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HYDROXYCHLOROQUINE AS A TREATMENT OPTION FOR COVID 19 AND SOME ADVERSE EVENTS - CASE REPORTS AND LITERATURE REVIEW

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ABSTRACT

Background: Hydroxychloroquine (HCQ) is a drug that has been used for many years in the treatment of malaria. However, due to its anti-inflammatory and immunosuppressive action, it is also used in the treatment of rheumatic diseases. In the emergency situation of the COVID 19 pandemic, HCQ is also included in the therapeutic protocols for the treatment of COVID 19.

Objective: We present two cases of adverse events during treatment with HCQ with cutaneous manifestations - a rare case of Acute Generalized Exanthematous Pustulosis (AGEP) with systemic involvement in 77 years old woman and a case of Urticaria factitia in a 70 years old woman. The symptoms of both patients disappeared after the treatment of the diseases.

Conclusion: Although the use of HCQ has a long history, HCQ is also used off-label and in the context of the COVID 19 pandemic, in combination with other drugs and in populations where it is not commonly used. Despite the fact that AGEP is a rare disease with reported incidence of 1-5 /1000,000 cases per year, it is a real severe adverse event of HCQ. In contrast, urticaria factitia is not a rare disease, but a correct diagnosis and association with a particular etiological agent could be difficult. AGEP and Urticaria factitia should be considered as possible adverse events of HCQ treatment, especially in the off-label use of the drug, so that they could be diagnosed early and treated properly.

Key words: Acute Generalized Exanthematous Pustulosis (AGEP), Urticaria factitia

INTRODUCTION

The Coronavirus Disease 2019 (COVID-19) was declared as a pandemic by the World Health Organization on March 11th, 2020. (1). As of 31.08.2021 the total number of reported cases of SARS-CoV-2 infection worldwide is close to 216 million, and the total number of COVID-19 deaths is almost 4.5 million (2). There is no definitive and specific therapy for COVID -19 (3) and the news and information of effective therapies are currently reflected on the WHO website with recommendations for treatment and prevention. In the absence of any definitive therapy, repurposing of some commonly used antivirals and immunomodulatory drugs has been tried to treat COVID-19. Among such drugs, hydroxychloroquine (HCQ) was one of the first drugs to be tested for COVID-19 and has been recommended in national treatmentguidelines in some countries such as India and theUSA (4). The emergency conditions imposed by the coronavirus disease 2019 (COVID-19)-pandemic have forced drug regulatory agencies, from the Food and Drug Administration to the European Medicines Agency, to allow the use of drugs that are not tested and approved for this precise condition. (5)

On 20.05.2020 Bulgarian Drug Administration (BDA) allowed the import and use of HCQ in Bulgaria and by order of the Minister of Health

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(13.04.2020) HCQ is allowed for treatment of COVID19.

Administration of HCQ as a potential treatment option during SARS-CoV-2, initially gained popularity, but later, its safe usage became questionable due to its cardiovascular safety, largely stemming from instances of cardiac arrhythmias in COVID-19. Moreover, in the setting of rheumatic diseases, in which patients are usually on HCQ for their primary disease, there is a need to scale the merits and demerits of HCQ usage for the treatment of COVID-19 (6).

In our practice we observed 2 cases of pruritus and acute generalized exanthematous pustulosis (AGEP) after treatment with HCQ and we believe that before starting treatment with HCQ it is necessary to consider the possibility of AGEP and new difficult-to-treat pruritus.Although AGEP is a rare disease with incidence of 1-5 cases per 1 million per year (7) in the conditions of COVID-19 pandemic appear reports of AGEP in patients with COVID-19 treated with HCQ and severe AGEP(8). AGEP is a disease whose severity varies from mild to very severe, overlap syndromes are known and lethal outcome is possible (9,10). AGEP should be considered in the treatment of HCQ, both in patients with COVID-19 and in patients with the usual indications for treatment with HCQ, especially in the context of the COVID-19 pandemic.

CASE PRESENTATION

Clinical case №1

We present a clinical case of AGEP in a 77-year-old woman. The patient was admitted via the emergency unit with impaired general condition with data for drug-induced rash. Data on the occurrence, course and relationship of the rash with medication were obtained from the patient. She also provided medical record of concomitant diseases and pre-hospital examinations. She reported that 2 days before the hospitalization she had noticed redness and a rash on her face, torso and limbs. She had unpleasant sensations in the areas with the rash, which she described as burning and mild itching. She denied having a change in her voice, a feeling of irritation in her throat, shortness of breath, swelling of her tongue or high fever. She associated the rash with taking HCQ for the first time and was the only medication she took daily. The patient denied intake of new foods, drinks, medications. She started taking an antihistamine two days before hospitalization at her own discretion, but due to the lack of effect on the rash she sought medical help. She denied the presence of allergic diseases and psoriasis in the personal and family history, they are not described in the accompanying medical records either. The patient had difficulty to move due to a disease of the musculoskeletal system - generalized osteoarthritis and 4 months before hospitalization she was treated for this disease with conventional doses Movalis (20 tablets), Flamexin (10 sachets) and Paratramal accidentally with increasing joint pain. After the treatment, control tests were performed - creatinine, complete blood count, AST, ALT - in reference values (2 months before hospitalization). In addition to HCQ during the last 2 weeks the patient occasionally took 1 tablet of Nurofen (Ibuprofen) every 2-3 days when the joint pain increased. During the hospitalization, the skin changes characteristic of AGEP on the torso, limbs and face were established **(Figure 1, 2, 3)** - generalized erythematous rash with widespread non-follicular, punctate pustules.

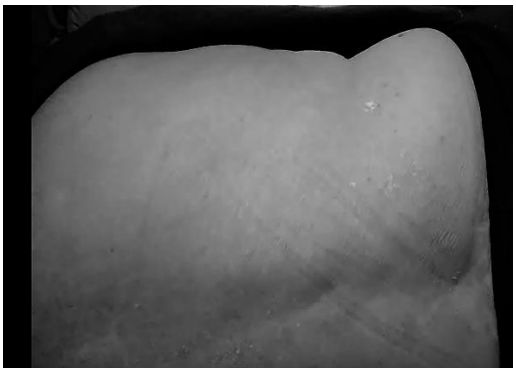

Figure 1. Skin rashes on the back

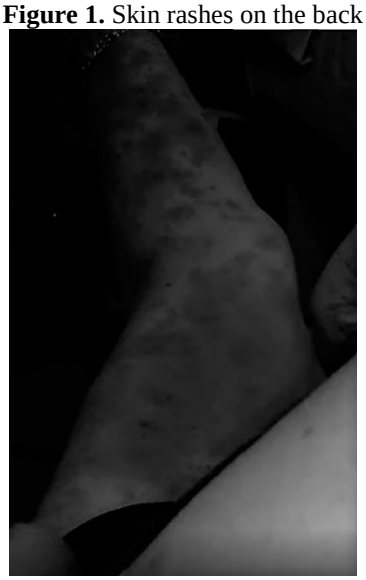

Figure 2. Skin rashes on the leg

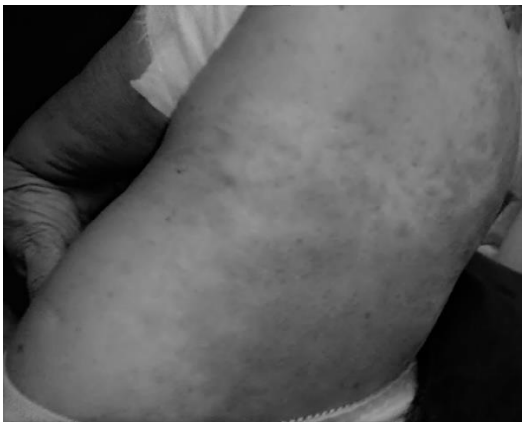

Figure 3. Skin rash on the upper extremities

The established changes in the musculoskeletal system corresponded to data on generalized osteoarthritis with involvement of the small joints of the arms, bearing joints and shoulder joints. Laboratory tests showed elevated levels of C-reactive protein (92.2mg / l; reference range 03-6 mg / l), leukocytosis (20.8 x109 / l; reference range 2.0-7.8x109 / l), with neutrophilia (17.8 x109). / l, reference range 1.6-7.4 109 / l). Serum creatinine was elevated (240 μmol / l; reference range 58-127 μmol / l). Liver enzyme levels were normal. Bacteriological examination for pustules was negative. A skin biopsy was not performed due to the patient's refusal. The diagnosis of AGEP was made according to the criteria of the European Severe Cutaneous Adverse Reactions study group for AGEP (Sidoroff, 2007) based on the rapid development of a typical pustular rash, a few days after starting X, typical skin changes, pronounced leukocytosis and neutrophilia (> 7 × 109 / L), negative microbiological examination of the pustule, resolution of the rash after discontinuation of the provocative drug, lack of personal or family history of psoriasis and psoriatic arthritis. HCQ was discontinued during hospitalization. Due to the presence of renal insufficiency, the initial treatment for AGEP was with systemic corticosteroids with gradual dose reduction and venous rehydration. During the clinical stay, the patient was afebrile, without lymphadenopathy or mucosal involvement, with stable vital signs. Laboratory parameters were monitored. The desquamation phase began during the hospitalization. After treatment and normalization of the laboratory parameters, with significant reduction of skin changes, the patient was discharged. At the follow-up examination 10 days later, there was no rash, and at follow-up within one month after discharge, the patient was calm, with no recurrence of the rash. In the present case, the diagnosis of AGEP was assessed with RegiSCAR, for sure (case 8 points) (7), although one of the indicators forming the assessment was impossible to apply because the patient refused a skin biopsy and the intake of Nurofen (Ibuprofen) may have compromised the assessment of the patient's high fever at the home and - an indicator that further forms points in the assessment.

Clinical case №2:

A 70-year-old woman in whom the treatment and diagnostic process were performed in an outpatient setting. The patient visited an allergy office because of severe intolerable itching on the body, which she associated with taking a new medicine - HCQ. That was the only drug that the patient took. The itching is excruciating, but skin eruptions do not appear spontaneously, only after scratching. After scratching, raised hyperemic and severely itchy traces of scratching appear on the patient's body **(Figures 4, 5, 6),** which disappear spontaneously. Skin itchiness increased at night. There was no evidence of any allergy in the medical history of the patient. The patient was diagnosed with COPD and is an ex-smoker. She didn´t receive treatment for COPD. She was not taking any other medications, including NSAIDs, except X. She has recently been diagnosed with a disease of the musculoskeletal system – rheumatoid arthritis and has been prescribed treatment with HCQ. During the physical examination, no deformities of the joints were found, no evidence of involvement of internal organs, no rash. The examination of the skin revealed evidence of dermographism. The laboratory tests performed with the exception of elevated CRP and ESR levels, did not show abnormalities. At the first visit, the patient was prescribed a second-generation antihistamine for 7-10 days without stopping X, as the patient's joint complaints responded well to HCQ. A new visit followed due to non-response of the symptoms and in order not to be stopped HCQ in case of side effects of the drug pruritus and dermographism, a second second-generation antihistamine was added for another 7 days. Again, pruritus and dermographism were unaffected by antihistamines, necessitating

discontinuation of HCQ. Two weeks after discontinuation of the drug, pruritus and rash resolved and did not recur. Antihistamines were also stopped. At 6 months follow-up, there was no recurrence of the skin complaints.

Figure 6. Skin rashes after scratching - close-up view

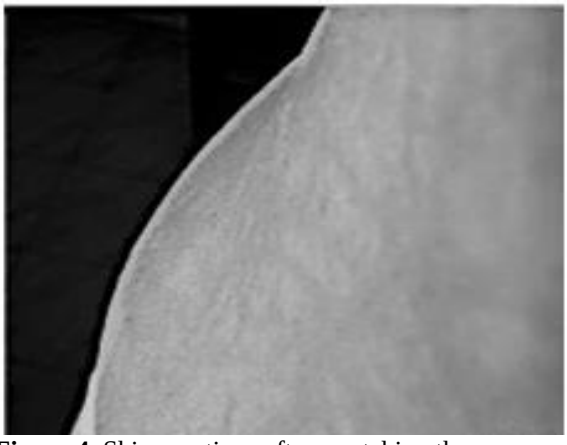

Figure 4. Skin eruptions after scratching the abdomen

Figure 5. Skin eruptions that occur after scratching the thigh

DISCUSSION

We suppose that the two presented clinical cases are of interest due to the increased use of HCQ in the COVID-19 pandemic, as well as due to the occurrence of two rare adverse events by treatment with HCQ. Both cases describe registered and known adverse events of treatment with HCQ, but with a significant difference in their severity - from mild, including only cutaneous symptoms to severe- generalized pustulosis with systemic symptoms. For both cases there is a chance that they will be misdiagnosed. The correct diagnosis can be easily mistaken if the complaints of itching in the 70-year-old patient were ignored, or the diagnosis of senile pruritus is incorrectly accepted. Pruritus when taking HCQ is a known and reported adverse event of treatment with HCQ, which has been described both in the Summary of the Product Characteristics and reported in the literature in recent years (11).

Urticaria factitia, also described as dermographism, is an adverse drug reaction, discussed mainly in the allergological literature and are of practical interest, as this type of urticaria is the most common subtype of physical urticaria (12), but less known by physicians without special knowledge in the field of allergology or dermatology. This type of urticaria could be overlooked, if the dermographism test is not performed during the examination, because the patient's skin during the physical examination is without rashes and the rash units do not appear spontaneously, but only under light pressure, or scratching, respectively. Despite the fact that this is not a severe and life-threatening adverse drug reaction, it causes serious discomfort to the patients and may lead to the need to discontinue the effective medication.

In the case of AGEP, the diagnosis could be delayed due to the fact that AGEP is a rare and little known disease, and systemic involvement and fever with neutrophilia would usually be associated with an inflammatory process. Acute generalized exanthematous pustulosis (AGEP) is a relatively recently described disease - in 1980 Beylot and co-authors first described several cases as AGEP (13). Roujeau and co-authors later identified AGEP as a rare skin disease that is

often caused by medication and in over 90% of cases by antibiotics (14). AGEP is characterized by an acute onset and diffusely distributed non-follicular punctate aseptic pustules covering the erythematous skin. This cutaneous exanthema is often accompanied by a slight rise in temperature (<38 C), leukocytosis and spontaneous discharge within 17 days, which is usually followed by desquamation. Numerous, non-follicular, intraepidermal or subcorneal sterile pustules up to 5 mm in size on an extensive erythematous background are typical, in the absence of bacterial infection, with neutrophils appearing after T-cell infiltration (15). The disease belongs to the group of adverse events of the delayed type, heterogeneous group of T-cell mediated hypersensitivity reactions, which include life-threatening conditions with severe skin side effects such as Steven-Johnson syndrome, toxic epidermal necrolysis and DRESS (drug reaction systemic symptoms) (16). The development of AGEP is usually provoked by medication (7).

Hydroxychloroquine has been described as a rare cause of AGEP. In the analysis of the publications for the period 1993 and 2007, only 16 reports for OGEP caused by the intake of HCQ for 14 years (17) were established, and for the period 2008-2018. Mohaghegh and co-authors (18) reported that they had identified 9 more publications. In a case report of AGEP induced by the intake of HCQ in a patient with COVID-19, the authors analyzed all articles published until April 2020 in the PubMed database, using search keywords: "hydroxychloroquine" and "Acute generalized exanthematous pustulosis" - 35 cases have been identified (8).

AGEP is a rare disease with a reported frequency of 1-5 cases per 1 million per year (7) and is among the adverse drug reactions associated with the use of Hydroxychloroquine (8, 17, 18). Hydroxychloroquine belongs to a group of medicines used to treat malaria. Its immunosuppressive and anti-inflammatory properties determine its use in the treatment of rheumatic and dermatological diseases (19). In the emergency imposed by the COVID-19 pandemic, HCQ was also used off -label to treat COVID-19 (5, 8, 20). On the other hand, HCQ used to treat COVID-19 is cited as a typical example of a wide range of skin side effects - AGEP, DRESS, lethal toxic epidermal necrolysis (11). Given the lack of clearly effective interventions for the treatment of COVID-19, HCQ has been used off-label in combination with drugs, in doses, and in populations where it would not traditionally be used (8).

The WHO does not currently recommend HCQ for both the treatment and prevention of COVID-19, given the increased risk of complications, but it is recommended for the treatment of autoimmune diseases and malaria, however, not COVID-19 (21). In view of this WHO recommendation, in the context of the pandemic, in patients with rheumatic diseases, who are undergoing treatment for their underlying disease with HCQ (as in our clinical cases), there is a need to assess the risk of treatment with HCQ (6).

CONCLUSION

On 20.05.2020 BDA allows the import and use of medicinal products containing HCQ in Bulgaria and by order of the Minister of Health (13.04.2020) HCQ is allowed for treatment of COVID19. The increasing use of HCQ in the context of the COVID19 pandemic, including in a larger number of patients with rheumatic diseases in Bulgaria, requires a good knowledge of the severe adverse events, even if they are relatively rare. HCQ has been described as a rare cause of AGEP, but in the emergency conditions imposed by the COVID-19 pandemic HCQ has been used off-label too for the treatment of various diseases, including COVID-19. The possibility of developing AGEP with HCQ treatment is a rare but real severe adverse event, that should also be considered and HCQ should be used with caution. HCQ has been used for decades in patients with various diseases. The increased use of HCQ, including for the treatment and prevention of COVID-19, has shown the need for careful monitoring and improvement in patients in whom HCQ treatment should be used to properly assess the benefit-risk balance. The adverse reactions we described should be considered in this assessment to minimize the risk of adverse reactions and, if they occur, to be diagnosed early and treated properly.

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