CASE REPORT ASIAN JOURNAL OF MEDICAL SCIENCES

Pancytopenia following rituximab therapy in a patient with rheumatoid arthritis: Could filgrastim be a temporary solution?

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Submitted: 22-03-2016 Revised: 23-05-2016 Published: 01-09-2016

ABSTRACT

Rheumatoid arthritis is a chronic inflammatory disease affecting the peripheral joints, and can also have extraarticular manifestations. The introduction of biological agents have opened new windows to its treatment. Rituximab is a monoclonal antibody directed against CD20 cells, thereby reducing the inflammation. There have been reports of neutropenia, but pancytopenia is an uncommon incident. Filgrastim, a human granulocyte colony stimulating factor, can stimulate neutrophil production. The patient being described is a case of rheumatoid arthritis, who developed severe pancytopenia following rituximab therapy. She was given filgrastim injections, which temporarily normalized her leucopenia and neutropenia. This report emphasizes the possibility of developing pancytopenia following rituximab injection and the need of regular follow up of complete blood counts. In such cases, filgrastim may be a temporary solution. Also special consideration should be given to the increased risk of infections after taking rituximab.

Key words: Pancytopenia, Rituximab, Filgrastim, Rheumatoid arthritis

Access this article online

Website: http://nepjol.info/index.php/AJMS

DOI: 10.3126/ajms.v7i5.14679

E-ISSN: 2091-0576

P-ISSN: 2467-9100

INTRODUCTION

Over the past few years, the treatment of rheumatoid arthritis (RA) have been revolutionized by the introduction of biologic disease - modifying antirheumatic drugs (DMRDs); which target cytokines and cell-surface molecules. Rituximab is a monoclonal antibody directed against CD20, which is a cell-surface molecule expressed by B lymphocytes. Some of the side effects of rituximab therapy include infusion reactions, progressive multifocal leukoencephalopathy and increased risk of infections. Pancytopenia is an uncommon adverse effect. This report is regarding a patient, with rheumatoid arthritis, who developed recurrent pancytopenia following rituximab therapy, and was temporarily treated with filgrastim, a human granulocyte colony stimulating factor (G-CSF). The patient was also susceptible to repeated infections after taking rituximab.

CASE REPORT

The patient was a 70 year old lady, staying with her son and family, who presented to Emergency department with complaints of extreme fatigue for the past 1 month, which had progressed over the past 10 days. She was diagnosed to have RA about 10 years ago; and was taking hydroxychloroquine 400 mg once daily and methotrexate 25 mg weekly once, and daily supplements of folic acid. Since she was still symptomatic in terms of her joint pain, she was given 1 dose of rituximab injection by her regular Rheumatologist. Following the injection, her joint symptoms improved slightly, but she started feeling lethargic. She also developed palpitations and dyspnoea on exertion which was progressive in nature. There were no other associated or systemic symptoms. She was not a diabetic or hypertensive.

On examination, she was conscious and oriented, moderately built and nourished. She was extremely pale. Her heart rate was 110 beats/minute, blood pressure 100/70 mmHg and respiratory rate of 22 breaths/minute. She was afebrile. Her systemic examinations were normal.

Her complete blood count showed pancytopenia with Hb of 5.5 g% (12 - 15), PCV 17% (36 – 52), total counts

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3000 cells/cmm (4,000 - 10,000) with differential counts as N75 L25, platelets 44,000 cells/cmm (150,000 - 450,000), MCV 97.5 fL (79 - 93), MCH 31.9 pg/cell (26 - 32) and MCHC 32.9 g% (32 - 36). Her random blood sugar, electrolytes, renal and liver functions were normal. Prothrombin time and activated partial thromboplastin time were normal. Her peripheral smear showed microcytic hypochromic anaemia with mild leucopenia and marked thrombocytopenia, with no abnormal cells. Her urine microscopy showed plenty of pus cells, with no evidence of haematuria and urine culture grew Klebsiella. She was started on injection meropenum, according to culture and sensitivity, and injection pantoprazole. Two units of packed cells were transfused. Her blood culture was sterile; and HIV, hepatitis B, hepatitis C, malarial smear, dengue serology and leptospirosis serology were negative. Antinuclear antibody, Coombs' test and serum protein electrophoresis were negative. Her stool occult blood was also negative. Chest Xray and ECG were normal.

On day 2, her Hb picked up to 8.1 g% but her total counts dropped to 1,700 cells/cmm with differentials as N60 L40. Her platelets were almost the same (53,000 cells/cmm). Over the next 5 days, her Hb did not show any further drop, total counts continued to be in the range of 1500-2100 cells/cmm, with differentials as N50 L48 E2, and platelets 25,000 – 40,000 cells/cmm. Her renal and liver functions continued to be normal. Her vitals were stable. Bone marrow examination showed a mildly hypo cellular marrow. Her repeat urine microscopy was normal and culture was sterile. Due to persistent leucopenia, she was given injection filgrastim 200 µg (5 µg/kg/day) subcutaneous once daily.

Three days following filgrastim injection, her Hb became 9 g%, total counts 5000 cells/cmm, differential N70 L30, and platelets 55,000 cells/cmm. By day 13 of admission, her total counts went up to 22,000 cells/cmm, due to filgrastim and the injection was withheld. She was discharged on day 18 of admission, with a stable blood picture i.e. Hb 9.2 g%, total counts 7000 cells/cmm, differential N68 L32, and platelet counts of 120,000 cells/cmm. She was asked to follow up every third day with complete blood counts, and to restart injection filgrastim and empirical antibiotics if necessary. She was also asked to continue hydroxychloroquine 400 mg once daily and folic acid. However, she did not review as advised.

About 1 month later, she presented again with fever, cough and breathlessness. She was pale. Her blood pressure was 90/60 mmHg. Her Hb was 6 g%, total counts 1300 cells/cmm, differential N72 L28, and platelets 150,000 cells/cmm. Her chest Xray showed left lower lobe pneumonia. She was intubated and put on mechanical ventilation. Injection piperacillin + tazobactum and levofloxacin were started, but patient expired within 8 hours of admission. Her cause of death was believed to be due to pneumonia with recurrent pancytopenia following rituximab therapy. The course of her pancytopenia has been outlined as line diagrams (Figures 1-3).

DISCUSSION

Rheumatoid arthritis is a chronic inflammatory disease, characterized by symmetric involvement of peripheral joints. A variety of extraarticular manifestations like subcutaneous nodules, pleural effusions, pulmonary nodules, interstitial lung disease, pericarditis, cardiomyopathy, peripheral neuropathy, vasculitis, haematological abnormalities etc occur in RA. It is commonly seen between 25 to 55 years of age, followed by a plateau till the age of 75 and then decreases. Genetic and environmental factors have been implicated in the

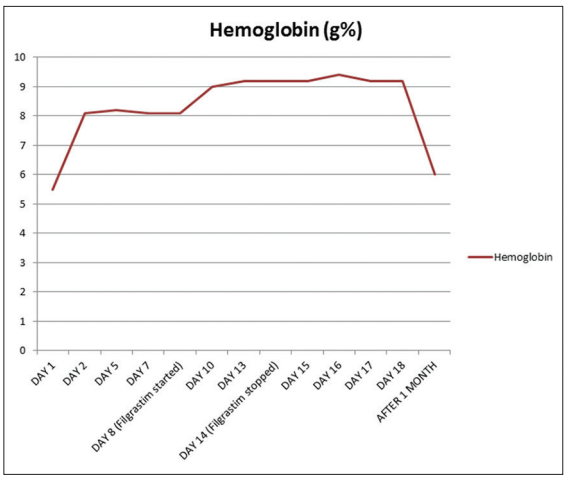

Figure 1: Course of pancytopenia in terms of haemoglobin

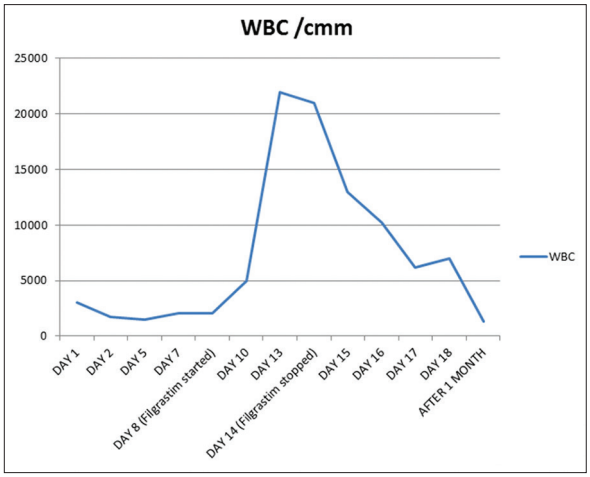

Figure 2: Course of pancytopenia in terms of WBC count

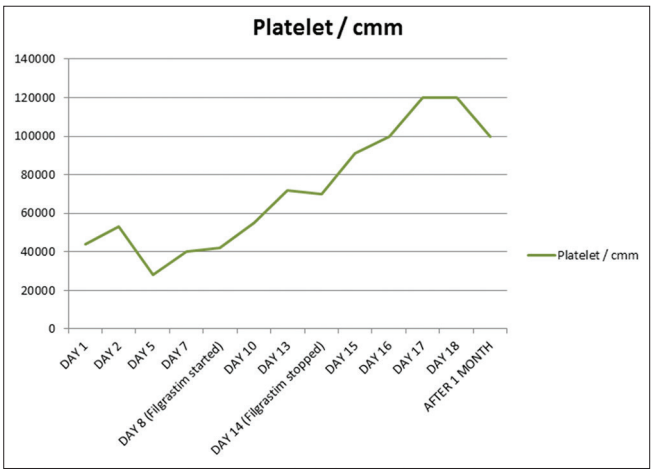

Figure 3: Course of pancytopenia in terms of platelet count

pathogenesis of RA. The onset is characterized by infiltration of the synovial membrane with lymphocytes, plasma cells, dentric cells and macrophages. CD4 T lymphocytes play a central role in interacting with the other cells in synovium. Cytokines and autoantibodies are formed from lymphoid follicles within the synovium. Synovial macrophages get activated which in turn produce inflammatory cytokines, resulting in swelling of the synovial membrane and damage to soft tissue and cartilage. There will be formation of inflammatory granulation called pannus over the articular cartilage, resulting in its destruction.[1]

The introduction of biological agents have revolutionized the management of RA. These drugs are reserved for patients with high density disease activity despite being treated with traditional DMRDs. Rituximab is a monoclonal antibody directed against the CD20 receptors expressed on B lymphocytes and plasma cells. It causes depletion of peripheral and synovial B cells.[1] Rituximab, in combination with methotrexate, has proved to be effective in treatment of refractory RA. There have been reports of infusion reactions. Also rituximab therapy may increase the risk of infections.[2] Progressive multifocal leukoencephalopathy has also been reported.[3,4] Haematological abnormalities like leukopenia, neutropenia and pancytopenia are other noted adverse effects following rituximab infusion.[5-7]

Filgrastim is a human granulocyte colony stimulating factor (G-CSF), produced by recombinant DNA technology. Colony stimulating factors are glycoproteins which act on hematopoietic cells by binding to specific cell surface receptors and stimulating proliferation, differentiation, and some end-cell functional activation. G-CSF regulates the production of neutrophils within the bone marrow and affects neutrophil progenitor proliferation.[8,9] Apart from various other indications, filgrastim has been used to treat drug induced pancytopenia.[10]

The patient being reported had received rituximab therapy for her RA and developed pancytopenia. The use of filgrastim had a transient effect on her leukopenia. However, the patient was subject to repeated infections and faced her death due to pneumonia in the presence of recurrent pancytopenia.

CONCLUSION

RA is a chronic inflammatory disease affecting the peripheral joints. Traditional DMRDs may be ineffective in the treatment of refractory RA. In such cases, biological agents like rituximab have proved to be beneficial. However, these drugs can have haematological adverse effects due to bone marrow suppression. Also there is increased risk of infections following therapy with rituximab. This case report highlights the risk of susceptibility to infections and the need for constant monitoring of complete blood count following rituximab therapy; and the probable use of filgrastim to overcome leucopenia in such situations.

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Authors Contribution:
RGM - Concept and design of case report, reviewed the literature, manuscript preparation, critical revision of manuscript and treating physician.

Source of Support: Nil. **Conflict of Interest:** None.