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Acute generalized exanthematous pustulosis induced by hydroxychloroquine prescribed for COVID-19

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1 **Title: Acute generalized exanthematous pustulosis induced by hydroxychloroquine**
2 **prescribed for COVID-19**

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39 **Clinical implication**

40 Hydroxychloroquine is now commonly used off-label for treatment of COVID-19 in
41 combinations with drugs, at doses and in populations where it is not typically used. We
42 present a case that highlights that even in short course therapy acute generalized
43 exanthematous pustulosis should be recognized as a potential adverse effect of
44 hydroxychloroquine.

45 Acute generalized exanthematous pustulosis (AGEP) is a rare drug reaction characterized by
46 acute, extensive formation of numerous non-follicular sterile pustules on a background of
47 edematous erythema.¹ Hydroxychloroquine (HCQ), is widely used to treat rheumatic and
48 dermatologic diseases, and is well known to cause AGEP.¹ At the end of 2019, a novel
49 coronavirus was identified as the cause of a cluster of pneumonia cases in Wuhan, city of
50 China. It rapidly spread in China and outside, and on March 12th, 2020, the WHO declared a
51 pandemic. HCQ has been reported to inhibit SARS-CoV-2 in vitro but clinical data evaluating
52 HCQ are limited, and its efficacy against SARS-CoV-2 is unknown. Nevertheless, given the
53 lack of clearly effective interventions, HCQ is being used off-label in combination with drugs,
54 at doses and in populations where it would not be traditionally used. Therefore, vigilance
55 needs to be applied especially if this drug is not being used in clinical trials settings where
56 adverse-event information and monitoring are more meticulous. Herein we report a case of
57 AGEP induced by HCQ prescribed for COVID-19. We also reviewed literature about HCQ
58 induced AGEP and efficacy of HCQ in COVID-19.

59 On March 23th, a 76-year-old patient with medical history of diabetes mellitus consulted the
60 emergency room (ER) for cough and diarrhea since March 17th. Chest computerized
61 tomography scan revealed bilateral patchy ground glass opacities consistent with COVID-19
62 disease. He did not present with any severity criteria and returned home. The day after,
63 clinical symptoms worsened with asthenia, fever, dyspnea. Thus, on March 24th, HCQ
64 (200mg three times daily) was introduced associated with azithromycin and ceftriaxone
65 (Figure 1). On March 29th, his condition worsened with acute respiratory distress syndrome
66 (ARDS). He required invasive mechanical ventilation and he was transferred to the intensive
67 care unit. HCQ was stopped after a cumulative dose of HCQ of 3600mg. The SARS-Cov-2
68 real time polymerase chain reaction test from the nasopharynx was positive. He received
69 bronchoscopy with bronchoalveolar lavage that identified *Aspergillus fumigatus* and *Candida*

70 *albicans*. Screening for other respiratory microbes (bacteria, fungi, mycobacteria and viruses)
71 was negative (ARDS infected COVID-19 patients have frequent bacterial and fungal super-
72 infection)². The patient did not take any corticosteroid during his clinical course. Although
73 COVID-19 improved with weaning of mechanical ventilation, the patient developed on April
74 3rd a pustular eruption on a background of edematous erythema of 2 days duration, which
75 began on intertriginous areas (intergluteal, axillary, inguinal) and rapidly affected 30% of
76 body surface area (Figure 2a, b, c). Oral and genital mucosae were normal. Diagnosis of
77 AGEP, symmetrical drug-related intertriginous and flexural exanthema (SDRIFE) and
78 staphylococcal scaled skin syndrome (SSSS) were suggested. In parallel, fever was noticed
79 and laboratory tests showed an increased leukocytosis with marked neutrophilia (from
80 $7 \times 10^9/L$ on 29th March to $13 \times 10^9/L$ on 3rd April). HCQ dosage was $325 \mu g/L$. Pustular smear
81 and culture were negative for bacteria and fungus. Cultures from common sites of *S. aureus*
82 colonization and blood cultures were negative too, excluding SSSS diagnosis. A skin biopsy
83 showed spongiform subcorneal and intracorneal pustules, some keratinocyte necrosis and a
84 dermal inflammatory infiltrate of neutrophils with perivascular accentuation, excluding
85 SDRIFE diagnosis (Figure 2c). Thus the diagnosis of AGEP was made, with a regiscar score
86 calculated to 11 (definite case > 8)¹, based on the rapid development of a febrile pustular
87 eruption a few days after beginning a drug treatment, the clinical finding of pustules on a
88 background of edematous erythema with flexural accentuation, a marked neutrophilia
89 ($> 7 \times 10^9/L$), a pustular smear and culture negative for microbes, a resolution of the rash after
90 drug discontinuation and histologic features including intra-corneal spongiform pustules and
91 some necrotic keratinocytes. The rash was already present the day when voriconazole was
92 started and 24 hours after the last dose of piperacillin-tazobactam (Figure 1) suggesting that
93 these were less suggestive of culprit drug compared with HCQ. The patient eventually died
94 from massive pulmonary embolism 10 days after the AGEP diagnosis.

95 HCQ has numerous skin side effects including maculopapular rash, cutaneous
96 hyperpigmentation, pruritus, AGEP, Stevens-Johnson syndrome or toxic epidermal necrolysis,
97 hair loss, and stomatitis, as previously reported³⁻⁵. In AGEP, the average duration of drug
98 exposure prior to onset of the symptoms depends on the causative drug. Antibiotics such as
99 amoxicillin consistently have a short latency of 24-72 hours, whereas other medications,
100 including HCQ, are often associated with latencies around 10-12 days or longer (16.2 days for
101 HCQ in our review)⁶. The latency period of 9 days in our patient was shorter than described.
102 The dysregulation of the Th17 pathway observed in cytokine storm induced by COVID-19
103 may explain a shorter delay of AGEP induced by HCQ. The PubMed database was searched
104 for all peer-reviewed articles published until April 2020 using the following search terms:
105 “hydroxychloroquine” and “acute generalized exanthematous pustulosis” and found 35 cases
106 (Table E-1).

107 Use of HCQ is included in Chinese treatment guidelines and was reportedly associated with
108 reduced disease progression. However, data supporting these claims are controversial. A
109 randomized trial of two different doses of HCQ in 62 COVID-19 patients, reported a better
110 outcome with higher doses⁷. However, the endpoints specified in the protocol differed from
111 those reported and the trial seemed to have stopped prematurely. In an open-label study of 36
112 COVID-19 patients, treatment with azithromycin and HCQ was associated with a more rapid
113 decline in viral RNA⁸. However, there were methodological concerns about the control
114 groups, and another observational study did not confirm these findings⁹. Additionally, in an
115 observational study of nearly 1400 patients with COVID-19 admitted to a hospital in New-
116 York, HCQ use was reported in 811 patients and was associated with a higher risk of
117 intubation or death (hazard ratio 2.37)¹⁰. Despite these facts, some clinicians argued that HCQ
118 is widely used and safe. Furthermore, amid the speculation regarding the beneficial roles of
119 HCQ in COVID-19, shortages are feared. A shortage in HCQ would create serious problems

120 for people with systemic lupus among others who are currently taking this drug. To conclude,
121 AGEP should be included in the potential side-effects of HCQ for the treatment of COVID-
122 19.

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203 **Figure legend**

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205 **Figure 1: Anamnestic, clinical and biological features of the patient**

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207 **Figure 2: clinical and pathological presentation of AGEP induced by HCO**

208 a, b, c) Several small pustules arising on a widespread erythema with typical flexural

209 accentuation of AGEP. d) Histopathological features of the skin biopsy include spongiform

210 subcorneal and intracorneal neutrophilic pustule, acanthosis, neutrophilic exocytosis and rare

211 necrotic keratinocytes (haematoxylin and eosin, x180 magnification).

Figure 1:

	17-23 Mar	24 Mar	25-28 Mar	29 Mar	30 Mar	31 Mar	1 Apr	2 Apr	3 Apr	4 Apr	5 Apr	6-8 Apr	9 Apr	10-11 Apr	12 Apr	13 Apr
<i>Day since HCQ introduction</i>		D1	D2-D5	D6	D7	D8	D9	D10	D11	D12	D13	D14-16	D17	D18-19	D20	D21
<i>HCQ PO</i>		200mg/8h														
<i>Azythromycin PO</i>		500mg/24h	250mg/24h													
<i>Ceftriaxone IV</i>		1g/24h														
<i>Piperacillin-Tazobactam IV</i>					4g/6h											
<i>VCZ IV</i>							600mg/12h	300mg/12h						300mg/12h		
<i>Cefepime IV</i>															2g/8h	
<i>Enoxaparin SC</i>					6000UI/L/12h											
<i>Covid-19 features</i>	Cough and diarrhea	Asthenia		ARDS requiring MV				Respiratory improvement						Respiratory worsening	Death by massive pulmonary embolism	
<i>Fever</i>	<38°C	38.3 to 39.5°C			<38°C		38.3°C to 39°C				<38°C			38.5°C to 39.7°C		
<i>Skin</i>	Normal						Folds pustular erythema <10% BSA	Pustular erythema extension	30% BSA	AGEP Regression			Post pustular scaled and post-inflammatory pigmentation			
<i>Drug levels and microbiology</i>				SARS-Cov2 PCR positive			BAL positive for C albicans and A fumigatus		HCQ random level 325µg/L		VCZ trough level 9.83mg/L (N=1-4mg/L)			VCZ trough level 5.37mg/L (N=1-4mg/L)	SARS-Cov2 PCR Negative	
<i>Inflammatory markers</i>				WBC=8.6x10 ⁹ /L N=7x10 ⁹ /L L=0.4 x10 ⁹ /L Eo= 0.0x10 ⁹ /L Mo=0.5 x10 ⁹ /L PCT=0.91µg/L CRP=200mg/L Il-6=521pg/mL Tg=0.69g/L ALT=43UI/L					WBC=13.9 x10 ⁹ /L N=13x10 ⁹ /L L=0.9 x10 ⁹ /L Eo=0.1 x10 ⁹ Mo=0.6 x10 ⁹ /L ALT 19UI/L							

Abbreviations: Mar: March, Apr: April, D: day, HCQ: Hydroxychloroquine, PO: per-os, IV: intra-venous, VCZ: voriconazole, SC: sub-cutaneous, PCR: polymerase chain reaction, BAL: bronchoalveolar lavage, BSA: body surface area, ARDS: acute respiratory distress syndrome, MV: mechanical ventilation, AGEP: acute generalized exanthematous pustulosis, N: normal range, WBC : white blood cells, N: neutrophil count, L: lymphocyte count, Eo: eosinophil count, Mo: monocyte count, PCT: procalcitonin, CRP: C-reactive protein, IL-6: interleukin-6, Tg: triglycerides, ALT: alanine aminotransferase.







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