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COVID-19 Short Communication

Transient plasma cell dyscrasia in COVID-19 patients linked to IL-6 triggering

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ABSTRACT

An unusual clonal gammopathy was reported in COVID-19 patient but whether this anomaly is related or not to the disease has not yet been clarified. To this aim, we selected a cohort of 35 COVID-19 patients swab positive and investigated serological levels of IL-6, immune response to major viral antigens and electrophoretic profile. Elevated levels of IL-6 were accompanied by a significative humoral response to viral Spike protein, revealing an altered electrophoretic profile in the gamma region. We can conclude that elevated levels of IL-6 triggers humoral response inducing a transient plasma cell dyscrasia in severe COVID-19 patients.

Severe Acute Respiratory Syndrome CoronaVirus-2 (SARS-CoV-2) is a novel coronavirus responsible for the 2019-20 pandemic [1].

SARS-CoV-2 infects the host via the respiratory tract and the first targets of viral entry access are mainly airway and alveolar epithelial cells, vascular endothelial cells and alveolar macrophages [2]. Then, viral RNA is transcribed and encodes at least four proteins: Spike (S), Membrane (M) and Envelope (E) protein are all expressed on the viral envelope whereas N is a component of the viral nucleocapsid. These proteins play a key role not only as structural viral elements, but also as the main target of humoral response [3,4].

Within 7 days after the onset of the disease, the immune system should eliminate the virus, giving rise to the patient's recovery. When this not does occur, the respiratory-like illness could progress to severe pneumonia, systemic inflammation often with a poor prognosis [5].

Emerging evidence suggests that severity and poor prognosis in COVID-19 patients could be related to an excessive response of the immune system, mainly characterized by the abnormal release of circulating cytokines, event known as "cytokine storm" [6]. Release of a plethora of cytokines plays a pivotal role in exacerbate patients conditions, from pneumonia through acute respiratory distress syndrome (ARDS), cumulating in systemic inflammation and ultimately multi-system organ failure [7]. Several cytokines such as IL-1, IL-2, IL-10, TNF-α and IFN-γ are responsible of this "storm" in COVID-19 patients, however, a crucial role seems to be played by IL-6, whose increased levels in the serum have been correlated with respiratory failure, ARDS, and adverse clinical outcomes [8]. However, mechanism/s triggered by IL-6 in the etiopathogenesis of Covid-19 is not yet fully understood.

IL-6 is a multifunctional cytokine that is promptly and transiently produced by T cell and macrophage in response to infections and tissue injuries, with a key role in host defense through the stimulation of acute phase responses, hematopoiesis, and immune reactions [9]. Several findings underline the pivotal role of IL-6 also in the differentiation of B-cells into antibody producing plasma cells and immunoglobulin secretion [10–12]. Aberrant levels of IL-6 have been demonstrated also in several autoimmune disease, in obesity as well as in Multiple Myeloma (MM) [13–15].

Recently, it has been described an unusual clonal gammopathy in COVID-19 patients [16]. However, is not clear whether modulation in the electrophoretic profile is related or not to the disease progression.

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On the light of this observation, aim of this study was to clarify the possible role of IL-6 in triggering of the immune response in COVID-19 patients. To this aim, we selected a cohort of COVID-19 patients, swab positive (RT-PCR positive), and evaluated at the diagnosis and six days later serological levels of IL-6, immune response to major viral antigens (Spike and/or N) and electrophoretic profile.

1. Patients and methods

1.1. Patients

Between March and November 2020, thirty-five COVID-19 positive patients cohort, 25 males (mean age 67 years) and 10 females (mean age 78,7 years), referred to the COVID-19 intensive care unit of the Policlinico Umberto I, "Sapienza" University of Rome, were enrolled in the study. All patients included in this study were swab positive (RT-PCR positive) for COVID-19. We collected two serum sample: 1st sample at the admittance and 2nd sample 6 day later.

1.2. Methods

1.2.1. Serum collection

All sera were acquired following a standard protocol. Briefly, samples were collected in a Yellow Top Vacutainer (Becton, Dickinson and Co., Plymouth UK) clotted 60–90 min and centrifuged for 10 min at 1300×*g*. The serum fractions obtained were then aliquoted in 1.5 ml Eppendorf tubes (Eppendorf S.r.l., Milano Italy) and stored at −80 °C until analysis.

1.2.2. IL-6 assay

The fully automated Elecsys system on a Cobas e801 platform (Roche Diagnostics, Basel, Switzerland) was used to measure IL-6 values. The Elecsys IL-6 immunoassay has been standardized against the National Institute for Biological Standards and Control first international standard 89/548IL-6 detection range was between 1,5 and 5.000 pg/ml, as a clinical cut-off we considered 7,0 pg/ml.

1.2.3. Antibody measurements

We measured SARS-CoV-2–specific antibodies with two established assays targeting immunoglobulin (IgM, IgG, and IgA) antibodies against the nucleoprotein (N) (Elecsys anti SARS-CoV-2 Roche) and IgM, IgG and IgA antibodies against the receptor binding domain (RBD) in the S1 subunit of the spike protein (pan-Ig anti–S1-RBD) (Elecsys anti SARS-CoV-2 Roche ROCHE).

Antibody against N: Elecsys anti SARS-CoV-2 provides a qualitative result with a sensitivity of 100.0% (95% CI 88.10–100.0) and a specificity of 99.81% (95% CI 99.65–99.91). A cut-off index (COI) ≥1 is regarded as positive. Antibodies titer above the reference limit of N antibodies was arbitrarily distributed in quartiles as follow: quartile I values from 1 to 10 COI; quartile II values from 11 to 50 COI; quartile III values > 50 COI.

Antibody against S: Elecsys anti SARS-CoV-2 provides a quantitative result with a sensitivity of 98.8% (95% CI 98.1–99.3) and a specificity of 99,98% (95%CI 99,91%). Measurement range 0,4<>250 U/ml. A cut-off index ≥0,8 U/ml is regarded as positive. Antibodies titer above the reference limit of S antibodies was arbitrarily distributed in quartiles as follow: anti-Spike antibody quartile I values from 1 to 10 U/ml; quartile II values from 10 to 100 U/ml; quartile III from 101 to >250 U/ml.

1.2.4. Serum proteins and immunotyping analysis

Collected sera were analyzed by Capillary Electrophoresis (CE) according to manufacturer instructions (Sebia Capillarys-2, Sebia 27 rue Léonard de Vinci CP 8010 Lisses - 91,008 Evry Cedex FRANCE). Protein electrophoresis is a technique routinely used in clinical laboratories for screening of serum and other fluids for protein abnormalities. Briefly, plasma proteins are resolved into few bands and are often used to detect Monoclonal band (M-band). The pattern of serum protein electrophoresis (protidogram) depends on the fractions of two major types of protein: albumin and globulins. In the interpretation of serum protein electrophoresis, most attention focuses on the gamma region (γ-region), which is composed predominantly of antibodies. In normal condition, this zone should appear as bell shaped curve (gaussian distribution), with no asymmetry or sharp peaks. The γ-globulins may be elevated (hypergammaglobulinemia), decreased (hypogammaglobulinemia), or have an abnormal peak or peaks.

1.2.5. Statistical analysis

The statistical significance of differences between the ab titer against S and N antigens was assessed using assessed using Fisher's exact two-tailed test. A p-value < 0.05 was considered statistically significant. Statistical analysis was carried out using MedCalc V 4.30 Software, Italy and Prism 5 Software, GraphPad, San Diego California–USA.

2. Results

2.1. Increased levels of IL-6 in COVID-19 patients

We started to assay IL-6 levels in a cohort of 35 patient at the hospital admittance. Thirty-three out of thirty-five patients showed higher levels of IL-6 (median IL-6 level was 31.5 pg/mL; IQR: 7 pg/mL) at the first withdrawal.

At the second withdrawal, 6 patients showed a normalization of amounts of IL-6, whereas 27 out of 33 patients showed higher levels of IL-6 (median IL-6 level was 52.0 pg/mL; IQR: 48.5 pg/mL) (Fig. 1).

2.2. Humoral immune response to viral spike and N antibodies in COVID-19 patients

Cytokine storm promoted by the altered level of IL-6 indeed represents a high risks factor and suggest the severe involvement of

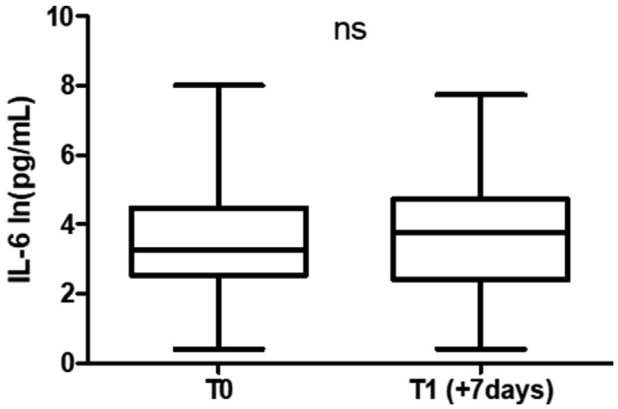


Fig. 1. IL-6 levels in Covid-19 patient cohort. The box plot analysis shows IL-6 levels in the first withdrawal round (T0) and in the second withdrawal round (T1) in 35 patient cohort. Statistical analysis was carried out using Wilcoxon test (W = −26.0, P = 0.11).

the immune system in response to viral infection. In order to correlate the severity of the immune response to the stimulation promoted by IL-6, we evaluated the presence of antibodies (ab) directed against the virus at the admittance (T0-1st sample) and 6 days post admission (T1-2nd sample). Ab levels were tested against the two major antigenic viral proteins: Spike (on the viral envelope) and N (nucleocapsid).

In the T0 ab values against S protein above the cut off were observed in 89% with an heterogenous distribution in all quartiles.

Six days following the first withdrawal (T1) we observed that seroconversion occurred in all patients. Moreover, ab levels against S were significantly increased in the III quartile range (62,8%).

Concerning N ab presence, in the T0, antibodies against N were grouped mostly in the I quartile range.

We then assayed ab expression in T1 and observed that N titer were moderately increased in the II quartile range and part were regressed in the I quartile range. Moreover, analyzing the group with higher ab titers (III quartile range), we also observed a statistically significative difference between anti-S ab respect to anti-N ab. This difference was detectable in the 1st (*P < 0,05) as well as in the 2nd (*P < 0,0015) withdrawal. Presented results are summarizing in Table 1.

2.3. Protidogram analysis and follow-up of COVID-19 patient cohort

Among the various anomalies observed in COVID-19 patients, recently it has been described an altered electrophoretic mobility of γ-globulins similar to that observed in monoclonal gammopathies [17] thus suggesting a strong stimulation of the immune system. In our study group we found/observed alterations in the γ-globulin profile in 82,2% of analyzed patients at first withdrawal (29/35) (Fig. 2 D). However, alterations of the electrophoretic profile were similar to the monoclonal band observed in Multiple Myeloma (MM) or in other monoclonal gammopathy of undetermined significance (MGUS). In Fig. 1 (A-B-C) we show a representative electrophoretic profile (CE) of three different patients. Comparison of IL-6 levels, anti S ab and anti N ab vs altered or normal CE is summarize in pie charts presented in Fig. 2 (E-F-G respectively).

We therefore wondered if there could be a correlation between these altered profiles with IL-6 levels. We observed that elevated levels of this cytokine are generally related to an altered protidograms, although four patients, despite high levels of IL-6, did not show a relevant alteration in the electrophoretic profile. Indeed, we observed that 95% of patients with an altered profile showed high ab titers against Spike, since 72,4% of the altered curves were associated to an elevated anti-Spike titer (III quartile group), 20,7% to the II quartile and only il 6,9% in the I quartile. Otherwise, only 25% of patients with elevated ab titers against N protein showed protidogram alteration, thus the anti-N levels did not seem to have a specific correlation with the alteration of the curve.

During the evolution of the disease, we analyzed the electrophoretic profile 6 days after the first withdrawal. As shown in Fig. 3, we observed that alteration of the γ-globulin regions could rapidly change in few days (Fig. 2 A(ii), B(ii), C(ii) panels) respect to the admittance withdrawal (Fig. 2, A (i), B (i), C (i) panels). Curves mobility showed a different behavior: in some case we observed a shift in the electrophoretic peak; in other cases, protidogram evolved in a hypergammaglobulinemia or in a hypogammaglobulinemia (data not shown). Moreover, as shown in Fig. 2, the γ-region of the electrophoretic profile of the γ-region returned to a normal distribution in patients with an improved clinical manifestation of disease (Fig. 3 B (iii) and C (iii) panels). In these patients, jointly with the profile normalization, we observed decreasing levels of IL-6. However, ab titers against S antigen were still persistent.

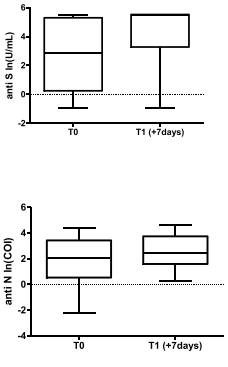
3. Discussion and conclusions

Cytokines are known to regulate cellular and humoral responses against virus [18] but in the case of SARS-CoV-2, this mechanism is aberrantly exacerbated during severe infections representing a poor prognosis risk factor.

In order to evaluate the natural history of the events that occur between viral infection and immune response in COVID-19, in the present paper we compared the IL-6 expression with the humoral response in a group of patients SARS-CoV-2 swab positive (molecular test) at the hospital admittance. According to previous reports, we observed that increased levels of IL-6 indicate a severe stimulation of the immune response followed by aberrant immunoglobulins productions against viral Spike protein. Since this protein mediate the viral entry via ACE-2 receptors, it is likely to represent the first and most abundant viral antigen presented by APC cells to the immune system. Otherwise, the nucleocapsid protein N, could have a different timing in humoral response. Such observation is supported by the

Table 1
Ab titers against Spike and N in COVID-19 cohort patients. Antibodies titer against S and N proteins have been evaluated at T0 (1st withdrawal) and six days later T1 (2nd withdrawal). Data were log transformed, and paired t-test was performed accordingly; no analysis was performed on anti S for 2nd stage sampling showed almost all saturated results (i.e. >250U/mL) whilst anti N level changed significantly between sampling stages (P = 0.012).

	%Positive q1	%Positive q2	%Positive q3	%Negative
Anti Spike (U/mL)	*1-10*	*11-100*	*101-250*	*<1*
T0	31.4	20.0	37.2	11.4
T1	11.4	25.7	62.8	0
Anti N (COI)	*1-10*	*11-50*	*51-100*	*<1*
T0	37.2	31.4	14.2	17.1
T1	42,8%	32,2	22.8	0



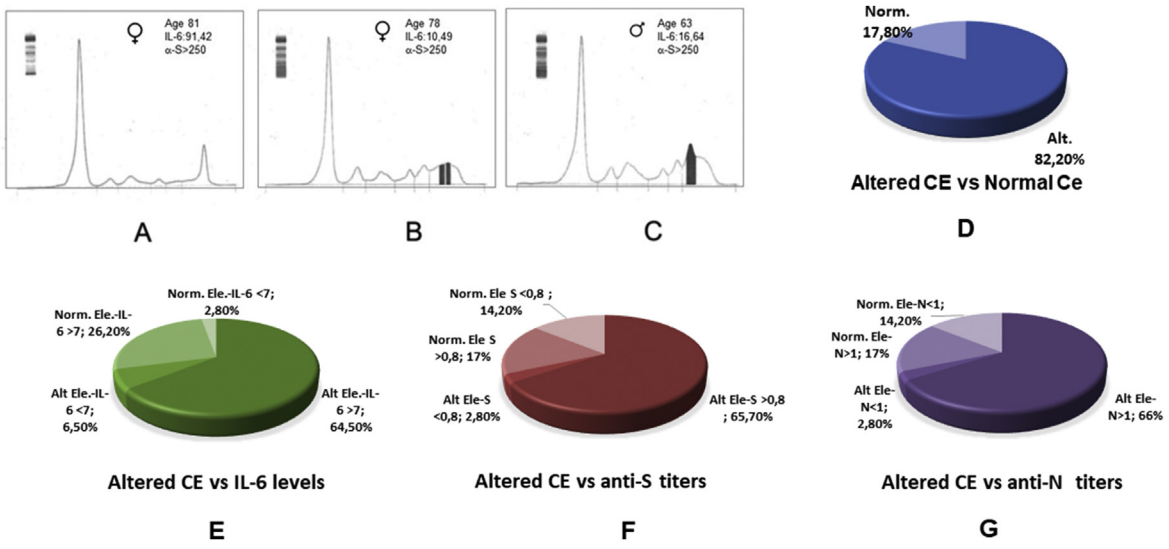


Fig. 2. Protidogram of Covid-19 patients. **(A, B, C)** Representative electrophoretic profiles of three different Covid-19 patients performed at the admittance. **(D)** Pie chart representing percentage of Normal vs Altered (Alt.) γ-globulins electrophoresys (CE). (**E,F,G**) Pie charts representing percentage of Normal (Norm.) or Altered (Alt.) γ-globulins electrophoresys vs IL-6 (>7 high; <7 normal), vs Spike titers (>0,8 positive; <0,8 negative) and vs N titers (>1 positive; <1 negative) respectively.

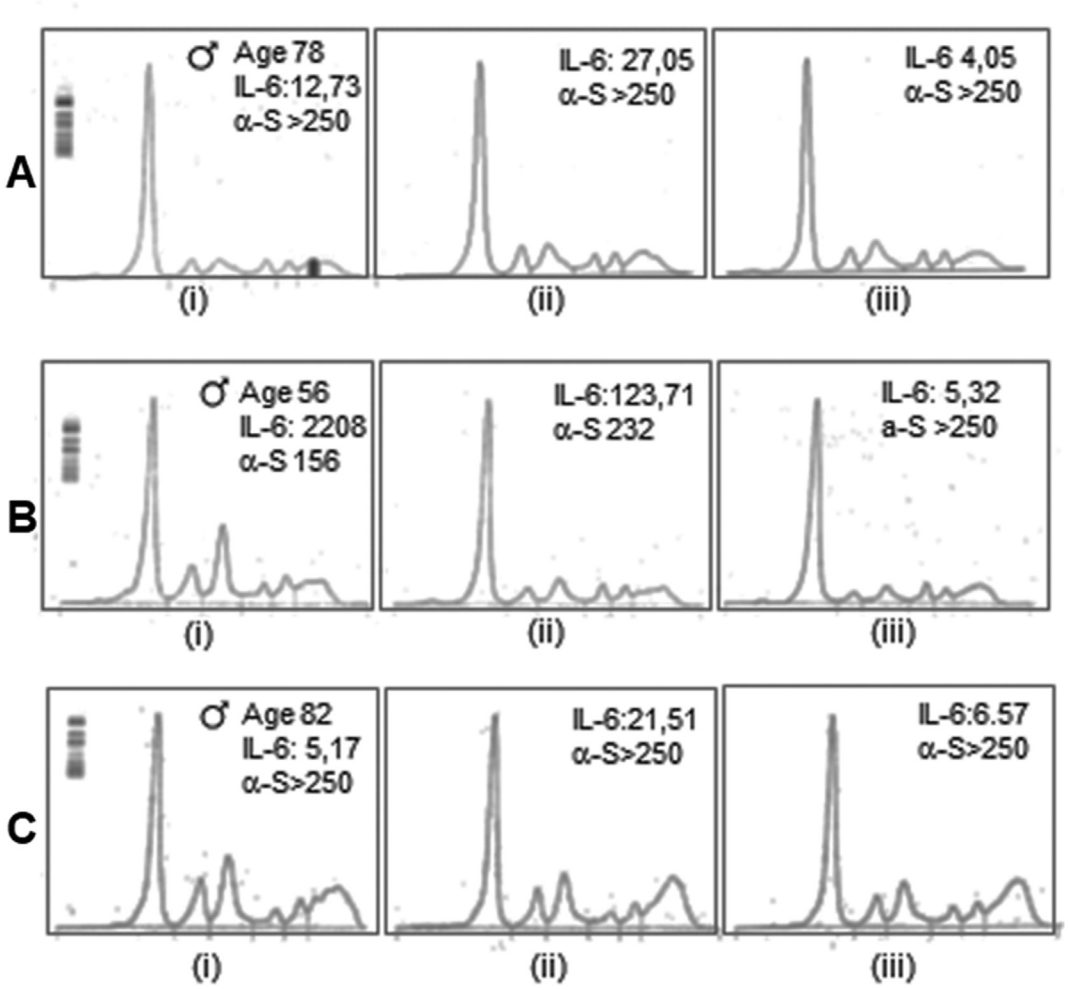


Fig. 3. Follow up protidograms of COVID-19 cohort patients. (**A-B-C**) Representative electrophoretic profiles of three different Covid-19 patients. Electrophoretic analysis has been performed at the admittance (i), 6 days following the first withdrawal (ii) and 12–14 days after the second withdrawal (iii).

evidence that here we found a delayed immune response to N protein. This is not unexpected because similar behavior has been described also in several human RNA respiratory viruses and in Herpesvirus infections: in EBV (Epstein–Barr Virus) the early lytic protein BFRF1 is highly expressed in several associated EBV tumors and immune disorder, but in other EBV related disease a prolonged viral replication is necessary to elicit a detectable humoral response to this protein [19–21].

According to our results, the severe involvement of the immune system is mainly sustained by high levels of IL-6 and anti-S ab and become evident with/by the transitory plasma cell dyscrasia detectable on the electrophoretic profile. The reduced stimulation of the humoral response is affected by the decreasing levels of IL-6 and protidograms start to normalize although, as expected, ab titers to S were persistently present.

Previous case-report reported the appearance of M-bands (monoclonal band) in the protidogram of older COVID-19 patients suggesting an age-related subclinical plasma cells disorder [16]. Monoclonal-bands (M-bands) are the typical electrophoretic signature of monoclonal gammopathies [22]. Since we observed that the appearance of M-band, in a high percentage of the population examined within different ranges of age, we can say that is not related to the age of patients but rather associated to an hyperstimulation of the humoral response. Although the M-band detectable in the electrophoretic profile is similar to the described monoclonal peaks of plasma dyscrasia (i.e. MM, MGUS etc.) [17,23], in COVID-19 patient this event should be considered a transient modulation due to the immunoglobulins aberrant production.

This observation is strengthened by the evidence that elevated levels of ab titers (i.e. against Spike protein) seems to be a good prerequisite to present an altered electrophoretic profile. Moreover IL-6 is known to promote the differentiation of B lymphocyte in plasmacells, which physiologically produce immunoglobulins [24].

Generally, serum proteins concentration is tightly controlled to balance their physiological functions in areas of immunity, coagulation, small molecule transport and inflammation. Any dysfunction and out-of-balance in their concentration can cause or is the results of a disease process [25] thus should not be disregarded. Monitoring protidogram in COVID-19 patients thus could represent a (fast and low cost) useful tool to point out high risk cases, the good clinical outcome or immune response to future vaccines.

The transient plasma cell dyscrasia reported here is indeed an unexpected event: is the first time that such anomaly is described in association to a viral infection. It would be interesting to evaluate whether aberrant Ig accumulation could give raise to the clinical signs observed in COVID-19 patients.

Thus concluding, further studies are needed to evaluate whether the hyperstimulation of the humoral response is only an end point of COVID-19 or a starting point for other diseases.

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Ethical statement

All procedures performed in this study were in accordance with the ethical standards of the Azienda Ospedaliera-Universitaria Policlinico Umberto I and University of Rome “La Sapienza”, National Research Committee and are in accordance with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. All experimental protocols of the study were approved by Azienda Ospedaliera-Universitaria Policlinico Umberto I and are routinely used to monitor patients. Informed consent was obtained from all individual participants included in the study.

Author contributions statement

A.F, E.A. conceived the experiment(s), A.F., R.L and V.V. conducted the experiment(s), R.L., M.S and M.L. recruits samples; C.I. and A.F. performed the statistical analysis; A.F., R.L., E.A and A.A analyzed the results. All authors reviewed the manuscript.

Declaration of competing interest

None.

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