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1 **Persistent IgG anti-cardiolipin autoantibodies are associated with post-covid syndrome**

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23 **Word Count:** 610

24 **Highlights:**

25 • No biological marker has been yet proposed to predict post-COVID syndrome (PCS)

- 26 • IgG anti-cardiolipin autoantibodies (aCL) are associated with COVID-19 severity
- 27 • We report here a persistent IgG aCL positivity in a patient developing PCS
- 28 • Persistence of aCL positivity could be a potential biological predictor of PCS

29

## 30 **Abstract**

31 Persistence of various symptoms in patients who recovered from COVID-19 was recently defined as  
32 long COVID or post-COVID syndrome (PCS). We report a case of a 58-year-old woman who,  
33 although recovering from COVID-19, has novel and persistent symptoms such as neurological  
34 complications, not explained by another cause apart from PCS. In addition to a low inflammatory  
35 response, we found a persistence of IgG aCL positivity and eosinopenia, one year after the COVID-  
36 19 acute infection, both previously defined as independent factors associated with disease severity.  
37 The pathophysiological mechanism of PCS is not known, but the possibility of persistence of the  
38 virus, especially in the nervous system, could be suggested, with a post-infectious inflammatory or  
39 autoimmune reaction.

40

## 41 **Introduction**

42 Growing data show the persistence of various symptoms in patients who recovered from COVID-19,  
43 recently defined as long COVID or post-COVID syndrome (PCS) (Tenforde et al., 2020). While  
44 markers associated to COVID-19 severity such as IL6, IgG anticardiolipin autoantibodies (aCL),  
45 eosinopenia, hemogram-derived ratios, have been described in the acute phase of the disease (Bertin  
46 et al., 2020; Liang et al., 2020; Lindsley et al., 2020; Zhou et al., 2020) , no biological marker has  
47 been yet proposed to predict PCS.

## 48 **Case presentation**

49 With a one-year follow-up, we report a case of a 58-year-old woman who, although recovering from  
50 COVID-19, has novel and persistent symptoms such as neurological complications. COVID-19 was

51 diagnosed in March 2020, on the basis of positive SARS-CoV-2 RT-PCR, followed in June 2020 by  
52 positive anti- SARS-CoV-2 serology (Table 1). She had asthma, arterial hypertension, insulin-  
53 dependent diabetes and overweight in her medical history (BMI =35.3kg/m<sup>2</sup>). During the acute phase,  
54 the patient presented febrile hypoxemic pneumonia with dyspnea and cough, which required  
55 hospitalization in intensive care unit without intubation and was treated by azithromycine,  
56 hydroxychloroquine and then ceftriaxone for one week. One year later, she still complains of asthenia,  
57 weekly sleepless headaches, memory problems related to dysexecutive syndrome, exertional dyspnea  
58 (stage 2 according to MMRC scale), chest pain and digestive disorders such as intermittent diarrhea,  
59 bloating, and belching. The scores on the neuropsychological tests were 23/30 on the Mini-Mental  
60 Score, 14/18 on the Frontal Assessment Battery, while the word memorization test revealed a deficit  
61 of information recall without encoding disorder. Cardiological examination showed minimal left  
62 ventricular hypertrophy with preserved ejection fraction. Pertinent laboratory data on admission and  
63 in the follow-up of the patient summarized in Table 1, showed persistent inflammatory biological  
64 syndrome with elevated CRP and fibrinogen, but not IL6. Interestingly, among antiphospholipid  
65 autoantibodies tested, only aCL IgG was positive and persistent one year later. A light but persistent  
66 eosinopenia was also observed. Other biological data were normal. Apart from the headaches, which  
67 persist, without a definite etiology, the clinical examination did not find any clinical sign of  
68 antiphospholipid syndrome (absence of skin lesion, renal or cardiac involvement or thrombosis). She  
69 has 5 children, and no known history of miscarriage or thrombosis.

70 Because of persistent neurological complaint, cerebrospinal fluid (CSF) analysis was performed and  
71 showed normal CSF-protein, without oligoclonal band nor pleiocytosis. Cerebral MRI showed  
72 isolated temporal lacunar stroke of old appearance. Cerebral 18F-FDG-PET scan showed moderate  
73 hypometabolism of amygdala, and mild hypometabolism of fronto-mesial lobe, insula, brainstem and  
74 cerebellum, as it has already been described in patients with long COVID (Guedj et al., 2021). Whole  
75 body 18F-FDG-PET scan did not show any systemic pathological hypermetabolism.

## 76 **Discussion**

77 Until now, most of the clinical studies of COVID-19 have focused on symptoms during the acute  
78 phase of the disease. Mainly, patients present fever ( $\geq 38\text{ }^{\circ}\text{C}$ ), cough, chest pain, dyspnea, diarrhea  
79 and fatigue or myalgia, and in about 15% of case, they may develop acute respiratory distress  
80 syndrome (ARDS) or end-organ failure. More recently, a “post-covid syndrome” (PCS) has been  
81 described in patients who exhibit at least one persistent symptom, 12 weeks after disease onset, which  
82 cannot be explained by another cause (Tenforde et al., 2020). This syndrome seems to be frequent  
83 after COVID-19 acute infection, and not only after a severe form of the disease. The most common  
84 signs of this clinical picture are persistent fatigue, dyspnea, and anosmia or memory complaint. In  
85 this case, we evidenced neurological disorders, not explained by another cause apart from PCS. In  
86 addition to a low grade inflammatory process, we evidenced the persistence of IgG aCL positivity  
87 and eosinopenia, one year after the COVID-19 acute infection, and both previously defined as  
88 independent factors associated with disease severity. They could be potential biological predictors of  
89 the PCS. Positive aCL have been reported in 13.9% of COVID-19 patients (Taha et al, 2021) and  
90 more than 50% of those suffering from the severe form of the disease whereas aCL prevalence was  
91 only 1.5 % in individuals from general population (Selmi et al, 2020). At the moment, the prevalence  
92 of aCL in post-COVID remains unknown as well as the pathophysiological mechanism involved in  
93 PCS, but are suggested the possibility of 1- persistence of the virus, especially in the nervous system,  
94 2- a post-infectious inflammatory or autoimmune reaction, or 3- microglial involvement (Matschke  
95 et al., 2020). The aCL could be associated with viral infections and may have in this context persistent  
96 pro-inflammatory effects, as recently described (Müller-Calleja et al, 2021).

## 97 **Declaration of competing interests**

98 The authors declare that they have no known competing financial interests or personal relationships  
99 that could have appeared to influence the work reported in this paper.

100 The authors have no conflict of interest to declare.

101 **Authors' contribution**

102 EK, BF, AM: treatment, care of the patients, and sample collection. NB, JLM, RA, DB drafted the  
103 manuscript. SW, BB collected clinical and biological data. All authors critically revised the report,  
104 commented on drafts of the manuscript, and approved the final report.

105 **Ethical Approval**

106 Informed consent was obtained from the patient's family for publication of this case report.

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109

110 **References**

111 Bertin et al, 2020 D. Bertin, A. Brodovitch, A. Beziane, S. Hug, A. Bouamri, JL. Mege, et al.  
112 Anticardiolipin IgG Autoantibody Level Is an Independent Risk Factor for COVID-19 Severity.  
113 Arthritis Rheumatol. Hoboken NJ 2020;72:1953–5.

114 Guedj et al, 2021 E. Guedj, M. Million, P. Dudouet, H. Tissot-Dupont, F. Bregeon, S. Cammilleri, et  
115 al. 18F-FDG brain PET hypometabolism in post-SARS-CoV-2 infection: substrate for  
116 persistent/delayed disorders? Eur. J. Nucl. Med. Mol. Imaging 2021; 48:592–5.

117 Liang et al, 2020 W. Liang, H. Liang, L. Ou, B. Chen, A. Chen, C. Li , et al. Development and  
118 Validation of a Clinical Risk Score to Predict the Occurrence of Critical Illness in Hospitalized  
119 Patients With COVID-19. JAMA Intern. Med. 2020;180:1081–9.

120 Lindsley et al, 2020 AW. Lindsley, JT. Schwartz, ME. Rothenberg. Eosinophil responses during  
121 COVID-19 infections and coronavirus vaccination. J. Allergy Clin. Immunol. 2020;146:1–7.

122 Matschke et al, 2020 J. Matschke, M. Lütgehetmann, C. Hagel, JP. Sperhake, AS. Schröder, C. Edler,  
123 et al. Neuropathology of patients with COVID-19 in Germany: a post-mortem case series. Lancet  
124 Neurol. 2020;19:919–29.

125 Müller-Calleja et al, 2021 N. Müller-Calleja, A. Hollerbach, J. Royce, S. Ritter, D. Pedrosa, T.  
126 Madhusudhan, et al. Lipid presentation by the protein C receptor links coagulation with  
127 autoimmunity. *Science* 2021;371.

128 Selmi et al, 2020 Selmi C, De Santis M, Battezzati PM, Generali E, Lari SA, Ceribelli A, Isailovic N,  
129 Zermiani P, Neidhöfer S, Matthias T, Scirè CA, Baldassarre D, Zuin M. Anti-phospholipid antibody  
130 prevalence and association with subclinical atherosclerosis and atherothrombosis in the general  
131 population. *Int J Cardiol.* 2020 Feb 1;300:209-213. doi: 10.1016/j.ijcard.2019.10.042. Epub 2019  
132 Nov 5. PMID: 31757648.

133 Taha et al, 2021 Taha Muhanad, and Lobelia Samavati. Antiphospholipid antibodies in COVID-19: a  
134 meta-analysis and systematic review. *RMD open* vol. 2021 7,2: e001580. doi:10.1136/rmdopen-  
135 2021-001580

136 Tenforde et al, 2020 MW. Tenforde, SS. Kim, CJ. Lindsell, E. Billig Rose, NI. Shapiro, DC. Files , et  
137 al. Symptom Duration and Risk Factors for Delayed Return to Usual Health Among Outpatients with  
138 COVID-19 in a Multistate Health Care Systems Network - United States, March-June 2020. *MMWR*  
139 *Morb. Mortal. Wkly. Rep.* 2020;69:993–8.

140 Zhou et al, 2020 F. Zhou, T. Yu, R. Du, G. Fan, Y. Liu, Z. Liu, et al. Clinical course and risk factors  
141 for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study.  
142 *Lancet Lond. Engl.* 2020;395:1054–62.

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145 **Table 1: Longitudinal follow-up of biological markers**

		<i>Normal Values</i>	<i>Date</i>					
			<i>2020/03/26</i>	<i>2020/06/17</i>	<i>2021/01/13</i>	<i>2021/02/17</i>	<i>2021/03/29</i>	<i>2021/04/07</i>
<b><i>COVID-19</i></b>	PCR SARS-CoV2		Positive Ct = 28	N.A	N.A	Negative	N.A	Negative
	Serology SARS-CoV2		N.A	N.A	N.A	Positive	Positive	Positive
	Hemocultures		Sterile	N.A	N.A	N.A	N.A	N.A
<b><i>Hemogram</i></b>	Red Blood Cells (T/L)	(4 - 5)	4,28	4,61	N.A	4,86	4,72	4,7
	Hemoglobin (g/dL)	(12 - 15)	11,3	12,2	N.A	12,4	12,4	12
	Platelets (G/L)	(150 - 400)	229	377	N.A	398	377	408
	WBC (G/L)	(4 - 10)	4,4	6,1	N.A	6,1	6,5	5,9
	Neutrophils (G/L)	(2 - 7,5)	2,8	2,6	N.A	2,3	3,1	2,9
	Eosinophils (G/L)	(0,1 - 0,5)	0	0,07	N.A	0,1	0,08	0,06
	Basophils (G/L)	(0 - 0,2)	0,01	0,02	N.A	0,02	0,02	0,01
	Lymphocytes (G/L)	(1 - 4)	1,4	3	N.A	3,3	3	2,6
	Monocytes (G/L)	(0,2 - 1)	0,17	0,42	N.A	0,39	0,36	0,29
	Neutrophil-to-lymphocyte ratio	(< 6,63)	2	0,87	N.A	0,7	1,03	1,12
	Platelet-to-lymphocyte ratio	(< 2,98)	1,64	1,26	N.A	1,21	1,26	1,57
	Neutrophil-to-platelet ratio	(< 2,98)	1,22	0,69	N.A	0,58	0,82	0,71
	Systemic immune-inflammation index (SII)	(< 13,87)	4,58	3,27	N.A	2,77	3,9	4,55
<b><i>Haemostasis</i></b>	Prothrombin Time (%)	(> 70)	110	122	112	110	122	106
	aPTT ratio	(< 1,2)	1,1	0,9	0,9	0,9	0,9	1
	D-Dimers (µg/ml)	(0 - 0,5)	N.A	0,39	0,41	0,62	N.A	0,53
	Fibrinogen (g/L)	(1,8 - 4)	6,95	5,36	5,49	5,85	N.A	5,34
<b><i>Inflammatory markers</i></b>	CRP (mg/L)	(0 - 5)	130	7,8	7,9	12,1	14,1	15,9
	Ferritin (µg/L)	(30 - 280)	N.A	N.A	N.A	N.A	N.A	N.A
	IL-6 (pg/mL)	(< 55)	N.A	N.A	7,76	14,82	20,63	9,82
<b><i>Blood ionogram</i></b>	Na (mmol/L)	(136 - 145)	136	140	139	138	138	139
	Cl (mmol/L)	(98 - 107)	99	103	101	102	99	102
	K (mmol/L)	(3,4 - 4,5)	4,16	4,72	5,24	4,64	4,13	4,73
	Ca (mmol/L)	(2,15 - 2,50)	2,17	N.A	N.A	N.A	2,49	N.A
<b><i>Renal function</i></b>	Creatinine (µmol/mL)	(45 - 84)	62,9	61,6	64,6	89	71	79
	GFR (CKD-EPI) (mL/min/1,74m <sup>2</sup> )	(> 90)	95	97	92	62	82	72
<b><i>Liver markers</i></b>	AST (UI/L)	(0 - 35)	31	N.A	N.A	21	20	18



	ALT (UI/L)	(0 - 35)	25	N.A	N.A	28	28	24
	GGT (UI/L)	(0 - 40)	71	N.A	66	58	60	52
	Total Bilirubin (µmol/L)	(0 - 21)	4	N.A	5	5	6	7
	Alkaline Phosphatase (UI/L)	(35 - 105)	74	N.A	N.A	97	106	91
<b><i>Tissue damage markers</i></b>	Lactate dehydrogenase (UI/L)	(135 - 214)	303	N.A	192	N.A	194	N.A
	Creatine Kinase (UI/L)	(0 - 170)	87	N.A	N.A	N.A	120	N.A
<b><i>Immunology :</i></b>	Antinuclear antibodies	(< 160)	N.A	N.A	Negative	Negative	Negative	Negative
<b><i>Conventional</i></b>	Anti-cardiolipin IgG (U/mL)	(< 15)	N.A	53,28	21,19	N.A	20,41	24,4
<b><i>Antiphospholipid</i></b>	Anti-cardiolipin IgM (U/mL)	(< 15)	N.A	0,77	0,46	N.A	2,06	1,75
<b><i>Antibodies</i></b>	Anti-B2GP1 IgG (U/mL)	(< 8)	N.A	1,17	1,42	N.A	0	0,68
	Anti-B2GP1 IgG (U/mL)	(< 8)	N.A	1,17	1,42	N.A	0	0,68
	Anti-B2GP1 IgM (U/mL)	(< 8)	N.A	2,3	0,57	N.A	0,23	1
	Lupus Anticoagulant		N.A	Negative	Negative	Negative	N.A	Negative

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147 N.A: non-available data