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Rituximab Induced Late Onset Neutropenia

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Authors' contributions

This work was carried out in collaboration among both authors. Author KHBPF did the Conceptual work and wrote the manuscript, also edited and formatted the manuscript to journal specifications and patient management. Author JB recorded the patient details and performed patient diagnosis and follow up. Both authors read and approved the final manuscript.

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Case Study

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ABSTRACT

Rituximab is a monoclonal antibody against CD20 a leucocyte cell marker expressed on normal and neoplastic B lymphocytes .Although first used for treatment of CD20 positive non-hodgkin's lymphoma it's use has expanded to include a varied spectrum of diseases mostly autoimmune disorders. Thus it is used in the treatment of autoimmune haemolytic anaemia, immune thrombocytopenia, rheumatoid arthritis, pemphigus vulgaris, vasculitis and many more autoimmune conditions.

Rituximab is generally a well tolerated drug although many acute and delayed adverse effects are noted. Rituximab induced late onset neutropenia [LON] is a rare and life threatening adverse effect which needs to be suspected in patients presenting with neutropenia after four weeks of completing Rituximab therapy.

We report a case of a 73year old man who presented with severe grade 4 neutropenia of $0.04x10^9$/L and life threatening sepsis 19 weeks after treatment of autoimmune haemolytic anaemia with four doses of Rituximab. He recovered with prompt initiation of G-CSF and made a complete recovery.

LON is a delayed drug-induced reaction, which appears several months (usually 1 to 5 months) after cessation of rituximab treatment. With widespread use of Rituximab for autoimmune diseases in different medical disciplines it is important that these physicians are aware of and monitor patient's post-Rituximab therapy for this delayed reaction.

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ABBREVIATIONS

LON : Late Onset Neutropenia
G-C SF : Granulocyte Colony Stimulating Factor

1. INTRODUCTION

Rituximab is a monoclonal antibody against CD20, a leucocyte cell marker expressed on normal and neoplastic B lymphocytes .It was used initially for treatment of CD 20 positive non-hodgkin's lymphoma [1,2,3].

Since then it has been successfully used in the treatment of immune thrombocytopenia, autoimmune haemolytic anaemia, rheumatoid arthritis, vasculitis and many more autoimmune disorders. It has shown efficacy as a first line, second or third line treatment option together with other immunosuppressants or as a sole agent [4,5].

Rituximab is given as an infusion once a week for a total of four weeks and is generally well tolerated. Infusion reactions, mainly anaphylaxis and allergic reactions are the most common serious adverse effects encountered [6]. Other side effects include cytopenias, mainly lymphopenia, infections, dermatological manifestations, arrhythmias, Myocardial infarctions, respiratory complications and progressive multifocal leucoencephalopathy [6].

Late or delayed onset neutropenia (LON) is a documented adverse effect of Rituximab that is defined as an unexplained absolute neutrophil count (ANC) of ≤1.5 × 10^9/L starting from 4 weeks after completing rituximab therapy, in patients with no signs of pre-existing chronic neutropenia and who have recovered from chemotherapy-induced neutropenia [7].

The exact mechanism is not known but several mechanisms have been postulated. This includes autoantibody mediated neutrophil destruction [8], Rituximab induced proliferation of large granular lymphocytes secreting Fas and Fas ligand leading to neutrophil apoptosis [7,9], hematopoietic lineage competition due to an excessive BAFF-induced B-cell recovery leading to increased lymphopoiesis and suppression of granulopoeisis [10].

The incidence of Late onset neutropenia ranges from 5.6 % to 27.3 % in study series involving treatment of NHL [7,8,11-16]. This was much lower in patients treated for rheumatoid arthritis, 1.3 - 5% [17,18] and other autoimmune disorders, 2.3 % [17].

Although occurrence of LON in patients treated with Rituximab for autoimmune haemolytic anaemia is reported the exact incidence is unknown. In a small case series of 12 patients with LON following Rituximab, 02 had received Rituximab [18]. In another study of 27 patients with AIHA treated with Rituximab one patient developed neutropenia [19].

The time frame for occurrence of neutropenia varies but ranges from 1 and 5 months after rituximab. [8].

The neutropenia resolves spontaneously in the majority of patients but a few need treatment with G-CSF for recovery. Late onset neutropenia in patients treated with Rituximab for autoimmune disorders report a higher incidence of infections than those who received Rituximab for non hodgkin's lymphomas [7].

2. CASE REPORT

A 73 year old man presenting with symptoms of anaemia had a haemoglobin of 8.3g/dl with normal white cell and platelet counts. The diagnostic work up revealed primary mixed autoimmune haemolytic anemia.

He was commenced on prednisolone but showed no response. Chlorambucil was added initially at a dose of 2mg daily and increased to 6mg. At this dose he maintained his Haemoglobin between 6.8 and 8.5 g/dl and needed transfusions monthly. Due to the poor response to steroids and alkylating agents Rituximab was administered at a dose of 375mg/m^2 weekly for 4 consecutive weeks.

Rituxumab was given uneventfully and he continued to be monitored at the clinic. Steroids were gradually tailed off but Chlorambucil was continued. The autoimmune haemolytic process only showed a partial response to Rituximab and he continued to maintain his Hb between 7.5 g/dl to 8.5 g with less frequent transfusions than before. The white cell counts and platelets were within normal range.

19 weeks after completion of Rituximab he presented with high grade fever of four days, confusion and sepsis. The Full Blood count revealed marked leucopenia and severe grade 4 neutropenia (WBC - 0.6 X 10^9/L and absolute neutrophil count 0.04 X 10^9/L). His Hb was within normal range for him and the platelet count was normal. The CRP was 162 mg/L. A diagnosis of neutropenic sepsis was made and he was commenced on IV Meropenem 500mg tds with subcutaneous GCSF 300ug daily after initial cultures and septic screen. With 3 doses of GCSF his counts improved to a total WBC of 4.7 X 10^9/L and neutrophils of 4 X 10^9/L. The counts were 15.3 X 10^9/L and 10.2 X 10^9/L respectively on discharge. His showed marked clinical improvement with resolved fever and reduction in CRP by day 3. He was discharged 7 days after admission and continues to be followed up at the haematology clinic.

3. DISCUSSION

Rituximab is well tolerated monoclonal antibody used in the treatment of NHL and autoimmune disorders. Although acute infusion related reactions are the most common adverse effects encountered delayed complications including progressive multifocal leucoencephalopathy and Late-onset neutropenia (LON) are also seen.

Late-onset neutropenia has been reported in 5–27% lymphoma patients by a number of groups [7–16]. The incidence of LON occurring in patients treated for lymphomas is 5-27% [7-16] and recent case reports suggest that LON also occurs in rituximab-treated patients with autoimmune disease.

LON is defined as an unexplained absolute neutrophil count (ANC) of ≤1.5 × 10^9/L (corresponding to neutropenia of grade 2–4 according to National Cancer Institute Common Toxicity Criteria) starting from 4 weeks after termination of rituximab therapy, in patients with no signs of pre-existing chronic neutropenia and who have recovered from chemotherapy-induced neutropenia. Our patient presented with severe grade 4 neutropenia which was responsible for the severe infection. The time frame of 19 weeks (approximately 4½ months) corresponds to the time frame given in many studies.

Many studies describe the occurrence, time frame and recovery of LON in patients treated for NHL and rheumatoid arthritis but literature for LON in autoimmune haemolytic anemia is scarce. A recent study in 2019 regarding, Incidence and Time Course of Neutropenia in Patients Treated with Rituximab-Based Therapy for Non-Malignant Immune-Mediated Hematologic Diseases [20] describes LON in 94 patients with ITP and 34 patients with autoimmune haemolytic anaemia. The 1-year estimated probability of developing neutropenia (ANC<1.5) was 18% and of those who developed neutropenia, the median ANC nadir and time to neutropenia from initial RTX infusion was 1.2 x 10^9/L and 4.4 months, respectively [20].

Although the reason is still unclear it has been documented that autoimmune patients appear to have more infections during the neutropenic period than lymphoma patients. This was seen in our patient too.

While a majority of patients who developed LON showed spontaneous recovery with normalization of neutrophil counts those with infections needed G-CSF treatment. Since our patient presented with life threatening sepsis and sever neutropenia G CSF was commenced administered with broad spectrum antibiotics.

Literature records good recovery of patients with very low mortality rates and our patient too made a rapid recovery over the first three days.

The true incidence, predisposing factors and mechanisms of LON are yet poorly defined and therefore it is still difficult to predict which patient will develop LON after treatment with Rituximab. A high degree of clinical suspicion and vigilant monitoring of counts in the outpatient follow up of Rituximab treated patients will help identify affected patients.

4. CONCLUSION

LON is a delayed drug-induced reaction, which appears several months after cessation of rituximab treatment. As Rituximab is used by different medical disciplines specially in the treatment of autoimmune disorders it is important that these physicians are aware of and monitor patients post Rituximab therapy for this delayed reaction.

AVAILABILITY OF DATA AND MATERIALS

Patient management details are available in his hospital records and clinic notes and copies can be made available.

CONSENT

The patient has provided informed consent for the 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.

ETHICAL APPROVAL

As per international standard or university standard written ethical approval has been collected and preserved by the author(s).

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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