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Favorable outcome of granulocyte colony-stimulating factor use in neuromyelitis optica patients presenting with agranulocytosis in the setting of rituximab

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Abstract

Neuromyelitis optica is a severe autoimmune condition affecting the central nervous system characterized by a relapsing disease course. Rituximab is a chimeric monoclonal antibody against the protein CD20, and is one of the most utilized medications for management of this disease. A known complication of rituximab use is neutropenia. We report on two patients who developed symptomatic early-onset rituximab-induced agranulocytosis who safely received granulocyte colony-stimulating factor. Neutrophil counts recovered quickly and both patients continue to receive rituximab without further incident.

Keywords

Neuromyelitis optica; NMO; G-CSF; Agranulocytosis; Rituximab; Neutropenia

1. Introduction

Neuromyelitis optica (NMO) is a severe autoimmune condition affecting the central nervous system characterized by a relapsing disease course. While there have been no placebo-controlled trials of immunosuppressive medications to manage the disease, rituximab is the most studied and one of the most utilized medications currently in use. Rituximab is a chimeric monoclonal antibody against the protein CD20, which is primarily found on the surface of immune system B cells. Rituximab depletes circulating B cells and is approved by the Food and Drug Administration (FDA) for the treatment of B cell malignancies, as well as autoimmune diseases including rheumatoid arthritis (RA) and Wegener's granulomatosis. It has also been used in other autoimmune diseases off-label, including Sjogren's syndrome, systemic lupus erythematosus (SLE), multiple sclerosis and NMO, in part because of the relatively favorable safety profile of the medication over time. However, one known complication of rituximab use is neutropenia (Tesfa et al., 2011; Wolach et al., 2010).

Late-onset neutropenia has been associated with rituximab treatment in B cell malignancies with an estimated incidence of 3–27% (Wolach et al., 2010). While only a few cases have been reported in autoimmune diseases, several retrospective analyses estimate the incidence to be 5–6%, predominantly seen in pemphigus vulgaris (Goh et al., 2007), RA, SLE, and

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Wegener's granulomatosis (Tesfa et al., 2011). Most patients were either on simultaneous or successive immunosuppression that complicates these findings. Rarer yet is the effect of drug-induced agranulocytosis (stage 4 neutropenia) after rituximab administration, defined as a decrease in peripheral neutrophil count to less than 0.5×10^9 cells/L due to immunologic or cytotoxic mechanisms (Plate et al., 2014).

Most cases of rituximab-induced agranulocytosis and neutropenia are due to delayed or late-onset neutropenia (LON) occurring a median of 38 to 175 days following the last rituximab dose (Wolach et al., 2010; Tesfa et al., 2011). The mechanism of rituximab-induced LON is unknown but is not thought to be due to direct drug toxicity. One case of LON has been reported in an NMO patient (Plate et al., 2014). In contrast, early-onset rituximab-induced neutropenia has been described in SLE (Gottenberg et al., 2005; Enríquez et al., 2007), and early-onset agranulocytosis has also been reported (Arroyo-Ávila et al., 2015) but early-onset agranulocytosis has not yet been reported in NMO. We reported two cases of early-onset rituximab-induced agranulocytosis in NMO.

2. Methods and results

2.1. Case report 1

A 32-year-old Caucasian woman meeting 2006 criteria for NMO (Wingerchuk et al., 2006) was diagnosed in 2009 following longitudinally-extensive transverse myelitis, optic neuritis and anti-AQP4 seropositivity. She was started on rituximab at the time of diagnosis, receiving 1000 mg intravenously on days 0 and 14 at initiation of therapy, and a single 1000 mg intravenous dose every five months thereafter for a total of 14 total doses over 58 months. Pre-medication included acetaminophen 1000 mg by mouth, diphenhydramine 50 mg intravenously, and dexamethasone 4 mg intravenously. Her disease was in remission since beginning this regimen. The patient received her normal rituximab regimen on day 0, after having baseline laboratory work-up that revealed absolute neutrophil count (ANC) of 2.38 k/ μ L and total white blood cell count (WBC) of 4.40 k/ μ L. The following evening, she developed a headache, fatigue, chills, and fever of 38.4 °C. On day 3, she was afebrile with resolution of chills and improvement in fatigue, but experienced gum sensitivity and inflammation. She also developed submandibular lymph node tenderness and inflammation along with jaw pain and sore throat. Basic laboratory work was drawn the next day and she was started on amoxicillin/clavulanate for presumed sinus infection. One week after rituximab, the patient presented with an ANC of 0.0 k/ μ L and total WBC of 1.45 k/ μ L; at this point her symptoms included extreme fatigue, rectal pain and gum inflammation. Patient was admitted to the hospital and received filgrastim 300 μ g as a single subcutaneous dose the next day. Two days later, her ANC recovered to 5.05 k/ μ L and WBC to 9.36 k/ μ L with symptom resolution. Patient continues on a single dose of rituximab at 1000 mg intravenously every 5 months and ANC and WBC have remained stable (most recent 2.11 k/ μ L & 4.22 k/ μ L, respectively). The patient was on the following medications at the time of the event: cephalexin 250 mg daily by mouth, and over-the-counter multi-vitamin, cholecalciferol, B complex, and fiber supplements.

2.2. Case report 2

A 32-year-old Caucasian woman meeting 2007 criteria for NMO Spectrum Disorder (Wingerchuk et al., 2007) was diagnosed in 2012 following a longitudinally extensive transverse myelitis and anti-AQP4 seropositivity. She was started on rituximab at the time of diagnosis, receiving 375 mg/m² intravenously on day 0 and 500 mg/m² on day 14. Pre-medication included acetaminophen 1000 mg by mouth, diphenhydramine 50 mg intravenously, and methylprednisolone 1000 mg intravenously. She developed no clinical inflammatory events in the interim. At month 3, the patient's B cells remained depleted, but she was erroneously given paired doses of 1000 mg/m² (1720 mg) of rituximab on days 0 and 14 at an outside institution. Prior to the infusions, her ANC was 6.2 k/μL and WBC was 8.7 k/μL. She was symptom-free until 2 weeks later when she developed cold-like symptoms including fatigue, fever of 38.1 °C, followed by the development of mouth sores. Basic laboratory work was drawn which revealed an ANC of 0.4 k/μL and a total WBC of 3.6 k/μL. The patient received filgrastim 333 μg as a single subcutaneous dose; counts recovered quickly to ANC of 13.8 k/μL and a total WBC of 17.9 k/μL by the next day. The patient continues on her rituximab regimen, dosed at 1000 mg intravenously at days 0 and 14; ANC and WBC have remained stable (most recent ANC 4.4 k/μL and WBC 6.8 k/μL). Patient was on the following medications at the time of the event: acyclovir 400 mg daily by mouth, sulfamethoxazole/trimethoprim three times weekly by mouth, docusate sodium 100 mg daily by mouth, vitamin D3 1000 IU daily by mouth, magnesium chloride supplement daily by mouth, calcium citrate + vitamin D supplement daily by mouth, calcium citrate + vitamin D and temazepam 15 mg by mouth as needed for sleep.

3. Discussion

These two cases likely illustrate early-onset rituximab toxicity leading to agranulocytosis with symptomatic outcomes. In one case, the patient received excessive treatment with rituximab suggesting a dose-related effect. These patients were concurrently on other medications that also rarely cause neutropenia, cephalexin and trimethoprim sulfa, respectively, which may have contributed to their agranulocytosis. Both patients continue on rituximab for management of their NMO without further complications.

A previous report of an NMO patient in the midst of initial disease presentation received filgrastim with worsening of his acute central nervous system lesion (Jacob et al., 2012). The authors also showed evidence of neuronal granulocyte colony-stimulating factor (G-CSF) up-regulation within lesions in NMO patients and concluded that filgrastim is detrimental in NMO. In our cases, the two NMO patients who received filgrastim were not in the midst of a relapse and did not have an adverse reaction suggesting that filgrastim may be safe in NMO patients who are in remission. As noted, both patients had quick recovery of neutrophils and continue on their rituximab with ongoing monitoring without further incidence and neither had exacerbation of their disease at the time of filgrastim administration. Also of potential significance, these patients exhibited infectious symptoms within 1.5 and 14 days, respectively, of their last rituximab infusion which differs from the delayed-onset typically associated with rituximab use. This suggests that monitoring of

patients' neutrophils while on rituximab therapy may be appropriate even in the acute period and/or short-term use.

The earlier case report of a patient with stage 4 neutropenia/agranulocytosis ($<0.5 \times 10^9$ cells/L) in an NMO patient receiving rituximab monotherapy was not symptomatic and did not receive treatment with G-CSF (Plate et al., 2014). This patient's ANC recovered despite ongoing rituximab treatment. In other autoimmune diseases with rituximab-induced neutropenia, recovery of ANC was usually noted within 9–20 days in untreated patients (Tesfa et al., 2011) suggesting that filgrastimis only useful in cases of symptomatic agranulocytosis in NMO.

Abbreviations

NMO	neuromyelitis optica
G-CSF	granulocyte colony-stimulating factor
AQP4	aquaporin 4
LON	late-onset neutropenia

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