MedCrave
Step into the World of Research

Journal of Cardiology & Current Research

Case Report

Open Access

CrossMark

A unique combination of dilated cardiomyopathy and non- compaction cardiomyopathy in 75-year-old female with lupus erythematosus and hydroxychloroquine use

Abstract

Systemic lupus erythematosus (SLE) is an autoimmune, chronic, and heterogeneous disease. Antimalarial drugs, such as hydroxychloroquine (HCQ) is still an important immunomodulator medicine for the treatment of SLE. Rarely, HCQ toxicity can occur. We report a case of a patient who was admitted to our hospital with clinical symptoms of heart failure with a background of history of SLE and chronic HCQ use. Dilated cardiomyopathy in parallel with increased left ventricular apical trabeculation consistent with left ventricle non-compaction cardiomyopathy (LVNC) was diagnosed.

We aim to pinpoint two rare manifestations presenting in the same patient, simultaneously a) the reversible dilated cardiomyopathy after modification of the dose of HCQ and b) the non-reversible left ventricle non compaction cardiomyopathy most likely associated with her underlying disease. HCQ cardiomyopathy is rare but occasionally correlated with undesirable side effects. It is crucial to consider it in any patient taking for prolonged time the medication, who presents with symptoms of heart failure.

Keywords: Hydroxychloroquine, cardiotoxicity, dilated cardiomyopathy, left ventricular non-compaction cardiomyopathy, systemic lupus erythematosus

Volume 17 Issue 3 - 2024

Foula Vassilara MD,[1] PhD, Spiridon Kois MD,[1] Ioannis A Papadopoulos MD,[1] Triantaphilli Nikolopoulou MD,[1] Aikaterini Kouki MD, [1] Georgakopoulos Nikolaos MD[2]

[1]5th Department of Internal Medicine, Hygeia Hospital, Athens, Greece

[2]Department of Cardiology, Hygeia Hospital, Athens, Greece

Correspondence: Foula Vassilara, MD, PhD, Head of 5th Internal Medicine Department, Hygeia Hospital Athens, Greece, Email fvassilara@hygeia.gr

Received: June 24, 2024 | **Published:** July 18, 2024

Introduction

Drug-induced cardiomyopathy in patients treated with hydroxychloroquine is an essential consideration that might be missed by physicians, leading to preventable side effects. Hydroxychloroquine (HCQ) is a widely used medication for treating systemic lupus erythematosus (SLE) and rheumatoid arthritis. It is well known from reported cases that HCQ causes hypertrophic, restrictive or dilated cardiomyopathy, which often is underestimated at the early stages until the patients present with symptoms of cardiac failure.[1-3] Furthermore, it has been rarely reported, the exceptional manifestation of left ventricular non-compaction cardiomyopathy (LVNC), in patients suffering from SLE.[4-6]

Case presentation

A 76-years old female patient presented to the Emergency Depatrement (ED) because of progressive exertional dyspnea of 6 months in duration associated with fatigue and pre-syncope episode.

She had been diagnosed with SLE with musculoskeletal, skin and Raynaud manifestations. She had been treated with hydroxychloroquine 400mg once daily for the last five years. Two months before the current admission, leflunomide 10mg once daily was added to her treatment.

She was diagnosed with bronchial asthma 2 years ago and she was treated with b2 adrenergic agonists.

Physical examination revealed ABP 160/78mmHg, pulse rate 83/min, SpO2 98% on ambient air. On auscultation of the lungs, fine rales were heard over the two bases of the lungs. On cardiac auscultation S1, S2 were clear, and a systolic murmur was loudest at the left lower sternal border. The actual body weight was75 kg.

Laboratory and imaging studies were as follows: ECG recorded sinus rhythm 83/min. A 24-hour Holter rhythm monitoring on an outpatient basis showed supraventricular tachycardia (SVT) and frequent premature ventricular contractions (PVC's) (Strips 1&2). A panel of PCR for upper respiratory pathogens revealed respiratory syncytial virus (RSV).

An echocardiography revealed depressed EF 30-35% with hypokinesia in all the walls with akinesia in the inferior wall, telodiastolic volume 188 ml (normal values for women <117ml), pulmonary hypertension RVSP 60-65mmHg, mitral insufficiency 1+/4+, tricuspid insufficiency 2+/4+, myocardial mass 57gr/m2, enlarged left atrium 52cm.

An invasive coronary angiography was performed which showed normal coronary vessels.

An MRI of the heart detected EF=43%, hypokinesia in the inferior wall without transmural thinning, dilatation of the left ventricle, increased trabeculation in the apical part of the left ventricle, a finding consistent with cardiomyopathy (non – compaction cardiomyopathy). No imaging manifestations of infarction or myocarditis were visualized. Mild to moderate insufficiency of the mitral valve and dilatation of the left atrium was demonstrated.

NT-pro BNP was 621.0 pg/ml (normal values less than 450) troponin was negative. Continues ECG monitoring showed minimum heart rate 47/min, maximum 88/min, supraventricular tachycardia 3QR S.

Her current medication consisted of bisoprolol 10mg 1x1, ramipril 5mg 1x1, L-thyroxine 100 mcg 1x1, atorvastatin 20mg 1x1, furosemide 20mg 1x1, hydroxychloroquine 400mg 1x1, leflunomide

10mg 1x1. Furosemide was modified to 20 mg twice daily IV, and eplerenone 25mg was added per os. HCQ was discontinued, given the clinical suspicion of hydroxychloroquine toxicity.

The patient was readmitted to the hospital 2 months later because of persistent dyspnea. An echocardiography showed depressed EF 45%, diffuse hypokinesia of the left ventricle, more prominent in the inferior wall, and trabeculation in the apex of the left ventricle. The left ventricle appeared with normal dimensions with moderate systolic dysfunction. Bilateral atrium dilatation was depicted with mitral regurgitation 2+/4+, tricuspid regurgitation 1-2+/4+ and RVSP 50mmHg.

BNP was normal. A modification to her previous treatment had been performed by her family cardiologist which remained unchanged during the second hospitalization. Her treatment consisted of bisoprolol 5mg daily, empagliflozin 10mg daily, sacubitril /valsartan 24mg /26 mg twice daily, furosemide 20mg daily, L-thyroxine 100mcg daily, atorvastatin 20mg daily.

At the second admission a further investigation for her dyspnea included chest CT, spirometry and lung diffusion and polysomnographic study for obstructive sleep apnea were performed, without any significant abnormal findings.

One month after the second admission the attending rheumatologist in consultation with her family cardiologist restarted the HQC in reduced dose 200 mg/daily considering that the lower dose would be safe and effective in avoid the relapse of her disease. The patient was on close follow up by her cardiologist and consecutive echocardiography every three months showed a progressive improvement in the systolic function of the heart.

Fifteen months after her last admission the most recent echocardiography showed EF 65%, RVSP 30-35mmHg, mitral insufficiency 1+/4+, tricuspid insufficiency 2+/4+, enlarged left atrium 52cm.

At the same time a new MRI of the heart showed remission of dilated myocardiopathy, EF 57% and unchanged trabeculation in the apical part of the left ventricle (Figures 1&2). NT Pro BNP 463 pg/ml (normal values less than 450).

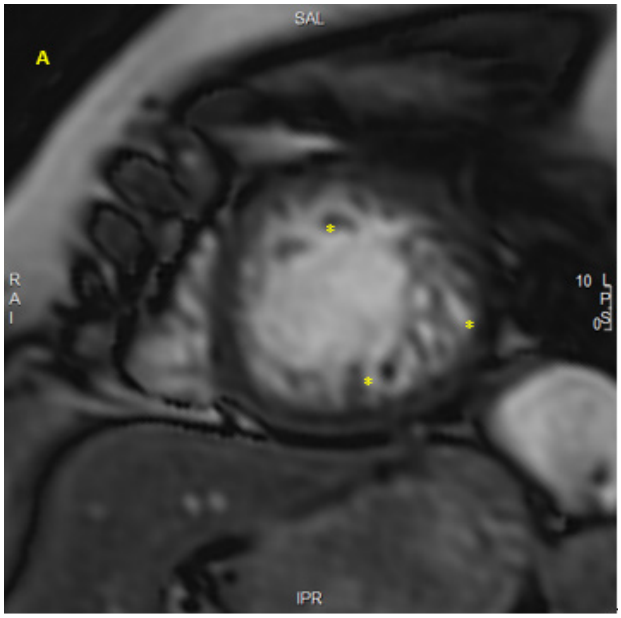


Figure 1 MRI apical short axis image at end-diastole 2023 showing trabeculations (asterisk) and decreased systolic function.

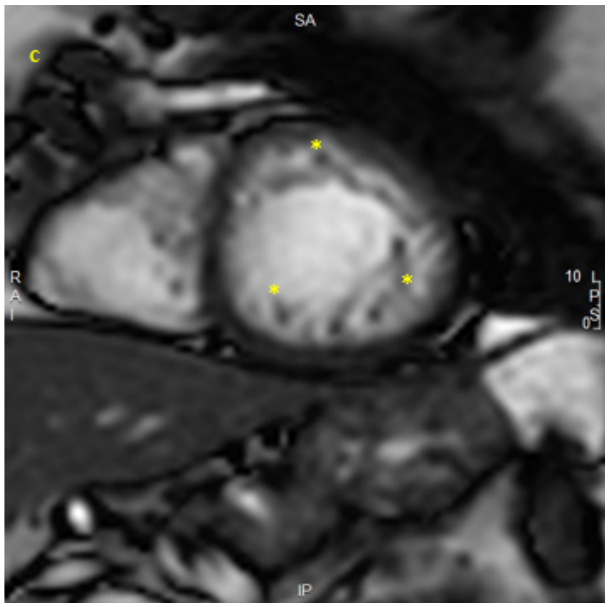


Figure 2 MRI apical short axis image at end-diastole 2024 showing the unchanged trabeculation (asterisk) and improvement of systolic function.

Discussion

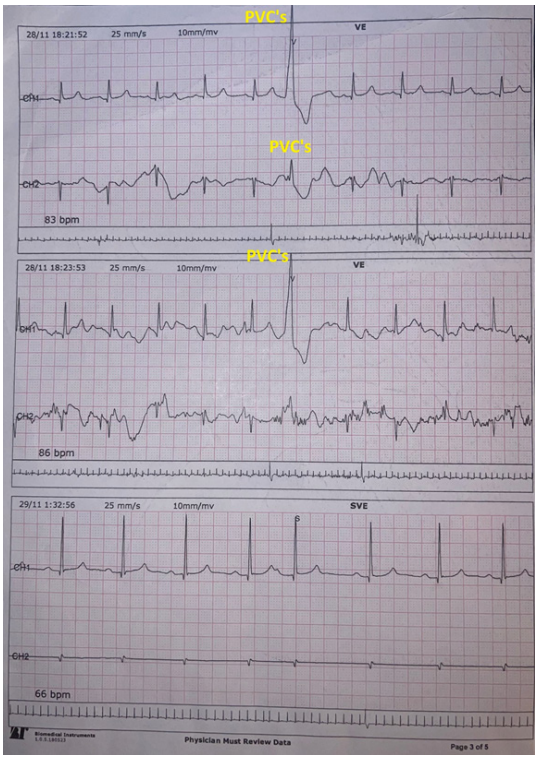
Hydroxychloroquine and cardiotoxicity

Hydroxychloroquine (HCQ) was initially used as an antimalarial agent and later as an immunomodulatory medication in autoimmune diseases mainly systemic lupus erythematosus ad rheumatoid arthritis. When administered orally, the drug has high bioavailability, long elimination half-life (30-60 days) and steady-state concentrations are reached after 4 to 6 months of therapy.[7]

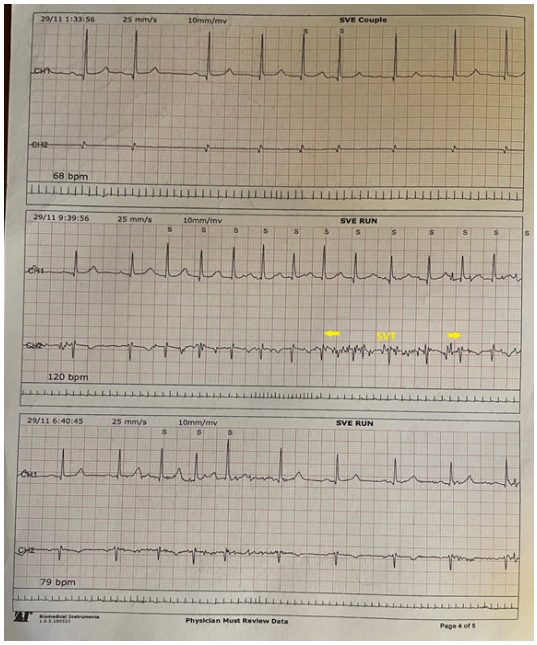
HCQ was considered as a safe medication until life -threatening adverse events included cardiomyopathy and conduction defects have been published, more recently. Its side effects were highlighted much more after its wide use in the initial period of COVID-19 pandemic.[8] HCQ produces multiple effects on cardiac electrical conduction, like class IA antiarrhythmic medication, via sodium and potassium channels. These effects lead to the classic PQ prolongation, QRS complex widening, and QT prolongation which predisposes to torsades de pointes.[8] In our patient arrhythmia was a great concern. On outpatient basis, consecutive 24-Holter rhythm monitoring detected supraventricular arrhythmia and PVC's (strips 1&2). HCQ accumulates in the lysosomes and myocardial biopsies are an adjunctive tool to point out its cardiotoxic effect. HCQ increases lysosome PH and inhibits lysosomal enzymes leading to formation of a type of acquired lysosomal storage disease.[9] The cumulative dose of HCQ and the duration of treatment is correlated with cardiotoxicity. A daily dose above 5mg/Kgr was the main risk factor for retinopathy.[10] In addition, impairment in renal function has been proposed as a mechanism for toxicity because HCQ renal and hepatic excretion.[2,7] Other risk factors for systemic toxicity are the older age, female gender, high body mass index, tamoxifen use and genetic predisposition.[11] It is less well studied what is the toxic daily dose for cardiomyopathy. Variable tissue concentrations might be found after administration of standardized doses because of significant interindividual pharmacokinetic variability. Variable total cumulative doses from 560.6 gr to 3916.4 gr in a review from Mayo clinic have been reported, even less in other publications in patients with normal renal function. It should be calculated in the actual body weight rather

Citation: Vassilara F, Kois S, Papadopoulos IA, et al. A unique combination of dilated cardiomyopathy and non- compaction cardiomyopathy in 75- year-old female with lupus erythematosus and hydroxychloroquine use. *J Cardiol Curr Res.* 2024;17(3):79–83. DOI: 10.15406/jccr.2024.17.00609

than in the ideal body weight. Undesirable side effects are rarely presented in patients taking HCQ for less than one year, except in the cases of acute poisoning and renal failure. The patient was treated with HCQ 400 mg per day for five years which exceeded the 5 mg per day, calculated in actual body weight, the total dose was730gr. Despite that most cases of cardiomyopathy associated with the use of HQC were prescribed in patients who have been treated > 10 years, the cumulative doses rather than the duration of time are more important. Genetic polymorphisms in enzyme activity in the metabolism of chloroquine could play an additional factor in cardiotoxicity.[12,8]



Strip 1 Showing premature ventricular contractions (PVC's)



Strip 2 Showing a short supraventricular tachycardia (SVT)

In our patient trabeculation in the left ventricle was noted on an echocardiography. In MRI this trabeculation fulfilled the criteria for non-compaction myocardiopathy. Classically, left ventricular non-compaction cardiomyopathy (LVNC) has been characterized as a primary cardiomyopathy of genetic origin, mainly in children.[13] There is an increased ratio 2.3 of the thick sponge -like, trabecular layer and the thinner compacted myocardial layer.[14] However, recent data highlights that the presence of trabeculation could be a finding in healthy individual in pregnancy, and in athletes. Despite the scarce data regarding the presence of non-compaction cardiomyopathy in drugs other than the antineoplastic drugs especially in hematologic patients, we would like to raise the question if HCQ could accelerate the progress of non-compaction cardiomyopathy.[15,16] On the other hand, very limited knowledge exists regarding the connection between SLE and other rheumatic diseases and non-compaction cardiomyopathy. Not surprisingly, a few cases reports, describing the connection between left ventricular non-compaction and systemic lupus erythematosus have been published.[4-6]

Dilated cardiomyopathy is the most common form of cardiomyopathy. It is characterized by reduced systolic left ventricular function and dilatation of the left or both ventricles. Its etiology is multifactorial, and the addition of genetic testing could bring in the light unknown variants.[17] Cardiac magnetic resonance is considered as the gold standard for measuring the volume, mass, and ejection fraction of both ventricles.[18] Moreover, myocardial trabeculations and non- compaction is reported as a different phenotype in patients with dilated cardiomyopathy. The prognostic value of this phenotype is currently uncertain.[19]

Dilated cardiomyopathy is well established manifestation of HCQ toxicity. A recent article from Spain suggests that HCQ – induced cardiac toxicity should be suspected in any patient who is taking the drug and presents with ventricular dysfunction. Other cardiopulmonary adverse effects include hypokinesia, pulmonary arterial hypertension valvular dysfunction and biatrial dilatation all these findings corresponded perfectly to our patient.[20] The certainty of diagnosis varies from pathognomonic demonstration of curvilinear bodies in myocardial biopsies in electron microscopy, and a high index of clinical suspicion.[9,21-23]

A relative drawback of our presentation is the lack of endomyocardial biopsy. However, until 2012 70 cases report with HCQ cardiotoxicity has been published. In less than half of them, cardiac biopsies were performed to establish the diagnosis. In the others, diagnosis was made using clinical and imaging findings.[24] Although endomyocardial biopsy is thought to be the gold standard in demonstrating the curvilinear bodies, the invasiveness of the method with 6% risk of complications and sampling error makes clinicians hesitant to perform the test. In addition, in the context of unexplained heart failure, cardiac MRI was as effective or superior to endomyocardial biopsies for diagnosing cardiomyopathy etiology. In a recent study from Mayo clinic, where MRI of the heart was used as an adjunctive tool in diagnosing HCQ cardiotoxicity besides the gold standard of myocardial biopsies 6 out of 6 patients found to have almost identical imaging findings with our patient. All six had abnormal ventricular wall thickness and volume, abnormal ventricular function, regional wall motion abnormalities, hypokinesis, akinesis as well as valvular abnormalities.[25]

Thankfully, when the drug was discontinued for three months and was restarted in half of the initial dose the ventricular volume returned to normal. By rheumatologic point of view HCQ has been considered to confer a survival benefit in patients with SLE. The decision on

dose lowering rather than the permanent omission is an acceptable option in patients, who derive a significant clinical benefit from the drug.[7] However, in some patients the side effects are not reversible and cardiac transplantation has been reported.[26,27]

Concomitantly, we would like to mention the additional benefit from the addition of sacubitril/ valsartan to the treatment of dilated cardiomyopathy. Sacubitril/ valsartan demonstrated a 20% reduction in heart failure hospitalizations and cardiovascular deaths.[28] Recent data have demonstrated a favorable effect of sacubitril/valsartan on left ventricular reverse remodeling and the improvement of systolic function in parallel with decrease in episodes of arrhythmia in 57.7% of patients.[29] We offered all the possible therapeutic options to the patient a) primarily, to discontinue HCQ for three months and later to decrease the dose in a half b) to add sacubitril/valsartan for the best clinical outcome. There is a report describing the LVNC as a causative factor for heart failure, which improved with the administration of sacubitril/valsartan.[30] Thanks to the advanced medical imaging modalities more than one parameter could be uncovered as coexisting factors in etiology of heart failure.

Conclusion

Cardiac disease is an under recognized and potentially serious complication of prolonged HCQ therapy. Despite the lack of guidelines for the interval of cardiac imaging in patients who are chronically treated with HQC, physicians should be aware of drug cardiotoxicity and should discontinue the therapy or modify the daily dose on the grounds of clinical suspicion and supporting imaging data. More importantly, treatment with HQC should be reconsidered in patients with preexisting cardiac conditions. Recently, the rate of non-compaction cardiomyopathy has increased thanks to improvements in echocardiographic and magnetic resonance imaging. It should be kept in mind that non -compaction cardiomyopathy could be recognized much more, in patients with rheumatic diseases who are subjected to cardiac MRI. Although non-compaction cardiomyopathy is considered a benign disease, in some patients, may lead to heart failure and lethal arrhythmias and the timely diagnosis is very crucial. Addition of sacubitril/valsartan seems to offer an additional benefit in the treatment of heart failure. Multidisciplinary collaboration is very essential for the good of our patients.

Acknowledgments

None.

Conflicts of interest

Authors declare that there is no conflicts of interest.

References

1. Yogasundaram H, Hung W, Paterson ID, et al. Chloroquine–induced cardiomyopathy: a reversible cause of heart failure. *ESC Heart Fail.* 2018;5(3):372–375.
2. Otero D, Petrovic M, Narayana Sarma V, et al. Hyderoxychloroquine–induced dilated cardiomyopathy. A case report. *AIM Clinical Cases.* 2022;1(5).
3. Tselios K, Deeb M, Gladman DD, et al Antimalarial- induced cardiomyopathy in systemic lupus erythematosus: as rare as considered? *J Rheumatol.* 2019;46(4):391-396.
4. Dobranici M, Tocitu A, Delcea C, et al. Left Ventricular noncompaction in a patient with systemic lupus erythematosus. *Rom J Intern Med*. 2019;57(1):78–82.
5. Ozkok a, Acar G. Cardiomyopathy mimicking left ventricular noncompaction in a patient with lupus nephritis. *CEN Case Rep*. 2012;1:69–72.
6. Rabelo CF, Batistella F, Godinho RN, et al. Systemic lupud erythematosus and transient left ventricular noncomaction. *Acta Reumatol Port.* 2014;39(3):274–276.
7. Yusuf IH, Issa PC, Ahn SJ. Hydroxychloroquine–induced Retinal Toxicity. *Front Pharmacol.* 2023;14:1196783.
8. Gagnon LR, Sadasivan C, Yogasundaram H, et al. Review of hydroxychloroquine cardiotoxicity: Lessons from the COVID–19 pandemic. *Curr Heart Fail Rep.* 2022;19 (6):458–466.
9. Nadeem U, Raafey M, Kim G, et al. Schulte chloroquine–and hydroxychloroquine– induced cardiomyopathy: A case report ad brief literature review. *Am J Clin Pathol.* 2020;aqaa253.
10. Liu PC, Luo SL, Lv MN, et al. Effect of hydroxychloroquine blood concentration on the efficacy and ocular toxicity of systemic lupus erythematosus. *Sci Rep*. 2024;14(1):7674.
11. Myller R. Systemic toxicity of chloroquine and hydroxychloroquine: prevalence, mechanisms, risk factors, prognostic and screening possibilities. *Rheumatology International.* 2021;41:1189–1202.
12. Chatre C, Roubille F, Vernhet H, et al. Cardiac complications attributed to chloroquine and hydroxychloroquine: a systematic review of the literature. *Drug Saf.* 2018;41(10):919–931.
13. Petersen SE, Jensen B, Aung N, et al. Excessive trabeculation of the Left Ventricle. *JACC Cardiovasc Imaging.* 2023;16(3):408–425.
14. Singh DP, Horenstein MS, Rout P, et al. *Left ventricular noncompaction cardiomyopathy*. 2024.
15. Hirano M, Kimura K, Ishigaki T, et al. High prevalence of left ventricular non–compaction and its effect on chemotherapy –related cardiac dysfunction in patients with hematological diseases. *Circ J*. 2020;84(11):1957–1964.
16. Luo C, Yang Y, Yang C, et al. Do antineoplastic drugs play an additional role in the progression of no–compaction cardiomyopathy? A case report. *Case reports in clinical medicine*. 9(6):144–153.
17. Hanselmann A, Veltmann C, Bauersachs J, et al. Dilated cardiomyopathies and non–compaction cardiomyopathy. *Herz.* 2020;45(3):212–220.
18. Ponikowski P, Voors AA, Anker SD, et al. 2016 ESC guidelines for the diagnosis and treatment of acute and chronic heart failure: the task force for the diagnosis and treatment of acute and chronic cardiac failure of the European society of cardiology (ESC). Development with the special contribution of the heart failure association (HFA) of the ESC. *Eur Heart J*. 37(27):2129–2200.
19. Amzulescu MS, Rousseau MF, Ahn SA, et al. Prognostic impact of hypertrabeculation and noncompaction phenotype in dilated cardiomyopathy: A CMR study. *JACC: Cardiovascular Imaging.* 2015;8(8):934–946.
20. Yogasundaram H, Putko BN, Tiem J, et al. Review hydroxychloroquine–induced cardiomyopathy: case report, pathophysiology, diagnosis, and treatment. *Can J Cardiol.* 2014;30(12):1706–1715.
21. Girolamo FD, Claver E, Olive M, et al. Dilated cardiomyopathy and hydroxychloroquine –induced phospholiposis: from curvilinear bodies to clinical suspicion. *Rev Esp Cardiol (Engl Ed).* 2018;71(6):491–493.
22. Ezzeddine FM, Giudicessi JR, Maleszewski JJ, et al. Unmasking hydroxychloroquine cardiotoxicity in a patient with heart failure and chronotropic incompetence. *JACC: Case Rep.* 2021;3(7):997–1001.
23. Joyce E, Fabre A, Mahon N. Hydroxychloroquine cardiotoxicity presenting as a rapidly evolving biventricular cardiomyopathy: key diagnostic features and literature review. *Eur Heart J Acute Cardiovasc Care.* 2013;2(1):77-83.

24. Yoshida A, Ishibashi –Ueda H, Yamada N, et al. Direct comparison of diagnostic capability of cardiac magnetic resonance and endomyocardial biopsy in patients with heart failure. *Eur J Heart Fail.* 2013;15(2):166–175.

25. Schneider A, Sadhana J, Menindez MD, et al. Hydroxychloroquine induced cardiotoxicity: A case series. *Rom J Intern Med.* 2024;62(2):210-215.

26. Malhotra A, Pathak MA, Dalia T, et al. Endomyocardial biopsy – proven hydroxychloroquine– induced cardiomyopathy in a patient with rheumatoid arthritis. BMJ Case Rep. 2023;16(4):e252327.

27. Muthukumar L, Jahangir A, Jan MF, et al. Double jeopardy cardiomyopathy requiring heart transplant: hydroxychloroquine and rheumatoid arthritis. *CASE (Phila).* 2020;4(5):382–385.

28. McMurray JJ, Packer M, Desai AS, et al. Angiotensin - neprilysin inhibition versus enalapril in heart failure. *N Engl J Med*. 2014;371(11):993-1004.

29. Paolini C, Mugnai G, Valle CD, et al. Effects and clinical implications of sacubitril/valsartan on left ventricular reverse remodeling in patients affected by chronic heart failure: 24 -month follow-up. *IJC Heart and Vasculature.* 2021;35:100821.

30. Bonatto MG, Albanez R, Cury Salemi VM, et al. Use of sacubitril/valsartan in non–compaction cardiomyopathy: a case report. *ESC Heart Fail.* 2020;7(3):1186–1189.

Citation: Vassilara F, Kois S, Papadopoulos IA, et al. A unique combination of dilated cardiomyopathy and non- compaction cardiomyopathy in 75- year-old female with lupus erythematosus and hydroxychloroquine use. *J Cardiol Curr Res*. 2024;17(3):79–83. DOI: 10.15406/jccr.2024.17.00609