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Original Article

Aplastic anemia and COVID-19: how to break the vicious circuit?

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Abstract: Aplastic anemia (AA) is a type of anemia that is caused by an intrinsic defect of hematopoietic progenitors or an extrinsic immune mediated destruction of stem cells. Patients commonly presented with pancytopenia, particularly leukopenia that renders patient susceptible to various infections. COVID-19 is one of these infections that could be life threatening and highly contagious. Infection with COVID-19 is expected in a patient who developed fever, respiratory manifestations, leukopenia and lymphopenia together with history suggestive of exposure to infection. Furthermore COVID-19 was found associated with thrombocytopenia, agranulocytosis and monocytopenia in severe cases. Thus the relationship between COVID-19 infection and AA would be a vicious circle as both cause leukopenia and lymphopenia. This study aimed to break this circle, through proposing risk stratification of vulnerability to COVID-19 in AA patients who were admitted in our institution in the period from Mar. 2018 to Mar. 2020 followed by a strict preventive plan tailored for each risk group. 79% of AA patients were at high risk of acquiring COVID-19 infection if exposed. This group of patients have to be targeted with more aggressive preventive plan than normal healthy persons. In conclusion this study proposed next step in combating COVID-19 infection through mass survey of high risk people then application of specific precautions to them, perhaps they could be candidate for future vaccine or prophylactic treatment.

Keywords: Aplastic anemia, COVID-19, vicious circle

Introduction

AA is a rare and heterogeneous disorder. It is defined as pancytopenia with a hypocellular bone marrow in the absence of an abnormal infiltrates, marrow fibrosis or dysplastic changes. To diagnose AA a hematologist must exclude other causes of pancytopenia [1-3].

The majority (70-80%) of AA cases are idiopathic [1-3]. The incidence of AA is 2-3 per million per year in Europe, but higher in East Asia. There is a biphasic distribution of AA, with peaks at 10-25 years and over 60 years [4].

The recent COVID-19 epidemic is dated back to December 2019, where case#0 was reported in Wuhan, China. Although the symptoms of COVID-19 often resemble those of influenza, including fever and cough, COVID-19 appears to be far more contagious than the flu and it has a fatality rate 10 times higher than that of influenza. The crude case fatality rate, based solely on reported numbers of cases and deaths, appears to be 3.96%, the actual risk of death from COVID-19 is unclear because the testing and supportive care for SARS-CoV-2 infection vary widely across the world. Actual death rates vary enormously, from 7.3% in Italy to 0.9% in South Korea. Until now, the reasons for these wide disparities in fatality rates are properly unidentified. Age, > 70 years, underlying medical conditions such as hypertension, cardiovascular and pulmonary diseases are candidate reasons for this escalating fatality rate. Conversely, in contrast to the H1N1 swine flu epidemic of 2009, rates of symptomatic COVID-19 infection and serious illness among children and adolescents are significantly lower than for older adults [5-8].

Global enormous efforts are directed to discover an effective vaccine for COVID-19. However,

a provisional vaccine is still undeveloped yet. Traditional measures for epidemic control of respiratory illness such as influenza could function for COVID-19. These measures include social distancing, frequent hand washing, and avoiding touching one's eyes, nose, or mouth. A self-quarantine up to 14 days is obligatory for persons contacted with COVID-19 patient. These measures have resulted in partially positive results in attenuating the infection and hence the fatality rate of COVID-19 infection. The average incubation period of COVID-19 is 5-7 days, but some cases have experienced longer incubation periods up to 12-14 days after exposure [9].

AA patients have high potential risk of attracting COVID-19 infection due to:

- The nature of the disease with leukopenia and pancytopenia, with lowered immunity.

- The follow up schedule of the patient, which entails regular visits to tertiary hospital. These health facilities may be faraway requiring patient travel, which is via crowded public transport means, particularly in developed countries and rural areas.

- Finally, the main treatment for AA is hematopoietic stem cell transplantation (HSCT), immunosuppressive therapy (IST) and thrombomimetics (Eltrombopag), in severe cases, all render patient immunocompromised.

The COVID-19 infection was found to be complicated with anemia, lymphopenia, neutrophilia, agranulocytosis, monocytopenia and atypical reactive lymphocytes, particularly in severe cases [10]. Accordingly the relationship between COVID-19 and AA would be a vicious circle.

AA exerts a social and economic burden on both patients and communities as a recent study in Egypt revealed [11]. Thus, AA patients have to follow even more restrictive measures than ordinary candidates for combating COVID-19 infection. This was the main motive for this study.

The objectives of this study were:

1. Identifying statistically the high risk groups of acquiring COVID-19 infection among AA patients.

2. Proposing specific preventive measures of COVID-19 infection tailored for each risk group.

Subjects and methods

Patients and settings

AA patients (idiopathic and secondary), diagnosed/admitted at the Clinical Hematology Unit of Internal Medicine Department, Assiut University Hospital, in the period from Mar. 2018 to Mar. 2020, were retrospectively enrolled in the study. This group of patients is on regular follow up at the outpatient clinic according to their treatment plan. Furthermore they usually reported to the emergency department for blood transfusions and other life critical medical services. Patients with inherited bone marrow failure syndrome were excluded from the study.

Data collection and patient categorization

Demographic, medical history, clinical, and the last hematologic data of the study patients were collected from their hospital records. Data concerning treatment plan and frequency of admission per year were also recorded. Diagnosis of AA and assessment of disease severity were carried out according to the modified Cammita criteria as following: 1) Very Severe AA (VSAA), with criteria of absolute neutrophil count ANC < 0.2 × 10^9/l, reticulocyte count < 20 × 10^9/l, platelet count < 20 × 10^9/l plus bone marrow cellularity < 25%, 2) Severe AA (SAA) similar to VSAA however ANC < 0.5 × 10^9/l, 3) Non SAA are patients who did not fulfill the criteria for VSAA or SAA [1, 2, 12].

All patients were treated with general supportive measures, and treatment of the cause if it is acquired AA. IST was prescribed for patients with non SAA who need treatment and for VSAA or SAA who lack matched sibling donor (MSD) or are over 50 years old. MSD hematopoietic stem cell transplantation (HSCT) was recommended in young adults with SAA [13, 14]. Eltrombopag was used for SAA refractory to IST [15].

Calculation of risk of acquiring COVID-19 infection in the study patients

Next patients' risk of acquiring COVID-19 infection was assessed according to proposed risk variables (**Table 1**). These variables included 1) patient's age which was substratified into 3-age

Table 1. Proposed risk stratification of vulnerability to COVID-19 infection for aplastic anemia patients included in the study

Risk variable	Risk value		
	0	1	2
Age (years)	< 55	55-65	> 65
Co-morbidities	No	1	≥ 2
WBCs × 10^9/L	4-10		< 4
Lymnphocyte count × 10^9/L	≥ 1.0		
HSCT or IST	No		Yes

N.B. WBCs = white blood cells count, HSCT = hematopoietic stem cell transplantation, IST = immunosuppressive therapy.

groups, based on the results of other studies that reported higher incidence of infection with COVID-19 in older ages 60-70 years with higher severity and fatality. 2) Presence or absence of other medical co-morbidities and the number of these co-morbid conditions, as the higher the number of associated co-morbidities the risk could have increased. 3) Total leukocyte count and 4) lymphocyte count as 33.7% and 83.2% of COVID-19 infected subjects had leukopenia and lymphopenia at presentation, respectively. 5) Treatment with HSCT or IST [5-8].

According to this risk characterization patients were grouped into 3 risk categories of susceptibility for infection with COVID-19 if they were exposed. These are low risk group with risk value (0), intermediate risk (1-2), and high risk (> 2). Patients with history of traveling to an area with COVID-19 epidemic or contacting a patient with COVID-19 infection over the past 2-weeks were considered high risk regardless of other parameters.

Preventive plan for each risk group

We assumed that the next most important step for adequate primary prevention of COVID-19 infection is to identify the high risk groups in each health care facility. Then, adequate preventive measures should be applied specifically for these groups. Accordingly we put the following plan that was tailored for each patient according to the above mentioned risk stratification.

1. Preventive measures for all risk groups and the low risk group: In addition to the general supportive and preventive measures provided to AA patients, they have to follow the general preventive measures provided by the World Health Organization (WHO), national and local health authorities for COVID-19 prevention [16]. Patients should update their contact details and notify their health care provider if they travelled abroad or contacted persons with suspected COVID-19 infection. They should continue their regular medical appointments and treatments however they should contacted their physician first and obsolete unnecessary visits. Have enough calm sleep, avoid stress, and exercise regularly. Consume balanced nutritious diet rich in vitamin C as in Mango and Guava. Keep well hydrated by drinking enough water and vitamin C-rich juices as orange and lemon juices. They should not be panic about COVID-19 infection just update their knowledge regularly and follow the national and institutional preventive plans.

2. Preventive measures for the intermediate risk group: including measures mentioned in 1 and self-monitoring for fever, sore throat or dyspnea, if any manifestation or symptoms consult their physician. If for any reason patients were admitted at hospital they have to be isolated from others. Every effort has to be exerted to avoid infection and contact with infected persons as the neutropenia and leukopenia of AA more persistent than that in those with malignancy under chemotherapy. Patients have to follow a neutropenic diet [17].

3. Preventive measures for the high risk group: including measures mentioned in 1 and 2 in addition to self-quarantine. Patients should consider wearing mask if they plan to go out but learn how to use it properly. They should ensure a 3-month supply of their medications and consult physician about blood transfusions. Avoid unnecessary medications and vaccinations particularly influenza vaccine. However patients have to consult their physicians about adding growth factors as granulocyte monocyte colony stimulating factor (GM-CSF) to their treatment regimen, particularly in those with acquired NSAA. Antiviral prophylaxis could be beneficial in this group of patients.

Statistical analysis

Statistical analyses were carried out by SPSS version 20 statistical package (SPSS, Chicago, IL, USA). Microsoft Excel software package was also used for creation of figures. Descriptive data were presented as median, range or means ± SD for quantitative variables while

Table 2. Descriptive statistics of age and complete blood count (CBC) parameters of aplastic anemia patients included in the study

Variable	Mean	Median	SD	Max	Min
Age (years)	32.21	25	15.41	65	18
Frequency of Hospital admission/year	2	2	1.36	7	1
Hospital days/year	13	10	9.39	40	3
WBCs × 10^9/l	2.48	1.75	2.14	9.4	0.3
ANC × 10^9/l	1.02	0.6	1.39	6.3	0.02
Hb mg/dl	8.42	8.4	2.33	13	3.5
Platelets × 10^9/l	35.25	29.5	26.06	109	6
Lymphocytes × 10^9/l	1.16	0.95	0.8	3.8	0.01
Reticulocyte %	1.24	0.5	1.38	5.2	0.1

N.B. WBCs = white blood cells, ANC = absolute neutrophil count, Hb = hemoglobin.

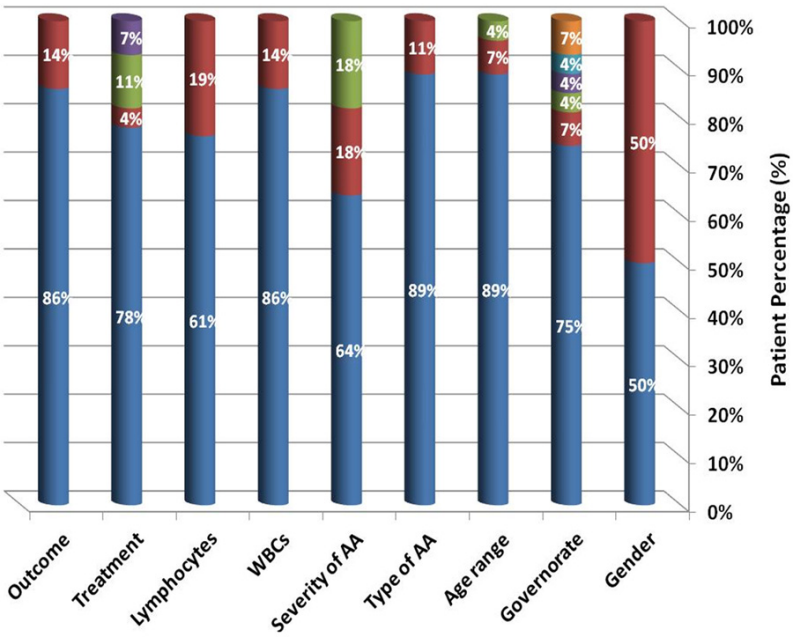

Figure 1. Distribution of categorical variables in aplastic anemia patients of the study under concern.

percentages represent categorical variables. Patients were categorized according to their risk of acquiring COVID-19 infection into three categories low, intermediate and high risk after calculating their risk score by submitting risk value for each individual patient (**Table 1**).

Results

Study patients

28-patients with AA were included in the study, 4- of them died from disease complications and one following allogeneic HSCT during the period of the study thus they were excluded from further analyses. None of our patients reported traveling to areas with high incidence of COVID-19 or contacting a patient with COVID-19 infection over the past 2-weeks.

Characteristics of aplastic anemia patients included in the study

(**Table 2**) showed descriptive statistics of age and hematologic parameters of AA patients included in the study. The median age of the study patients was 25-years and the range was 18-65 years. The maximum frequency of hospital admissions per year was 7 times and 40- were the longest hospital stay days. The median WBCs, lymphocytes and platelets were 1.75, 0.95, and 29.5 × 10^9/l, respectively.

(**Figure 1**) and (**Table 3**) showed demographic , disease characteristics, therapeutic regimens and outcome of the study patients based on data collected during the last follow up visit. The male to female ratio was 1:1 and 75% were from Assiut Governorate, where the study was conducted. 89% were idiopathic AA and 64% were NSAA. 89% and 61% were leukopenic and lymphopenic respectively, only one patient had relative lymphocytosis. Nearly three fourths of patients were treated with immunosuppressive therapy. The vast majority of patients (86%) have no associated medical co-morbidities, 7% have diabetes mellitus and hypertension was present in another 7%. 14% of the study patients died during the period of the study.

Risk of susceptibility to COVID-19 infection in AA patients included in the study

(**Figure 2**) showed risk liability of COVID-19 infection, if exposed, of AA anemia patients

Table 3. Demographic and disease characteristics of the studied aplastic anemia patient group

Gender		Governorate		Age range		Type of AA		Severity of AA	
M	50%	Assiut	75%	< 55	89%	Idiopathic	89%	NSAA	64%
F	50%	Qena	7%	"55:65"	7%	Acquired	11%	SAA	18%
		Sohag	4%	> 65	4%			VSAA	18%
		Alexandria	4%						
		Aswan	4%						
		ElMinya	7%						
WBCs		Lymphocytes		Treatment		Outcome		Co-morbidities	
< 4	86%	< 1.0	61%	IST	78%	Living	86%	None	86%
> 4	14%	> 1.0	19%	HSCT	4%	Died	14%	DM	7%
				IST+Eltrombopag	11%			HTN	7%
				Supportive only	7%				

N.B. M = males, F = females, WBCS = white blood cells, IST = immunosuppressive therapy, HSCT = hematopoietic stem cell transplantation, NSAA = non Severe aplastic anemia, VSAA = very SAA, DM = diabetes mellitus, HTN = hypertension.

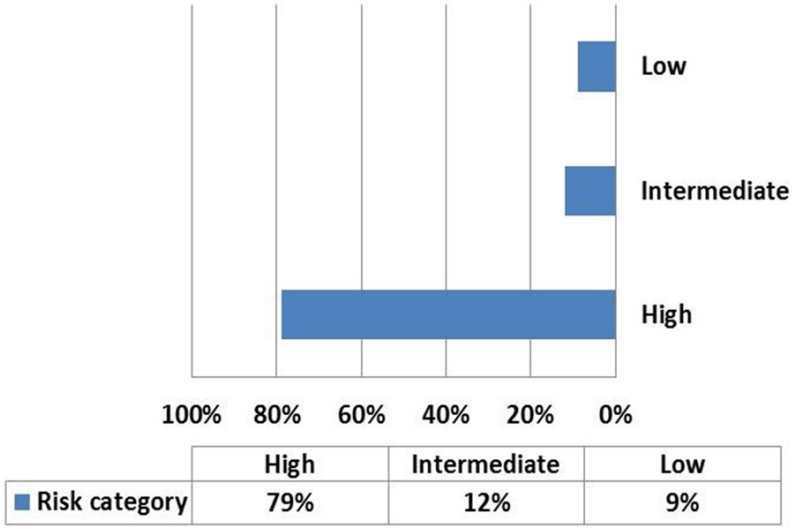

Figure 2. Distribution of risk of COVID-19 infection among aplastic anemia group under concern.

included in the study according to the above mentioned risk stratification (**Table 1**). It revealed that only 9% had low risk while 79% were in high risk category. The remaining 12% were in the intermediate risk group.

Discussion

COVID-19 is a recent viral infection that is rapidly spreading leading to a worldwide corona pandemic. Several studies were conducted to investigate susceptibility and risk factors of morbidity and mortality in COVID-19 infected subjects. Most of them concluded that elderly age and medical co-morbidities as hypertension or diabetes are the most important poor prognostic markers in COVID-19 patients [18]. This work was done to assess the relationship between AA and risk of COVID-19 infection through proposing a risk stratification of vulnerability to infection in AA.

The results of this study were in accordance with Asian studies and contradictory to Western ones where AA showed unimodal age distribution without second peak in those > 60 years old. However there was no sex predilection in the current study [19, 20].

Findings of the current study revealed that 96% of AA patients were < 65-years old, and only 14% of them had medical co-morbidities. Even though when we applied our proposed risk stratification to them to assess their vulnerability to COVID-19 infection the vast majority of them were at high risk if they are exposed. This was explained by the disease and clinical characteristics of the study patients, as most of them were leukopenic, lymphopenic and on regular IST. On the other hand exposure to COVID-19 infection was not documented in the study patients, nevertheless higher frequency of hospital admission and longer stay at hospital would be a definite risk of acquiring infection. This assumption was supported with the

findings of Liang and his co-workers who reported higher incidence of infection and mortality with COVID-19 in cancer patients. They attributed these poor outcomes to the frequent visits and stay at hospitals as a part of the management schedules for these patients [21].

Patients with malignancy often undergo management in a hospital setting; receive chemotherapy, radiotherapy or immunotherapy or even a combination of those. This motivated Yu and his colleagues to assess the incidence and clinical outcomes of COVID-19 infection in cancer patients. They reviewed hospital records of 1,524 cancer patients admitted to the department of radiation and medical oncology in their institution from 30th of Dec. 2019 to 17th of Feb 2020. They reported 12 of them with infection; the infection rate was 0.79%. This rate was double or more the estimated cumulative incidence 0.37% in Wuhan in the same period. Therefore, the researchers, Yu and his colleagues, had proposed more aggressive preventive measures for cancer patients to decrease frequency of hospital admissions or visits during the viral epidemic. For those patients in need for treatment, strict isolation protocols have to be established to mitigate the infection risk of SARS-CoV-2 [22].

Although AA is a benign disorder however the disease presentation, clinical symptoms, disease course and even treatment and follow up plan is nearly similar to that of hematological malignancy. Accordingly we suggested applying the strategy of Yu et al. to AA patients during COVID-19 pandemic. Furthermore, we recommend that Hematology Units, Departments and outpatient clinics should remain free from infection with the new Corona virus and should be concerned solely with management of hematological diseases. Not only this but hematologists and other health care workers in these departments or Units have to be cautious and avoid to be an infection transmission route through proper isolation from COVID-19 infected subjects.

Interestingly the vast majority of patients in this study were NSAA, however when we applied the proposed risk assessment to them, 79% of them were at high risk of acquiring COVID-19.

Based in these results we recommend, that in the era of COVID-19 pandemic we have to think about revising regimens of treatment of AA patients and think in a regimen that would boost their immune system non-specifically, perhaps with adding growth factors [1]. Eltrombopag was found to produce a trilineage increment on blood cell counts in patients with AA, [15] accordingly it could be combined with the usual treatment of high risk patients for 4-weeks. However the use of prophylactic hydrochloroquine or antivirals is still questionable [23-25].

Conclusions

In conclusion, we found that most patients with AA at higher risk for COVID-19 infection if they were exposed and they are more prone to develop severe form of the disease as they are immune deficient either by the disease itself or by treatment. These findings obligate the importance of specific preventive measures for those patients as earlier as possible and strict self-quarantine and limitation of exposure to infected subjects. Clinicians should provide each patient with his appropriate preventive plan according to his risk category. However, additional clinical trials evaluating the possible value of prophylactic antiviral and chloroquine in high risk patients is needed. Furthermore, patients with high risk AA could be candidates for future vaccine for COVID-19.

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Disclosure of conflict of interest

None.

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