Serum Sickness Following Rituximab Treatment in Childhood-Onset SLE: A Single Center Experience

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BACKGROUND

•Systemic Lupus erythematosus is a chronic autoimmune disease characterized by multi-organ involvement. As in adults, the childhood form (cSLE) often requires comprehensive anti-inflammatory, immunolytic and immunomodulatory therapies to achieve adequate disease control and eventual disease remission. With the knowledge of the critical role of B cells on the immune dysregulatory processes in SLE, the effectiveness and safety of focused B cell depletion has thus been well defined. Rituximab, a chimeric monoclonal antibody that binds to CD20 expressed on B lymphocytes initiating B cell lysis and subsequent depletion of antibody burden, has so far provided the most data along this therapeutic pathway. An uncommon adverse reaction is serum sickness, an immune complex-mediated ("type III") hypersensitivity characterized as a triad of rash, fever and polyarthritis/arthralgias. Though not commonly documented, rituximab-induced serum sickness has been noted in patients with underlying autoimmune diseases, and reported disorders including Sjogren's syndrome, chronic ITP, and rheumatoid arthritis. There is to date a paucity of data as to the true incidence of serum sickness following rituximab in both adult and cSLE. Our study describes occurrence of serum sickness in our cohort of cSLE.

PURPOSE

•A review of cases of serum sickness developing after Rituximab administrated noted in patients with juvenile systemic lupus erythematosus. Presenting manifestations, therapy and clinical course were defined. Described as well is a small cohort of this rare rheumatologic disorder at Texas Children's Hospital.

METHODS

With a local IRB approval, a retrospective review of the electronic health records of patients with cSLE from July 2011 to May 2019 was performed. Patients who developed serum sickness following Rituximab treatment were included. Descriptive analyses were done to ascertain similarities amongst the patients, possible risk factors for the development of serum sickness, response to treatment and use of other anti-CD20 medication use.

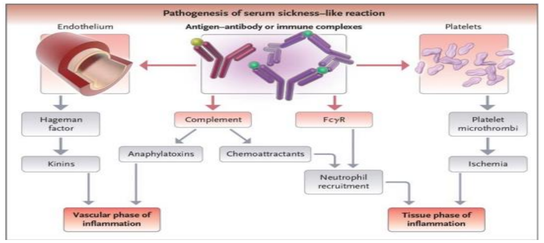

Fig 1: Type III Hypersensitivity Pathway

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5
Age/Gender/ Ethnicity/ SLEDAI at time of Rituximab Administration	16 yo F Hispanic SLEDAI: 4	19 yo F Hispanic SLEDAI: 8	15 yo M Hispanic SLEDAI: 11	18 yo F Hispanic SLEDAI: 6	16 yo F Hispanic SLEDAI: 4
Duration of SLE at time of Rituximab (in months)	36 mo	72 months	36 mo	60 mo	24 mo
Immunologic features at time of rituximab	(+) ANA, (+) smith, (+) dsDNA, (+) APLA (aCL, LAC), (+) RNP (+) SSA Hypocomplementemia	(+) ANA, (+) smith, (+) RNP, (+) DAT IgG Hypocomplementemia	(+)DAT IgG, (+) ANA, (+) LAC (+) dsDNA Hypocomplementemia	(+) ANA, (+) dsDNA, (+) APLA (LAC, B2G), (+) RNP Hypocomplementemia	(+) ANA, (+) smith, (+) LAC, (+) DAT IgG, (+) RF, (+) SSA (+) SSB Normal complements
Serum Sickness Clinical Manifestations	Fever, myalgias, rash and hand swelling/arthritis	Fever, arthritis, hypotension, urticaria	Tenosynovitis, and urticaria rash and shortness of breath	Fever, rash, arthritis, myalgias	Fever, myalgias, rash, chills
Treatment	Steroids + hydroxyzine	Steroids	Steroids + hydroxyzine	Steroids	Steroids
1st or 2nd Rituximab	1st	1st	1st	1st	2nd
Time interval from Rituximab administration to development of SS (in days)	9 days	10 days	7 days	13 days	8 days
History of prior Rituximab treatment/dose	Yes -- previous cycle 24 months prior -1000 mg x2	Yes -- previous cycles 15 months - 575mg x3, and 79 months prior - 1000 mg x2	Yes -- previous cycle 13 months prior -- 1000 mg x 2	No	No
Treatment with Ofatumumab	Yes	No	Yes	No	No

Table 1:Cohort of 5 cSLE patients

RESULTS

Of the 210 cSLE patients being actively followed, 20 patients had received Rituximab.

6 patients (30%) developed serum sickness. One patient was then excluded due to incomplete record

83% were female and all were Hispanic, with a mean age of 16.6 year old (range of 15 to 19 years).

Mean disease duration was 3.8 years (Range: 2 to 6 years). Clinical indication for rituximab therapy was significant disease flare.

Mean SLEDAI score at time of treatment was 6.6 (Range: 4 to 11); 1 patient had polyclonal hypergammaglobulinemia.

Additional immunosuppression included steroids (4/5), mycophenolate (2/5), hydroxychloroquine (5/5).

3 patients had history of prior rituximab treatment with a mean dose of 858 mg/dose (575mg/dose to 1000 mg/dose) and mean interval from previous to most recent dose of 17.3 months.

Mean time from drug exposure to serum sickness manifestation was 9.8 days (Range: 7-13 days).

Anti-rituximab antibody was not determined at time of SS diagnosis.

2 patients received and tolerated alternative B-cell depletion (Ofatumumab).

CONCLUSION

• We described a small cohort of cSLE who developed SS following rituximab treatment.

•Clinical manifestation of SS included fever, cutaneous, musculoskeletal (myalgias and arthritis), features which mimic that of active lupus

•1 patient with significant hypergammaglobulinemia at time of rituximab treatment. Limited data suggested that this an important immunologic feature of adult with rheumatic disease who developed SS following rituximab treatment.

•While rituximab continues to be an important therapeutic tool in the management of cSLE, it is important to be aware that serum sickness may be an adverse effect.

•Amongst our limited cohort, common features included significant autoantibody burden that would suggest a predisposition for serum sickness

REFERENCES

1. *Case 10-2013: A 30-Year-Old Man with Fever, Myalgias, Arthritis, and Rash*. Stone. J. et al. n engl j med 368;13 nejm.org march 28, 2013