ mm3	- Hb decreased to a minimum of 5.9 (21/7), 2 PC given. - Platelets reduced to 14000 on 14/7, PRP given. - TLC reached a minimum of 2150 on 22/7, Filgastrim was started.
3	48y/M	Negative -18/6/20 Positive – 23/6/20	18/6/20 – Hb 8.5 g/dl TLC – 450/mm3 Platelets – 24000/mm3	- 20/6 - Hb dipped to 6.7, TLC to 230 when Filgastrim was started. - TLC rose to 1690 on 22/6, but platelet dropped to 4000; Filgastrim was stopped and PRP given. - Deranged liver functions, remdesivir not given.
4	48y/M	Positive-21/7/20	24/7/20 – Hb - 7.9 g/dl TLC 2360/mm3 Platelets – 195000	- Hb was maintained in the same range throughout. - TLC rose, but was within normal limit throughout.

				- Platelets were around 2 lakhs throughout ICU stay.
5	13y/F	Positive-18/8/20	16/8/20 – Hb – 6.2 g/dl TLC 2600/mm3 Platelets – 24000/mm3	- PC transfused. - Filgastrim was started in ward, continued in ICU.
6	30y/M	Positive- 31/8/20	25/8/20 – Hb – 8.6 g/dl TLC – 2100/mm3 Platelets – 60000/ mm3	- Patient expired the same day as ICU admission, no follow up investigations available.

Abbreviations: Hb (Haemoglobin), TLC (Total Leucocyte Count), PC (Packed Cells), PRP (Platelet Rich Plasma), INR (International Normalized Ratio)

Discussion

All the cases from our series are from a single centre, which caters to both COVID as well as non-COVID patients, during the months of May to August 2020. In the initial days of pandemic, with the lockdown in place, only emergency services were active, and treatment of patients with haematological malignancies was delayed. But eventually, admission of such patients for chemotherapy on a semi-emergency basis was associated with an increased exposure to SARS-CoV2, and a sizeable number of these patients turned positive. An exception was the 48-year-old patient who was diagnosed with follicular lymphoma only after being admitted to the hospital for COVID-19. Follicular lymphoma is a type of Hodgkin's lymphoma which has a good prognosis even with COVID superinfection. Chemotherapy was a common precedent in most of these cases (5 out of 6), and the fact that patients turned positive during hospital admission questions elective chemotherapy in present scenario. In fact, apart from chemotherapy being delayed/stopped in the COVID-19 positive patients, it has been further advised to delay hematopoietic stem cell transplant in COVID-19, or increase the interval of Rituximab therapy [9,10].

The Italian Haematology Alliance (Passamonti et al [11]) collected data from various small studies regarding the outcomes of patients with WHO-defined haematological malignancies and COVID-19 infection. They found that out of a total of 536 enrolled patients, 37% died within the timeframe of the study. The patients admitted to ICU had a poorer outcome (63% mortality) compared to those not requiring ICU admission (32% mortality). The authors also concluded that patients with AML, non-Hodgkin's lymphoma and plasma cell neoplasms had a worse outcome.

He et al [12] conducted a cohort study at two centres in Wuhan, of 128 hospitalised subjects with haematological cancers, 13 (10%) of whom developed COVID-19. They also included 226 health care providers in the study, 16 of whom developed COVID-19 and 11 of whom were hospitalised. It was found that the 13 subjects with haematological cancers had more severe infection and more deaths compared with hospitalised health care workers with COVID-19. Case fatality rates were 62% and 0 (P = 0.002) respectively.

The Spanish Transplant Group and Cell Therapy (Piñana et al [13]) conducted a multicentric retrospective observational study in 367 paediatric and adult patients living with blood cancers, including some who received stem cell transplantation. The prognostic factors for higher COVID-related mortality rate identified were elderly patients (age >70yrs), neutropenia, C-reactive protein > 20mg/dL and uncontrolled haematological malignancies. Auto/allogenic stem cell transplantation in these patients was seen as a protective factor in Covid-19, along with some role of Azithromycin and steroids in the treatment.

Malard et al [3] conducted a single centre study in Paris in which 48 patients with haematological cancers were screened, out of which 25 found to be COVID positive. Thirteen patients developed ARDS, out of which 6 needed mechanical ventilation. Nine patients with ARDS expired during the duration of assessment. The authors concluded that patients with hematologic malignancies harboured a higher risk of developing a severe form of COVID-19 with ARDS, requiring mechanical ventilation, compared to those in the general population without an underlying medical condition.

The American Society of Hematology Research Collaborative (ASH RC) [14] formed the ASH RC COVID-19 Registry for Hematology, on 1st April 2020, to collect data on patients with COVID-19 and underlying hematologic disorders. They published and presented data from 656 patients from across various countries, out of which 57% had leukaemia, followed by lymphoma (25%) and plasma cell malignancies (18%). Researchers found that the overall COVID-related mortality rate was 20%, but differed markedly by disease severity (33% mortality for those needing ICU care). They also noted a relationship between cancer-related life expectancy and mortality, with better outcomes in patients who had a better pre-COVID prognosis.

Conclusion

The purpose of our case series is to highlight the fact that patients with hematologic malignancies appear to be

very vulnerable to COVID-19 infection. Therefore, these patients need to remain in COVID-19 free zones of the hospital, dedicated solely to hematologic treatment. Furthermore, early testing for SARS-CoV2 must be considered in these patients, even with atypical symptoms. An early ICU admission may be warranted for this population in view of increased chances of development of severe COVID infection and ARDS. Chemotherapy seems to be associated with a poorer outcome, and should be initiated only when COVID-19 has been ruled out. Therapies to enhance immunity in such patients like GCSF and bone marrow transplant may be beneficial, although more studies need to be done to find out their benefit in survival.

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