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Editorial – COVID-19, more than a viral pneumonia

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COVID-19 is globally becoming one of the most important issue for the public health. Despite several weeks elapsed since the first epidemic outbreak, globally virological, immunopathological and clinical aspects of the 2019-nCoV and related syndrome are still under investigation[1-3].

Currently, what we know about the COVID-19 is mainly related to clinical aspects being characterized by a prodromal phase including fever, dry cough, myalgia, fatigue, and diarrhea, with possible development of dyspnea and lymphopenia. Furthermore it has also been found that the median time from symptoms onset to ARDS is about 8 days[4] and during the infection process, the white blood cell count in peripheral blood in the early stage of the disease is normal or slightly low, and lymphopenia is observed in patients[4,5].

Complications of COVID-19 include therefore acute respiratory distress syndrome, acute cardiac injury and secondary (super-)infections in patients in the intensive care unit (ICU)[5,6].

The immunopathological phenomena subtended to these clinical findings are poorly understood and some of the possible mechanisms have been hypothesized to be related to SARS and MERS models. Currently, we have reports showing that an initial increased plasma levels of pro-inflammatory cytokines, such as IL-1β, IL-1Rα, IL-7, IL-8, IL-9, IL-10, and IL-6 coupled to vascular endothelial growth factor concentrations are present in 2019-nCoV-infected patients compared to healthy controls[4,5]. Furthermore, those cytokine environments seem to be more prominent in ICU patients showing higher plasma levels of those with also imbalance of lymphocytes subsets[4-6]. According to recent articles showing early histopathological features in COVID-19, the inflammation has been found to be predominantly lymphocytic, with the presence of multinucleated giant cells alongside large atypical pneumocytes, but without any definitive evidence of viral inclusions in several anatomical district[7,8].

These results strongly suggest that inflammation due to possible immune imbalance between natural and acquired immune system may be crucial playing a relevant role in the development of disease severity due to cytokine storm and inflammation environments in a systemic way.

Indeed, based on this idea and according to our previous experiences on immunopathogenesis in viral infections[9], at the beginning of March 2020 we started to evaluate several markers of immune system dysregulation as LAC screening.

Our preliminary results showed that patients admitted in ICU with severe pneumonia and systemic inflammatory response characterized by increase of CRP and IL-6 had higher levels of LAC screening compared to those not admitted in the intensive care (Table I). This data, according to previous experimental evidence and current hypotheses on vascular damage during COVID-19[9,10] seem to propose that possible pathogenesis of COVID would be related to immune system dysregulation with possible production of autoantibody and hyper-triggered response rather than viral infection consequence.

In this possible scenario, the disease evolution of COVID-19 could not be simply related to the effect of virus on the targeted tissues, but the histological damage of lung, kidney and other organs would be the result of a systemic immune mediated inflammatory environment, involving endothelium and tissues infected by the SARS-CoV-2[11]. This hypothesis could also explain why an approach based on chloroquine or monoclonal antibodies targeting cytokines receptors seem to improve disease clinical evolution reducing inflammatory environments[12]. In this perspective, the monoclonal antibodies used for other pathologies could find an important therapeutic space[13-15]. Currently, in our country, a clinical trial on to-

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Table I. Demographics and immunity assay of patients with COVID-19.

	No. (%)	
	ICU (n = 10)	Ward (n = 6)
CHARACTERISTICS (MEDIAN, IQR, RANGE)		
Age	53 (47-67)	53 (41.25-62)
Sex		
Male	10 (100%)	9 (90%)
Female	0 (0%)	1 (10%)
IMMUNITY ASSAY		
P-ANCA	Neg	Neg
C-ANCA	Neg	Neg
ANA	Neg	Neg
ENA	Pos	Neg
ASMA	Neg	Neg
LAC-Screening Ratio*	1.81 (1.5-2)	Neg

*LAC Screening Ratio according to DRVTT (diluite Russel's viper venom test).

cilizumab to verify its effectiveness on the hyper-response of the immune system is underway. Therefore, future researches should focus on this hypothesis to start new therapeutic approaches aimed not only to control viral replication but to modulate the immune response too.

Conflict of Interest

The authors declare that they have no conflict of interests.

References

1) Zhong N, Zheng B, Li Y, Poon, Xie ZH, Chan KH, Li PH, Tan SY, Chang Q, Xie JP, Liu XQ, Xu J, Li DX, Yuen KY, Peiris, Guan Y. Epidemiology and cause of severe acute respiratory syndrome (SARS) in Guangdong, People's Republic of China, in February 2003. Lancet 2003; 362: 1353-1358.
2) Perrella A, Carannante N, Berretta M, Rinaldi M, Maturo N, Rinaldi L. Novel Coronavirus 2019 (Sars-CoV2): a global emergency that needs new approaches? Eur Rev Med Pharmacol Sci 2020; 24: 2162-2164.
3) Ceccarelli M, Berretta M, Venanzi Rullo E, Nunnari G, Cacopardo B. Differences and similarities between Severe Acute Respiratory Syndrome (SARS)-CoronaVirus (CoV) and SARS-CoV-2. Would a rose by another name smell as sweet? Eur Rev Med Pharmacol Sci 2020; 24: 2781-2783.
4) Guan WJ, Ni ZY, Hu Y, Liang WH, Ou CQ, He JX, Liu L, Shan H, Lei CL, Hui DSC, Du B, Li LJ, Zeng G, Yuen KY, Chen RC, Tang CL, Wang T, Chen PY, Xiang J, Li SY, Wang JL, Liang ZJ, Peng YX, Wei L, Liu Y, Hu YH, Peng P, Wang JM, Liu JY, Chen Z, Li G, Zheng ZJ, Qiu SQ, Luo J, Ye CJ, Zhu SY, Zhong NS; China Medical Treatment Expert Group for Covid-19. Clinical characteristics of 2019 novel coronavirus infection in China. N Engl J Med 2020. Doi:10.1056/NEJMoa2002032.
5) Wang D, Hu B, Hu C, Zhu F, Liu X, Zhang J, Wang B, Xiang H, Cheng Z, Xiong Y, Zhao Y, Li Y, Wang X, Peng Z. Clinical characteristics of 138 hospitalized patients With 2019 novel coronavirus-infected pneumonia in Wuhan, China. JAMA 2020. doi: 10.1001/jama.2020.1585. [Epub ahead of print].
6) Wan SX, Yi QJ, Fan SB, Lv J, Zhang X, Guo L, Lang C, Xiao Q, Xiao K, Yi Z, Qiang M, Xiang J, Zhang B, Chen Y. Characteristics of lymphocyte subsets and cytokines in peripheral blood of 123 hospitalized patients with 2019 novel coronavirus pneumonia (NCP). MedRxiv 2020. Doi:10.1101/2020.02.10.20021832.
7) Hanley B, Lucas SB, Youd E, Swift B, Osborn M. Autopsy in suspected COVID-19 cases. J Clin Pathol 2020; 73: 239-242.
8) Yao XH, Li TY, He ZC, Ping YF, Liu HW, Yu SC, Mou HM, Wang LH, Zhang HR, Fu WJ, Luo T, Liu F, Chen C, Xiao HL, Guo HT, Lin S, Xiang DF, Shi Y, Li QR, Huang X, Cui Y, Li XZ, Tang W, Pan PF, Huang XQ, Ding YQ, Bian XW.

A pathological report of three COVID-19 cases by minimally invasive autopsies. Zhonghua Bing Li Xue Za Zhi. 2020; 49: E009.

9) Perrella A, D'Antonio A, Sbreglia C, Sorrentino P, Conca P, Atripaldi L, Conti P, Perrella O. CD4+/CD25+ T cells suppress autologous CD4+/CD25- lymphocytes and secrete granzyme B during acute and chronic hepatitis C. Pathog Dis 2014; 72: 124-130.
10) Channappanavar R, Perlman S. Pathogenic human coronavirus infections: causes and consequences of cytokine storm and immunopathology. Semin Immunopathol 2017; 39: 529-539.
11) Lin L, Lu L, Cao W, Li T. Hypothesis for potential pathogenesis of SARS-CoV-2 infection-a review of immune changes in patients with viral pneumonia. Emerg Microbes Infect 2020; 9: 727-732.
12) Wang M, Cao R, Zhang L, Yang X, Liu J, Xu M, Shi Z, Hu Z, Zhong W, Xiao G. Remdesivir and chloroquine effectively inhibit the recently emerged novel coronavirus (2019-nCoV) in vitro. Cell Res 2020; 30: 269-271.
13) Semeraro F, Russo A, Delcassi L, Romano MR, Rinaldi M, Chiosi F, Costagliola C. Treatment of exudative age-related macular degeneration with ranibizumab combined with ketorolac eyedrops or photodynamic therapy. Retina 2015; 35: 1547-1554.
14) Costagliola C, Semeraro F, Cipollone U, Rinaldi M, della Corte M, Romano MR. Changes in neovascular choroidal morphology after intravitreal bevacizumab injection: prospective trial on 156 eyes throughout 12-month follow-up. Graefes Arch Clin Exp Ophthalmol 2009; 247: 1031-1037.
15) Biggioggero M, Crotti C, Becciolini A, Favalli EG. Tocilizumab in the treatment of rheumatoid arthritis: an evidence-based review and patient selection. Drug Des Devel Ther 2018; 13: 57-70.