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SARS-CoV-2 infection anxieties and general population restrictions delay diagnosis and treatment of acute haematological malignancies

Acute leukaemias remain a very serious group of diseases often associated with major complications and substantial morbidity and mortality. Diagnosis and appropriate anti-leukaemic therapy together with any needed supportive therapy should be started as soon as possible. Any delay in diagnosis or treatment increases the probability of additional medical complications, including hyperleukocytosis with related leukostasis, tumour lysis syndrome and coagulopathies or myeloid extramedullary masses. In addition, patients with acute leukaemias are highly susceptible to infectious diseases unrelated to the disease itself, to treatment side effects and to individual risk factors.

- Severe infectious diseases, such as the plague, cholera and yellow fever, have been the cause of pandemics throughout recorded human history including in the past two centuries. For example, 14 international conferences were held

between 1851 and 1938 to coordinate responses to major infectious outbreaks. Restrictive measurements including quarantine and social distancing measures were established and guidelines for sanitary management of contagious disease were developed.¹ These conferences aimed to maximize protection from disease with minimum effects on trade and travel.

From its emergence in China, SARS-CoV-2 virus has spread all around the world, representing the most serious health, economic and social crisis of the new millennium.² Since the beginning of the SARS-CoV-2 epidemic in Italy, the Italian Government has implemented several restrictive measures to contain the spread of infection. Among these measures, the lockdown implemented on 9 March 2020 has a positive impact on disease propagation, in particular in the central and southern regions of Italy.³ Unfortunately, the

overwhelming information on the explosive growth of the number of SARS-CoV-2 cases, the large number of virus-caused deaths and the necessity to avoid interpersonal contacts have combined to produce significant anxiety in the general population. This anxiety has led to underdiagnoses of symptoms in patients with haematological disorders other than fever and respiratory failures, postponement of haematological laboratory and radiological tests and deferrals of medical and haematological examinations. Delays in chemotherapy initiation often negatively affect prognosis, particularly in young patients with low- or intermediate-risk haematological disease. Moreover, any postponement of diagnosis and treatment might result in patients progressing to a high-risk disease state and acquiring additional genetic abnormalities and hyperleukocytosis.⁴

Here we report on eight cases of hyperleukocytosis observed from 17 March 2020 to 22 April 2020 in patients who went to the hospital emergency room after postponing their medical check-up for fear of SARS-CoV-2 infection. In four cases, the clinical pictures were complicated by fever and pulmonary symptoms, the proximal reason for the hospital visit due to the strong suspicion of a SARS-CoV-2 infection. One patient had acute kidney failure and another presented with a bowel sub-occlusion and spleen infarction causing severe abdominal pain. Another patient was documented with a pulmonary infection and femoral artery thrombosis causing intense pain and claudication. Signs and symptoms of anaemia and asthenia were present in all cases. Each case was tested twice or three times for SARS-CoV-2 before admission to the haematologic ward and all were negative. Three cases had acute myeloid leukaemia (AML), one was determined to have chronic myeloid leukaemia (CML) in the accelerated phase, one CML in blast crisis (BC), one was confirmed to have acute lymphoblastic leukaemia (ALL) and one was diagnosed with mantle cell lymphoma (MCL) in the leukaemic phase. All patients arrived at the hospital with hyperleukocytosis (77–326 white blood cells [WBC]/ μ l) 21–45 days after the occurrence of symptoms that appeared following the implementation of restrictive measures to delay the spread of SARS-CoV-2. To date, three patients are on induction therapy started 17, 15 and 23 days after hospital admission and 27, 45 and 33 days, respectively, from the occurrence of symptoms or clinical signs. Three other patients are on antibiotics and supportive therapy, and one patient died three days after arrival at the hospital on salvage haemodialysis. The patient in CML (accelerated phase) has just started on hydroxycarbamide (Table I). Although the age of two patients, at 60 and 63 years respectively (one AML and one BC-CML) makes them potentially eligible for intensive treatment, significant pre-existing co-morbidities postponed the start of treatment (still not started), and suggested a less intensive treatment regimen.

The fear of diseases, a well-known psychological phenomenon which most people experience at least once during their lives, is the consequence of a complex mix of cultural,

epidemiological, familial, social and psychological factors. During history, various human populations have faced naturally occurring or human-made disasters, but nothing in our lifetimes compares to the 2020 health crisis. Over the last century, comparable events include the Spanish flu pandemic of 1918 and subsequent epidemics such as polio, HIV, ebola, SARS and swine flu that were more virulent, but smaller in scale and in duration, and less disruptive globally. The HIV epidemic bears some similarity to SARS-CoV-2, but the key psychological factors causing the delay in diagnosis and treatment are different in the two situations. In the case of HIV, guidelines recommending HIV testing every 3–6 months were not followed by the majority of high-risk individuals. These results highlighted the importance of HIV stigma as the principal barrier to HIV testing due to fear of affective, social, healthcare and behavioural consequences.⁵ In contrast, the main objective during the present pandemic has been to avoid SARS-CoV-2 infection and individuals who are psychologically or socially more fragile may have exaggerated their implementation of containment measures.

The rapid expansion of SARS-CoV-2 in Italy has led to the widespread adoption of screening measures with two major aims: (i) to limit interpersonal contact and therefore viral spread; and (ii) to avoid the collapse of hospitals, in particular intensive care units, due to the exceptionally large volume of patients with SARS-CoV-2 or SARS-CoV-2-like symptoms. Accordingly, Italian health authorities have indicated that in cases of fever, cough or mild signs of dyspnoea, patients should remain at home, remaining isolated as much as possible until SARS-CoV-2 swab results are obtained. Unfortunately, fear and anxiety about a disease such as SARS-CoV-2 is often overwhelming, causing difficulties in assessing proper health status and undertaking corrective procedures. Many haematological diseases, including acute leukaemia, have an asymptomatic onset, or initial signs indistinguishable from those present in SARS-CoV-2 infections. The majority of acute leukaemias, however, rapidly deteriorate with severe co-morbidities, and producing a rapid diagnosis and prompt organization of supportive care is crucial. Complications are typically present in patients with acute leukaemia, particularly in those who experience delays in diagnosis or start of treatment. The consequence may be a worsening of the disease due to the acquisition of molecular abnormalities or treatment with a less intensive schedule to avoid potentially fatal risks. A complete haematological assessment at the time of onset of asthenia and/or fever would normally be the course of action in order to identify the most appropriate treatment path and potentially a more successful outcome of these haematological disorders (Table II).

Little is known about the impact of SARS-CoV-2 on non-haematological diseases. In a study conducted in Hong Kong, the authors reported delays in seeking medical help by seven ST elevation myocardial infarction (STEMI) patients. These delays, measured in the time from symptom onset to first

Table 1. Clinical and biological characteristics of patients diagnosed with haematological disorders.

Gender (M/F)	Age (years)	Date of diagnosis	Swabs for COVID-19 testing after diagnosis (number/result)	Diagnosis	Molecular and/or cytogenetics	WBC/ μ l at baseline	Estimated days of symptoms before going to the emergency room	Symptoms before diagnosis	Comorbidities associated with HL at diagnosis	Follow-up
F	57	03/17/2020	2/negative	Blast crisis in chronic myeloid leukaemia	P190 BCR/ABL t(9;22)	299 000	23	Weakness, diffuse purpura, conjunctivitis	Acute kidney failure (creatinine value: 8–6 mg/l)	Death after two days of salvage haemodialysis
F	65	03/18/2020	2/negative	Acute myeloid leukaemia	NPM1 46XX	326 000	27	Fever unresponsive to antibiotics, hypoaecia	Infective lung nodule (9 × 5 cm), severe respiratory insufficiency	On induction chemotherapy after 3 weeks of i.v. antibiotics and antifungal therapy
M	71	03/22/2020	2/negative	Mantle cell lymphoma	t(11;14)	190 000	45	Low-grade fever, night sweats, intermittent abdominal pain	Bowel sub-occlusion, spleen infarction	On chemotherapy after 2 weeks of surgical surveillance
M	74	04/03/2020	3/negative	Acute lymphoblastic leukaemia	46XY	137 000	33	Weakness, persistent low-grade fever, sore throat	Acute kidney failure (creatinine value: 4–6 mg/l), gram positive sepsis	On induction chemotherapy after 2 weeks of salvage haemodialysis and 2 weeks of i.v. antibiotics
M	65	04/09/2020	2/negative	Acute myeloid leukaemia	FLT3 ITD and FLT3 TKD 46XY	86 000	35	Persistent low-grade fever, pain on right lower limb associated with initial claudication	Pneumonia, superficial thrombosis of femoral arteries	On treatment with i.v. antibiotics and anticoagulant therapy (chemotherapy not yet started)
F	65	04/14/2020	3/negative	Acute myeloid leukaemia	FLT3 ITD and NPM1 46XX	95 000	42	Fever unresponsive to antibiotics, persistent cough	Interstitial pneumonia	On treatment with i.v. antibiotics (chemotherapy not yet started)
F	63	04/20/2020	2/negative	Blast crisis in chronic myeloid leukaemia	P190 BCR/ABL t(9;22); +8 in 4 metaphases	77 000	21	Fever unresponsive to antibiotics	Pneumonia	On treatment with i.v. antibiotics (chemotherapy not yet started)
F	51	04/22/2020	2/negative	Accelerated phase in chronic myeloid leukaemia	P210 BCR/ABL t(9;22)	175 000	33	Weakness, fever unresponsive to antibiotics	Pneumonia	On treatment with i.v. antibiotics (chemotherapy not yet started)

M, male; F, female; WBC, white blood cells; HL, hyperleukocytosis; i.v., intravenous.

Table II. Possible measures to prevent potential delays in haematological disease diagnosis during the SARS-CoV-2 pandemic.

Primary measures	
Family doctors	<ul style="list-style-type: none"> Telephone calls, telemedicine or digital platforms should be utilized to screen patients for potential haematological symptoms such as persistent or low-grade fever unresponsive to antibiotics, cough, weakness, fatigue, weight loss, night sweats, bleedings, lymphadenopathies and exposure history that potentially could identify patients with SARS-CoV-2 infection. Appropriate personal protective equipment (PPE) should be provided to allow patients to be seen at home especially in the elderly setting if required by critical clinical conditions. Home care services should be promptly activated or, if symptoms persist for >72 h, refer patients to specific departments.
Home care services	<ul style="list-style-type: none"> Develop home care services with dedicated staff (e.g., nurses equipped with appropriate PPE) capable of performing a SARS-CoV-2 swab and blood analysis including blood cell count and assessment of coagulation parameters. These exams should be processed quickly, within a few hours. If alterations of blood cell count or coagulation parameters are noted, patients should be immediately referred to a haematology department or seen by a specialist, regardless of SARS-CoV-2 results

medical contact, were observed after the initiation of SARS-CoV-2 control measures, compared to STEMI patients before the outbreak.⁶ Another study in an Italian paediatric hospital research network reported 12 cases of delayed access to hospital care during the week of March 23–27 across five hospitals.⁷ These studies further show how public health emergencies can impact healthcare in patients unrelated medical conditions.

As a result of the SARS-CoV-2 crisis, management authorities of all Italian hospitals have produced regulations regarding suspension of outpatient visits for non-urgent situations, limiting therapies to those that cannot be postponed. Scientific societies such as the Italian Society of Haematology (SIE) and the Italian Group for Marrow Transplantation (GITMO) have suggested to proceed with the current haematological treatment as long as possible, isolating inpatients from visitors and restricting outpatients to waiting rooms and day hospitals. Our experience indicates that the need for some haematological patients to be analysed in a hospital setting is at least as urgent as a patient with a strong suspicion of SARS-CoV-2 infection, because any delay in a diagnosis of acute leukaemia can have a deleterious effect on medium- or long-term survival. In this period of worldwide health crisis and unprecedented stress on healthcare systems,

haematologists should expect to continue to provide rapid diagnoses and treatment options to those with more advanced forms of haematological diseases.

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Author contributions

MM and PDF designed the study and wrote the paper. CM and PN collected clinical data. IC and AP did the immunophenotype studies and diagnoses. PDF supervised the study. All authors gave their final approval to the manuscript.

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