Case Report

A novel case of lupus nephritis and mixed connective tissue disorder in a COVID-19 patient

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ABSTRACT

Introduction: Mixed connective tissue disease (MCTD) was initially identified in 1972 as a condition characterized by overlapping characteristics of systemic sclerosis, systemic lupus erythematosus (SLE), and polymyositis [1]. Because the signs and symptoms of these three diseases may not always emerge simultaneously, diagnosing MCTD can be difficult. SLE is a chronic inflammatory autoimmune disease that presents a wide range of clinical symptoms owing to its influence on several organ systems, with Lupus Nephritis (LN) being one of the disease

1. Introduction

Mixed Connective Tissue Disease (MCTD) was initially identified in 1972 as a condition characterized by overlapping characteristics of systemic sclerosis, systemic lupus erythematosus (SLE), and polymyositis [1]. Because the signs and symptoms of these three diseases may not always emerge simultaneously, diagnosing MCTD can be difficult. SLE is a chronic inflammatory autoimmune disease that presents a wide range of clinical symptoms owing to its influence on several organ systems, with Lupus Nephritis (LN) being one of the disease

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manifestations. LN affects up to five out of ten people with SLE and can manifest clinically as weight gain, hypertension, and foamy urine [2]. Despite emerging developments in the treatment of Lupus Nephritis, guidelines for management are not definitive and only consist of symptomatic relief globally [3].

Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), which causes Coronavirus Disease-2019 (COVID-19), has been a global epidemic for the past two years. COVID-19 causes a broad spectrum of clinical symptoms that impact various body systems, often appearing with respiratory signs and symptoms, such as flu-like illness exacerbated by acute respiratory distress syndrome (ARDS) and lung failure [4,5]. Additional symptoms and risks include severe metabolic syndrome, acute renal injury, neurological diseases, cardiovascular and thrombo-embolic events such as encephalopathy, seizures, and stroke [6-10]. A possible relationship between COVID-19 and autoimmune diseases such as SLE has also been recently documented in many case reports within the literature [11-13]. However, there is a lack of data and knowledge on LN in conjunction with MCTD in COVID-19 positive patients. Given the clinical importance of COVID-19 during the ongoing pandemic, the present paper elucidates a rare case of newly diagnosed LN in combination with MCTD in a PCR-confirmed COVID-19 patient. A review of the literature was conducted to analyse all linked clinical case reports and case series to provide an in-depth understanding of the relationship between COVID-19 and renal manifestations of Lupus.

2. Case Presentation

A 22-year-old COVID-19 positive female presented to the emergency department via an ambulance with fever, weight loss (20 kg), shortness of breath, loose stools, and multiple skin lesions present for the previous eight months. The fever was mild, intermittent, and alleviated by antipyretics. This was accompanied by frequent bowel movements (4-5 times per day) and progressive shortness of breath at rest and during exertion. However, there were no reports of orthopnea or paroxysmal nocturnal dyspnea. She also complained of polyuria and hematuria for the last two days. Her past medical history was insignificant, and other aspects of her health, including menstrual health, were unremarkable. There is no history of chronic disease in her family.

Upon presentation to the emergency department, she was a-febrile, tachycardic but hemodynamically stable, and well orientated to time and place. On inspection, there was a noticeable pallor, indicating a positive anaemic state. Dehydration, bilateral pitting edema up to the shin, and periorbital swelling were also seen. Posterior cervical lymph nodes (less than 8 mm) were deranged, with a high leukocyte count and thrombocytopenia. Further investigation included viral markers, which were tested negative. On suspicion of autoimmune disorders [Table 2], antinuclear antibodies (ANA) titers were carried which were found to be elevated. Along with this, Extractable Nuclear Antigen (ENA) profile revealed an increase in antibody titers to the anti-smith (Sm) and U1 small nuclear ribonucleoprotein (U1-RNP). Moreover, she was tested positive for Rheumatoid factor, while C3 and C4 complement levels were within normal ranges.

2.1. Clinical Evaluation

Baseline Laboratory Investigations

| Test Name                        | Results | Normal Ranges |
|----------------------------------|---------|---------------|
| Complete blood count [CBC]       |         |               |
| Hemoglobin                       | 63 g/dL | 12-16 g/dL    |
| HCT                              | 20.10   | 0.37-0.47     |
| MCV                              | 82 fl   | 80-100 fl     |
| MCH                              | 25.7 pg | 21-32 pg      |
| MCHC                             | 31.3 Gm/dl | 33.4-35.5 Gm/dl |
| TLC                              | 17.5 u/L| 3.6-110 u/L   |
| Neutrophils                      | 73%     | 55-70%        |
| Lymphocytes                      | 21%     | 20-40%        |
| Monocytes                        | 4%      | 2-8%          |
| Eosinophils                      | 2%      | 1-4%          |
| PLT                              | 660 × 10^6 mcl | 150-450 × 10^9 mcl |
| Reticulocyte Count               | 1.3%    | 0.2-2%        |
| Inflammatory Markers            |         |               |
| CRP                              | 153 mg/L| <5 mg/L       |
| ESR                              | 102 mm/hr | 3-9 mm/hr     |
| Fasting Lipid Profile            |         |               |
| Cholesterol                      | 240 mg/dL | <200 mg/dL    |
| Triglycerides                    | 612 mg/dL | 35-135 mg/dL  |
| LDL                              | 140 mg/dL | <130 mg/dL    |
| Total Lipid                      | 1202 mg/dl | <150 mg/dl    |
| HDL                              | 26 mg/dl | <50 mg/dl     |
| Protein creatinine ratio         | 9.3 g/day | <0.2 g/day    |
| Urine Direct Report              |         |               |
| Quantity                         | 40 ml   | 800-2000 ml   |
| Colour                           | Dark Yellow | Pale Yellow  |
| Ph                               | 6.0     | 4.5-8.0       |
| Specific Gravity                 | 1.020   | 1.005-1.025   |
| Albumin                          | ++      | <30 mg/g      |
| Sugars                           | Nil     | 0-0.8 mmol/L  |
| Blood (RBCs)                     | ++      | <3            |
| Red Cells (per hpf)              | 12-13   | <2            |
| Pus cells                        | 2-4     | 0-4           |
| Nitrites                         | Nil     | Nil           |
| Granular Cast                    | ++      | Nil           |
| Amorphous urate                  | ++      | –             |
| Miscellaneous Tests              |         |               |
| Total Protein                    | 7.6 g/dL| 6.8-8.3 g/dL  |
| Serum Albumin                    | 1.3 g/dL| 3.4-5.4 g/dL  |
| Serum Globulin                   | 6.3 g/dL| 2.3-6.3 g/dL  |
| Albumin/Globulin ratio           | 0.21    | 1.1-2.5       |
| D dimer                          | 0.2     | <0.5          |
| Lactose Dehydrogenase (LDH)      | 514 U/L | 140-280 U/L   |

Fig. 1. Hyperpigmented lesion on the leg.
range (see Table 3). Ultrasoundography was performed to thoroughly assess breast tissue, which revealed several cystic regions in the right breast, primarily in the lower quadrants. One measured 16.2 × 9.4 mm and extended into the retro-areolar area, displaying diffused internal echoes. Multiple large lymph nodes measuring 16.0 × 9.4 mm were seen in the right axilla, along with hilar thickening. Multiple cystic regions were found dispersed throughout the parenchyma of the left breast, one of them being next to the areolar edge and measuring 15.8 × 6.8 mm. The discovered cysts were most likely complicated cysts. The left axilla showed a few swollen lymph nodes measuring 22.0 × 10.0 mm, as well as evidence of thinning of the hilum.

Echocardiography was performed to rule out cardiac involvement, which was expected. Along with an endoscopy, a color Doppler of the lower limbs was performed. Endoscopy revealed minor gastritis, and a biopsy was performed (results are awaited). A Doppler examination of the lower limbs revealed no indications of stenosis, occlusion, or thrombosis. However, it did indicate bilateral soft tissue edema and a benign-looking inguinal lymph node on the right side.

The on-call nephrologist ordered a renal biopsy for further confirmation, and the results are still pending. Based on the clinical findings and laboratory investigations, the patient was diagnosed with MCTD associated with a flare of LN.

Despite the initial concerns regarding the commencement of steroids in an active COVID-19 infection, the management team decided to control her lupus flare with a lower steroid dose (intravenous methylprednisolone 50mg once daily) throughout hospitalization, in addition to oral hydroxychloroquine 200mg once daily. The patient was also given 1g intravenous cyclophosphamide once a month. Her condition steadily improved, and she was stable on the 7th day of her hospitalization. She was discharged on oral steroid maintenance medication with prednisolone 50mg once daily) throughout hospitalization, in addition to hydroxychloroquine.

Laboratory investigations, the patient was diagnosed with MCTD, as well as ANA and Anti-U1 RNP Antibodies. The Sm-Antibodies, as well as ANA and Anti-U1 RNP Antibodies.

4. Results

Out of the total papers, eleven articles were from Asia [19,22,25,30,32,33,36,39,41,43,44], eight from Europe [15,17,18,20,24,27,38,45], eleven from North America [14,16,26,28,29,34,35,37,40,42,46], two from South America [21,31] and one from Africa [23].

These Lupus patients were predominantly female (female/male ratio: 27:10). Fourteen of the cases had underlying LN. At the same time, there was only one patient who had underlying MCTD [21]. Moreover, most of the cases had musculoskeletal involvement [15,19,23,24,27,28,31,34,39].

For lupus management, more than half (56.7%) of the patients were on hydroxychloroquine therapy. Moreover, about half of the patients were given corticosteroids, while only nine were on mycophenolate mofetil.

We have analyzed and classified COVID-19 based on its severity, including asymptomatic, mild, moderate, severe, or critical. The majority of the patients (83.7%) were infected with mild to moderate COVID-19. In contrast, seven (18.9%) of the patients had severe to serious COVID-19. Except for 14 individuals, everyone was given systemic steroid therapy. Eculizumab was administered to three of the patients [37]. Tocilizumab IV was administered to a single patient [24]. Furthermore, for acute renal injury, only one patient required hemodialysis [40]. COVID-19 was linked to seven cases of thromboembolic events [20,25,29,33,37,41].

The clinical symptoms of active SLE and COVID-19 infection are often overlapping. Fever, rash, arthralgia, malaise, acute renal damage, and cytopenias are also symptoms of both disorders. Only four instances were documented to have a flare of lupus during the COVID-19 infection, according to our research [21,22,27,46].

5. Discussion

The relation of acute exacerbations of rheumatic and connective tissue diseases with viral infections like HIV, poliomyelitis, and influenza [47,48]. Because of the current COVID-19 pandemic, attention has been drawn to the possible flare-ups seen in patients with SLE and MCTD associated with mild COVID-19 infection, including diffuse lymphadenopathy [21] and full-blown SLE vasculitis [38]. A study by Jose L Pablos et al. statistically demonstrated how severe COVID-19 infection was a risk factor in diagnosing connective tissue disease, omitting inflammatory arthritis [49]. Moreover, Cheng Chen et al. reported in their study that during the COVID-19 pandemic, patients diagnosed with SLE abruptly ceased taking immunosuppressive therapy, which led to rapid flare-ups in their autoimmune conditions [50].

In this case, the patient had SLE and MCTD symptoms that were not recognized until she experienced a suspected flare-up of LN. During her active course of COVID-19 infection, she developed new-onset hematuria, proteinuria, bilateral pitting pedal edema, and periorbital edema, all of which were suggestive of Lupus Nephritis flare-up. Our patient was tested for autoimmune serology and found to have elevated levels of Anti-SM Antibodies, as well as ANA and Anti-U1 RNP Antibodies. Certain clinical features that confirm the diagnosis of SLE with MCTD include posterior cervical lymphadenitis, rheumatoid skin nodules, elevated inflammatory markers (ESR, CRP), and a deranged cell lineage. Though our patient was not commenced on immunosuppressive therapy during her illness, it did not affect her normal daily activities. This created the notion that COVID-19 infection may be associated with flare-ups in autoimmune disorders such as SLE and MCTD, which has not previously been documented in the literature.

The literature search primarily yielded case reports and case series involving the aforesaid patient population. The cohort size in the included studies was mainly limited to individual cases given the dearth of data and evolving COVID-19 literature. Furthermore, the follow-up
Table 3
Summary of all the case reports and case series related to lupus in association with COVID-19.

| Authors            | Country     | Age, Gender | Disease duration | Disease system involvement | Lupus medications                                                                 | Severity of COVID-19 |
|--------------------|-------------|-------------|------------------|----------------------------|-------------------------------------------------------------------------------------|----------------------|
| Watchmake J.M. et al. | United States | 60 years, F | 33 days          | Respiratory, neurological   | Steroids, rituximab, methotrexate, remdesivir, apixaban                             | Mild                 |
| Kreuter, A. et al.  | Germany     | 79 years, M | NA               | Cutaneous, Musculoskeletal | Hydroxychloroquine 200 mg twice daily and tapered intravenous glucocorticosteroid therapy | Not infected but vaccinated |
| Brockman, T. et al. | United States | 71 years, F | 90 days          | Renal, respiratory, cardiac | Initially, Clopidogrel and heparin (discontinued later) followed by aspirin and colchicine | Severe               |
| Domínguez-Rojas, J. et al. | Peru | 11 years, F | 28 days          | Respiratory, renal, neurological | Low-dose methylprednisolone 120 mg IV for 2 repeated doses, tocilizumab (TCZ) at 600 mg, and Tazocilline. Two days later, corticoids were decreased to 80 mg for 2 days then 40 mg for 2 more days | Severe               |
| Yamaguchi, S. et al. | Japan       | 72 years, M | 39 days          | Respiratory, renal, musculoskeletal, neurologic | Hydroxychloroquine, Mycophenolate Mofetil 2 g a day Prednisone 20 mg a day with descending tapering | Mild                 |
| Roncati, L. et al.  | Italy        | 44 years, M | 8 days           | Respiratory, gastrointestinal | Hydroxychloroquine, Mycophenolate Mofetil 1 g a day (reinitiated) Prednisone 40 mg a day with descending tapering | Mild                 |
| Patil, S. et al.    | India        | 22 years, F | N.A              | Musculoskeletal, cutaneous | Hydroxychloroquine 200 mg twice a day                                                | Moderate             |
| Sang, J.H.Q. et al. | Singapore    | 30 years, M | 7 days           | Gastrointestinal, Vascular     | Hydroxychloroquine 200mg once daily                                                  | Methylprednisolone   |
| Pang, J.H.Q. et al. | Singapore    | 30 years, M | 7 days           | Gastrointestinal, Vascular     | Methylprednisolone 50mg daily and oral hydroxychloroquine 200mg once daily            | Mild                 |

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duration for all of the studies was noted to be homogenous. The ongoing debate regarding the plight of SLE diagnosed individuals for an increased risk of acquiring COVID-19 infection due to immune dysregulation has already been assessed in a study of more than 900 patients (91% females) with the negative outcome of this hypothesis in which SLE diagnosed patients taking immunosuppressant like hydroxychloroquine and mycophenolate mofetil were not found to have an increase in COVID-19 infectivity rate [51]. Similarly, another study showed the same results, stating that patients with Lupus and the general population share the same COVID-19 hospitalization risk factors [52]. However, Giuseppe A. Ramirez et al. [48] concluded that COVID-19 could have a moderately increased morbidity in patients suffering from SLE, even though the study had certain limitations and selection bias, rendering the possibility controversial. In addition, another complication arising from overlap in symptoms of rheumatic diseases such as our patient. Our case is the first in our region to describe a newly diagnosed nephritic illness coupled with SLE and MCTD in a PCR-confirmed COVID-19 infected woman. The rarity of this occurrence suggests that it should be included in the literature.

6. Conclusion

We presented a case report of a PCR-confirmed COVID-19 positive patient with LN in association with SLE and MCTD. Because of the overlapping clinical manifestations and laboratory findings between lupus and COVID-19 pneumonia, the diagnostic problems and treatment hurdles should be carefully addressed. In COVID-19 patients with LN and acute renal injury, it is critical to promptly treat symptomatic flares associated with autoimmune disorders such as SLE and MCTD that may have gone unnoticed to prevent morbidity from the addition of a respiratory infection. However, the commencement of steroids at lower doses to treat lupus flare should be considered with caution in an active COVID-19 infection. To validate or reject the current findings, more extensive prospective studies are needed.

Ethical approval

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Consent

Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal on request.

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Declaration of competing interest

N/A.

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