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Case Report

Severe Systemic Lupus Erythematosus in a Young Man Following mRNA COVID 19 Vaccinations: A Case Report

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Abstract

Background: Systemic Lupus Erythematosus (SLE) is a chronic systemic autoimmune disease with a wide clinical presentation. Despite the prevalence is highest among reproductive age and non-white women, SLE can be potentially manifested at any age, gender, or ethnic group. Multiple genetic, environmental, and immunologic factors have been linked to the SLE pathogenesis. Besides various hematological abnormalities are present in SLE, pancytopenia remains uncommon and usually responds well to steroids. The coexistence of arthritis and hematological abnormalities in SLE is not frequent. New onset SLE among previous healthy subjects vaccinated against COVID-19 infection have been recently described in literature. **Case presentation:** We report a case of 23-year-old male who developed severe SLE with polysynovitis and pancytopenia after Pfizer mRNA Covid-19 vaccination. On initial treatment with oral and intravenous pulse of corticosteroid, no significant clinical response was recorded. Further treatment has included Methotrexate (MTX), which was discontinued due to liver function tests derangement and Hydroxychloroquine (HCQ) without any clinical benefit. The patient has also received intravenous immunoglobulin treatment in the light of persistent disease activity and suspected concomitant infection. Clinical improvement was recorded after intravenous Rituximab (RTX) treatment. **Conclusions:** This was the case of severe SLE in a young otherwise healthy male following Covid-19 Pfizer m-RNA vaccination, which responded to IV RTX treatment.

Keywords: Systemic Lupus Erythematosus; COVID 19 Vaccination; Rituximab

Abbreviations: ANA Antinuclear Antibodies obtained by indirect immunofluorescence; ANCA Antineutrophil Cytoplasmic Antibodies; Anti ds-DNA Anti Double Stranded DNA confirmed by indirect immunofluorescence Crithidia Lucillae; ALT Alanine Transaminase; AZA Azathioprine; B2 GP1 Beta 2 Glycoprotein 1; CCP Cyclic Citrullinated Peptide; CRP C Reactive Protein; CYP Cyclophosphamide; ENA screen Extractable Nuclear Antigens; ESR Erythrocyte Sedimentation Rate; Hb Haemoglobin; HCQ Hydroxychloroquine; Ig Immunoglobulin; IVIG Intravenous Immunoglobulin; LAC Lupus Anticoagulant; MMF Mycophenolate Mofetil; MPO Myeloperoxidase; MTX Methotrexate; PLT Platelet Count; PR3 Proteinase 3; RTX Rituximab; SLE Systemic Lupus Erythematous; WBC White Blood Cell

Background

Systemic Lupus Erythematosus (SLE) is a chronic autoimmune condition involving almost all organs with variable intensity from mild to life threatening. It is considered to be a disease of childbearing age women and is rare among young males. Renal, central nervous and vascular system involvement is more common when it affects male patients [1]. Common haematological manifestations are including anaemia, leukopenia, and thrombocytopenia. While pancytopenia can occur, this is

infrequent [2]. Arthritis is usually uncommon among those presenting with haematological manifestations and both arthritis and haematological complications usually responds to conventional steroid treatment [3].

Glucocorticoids, Hydroxychloroquine (HCQ), and the immunomodulatory agent Methotrexate (MTX) Azathioprine (AZA) and mycophenolate mofetil (MMF) are currently the most frequently used medications [4]. In presence of persistent active or flaring extra-renal disease, additional treatment with belimumab (human monoclonal antibody that inhibits B-cell activating factor) is recommended, while Rituximab (RTX) or Cyclophosphamide (CYP) can be considered in severe, organ-threatening, or refractory disease [4,5]. In cases of persistent SLE disease activity and concomitant infection immunosuppressive drugs should be used with caution and Intravenous Immunoglobulin (IVIG) treatment may represent an alternative option [6]. Despite disappointing findings from clinical trials, in clinical setting RTX has shown often excellent and encouraging results especially in patients with SLE and severe and refractory haematological and musculoskeletal manifestations [5].

We report the case of 23 years old male who developed severe SLE with pancytopenia and polysynovitis following second dose of Pfizer Covid-19 vaccination. The patient did not tolerate MTX due to liver dysfunction and has showed poor response to combined treatment with high dosage of corticosteroid and HCQ. Clinical improvement was recorded after intravenous treatment with RTX.

Case Presentation

A 23-year-old Caucasian male, with no pre-morbidities or family history of autoimmune conditions, few days later after second dose of Pfizer-BioNTech COVID-19 vaccination developed abrupt onset of polysynovitis with main involvement of hands and right elbow associated with malar rash, Raynaud's phenomenon, fatigue, and night sweats. The patient denied any side effects after the first dose of Pfizer-BioNTech COVID-19 vaccination delivered ten weeks earlier. Initial laboratory test results displayed signs of pancytopenia, raised inflammatory markers, low complements, and multiple positive autoantibodies (Table 1). A diagnosis of SLE was established based on the 2019 American College of Rheumatology/European League against Rheumatism (ACR/EULAR) classification criteria [7]. The patient was commenced on Prednisolone 30 mg daily (gradually tapered down over four weeks period to 5 mg daily as maintained dosage), oral methotrexate 15 mg weekly and folic acid 5 mg weekly. After four weeks full blood count normalized alongside with inflammatory markers.

Laboratory test	Result (normal range)
WBC	2.9 x 10^9/l (4.0-11.0)
PLT	125x 10^9/l (150-400)
Hb	115 g/l (130-180)
ESR	94 mm/hour (0-15)
CRP	13 mg/l (<5)
ANA	1:640 homogenous pattern
Anti-ds-DNA	> 379 IU/ml (0-10.0)
Anti-Ig G cardiolipin antibody	32 GPL U/ml (normal range 0-10 U/ml)
Anti-B2 GP1 antibody	10 U/ml (normal range 0-7 U/ml)
LAC	present
Complement C3	0.51 g/L (0.75-1.65)
Complement C4	<0.08 g/L (0.14-0.54)
Anti-ENA screen	negative
ANCA screen	equivocal
Anti-MPO Antibodies	0.4 U/ml (0.0-3.5)
Anti-PR3 Antibodies	<0.2 U/ml (0.0-2.0)
RF (Rheumatoid Factor)	<10.0 IU/ml (0.0-14.0)
Anti-CCP Antibodies	2.4 U/ml (0.0-7.0)

WBC White Cell Count, PLT Platelet Count, Hb Haemoglobin, ESR Erythrocyte Sedimentation Rate, CRP C Reactive Protein, ANA Antinuclear Antibodies Obtained By Indirect Immunofluorescence, Anti Ds-DNA Anti Double Stranded DNA Confirmed By Indirect Immunofluorescence Crithidia Lucillae, Ig Immunoglobulin, B2 GP1 Beta 2 Glycoprotein 1, LAC Lupus Anticoagulant, ENA Screen Extractable Nuclear Antigens, ANCA Antineutrophil Cytoplasmic Antibodies, MPO Myeloperoxidase, PR3 Proteinase 3, CCP Cyclic Citrullinated Peptide.

Table 1: Laboratory results at baseline

After four months period of subjective clinical well-being, the patient voluntary decided to discontinue methotrexate in the absence of any side effects. Few weeks later, a gradual reoccurrence of polysynovitis was recorded. Prednisolone was re-increased up to 10 mg daily, oral MTX 15 mg weekly re-started and 200 mg daily twice a day (dosage adjusted according to ideal body weight) added. Due to further clinical deterioration and new development of erythematous malar and palmar skin rash the patient was admitted into hospital. Evidence of leukopenia (white cell count 2 x 10^9/l), neutropenia (neutrophil count 1.4 x 10^9/L), thrombocytopenia (platelet count 91 x 10^9/l) low RBC count (3.94 x 10^9/L) and low haemoglobin (106 g/l) were recorded at admission, alongside evidence of painful vesicular skin rash over left side of the chest wall suggestive of shingles. SLE Disease Activity Index (SLEDAI) at admission was 23. MTX was discontinued due to raised alanine transaminase (90 U/l) and acyclovir 400 mg five times daily was commenced for seven days.

Due to persistent disease activity the patient was treated with Intravenous (IV) infusion of Methylprednisolone 500 mg daily for three days, switched then to oral prednisolone 60 mg daily. Polysynovitis remained unchanged whilst an improvement of erythematous skin rash and laboratory results (white cell count 2.3 x 10^9/l, neutrophil count 1.9 x 10^9/l, platelet count 106 x 10^9/l, ALT 27 U/l) were noted.

Eight days after admission the patient developed spiking temperature (39.3 C°) with excessive sweating and raised protein-C reactive (81 mg/l, normal range < 5mg/l). Chest x-ray, blood and urine cultures showed no growth but in the suspicion of an infection IV antibiotic (Piperacillin 4g/Tazobactam 500mg) was delivered and oral prednisolone reduced to 30 mg daily. In the following days white cell and neutrophil count both temporary improved (4.2 x 109/l and 3.8 x 109/l, respectively), but platelet count dropped down to 41 x 109/L. Pyrexia was persistent with night sweats and oral prednisolone was further reduced to 20mg daily. Antibiotic was then changed from IV Piperacillin/Tazobactam to oral Ciprofloxacin in view of thrombocytopenia after consulting a microbiologist. Thorax, abdomen, and pelvis Computed Tomography (CT) scan was requested as further investigation and main findings were bibasal atelectasis of lungs and bilateral shallow pleural effusions. Repeated blood and urine cultures showed no growth, but the patient continued to remain febrile.

After further laboratory results deterioration (white cell count 2.8 x 109/L, haemoglobin 95 g/dl, neutrophil count 2.3 x 109/L, platelet count 47 x 109/L and CRP 86 mg/l), the patient was treated with IV Immunoglobulin (IG) treatment (135 g in total over 5 days) in view of persistent pancytopenia and disease activity and suspected underlying infection. After completion of IV IG treatment laboratory results showed white cell count 4.6 x 109/L, haemoglobin 105 g/l, platelet count 103 x 109/L and CRP 53 mg/l. The patient developed than tachycardia (110 beats/min) and a requested electrocardiogram was suggestive of sinus tachycardia whilst an echocardiogram showed trivial global pericardial effusion (<5mm) and moderate tricuspid regurgitation.

After transient improvement of joint symptoms night sweats and fever recurred and the patient was treated with IV RTX (1000 mg, two infusions two weeks apart) after completion of antibiotic treatment. Significant clinical response (SLEDAI = 11) and improvement of laboratory results (Table 2) were recorded. Overall trend of laboratory tests during hospital admission and under various treatment is displayed in Figure 1.

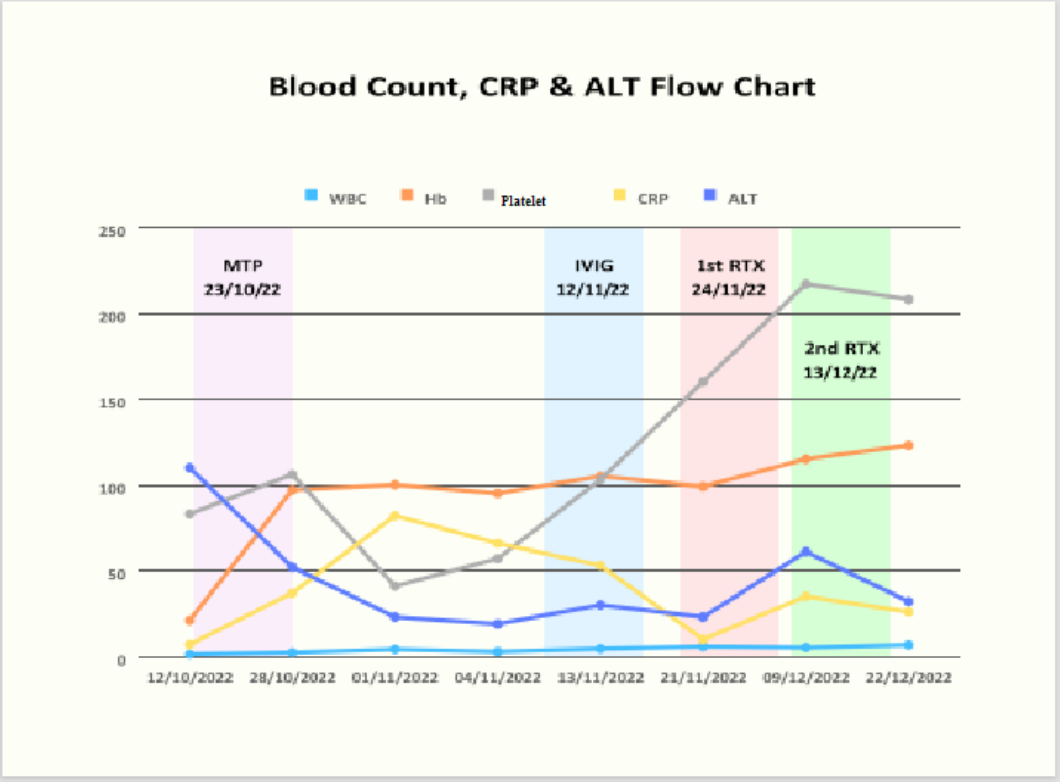

Figure 1: Performance of laboratory tests during hospital admission and treatment with pulse of IV MTP, IVIG and RTX. WBC white cell count, Hb haemoglobin, PLT platelet count, CRP C reactive protein, ALT alanine transaminase, MTP methylprednisolone, IVIG intravenous immunoglobulin, RTX rituximab.

	On Hospital Admission	Day	Day 10	Day 14	Day 23	Day 31	Day 49	Post discharge Day 8
WBC (x 10^9/L)	1.3	2.3	4.2	2.8	4.6	5.9	5.3	6.8
Hb (g/L)	115	97	100	95	105	99	115	123
PLT (x10^9/L)	83	106	41	57	103	160	217	208
CRP (mg/l)	7	37	82	66	53	10	35	26
ALT (U/L)	110	52	23	19	30	23	61	32
WBC White Cell Count, PLT Platelet Count, Hb Haemoglobin, CRP C Reactive Protein, ALT Alanine Transaminase								

Table 2: Laboratory results after hospital admission

Discussion

SLE is an autoimmune disease of unknown aetiology with variable multisystem involvement and heterogeneous clinical features, ranging from mild to life threatening. SLE is considered to be a disorder of childbearing age women. As it remains uncommon among men, little is known about SLE in male (1).

Few possible correlations between mRNA COVID 19 vaccination and new onset SLE have been reported in literature despite some uncertainty about exact mechanism [8,9]. The exact aetiology of SLE is also unknown and complex [10]. The B-cell hyperactivity leading to increased autoantibody production and activation of CD4 immune pathways have been shown to play a role in the pathogenesis of SLE and the activation of multiple pro-inflammatory pathways following mRNA vaccination may contribute to the mechanism [11].

In men SLE usually appear at older age with different comorbidities and higher mortality at one year compared to women with SLE [12]. Men with SLE have also a more complex clinical course and common renal, central nervous system and vascular involvement compared to women [1].

Cases of Cutaneous Lupus Erythematous (CLE) have been observed following Pfizer-BioNTech vaccine administration [13]. There is lack of clear evidence of direct association between Covid-19 vaccination and new onset SLE but, there are few case reports of SLE after Pfizer Covid-19 vaccination [8,9].

Haematological abnormalities are common findings in patients with SLE. When haematological abnormalities occur, it is important to distinguish whether these are manifestations of SLE disease itself, consequence of SLE treatment or part of separate and different haematological disorder. Leukopenia might be seen in 50–60% of patients with SLE and usually only a minority have a WBC count <1000/mm [2]. Thrombocytopenia has a reported prevalence ranging from 7 to 30% in large series of patients with SLE [15]. Anaemia is the most frequent haematological alteration in patients with SLE, occurring in more than 50% of cases [14]. Pancytopenia (defined as a reduction in red blood cell, white blood cell, and platelet counts) is less common than isolated cytopenia and can occur in SLE but, exact frequency is unknown [14].

P.K. Sasidharan, et al studied 108 patients with SLE in North Kerala, India and found that arthritis was uncommon among those who presented with haematological manifestations [3].

Our patient, who is a young male without any renal, central nervous system or vascular involvement had Pfizer Covid-19 mRNA vaccination developed SLE with pancytopenia and polysynovitis, which were both resistant to steroid and HCQ and required further treatment. MTX was also stopped due to suspected concomitant infection and liver function tests derangement. In cases of SLE resistant to conventional treatment and with possible concomitant infection as in our case, IVIG may represent safer and beneficial adjunct therapy [5]. It is also known that IVIG treatment can protect against infections which are a common clinical problem and one of the principal causes of mortality in SLE patients [6]. However, in our case IVIG treatment has improved the pancytopenia but not the joint involvement. Despite RTX performance in SLE clinical trials has been disappointing, case series and "real-world" clinical practice pointed to RTX having a role in controlling disease activity in SLE especially from hematologic and musculoskeletal standpoint [6]. In our case, IV RTX treatment has been followed by a significant clinical and laboratory improvement.

Conclusion

Abrupt onset of SLE cases following mRNA COVD-19 vaccinations have been recently reported in literature, although the precise mechanism of autoimmunity triggered by these vaccinations is not yet well established. We reported the case of severe SLE in a young otherwise healthy male following Covid-19 Pfizer m-RNA vaccine, which ultimately responded to IV RTX treatment. Further studies are needed to explore the association between COVID-19 vaccinations and new onset SLE.

Author Contribution

All authors contributed to the care of patient and data gathering. Dr Chauhan and Dr Ciapetti drafted the initial version. All authors offered corrections, read, and approved version.

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