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Case study of a patient of granulomatosis with polyangiitis successfully maintained on rituximab biosimilar for five years

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Abstract

Granulomatosis with Polyangiitis (GPA) or previously known as Wegener's Granulomatosis (WG), is a rare multi-system autoimmune disease. Here, we describe a case of GPA treated and maintained on Rituximab (Biosimilar Dr Reddy's Reditux RA) infusions every six months for five years. At that time, there was little research reporting use of Rituximab in these patients. The studies reported that it can be used for two years only. In our patient over five years of treatment with rituximab, most of the symptoms resolved with no adverse effects. This case emphasizes on Rituximab safety and efficacy for long-term therapy in a patient with refractory GPA.

Keywords

granulomatosis with polyangiitis; biosimilar; rituximab; computed tomography

Abbreviations

GPA : Granulomatosis with Polyangiitis; WG : wegener's Granulomatosis; HRCT : High-resolution computed tomography; CT: Computed Tomography; ESR: Erythrocyte Sedimentation Rate

Case Report

A 52-year-old Indian female was referred from a hospital to us, because of a cough persisting for three months, shortness of breath, right-sided chest pain, occasional fever, sleeplessness, loss of appetite and generalised weakness. She had no previous history of smoking, addiction, any specific allergy, hypertension, diabetes mellitus, or hyperlipidemia. No history of tuberculosis or any similar problem in the first-degree relatives had been recorded before.

On examination, she was alert and obeyed commands. Her skin was normal in appearance, texture, and temperature. Her scalp normal and pupils equally round, 4mm, reactive to light and accommodation, sclera and conjunctiva normal. Fundoscopic examination revealed normal vessels without haemorrhage. Tympanic membranes, external auditory canals, and nasal mucosa were normal. Oral pharynx was without erythema or exudate. Tongue and gums were normal. The neck was moveable without resistance. The trachea was midline and thyroid gland normal without masses. Carotid artery upstroke was normal bilaterally without bruits. Jugular venous pressure was measured as 8 cm with the patient at 45 degrees. No cyanosis, clubbing, or oedema was noted in the extremities. Peripheral pulses in the femoral, popliteal, anterior-tibial, dorsal-pedis, brachial, and radial areas were normal. No palpable nodes were found in the cervical, supraclavicular, axillary or inguinal areas.

Chest examination revealed scattered crepitation's on auscultation of the lungs bilaterally. Heart sounds were normal. No fourth heart sound or rub was heard. The abdomen was symmetrical without distention; bowel sounds were normal in quality and intensity in all areas. No masses or splenomegaly were noted; the liver span was 8cm by percussion. Normal rectal sphincter tone, no rectal masses were noted on exam. Pelvic exam reveals normal external genitalia, normal vagina, and cervix on speculum examination. Bimanual examination revealed no palpable uterus, ovaries, or masses. Cranial nerves examination were normal. Motor and sensory examination of the upper and lower extremities were normal. Gait and cerebellar function were also normal. Reflexes were normal and symmetrical bilaterally in both extremities. No other significant findings were reported on physical exam.

Chest radiograph revealed amulti-lobulated mass in the right mid-zone of the lungs; the impression was probably cancer. It was followed up by High-Resolution Computed Tomography (HRCT) chest which confirmed the presence of right lower apical segment mass and multiple well-defined nodules seen in the right upper lobe, right middle lobe, lingual and left lower lobe (**Figure 1**). The patient underwent bronchoscopy and bronchial sputum/smear specimens were negative for bacteria, Acid- Fast Bacilli (AFB), fungal elements and malignant cells. The patient then underwent CT-guided biopsies which showed necro-inflammatory debris without any evidence of granuloma/malignant cells/fungal elements. Tumour markers (CEA,CA-19-9 & CA-125) were negative. Blood tests and serology confirmed GPA with a strong cytoplasmic Anti-neutrophil cytoplasmic antibody (C-ANCA) positivity with anti-PR3 auto antibodies>200. C-Reactive Protein (CRP) (96), Rheumatoid factor (640) and Erythrocyte Sedimentation Rate (ESR) (140mm/hr) were elevated. Antinuclear Antibody (ANA) was negative. Urine examination revealed microscopic haematuria (10-15 RBC/HPF) with mild proteinuria (Spot urine for protein creatinine ratio 0.96).

Treatment

After the initial diagnosis, vaccination was completed before treatment begun. Birmingham Vasculitis Activity Score for Wegener's Granulomatosis (BVAS-WG) was 17. Initially, the patient was started on pulse therapy of methylprednisolone 500mg for five days. Following methylprednisolone, first pulse of IV Cyclophosphamide (750mg) given and 60mg of oral prednisolone started. In addition, supportive therapy was provided through antacids, antipyretics, multivitamins, nebulisation, and antibiotics. Subsequently, she received monthly pulse of cyclophosphamide (750mg) with tapering dose of steroids for the next 5 months. However, despite this, the patient's condition progressively worsened with increasing breathlessness, severe debilitating joint pains, headache and generalised weakness. She also developed hypertension and Magnetic Resonance Imaging (MRI) of brain was found to be normal. Computed Tomography (CT) of paranasal sinuses revealed mild mucosal thickening in sphenoid ethmoidal recess.

After 6 pulses of cyclophosphamide and steroids, ESR dropped to 80mm/hr and on physical examination of the respiratory system, the lungs were clear, but the patient still complained of shortness of breath on each follow-up visit. 15 days after the 6th dose of Cyclophosphamide, the patient developed sudden loss of vision which was confirmed to be retrobulbar optic neuritis by the ophthalmologist (**Figure 2**). She was given I.V. Methylprednisolone 1g daily for 5 days.

Due to refractoriness of the disease to the conventional treatment, and the progressive worsening of symptoms, it was decided to start with Rituximab Biosimilar. In March 2011, she received her first infusion of Rituximab Biosimilar 1g followed by a second infusion two weeks later. After this, her ESR dropped to 40mm/hr and urine examination became normal. She was given Zoledronic acid, a bisphosphonate, for her treatment of osteopenia. After induction doses of Rituximab Biosimilar, she received 1g infusion every six months for the next four years as she complained of mild breathlessness, fever and joint pains 4-5 months after each dose of Rituximab Biosimilar. This completed a total of ten infusions over five years with her last being in April 2015. A low dose of steroids was continued all throughout.

Immunoglobulin levels were done repeatedly throughout her treatment and infusions of Rituximab Biosimilar was delayed in between due to a decrease in IgG levels. She was clinically stable for the entire period, with no major flare-ups. Occasionally, she developed a cough and /or shortness of breath which was treated with symptomatic therapy of nebulisation and antibiotics based on sensitivity tests. In April 2016 follow up, Chest X-ray post-anterior view revealed fibrosis in the right mid-zone with the rest of the lung parenchyma appearing normal (**Figure 2**). Anti-PR3 antibodies were 0.24 and her clinical course seemed to have stabilised. BVAS-WG Score reduced to 1.

Discussion

GPA is a granulomatous lung disease characterised by inflammation of the upper and lower respiratory tracts, with necrotizing vasculitis affecting small and medium-sized blood vessels and, frequently, necrotising glomerulonephritis [1]. The American College of Rheumatology defined it by two of these four criteria: nephritic urinary sediment, abnormal chest finding, nasal or oral inflammation, and granulomatous inflammation on biopsy [2]. It is treated with a combination of corticosteroids and cyclophosphamide or other immunosuppressive agents (like methotrexate and azathioprine) [3]. In cases where this treatment had failed, rituximab has shown promise [4].

Rituximab is a chimeric monoclonal anti-CD20 antibody mainly used for the treatment of B-cell lymphomas. It has recently been used as salvage therapy in the treatment of various refractory autoimmune diseases [5]. Globally, the experience with rituximab has been used for a short period of time and the results have been variable [4,6]. Here, we discuss the success of using Rituximab Biosimilaras a long-term alternative for maintenance therapy. The available literature indicates that Rituximab has been used in GPA as rescue medication in cases of refractory disease or in patients with a contraindication to cyclophosphamide. Hundreds of cases of GPA treated with Rituximab have been studied and reportedas case series inthe medical literature (**Table 1).**

This patient had mild kidney disease but had life-threatening lung disease. She didn't respond adequately with cyclophosphamide and corticosteroids resulting in worsening of dyspnea and the development of Retrobulbar neuritis causing loss of vision. She responded very well to treatment with Rituximab Biosimilar symptomatically and as evidenced by her blood reports. She experienced mild flare-ups which were treated symptomatically and didn't require major interventions. No new manifestations of the disease were noted. Almost a year after 10 Rituximab infusions, she has remained well and in remission. Previous studies have shown a relapse rate of 30% (29/99) (**Table 1**), mainly through the first 12 months.

In conclusion, it can be assumed that Rituximab is a safe and efficacious alternative for patients with GPA. It has shown minimal side effects. This case report emphasizes that contrary to current literature this treatment can be safely continued for over five years in whom conventional immunosuppressive agents have failed or have contraindications to its use.

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Author's Contributions

Arindam Nandy Roy wrote the case presentations and supervised the writing of the discussion. The author has read and approved the final manuscript.

Tables

Table 1: Previous reports on the Use of Rituximab in GPA* (In Chronologically Order) [7]

Author/Year	Indication	No. pts	Dose	Previous Treatment	BVAS-WG	Results on ANCA Titer	Response Rate	Follow-Up (Months)	Relapses
Eriksson [8], 2005	Refractory/relapsing disease	7	375mg/m2/w x 2-4 infusions	Prd, Cyc, AZA, MMF	Reduced	Unchanged	6 CR, 1PR	6-24	2/7
Keogh [9], 2005	Refractory disease or Cyc intolerance	10	375mg/m2/w x 4 infusions	Prd, Cyc, MTX, MMF	Reduced	Decreased	9 CR, 1 PR	10-42	2/10
Omdal [10], 2005	Refractory/relapsing disease	3	375mg/m2/w x 4 infusions	Prd, Cyc, MTX, MMF, AZA	NS	Decreased	3 CR	24	3/3
Keogh [11], 2006	Refractory disease or Cyc intolerance	10	375mg/m2/w x 4 infusions	Prd, Cyc, AZA, MTX	Reduced	Decreased	10 CR	12	1/10
Aries [12], 2006	Refractory disease	8	375mg/m2/mth	Prd, Cyc, MTX, MMF	Unchanged	Unchanged	2 CR, 1 PR, 5 failures	NS	0/8
Stasi [13], 2006	Refractory or relapsing disease	8	375mg/m2/w x 4 infusions	Prd, Cyc, AZA, MTX, CyA, Ig, cotrimoxazol	Reduced	Decreased	7 CR, 1 PR	33	3/8
Golbin [14], 2006	Refractory or Cyc contraindicated	21	375mg/m2/w x 2-4 infusions	Prd	NS	Unchanged	NS	19-70	7/21
García [5], 2007	Severe WG	4	375mg/m2/w x4 infusions	Cyc, Prd	Unchanged	NS	1 PR, 3 failures	NS	1/4
Henes [15], 2007	Refractory disease	6	375mg/m2/w x 4 infusions	Prd, Leflunom	Reduced	Decreased	5 CR, 1 PR	12-21	1/6
Tamura [16], 2007	Refractory disease	2	375mg/m2/w x 4 infusions	Prd	Reduced	Normalized	2 CR	6-13	1/2
Brihaye [17], 2007	Refractory/relapsing disease	8	375mg/m2/w x 4 infusions	Prd, IS (not specified)	Reduced	NS	3 CR, 3 PR, 2 failures	NS	1/8
Sánchez-Cano [18], 2008	Refractory disease/ Cyc contraindicated	4	375mg/m2/w x 4 infusions	Prd, Cyc, MTX, AZA	Reduced	Decreased	2 CR, 2 PR	8-26	3/4
Seo [19], 2008	Refractory disease or Cyc intolerance	8	375mg/m2/w x 4 infusions	Prd, Cyc, MTX	Reduced	Decreased	8 CR	NS	5/8

*Only reports of 2 or more cases. Prd: Prednisone; Cyc: Cyclophosphamide; Aza: Azathioprine; MTX: Methotrexate; MMF: Mycophenolate; CyA: Cyclosporine A; Ig: Immunoglobulins; Leflunom: Leflunomide; NS: Not specified. CR: Complete response; PR: Partial response.

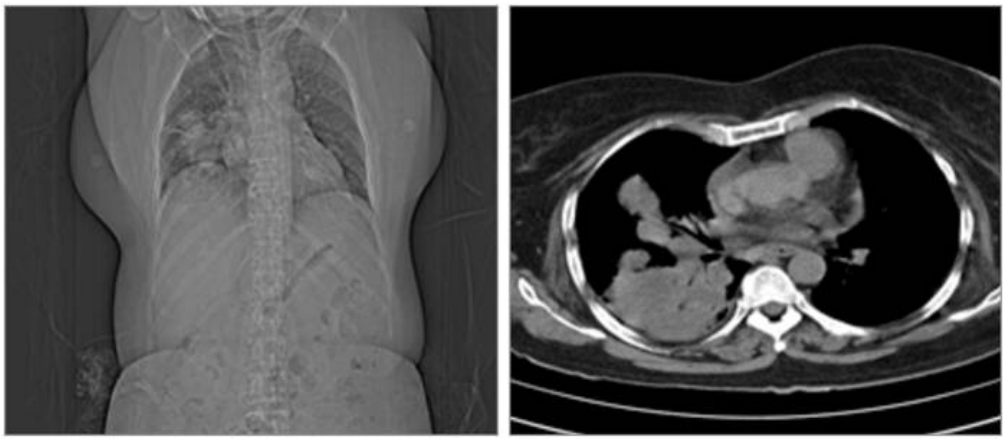

Figure 1: A) CT topogram of the chest reveals right lower lobe consolidation **B)** right lower and middle lobe consolidation.

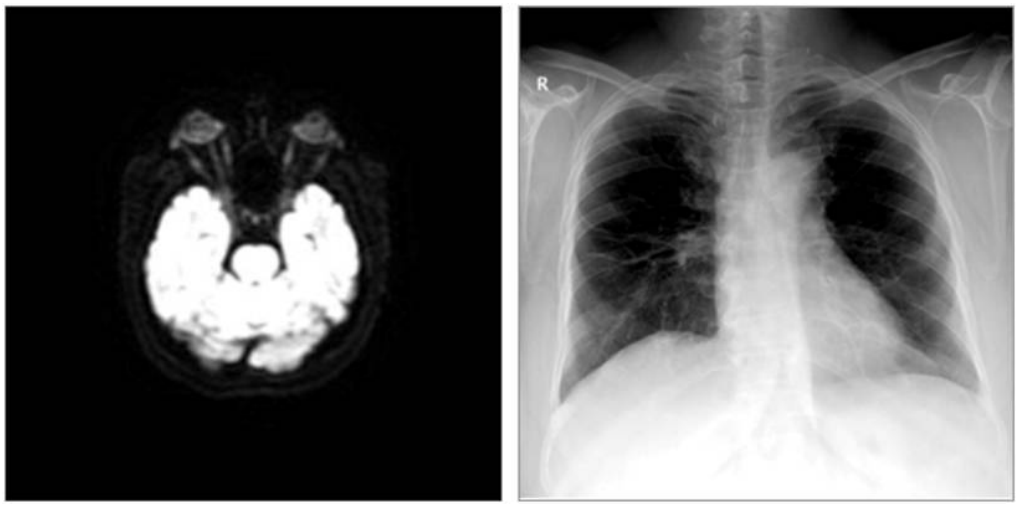

Figure 2: A) Right optic nerve on diffusion weighs images show the certain increase in a signal due to optic neuritis **B)** Complete resolution of right lower lobe consolidation with few fibrotic strands seen at the site of involvement in the right mid-zone.

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