COVID-19 infection and severe autoimmune haemolytic anaemia: A case report and review of the literature

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Abstract. During the ongoing coronavirus disease 2019 (COVID-19) pandemic, a number of autoimmune diseases have been found to be associated with severe acute respiratory syndrome-coronavirus 2 (SARS-CoV-2) infection, with thrombocytopenia being the most common. The present study describes the case of a female patient who tested positive for SARS-CoV-2 infection from samples from two nasopharyngeal swabs examined using RT-PCR; she was admitted to hospital for severe anaemia. The woman also tested positive to direct antiglobulin test (DAT). In addition, the literature was reviewed for cases of anaemia concomitant to COVID-19 and only cases of autoimmune haemolytic anaemia (AIHA) with positive DAT were considered. A total of 38 cases of AIHA concomitant to COVID-19 were identified. In the cases reported in the literature, both warm AIHA and cold agglutinin disease were observed, with a marked prevalence of CAD. The majority of the cases identified in the literature, including the patient described herein, have had a full recovery from both COVID-19 and AIHA; however, as some of the patients visited the hospital for observation when their condition was already at an advanced and severe stage, effective therapy could not be administered and they consequently succumbed. On the whole, as autoimmune anaemia may be a consequence of SARS-CoV-2 infection, it should perhaps be considered among the haematological autoimmune disorders secondary to COVID-19, along with thrombocytopenia.

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Introduction

The association between severe acute respiratory syndrome-coronavirus 2 (SARS-CoV-2) infection and the occurrence of autoimmune cytopenia has become a matter of concern during the coronavirus disease 2019 (COVID-19) pandemic. Since the early spread of the virus, pulmonary impairment has appeared to be the main feature of SARS-CoV-2 infection, in accordance with its primary transmission mode via droplets, not differing from the main characteristics of SARS-CoV (1,2). However, numerous cases of thrombocytopenia secondary to COVID-19 have appeared almost immediately, alongside several other different complications (3-8).

The present study describes the case of a female patient admitted to the Infectious Diseases Unit in 'Gaetano Martino' Hospital, Messina, Italy for severe anaemia and COVID-19; while the respiratory symptoms were absent during hospitalization, anaemia appeared to be the preponderant feature during the infection. The possible association between SARS-CoV-2 infection and autoimmune anaemia has to be considered as one of the potential complications of COVID-19, just as COVID-19 has already been recognized as having an important association with thrombocytopenia (9). Autoimmune haemolytic anaemia (AIHA) represents a heterogeneous group of pathologies characterised by the abnormal formation of autoantibodies that bind to antigens on the membrane of red blood cells (RBCs) and determine their destruction. Among the factors that may contribute to the development of AIHA, there are viral infections and inflammation.

In order to further evaluate the association between AIHA and SARS-CoV-2 infection, the present study performed a search of the literature for other reported cases of COVID-19-related autoimmune anaemia. The association between viral infections and autoimmune haematological disorders is well known. The development of numerous variants of the virus has posed the need for further investigations of COVID-19 (10,11).

Case report

The present study describes the case of a Caucasian 61-year-old female patient, weighing 67 kg; she had a clinical history of hypertension, asthma, a previous episode of leishmaniasis,

a previous cerebral stroke, and thyroid cancer treated with a total thyroidectomy; at the time of admission, she was in treatment with levothyroxine. There was no history of autoimmune diseases or anaemia.

Symptoms, such as coughing and throat ache commenced in late November, 2020, 1 month prior to hospitalisation; therefore, she began therapy with levofloxacin and betamethasone. At 1 week after the onset of the first symptoms, her coughing and throat ache disappeared; however, she tested positive to two nasopharyngeal swabs (via RT-PCR) for SARS-CoV-2. After 3 weeks, she presented with jaundice and fatigue, which led the patient to visit the 'Gaetano Martino' Hospital in Messina, Italy, on December 30, 2020. Blood tests revealed severe anaemia with haemoglobin (Hb) levels of 5.3 g/dl. The patient was admitted to the Infectious Disease Unit in 'Gaetano Martino' Hospital, after another nose-pharyngeal swab tested positive for SARS-CoV-2. Chest X-rays revealed basal bilateral parenchymal thickening and apical micronodules in the right lung.

Further blood tests were requested, which were performed by the Laboratory of Clinical Pathology, Microbiology and Immunometry of 'Gaetano Martino' Hospital. Initial blood test results confirmed anaemia with Hb levels of 5.1 g/dl (normal range, 12.1-15.1 g/dl). Other altered values were present at the blood count: RBCs, 1,540,000; mean corpuscular volume, 101 (normal range, 80-100); haematocrit, 15% (normal range, 38-46%); platelets, 183,000 (normal range, 150,000-450,000). In addition, increased levels of erythropoietin (Epo; 90 IU/ml; normal range, 2.6-18.5 IU/ml) were observed, which can indicate low O_2 levels in the blood, anaemia from bone marrow failure, thalassemia or iron deficiency. Ferritin levels were also high (614,00 ng/ml; normal range, 12-150 ng/ml). Total bilirubin levels were also increased 5.01 mg/dl (normal range, 0.2-1 mg/dl), as well as direct bilirubin levels (1.14 mg/dl); biomarkers of cholestasis usually increase in haemolytic anaemia due to the high rate of RBC destruction and the degradation of heme to bilirubin; lactate-dehydrogenase levels were also high (501 U/L; normal range, 150-460 U/L). The levels of this enzyme are usually increased in plasma when there is tissue damage, in various types of anaemia, and during acute infections and inflammation in general. DAT was positive; thus, the patient was diagnosed with severe AIHA. Reticulocytosis (7% with a range of 0.5-2.5% of the erythrocyte count) and a reduction in haptoglobin levels were also observed (2 mg/dl with a range of 30-200 mg/dl). The Hb trends during the period of hospitalisation are presented in Fig. 1.

During the period of hospitalisation, an abdomen ultrasound was performed to exclude conditions that may have resulted in an alteration of haemolytic markers: No sign of obstruction of the biliary tract was observed, and there were no alterations in the liver parenchyma and no splenomegaly. There was also no evidence of overt bleeding. The test results for antinuclear antibody, antineutrophil cytoplasmic antibody, anti-smooth muscle antibody, antiphospholipid antibodies and anti-dsDNA-Ab were negative. Screening for HBV, HCV and leishmania was also performed, and the results were negative. Mild hypothyroidism was found in the blood tests for thyroid function, tested using electrochemiluminescence immunoassay (ECLIA; with a COBAS 8000 analyser; Roche Diagnostics; cat. nos. 07027397190, 07027362190, 08443432190). The results were as follows: Free thyroxine, 16.30 pmol/l (normal range, 12-30 pmol/l); free triiodothyronine, 0.9 pg/ml (normal range, 2.3-4.1 pg/ml); and thyroid stimulating hormone, 6.06 u(IU)/ml (normal range, 0.35-5.5 uIU/ml). There was a mild prevalence in IgG levels (384 mg/dl), with normal IgA and IgM levels (78 and 40 mg/dl, respectively) (performed using the Abcam Human IgM/IgG/IgA ELISA kit; cat. no. ab195215, Abcam). Complement factors were normal with a C3 level of 89 mg/dl and a C4 level of 11 mg/dl. There were no temperature peaks or a need for O_2 therapy during the hospitalisation period. In the first few days since her admission, the Hb levels continued to slowly decrease (Fig. 1). A haematology consultation was requested to investigate the anaemia of the patient and to select a treatment.

On the third day of hospitalisation, treatment with methylprednisolone at 20 mg twice a day was commenced, according to haematologist's advice and given that steroids are considered standard clinical practice for AIHA. In addition, the patient was treated with low molecular weight heparin (LMWH) at 4,000 UI once a day for COVID-19 thromboembolic prophylaxis, as stated in the recommendations by the Italian Society on Thrombosis and Haemostasis of April, 2020 (12). Proton pump inhibitors were also added to the treatment regimen due to the increased risk of developing peptic ulcers caused by steroids, as well as the supplementation of cyanocobalamin and folic acid since erythropoiesis increases in response to haemolysis, which results in a greater demand for folate and cyanocobalamin (13).

During hospitalisation, a progressive improvement in the woman's clinical conditions and Hb levels were observed, with the normalisation of haptoglobin and cholestasis levels as the patient continued the treatment. Jaundice disappeared progressively with the normalization of bilirubin levels.

On the 13th day of hospitalisation, a nasopharyngeal swab for SARS-CoV-2 tested negative, and the final blood test results revealed an improvement in Hb levels and cholestasis markers. In addition, a reduction in the levels of reticulocytes and haptoglobin was observed. Upon agreement, on the 16th day of hospitalisation, the patient was transferred to the haematology unit for further assistance and monitoring for a further 6 days. Therapy with methylprednisolone was continued and progressively tapered; a gradual improvement in her clinical and laboratory conditions was observed. The woman was discharged on the 22th day following admission, in January, 2021, with Hb levels of 11.4 g/dl, a complete resolution of jaundice and fatigue, and with the indication to continue steroid therapy, switching from methylprednisolone to prednisone 25 mg, twice a day.

Discussion

In the present study, a search of the literature was also performed using 'COVID-19 + anaemia', 'SARS-CoV-2 + anaemia', 'warm autoimmune haemolytic anaemia + COVID-19 OR SARS-CoV-2', 'cold agglutinin disease + COVID-19 OR SARS-CoV-2', 'autoimmune anaemia + SARS-CoV-2' as key words. The articles were mainly obtained from PubMed and PMC. Among the articles identified, only the ones in the English language, studies on humans, and cases about patients with anaemia concomitant with COVID-19 and a positive direct

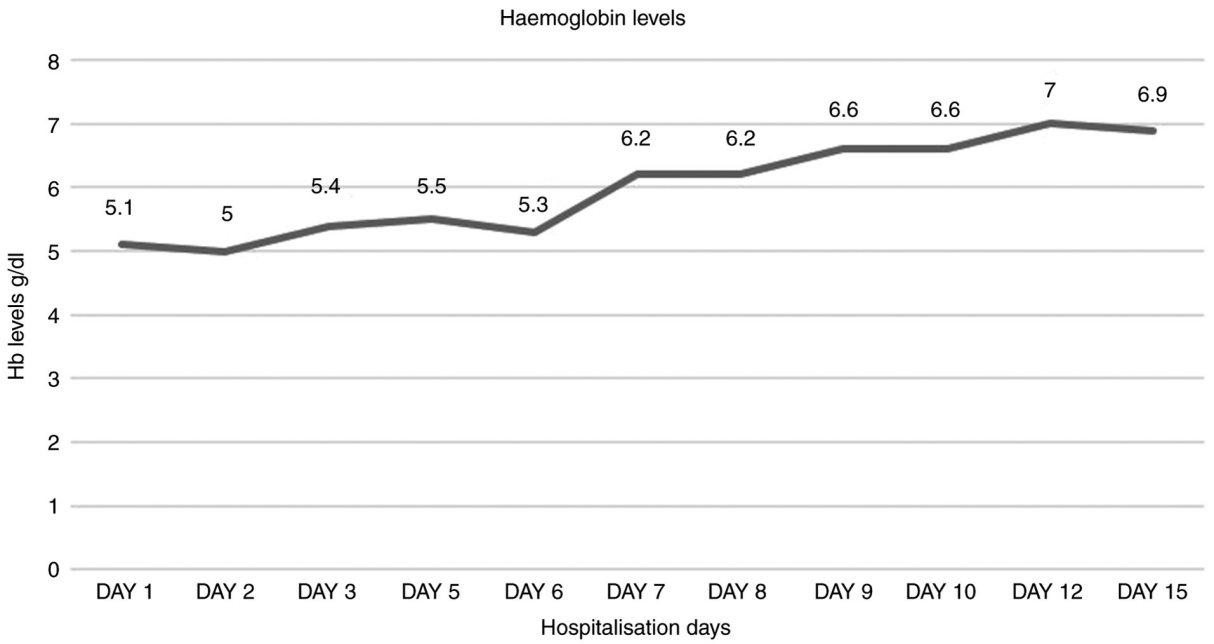

Figure 1. The patient's haemoglobin levels (g/dl) throughout her hospitalisation period.

antiglobulin test (DAT) and no previous history of AIHA were considered. For the majority of cases, the entire article was read; in a few cases, only the abstract was read. After selecting the articles which fulfilled these criteria, a few more articles about anaemia with COVID-19 and a positive DAT were found in the references and these were included as well.

While pulmonary involvement remains the main feature of SARS-CoV-2, there are a number of other manifestations caused by the viral infection and COVID-19-related complications that may lead to a worse outcome, such as neurological involvement or electrolytes impairment (14,15).

The patient described herein presented with features suggestive of haemolysis and was diagnosed with AIHA following a positive DAT. Other cases of AIHA in patients with COVID-19 reported in literature were also identified (Table I).The history of a patient with AIHA should include the following: Symptoms of anaemia (breathlessness, fatigue, chest pain), symptoms suggestive of intravascular haemolysis (dark urine, loin pain), recent infection, symptoms of cold-induced acrocyanosis, symptoms suggestive of underlying lymphoproliferative disorder (weight loss, night sweats, lymphadenopathy), recent transfusions to exclude delayed haemolytic reactions, a previous medical history stating if the patient is a solid organ or stem cell transplant recipient and a detailed drug history (16). There are numerous causes of AIHA (13). These include autoimmune, viral, lymphoproliferative disorders and immunodeficiency states. In the patient in the present study, there were no signs that may have suggested a new onset of cancer or a reactivation of her previous one, since the thyroid cancer had been successfully removed with the whole gland, and she had been in follow-up ever since, with the final check-up performed 1 month and a half prior to admission with no radiologic evidence of residual tissue. Moreover, there were no other causes that could have explained the features of AIHA or episodes prior to the one described. It is considered that hypothyroidism could have justified the acute anaemia, particularly since the patient was still in treatment with levothyroxine and had been for years prior to the onset of anaemia. An abdomen ultrasound performed during the hospitalisation period was negative for liver, biliary tract and spleen alterations, and a reduction in haptoglobin levels was observed, which is more suggestive of intravascular haemolysis. Haemolysis and other blood disorders secondary to viral infections are common findings, and it is known that COVID-19 infection is associated with immune dysregulation and that specific HLA antigens are associated with a more severe disease (17-20); thus, it was suspected that the patient had haemolytic anaemia secondary to COVID-19, as it probably induced the selection of anti-globulin antibodies, causing the haemolysis observed in this case.

In acute inflammation, there are numerous factors that contribute to the decrease in Hb levels, the most known being the cytokine-induced iron metabolism dysregulation and the inhibition of Epo formation. In COVID-19, there is the added risk of iatrogenic anticoagulation and the cross-mimicry between Spike-protein and some RBC surface proteins (21).

The results of a study conducted by the Reference Centre in Northern Italy for autoimmune cytopenia (AIC) suggested a lower than expected incidence of COVID-19 in patients previously diagnosed with AIC (22).

Even though anaemia is a common and very well-known consequence of inflammation caused from the dysregulation of iron homeostasis and the suppression of Epo, in SARS-CoV-2 infection, there is the added risk of iatrogenic bleeding or bleeding secondary to disseminated intravascular coagulation. Therefore, the patient in the present study was treated with a prophylactic dose of LMWH.

Molecular mimicry, which may be the cause of other autoimmune SARS-CoV-2-related diseases, should be considered as a potential trigger for AIHA, consisting of antibodies elicited against viral proteins that cross-react with self-antigens. Ankyrin-1, a protein present on erythrocyte membranes, appears

Table I. Cases of AIHA concomitant to SARS-CoV-2 infection reported in the literature.

Authors (year of publication)	Sex	Age, years	Comorbidities	DAT specificity	Ab Optimum Temp	Hb (g/dl)	Reticulocytosis	Haptoglobin (mg/dl)	Total bilirubin level(s) mg/dl	AIHA treatment	Outcome	(Refs.)
Maslov *et al* (2020)	M	48	Hypertension, insulin-dependent diabetes, obesity, end-stage renal disease	/	Cold	4.5	/	21	2.5		Exitus	(26)
Liput *et al* (2021)	F	33	Iron deficiency anaemia	IgG+C3	Warm	6.5	Yes	<10	3	Prednisone 1 mg/kg/day, blood transfusion	Recovery	(28)
Zama *et al* (2021)	M	15	/	IgG+C3d	Cold	3.7	/	/	3.51	Prednisone 2 mg/kg, ivig	Recovery	(34)
Ahmed *et al* (2021)	M	70	CAD, gout, chronic viral hepatitis B	C3d	Cold	3.4	Yes	<0.08	3.86	Dexamethasone 6 mg/day, blood transfusion	Recovery	(35)
Moonla *et al* (2020)	F	24	/	C3d	Cold	10.9	/	/	NR		Recovery	(36)
Raghuwanshi (2020)	M	45	/	/	Cold	6.9	Yes	/	7.76	Blood transfusion	/	(37)
Jacobs *et al* (2020)	F	33	Hypothyroidism	IgG+C3d	Cold	1.3	Yes	<8	2	Blood transfusions, prednisone 1 mg/kg, daily, rituximab 600 mg single dose	Recovery	(38)
Zagorski *et al* (2020)	F	46	Immune thrombocytopenic purpura (ITP), status post splenectomy, iron deficiency anaemia, asthma	IgG+C3d	Cold	5.3	Yes	Undetectable	9.2		Exitus	(39)

Table I. Continued.

Authors (year of publication)	Sex	Age, years	Comorbidities	DAT specificity	Ab Optimum Temp	Hb (g/dl)	Reticulocytosis	Haptoglobin (mg/dl)	Total bilirubin level(s) mg/dl	AIHA treatment	Outcome	(Refs.)
Capes *et al* (2020)	M	62	Hypertension, smoking, oropharyngeal squamous cell carcinoma in treatment with radiochemotherapy	IgG+C3d	Cold	6.9	Yes	0.13	1.3	Blood transfusion	Recovery	(40)
Kaur *et al* (2021)	M	61	Hypertension, type 2 diabetes mellitus, hypercholesterolemia, end-stage renal disease (ESRD), haemodialysis-dependent, anaemia of chronic disease, coronary artery disease, paroxysmal atrial fibrillation, obesity	C3d	Cold	4.5	Yes	/	3.1	Methylprednisolone 60 mg, blood transfusion	Recovery	(41)
Patil *et al* (2020)	F	51	Breast ductal carcinoma *in situ* post-mastectomy on chemoradiation	C3d	Cold	5.1	Yes	/	NR	/	Recovery	(42)
D'Aloisio *et al* (2020)	M	46	Hypertension, hereditary spherocytosis	/	Cold	6.2	/	244	1.8	Blood transfusion	Recovery	(43)
Huscenot *et al* (2020)	F	43	Obesity and untreated multiple sclerosis	/	Cold	6.1	/	/	NR	/	Recovery	(44)
Huscenot *et al* (2020)	M	63	Hypertension	IgG+C3	Warm	8.2	/	<0.08	NR	/	Recovery	(44)
Gupta *et al* (2021)	M	77	G6PD deficiency	C3d	Cold	8.8	/	/	1.9	Methylprednisolone, blood transfusion	Exitus	(45)

Table I. Continued.

Authors (year of publication)	Sex	Age, years	Comorbidities	DAT specificity	Ab Optimum Temp	Hb (g/dl)	Reticulocytosis	Haptoglobin (mg/dl)	Total bilirubin level(s) mg/dl	AIHA treatment	Outcome	(Refs.)
Nair *et al* (2021)	M	23	Bronchial asthma	IgG	Warm	3.6	Yes	/	6.95	Methylprednisolone 1 g/day, prednisolone 1 mg/kg/day, blood transfusion	Recovery	(46)
Hindilerden *et al* (2020)	M	56	Hypertension	IgG+C3d	Warm	4.3	Yes	11.5	2.95	IVIG, blood transfusion, prednisolone 1 mg/kg/day	Recovery	(47)
Lazarian *et al* (2020)	M	61	Hypertension, chronic renal failure	IgG+C3d	Warm	6	Yes	<0.1	NR	Steroids	/	(48)
Lazarian *et al* (2020)	F	89	Hypertension, chronic renal failure, atrial fibrillation	IgG+C3d	Warm	8.4	Yes	<0.1	NR	Steroids	/	(48)
Lazarian *et al* (2020)	F	62	Hypertension, cirrhosis	C3d	Cold	10.8	Yes	<0.1	NR	SteroidS, rituximab	/	(48)
Lazarian *et al* (2020)	F	69	Obesity	IgG+C3d	Cold	3.8	Yes	<0.1	NR	Steroids	/	(48)
Lazarian *et al* (2020)	M	61	Hypertension, chronic renal failure, diabetes, hypercholesterolaemia	C3d	Cold	7.2	Yes	0.8	NR	Blood transfusion	/	(48)
Lazarian *et al* (2020)	M	61	Diabetes	IgG	Warm	7	Yes	<0.1	NR	Steroids, rituximab	/	(48)
Lazarian *et al* (2020)	M	75	Diabetes, hypercholesterolaemia, cardiopathy, obesity, chronic obstructive bronchopneumopathy	IgG	Warm	7.1	Yes	<0.1	NR	Blood transfusion	/	(48)
Brazel *et al* (2021)	M	51	/	IgG+C3d	Mixed	3.1	Yes	<30	5.3	Prednisone 1 mg/kg, blood transfusion	Recovery	(49)
Rosenzweig *et al* (2020)	F	14	/	IgG+C3b C3d	Mixed	4	Yes	<10	NR	Blood transfusion, rituximab	Recovery	(50)
Al-Mashdali *et al* (2021)	M	39	/	IgG	NR	8.2	Yes	/	NR	Prednisolone 60 mg daily	Recovery	(51)

Table I. Continued.

Authors (year of publication)	Sex	Age, years	Comorbidities	DAT specificity	Ab Optimum Temp	Hb (g/dl)	Reticulocytosis	Haptoglobin (mg/dl)	Total bilirubin level(s) mg/dl	AIHA treatment	Outcome	(Refs.)
Al-Mashdali *et al* (2021)	M	2	β thalassemia major (transplant + GvHD)	IgA+/IgG +/IgM+/C 3c+/C3d+	Cold	2.3	/	/	2.94	Prednisone 2 mg/kg, blood transfusions	Recovery	(51)
Mausoleo *et al* (2021)	F	53	Autoimmune thyroiditis	IgA	NR	7	Yes	<0.07	NR	Methylprednisolone 500 mg, prednisone 1 mg/kg, blood transfusion, rituximab	Recovery	(52)
Huda *et al* (2021)	M	54	Diabetes mellitus	IgG	NR	9	Yes	30	1.4	Prednisone 80 mg	Recovery	(53)
Georgy *et al* (2021)	M	33	/	/	NR	7.5	Yes		1.23	Dexamethasone 40 mg/ day	Exitus	(54)
Jawed *et al* (2020)	M	50	Obstructive sleep apnoea and hypertension	C3d	NR	7.9	Yes	<30	7.84	/	Recovery	(55)
Lopez *et al* (2020)	F	46	Congenital thrombocytopenia	IgG+C3d	NR	9.7	Yes	/	NR	IVIG, blood transfusion, prednisone 60 mg/day	Recovery	(56)
Hernández *et al* (2020)	F	13	Psoriasis	IgG	NR	6.3	Yes	<7.38	1.9	Methylprednisolone pulses 250 mg/daily, prednisolone 1 mg/kg daily	Recovery	(57)
Ramos-Ruperto *et al* (2021)	M	53	/	IgG	NR	6.5	/	<7.75	1	Methylprednisolone	Recovery	(58)
Ramos-Ruperto *et al* (2021)	F	73	/	C3d	NR	7.4	/	<7.75	3.5	Blood transfusion	Recovery	(58)

Table I. Continued.

Authors (year of publication)	Sex	Age, years	Comorbidities	DAT specificity	Ab Optimum Temp	Hb (g/dl)	Reticulocytosis	Haptoglobin (mg/dl)	Total bilirubin level(s) mg/dl	AIHA treatment	Outcome	(Refs.)
Ramos-Ruperto *et al* (2021)	F	76	Hypertension, hypothyroidism and chronic lymphocytic leukaemia (CLL)	IgG	NR	8	/	<7.75	0.35	Methylprednisolone	Recovery	(58)
Woldie *et al* (2020)	M	24	AIHA	IgG+C3	NR	7.5	/	/	2.4	Prednisone (1.5 mg/kg), cyclophosphamide	Recovery	(59)

NR, not reported; /, none; Hb, haemoglobin; temp., temperature; AIHA, autoimmune haemolytic anaemia.

to have structural similarities with the viral spike protein, sharing an immunogenic-antigenic epitope with the SARS-CoV-2 surface glycoprotein known as Spike-protein (20). These factors contribute to the plethora of evidence that suggest that autoimmune diseases are potentially induced by SARS-CoV-2; therefore, it can be assumed that anaemia in COVID-19 can be sustained both from the viral infection itself and from the selection of auto-antibodies induced by SARS-CoV-2 (23).

In the case described herein, weakness and other anaemia-related symptoms were the first clinical manifestations that led the woman to seeking medical attention; at the time, she did not present any respiratory symptoms that are commonly associated with COVID-19, even though she had a cough and throat ache the month prior to her admission. The authors found very few other cases in literature in which there were only late pulmonary symptoms or no pulmonary manifestations (24,25). In other cases, there were coryzal symptoms prior to anaemia (23,26), the most common being dyspnoea, fever, cough, muscle aches, anosmia, ageusia. Regardless of the first symptoms, it is proven that a decrease in Hb levels during COVID-19 may lead to a worse prognosis (27,28), since the already compromised respiratory system has to deal with a significant reduction in Hb that cannot guarantee an adequate peripheral oxygenation.

Most typical COVID-19 symptoms were usually absent or manifested late in the cases found in the literature; therefore, testing for SARS-CoV-2 should be considered for patients that present anaemia-related features, along with the other common viruses. DAT needs to also be performed to reveal a possible autoimmune origin of anaemia. If possible, when AIHA is diagnosed, a titration of antiglobulin-Abs should be performed to test the type of autoantibodies involved.

The diverse types of AIHA, in fact, differ based on the optimal reactivity temperatures of the autoantibodies. Serologically AIHA cases are divided into the warm type (65%) known as wAIHA, the cold type (29%) which is cold hemagglutinin disease (CAD), 1% paroxysmal cold haemoglobinuria or mixed AIHA (mAIHA, 5%) (29,30). The concomitant or sequential association of AIHA with immune thrombocytopenia and sometimes neutropenia define Evans syndrome, a rare syndrome that represents 7% of AIHA cases (31). Among the different types, wAIHA is the most common, accounting for 70 to 80% of all adult cases and ~50% of paediatric cases (32).

Due to laboratory limitations, the authors were not able to perform a titration of antiglobulin-Ab to determine whether the case was a CAD or wAIHA case, even though it is known that cold agglutinins are often a complication of specific infections and malignancies. In the literature search, a marked prevalence of CAD was observed, with 17 cases out of 39 being CAD (44%) (24,27,33-45), 8 cases of wAIHA (20%) (28,46-48), 2 cases of mAIHA (5%) (49,50) and 12 cases (31%) where titration was not performed (51-59).

In the majority of cases, a DAT was performed and a marked prevalence of both the IgG and C3 type was observed. A peculiar case is the second one reported by Zama *et al* (34), regarding a 2-year old male patient who had a history of β-thalassemia major, who underwent an allogeneic haematopoietic stem cell transplantation and subsequently manifested graft vs. host disease (GvHD). At 6 months following transplantation, the

patient in that study manifested fever and weakness and tested positive for SARS-CoV-2, with blood tests revealing severe anaemia (Hb, 2.3 g/dl); DAT tested positive for cold agglutinins $IgA^+/IgG^+/IgM^+/C3e^+/C3d^+$, which may be interpreted as the result of alloimmunization due to the patient's recent history of transplantation and GvHD (34).

Excluding a case of macular haemorrhage (43), which could not justify the decrease in Hb levels, there was no evidence of overt bleeding in the other cases identified in the literature, similarly to the case of the patient in the present study. In the other cases in the literature, a high rate of hypertension as a comorbidity was found, followed in frequency by type II diabetes and hypercholesterolemia. The patient described herein also suffered from hypertension. Haematological disorders were present in 8 cases in the literature among the ones identified (27,38,40,42,50,55,57,58). Only another 2 patients had a clinical history of hypothyroidism, as in the case of the patient described herein (37,57). Another 2 cases had a history of solid cancer, with one being still in treatment during the episode of AIHA (39,41).

First-line therapy for AIHA involves the administration of corticosteroids. Treatment with low-dose corticosteroids for >6 months results in a lower incidence of relapse than in patients who discontinue the administration at an earlier stage (60-62). If the patient is not responsive to treatment after 3 weeks, treatment failure should considered, and therapy should be switched to intravenous immunoglobulin, if not contraindicated. In the case of a first-line failure, the second-line treatment consists of immunosuppression and rituximab, a chimeric human IgG1-κ monoclonal antibody against the protein, CD20, a therapeutic option for thrombocytopenia, AIHA and Evans syndrome that usually yields a response rate of 70-80% as the second-line treatment for AIHA; some cases of hypogammaglobulinemia have been observed consequentially to the use of rituximab (63).

Corticosteroid therapy was the first-line treatment in a number of cases in the literature. In 25 of the identified cases, steroids were administered following the failure of other treatments. Among the most commonly used there were methylprednisolone, prednisone and prednisolone. I the present study, it was decided not to perform a blood transfusion after consulting the haematologists.

The outcome of COVID-19 in patients with underlying AIHA has yet to be studied, even though studies concerning other underlying pathologies are already available (14,64,65). Hb levels, assessed in patients with COVID-19 at the time of hospital admission, indicate that patients with anaemia admitted to the intensive care unit (ICU) have a higher mortality rate than non-anaemic patients not in the ICU (22,66). Moreover, SARS-CoV-2-infected patients with AIHA appear to have had a longer hospitalisation period than COVID-19 patients with non-AIHA anaemia (27). Of course, SARS-CoV-2-targeted therapies and eventual O_2 therapy have to be administered along with treatment for AIHA, if not contraindicated for the anaemia, to treat the viral infection as well (67,68).

In the case in the present study, COVID-19 specific treatment was not administered, such as monoclonal antibodies, mostly due to the fact that they were not available at the time. However, they could have improved the cytokine storm caused by SARS-CoV-2 (69,70).

In 27 (69,2%) out of the 39 cases identified in the literature, the patients, including the one described herein, had a full recovery from both COVID-19 and AIHA (28,34-36,38,40-44,46,47,49-59). Of note, 4 patients (10,2%) succumbed (26,39,45,54). It has to be mentioned that some of the patients visited the hospitals for observation at a time when their condition was already at an advanced or severe stage; thus, effective therapy could not be administered and the patient succumbed. The outcome in 8 cases (20,5%) was not reported (37,48).

Even in the more severe cases, there appears to be a prevalence of a full recovery, which may be due to the early commencement of treatment. Among the various steroid regimens adopted, there does not appear to be a more effective one, while it is controversial the role played by IV-Ig, considering the autoimmune nature of AHIA, and rituximab, added just in a few of the cases taken into account.

However, even if they are not among the most common predictors of mortality in COVID-19 cases, AIHA and anaemia induced by SARS-CoV-2 need to be considered one of the most concerning aspects, as they could lead to severe consequences in combination with the other features of the viral infection (71).

In conclusion, the clinical case described herein has allowed for the re-evaluation of the complex associations that exist between autoimmune and infectious diseases, with reference to COVID-19. In particular, it is interesting to note that in the case described herein, there was a complete absence of respiratory symptoms at the time of admission and anaemia appeared to be the only presentation of COVID-19, excluding the mild coughing and throat ache the patient had manifested 1 month prior to her admission. While thrombocytopenia remains the most common autoimmune disease associated with SARS-CoV-2 infection, the increasing number of reported cases of AIHA has become a cause for concern and interest, particularly considering the still increasing number of cases of other haematological disorders, such as thrombocytopenia associated with COVID-19 and, in addition, how SARS-CoV-2 may affect patients with an underlying haematological disorder (9). Although the mechanisms of the interaction between SARS-CoV-2 and haemolytic anaemia are not yet fully understood and further studies are certainly required to evaluate these, the possible association between COVID-19 and AIHA cannot be ignored.

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Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

EVR, MC, GC, YR, GN, AM and CM were involved in the conceptualization of the study. YR, CM, EVR, MC, GC and GN were involved in acquiring, analysing and interpreting the patient's data. YR, CM, EVR, GN, MC, GC and AM were involved the drafting, writing, review and editing of the manuscript. All authors have read and agreed to the published version of the manuscript. YR and CM confirm the authenticity of all the raw data. All the authors agree to be accountable for all aspects of the work. None of the authors have performed any of the biochemical and blood test reported in the manuscript.

Ethics approval and consent to participate

Written informed consent was obtained from the patient whose case is described herein.

Patient consent for publication

Written informed consent was obtained from the patient for the publication of her case.

Competing interests

The authors declare that they have no competing interests.

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