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Chronic Severe Neutropenia Associated With Intravenous Immunoglobulin for Multifocal Motor Neuropathy

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ABSTRACT

Intravenous immunoglobulin (IVIG) is an immunomodulatory therapy derived from pooled donor immunoglobulins and used for treatment of various autoimmune conditions. Here we report the diagnosis and management of IVIG-induced chronic severe neutropenia with absolute neutrophil count $<0.5\times10^3/\mu L$ in a patient with multifocal motor neuropathy. Serial blood count showed a cyclical pattern of neutropenia: worsening 24–48 h post-IVIG, then gradually improving before the next infusion. IVIG-induced neutropenia is rare, with previous reports of predominantly mild transient neutropenia. Our case describes chronic severe neutropenia that developed years after starting IVIG. We summarize available evidence and management strategies for IVIG-associated neutropenia.

Intravenous immunoglobulin (IVIG)-induced chronic severe neutropenia with absolute neutrophil count (ANC) <0.5×103/μL is rare, and its presentation and management have not been described. While transient mild neutropenia following IVIG has been reported [1–6], chronic severe neutropenia caused by IVIG remains underrecognized. IVIG is widely used for various immune-mediated conditions, including neuromuscular disorders multifocal motor neuropathy (MMN), chronic inflammatory demyelinating polyneuropathy, and Guillain-Barré Syndrome [7]. Here, we report a case of IVIG-induced chronic severe neutropenia in a patient with MMN. MMN, characterized by progressive muscle weakness due to conduction blocks without sensory abnormalities [8], is primarily treated with IVIG, which has been shown to improve muscle strength and reduce disability [7].

A 56-year-old man with a 15-year history of MMN on maintenance IVIG (Privigen) was referred for chronic neutropenia with ANC <0.5×103/μL. He had been receiving IVIG for 10 years, initially every 4–6 weeks. Weakness between doses led to dose increases: 600 mg/kg every 4 weeks, then 900 mg/kg, and finally 1 g/kg every 3 weeks—with excellent symptom control. After nearly 5 years on this intensified regimen, routine bloodwork revealed severe leukopenia and neutropenia (white blood count 1.6×103/μL, ANC 0.3×103/μL). Hemoglobin and platelets were normal. Historical labs showed mild neutropenia (ANC 0.8–1.9×103/μL) over the previous 10 years on IVIG. However, no CBCs were available before IVIG initiation or since the dose intensification.

A comprehensive evaluation was performed. There were no nutritional deficiencies, infections, rheumatologic conditions, or hereditary syndromes. Bone marrow was normocellular for age without dysplasia, with a normal myeloid to erythroid ratio, normal myeloid maturation, and no increase in T large granular lymphocytes. There was a mosaic loss of the Y chromosome but

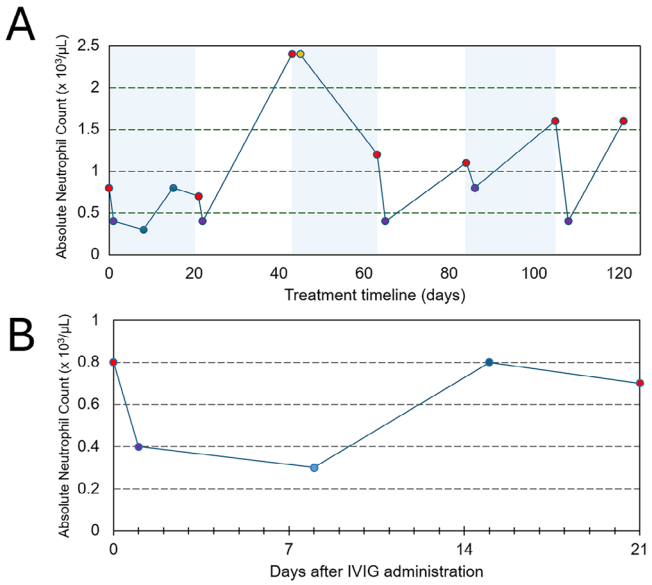

FIGURE 1 | Absolute neutrophil count (ANC) trend in relation to intravenous immunoglobulin (IVIG) administration. (A) ANC trend over a 6-month period, showing pre- and post-IVIG administration neutrophil counts for six cycles of IVIG administration (demarcated by alternating shading of blue and white). ANC drawn before each IVIG administration is noted in red. The neutrophil count drops each cycle on the day after IVIG administration (purple dot), except for Cycle 3 when the patient experienced a coronavirus disease 2019 (COVID-19) infection with an appropriate neutrophil response (denoted by a yellow dot on day 42 of the graph). The blue dots on days 8 and 15 represent the ANC from more frequent weekly draws during Cycle 1, and this cycle is further expanded in (B). The median ANC pre- IVIG is 1.1×103/μL. The median ANC post-IVIG is 0.3×103/μL. (B) An expanded graph showing the ANC trend over the 21 days after IVIG administration (this corresponds to days 1–21 of A). The pre-IVIG ANC is 0.8×103/μL (day 0), dropping to 0.4×103/μL on day 1, with a nadir at 0.3×103/μL on day 8, rising back to 0.8×103/μL by day 15.

no malignancy-associated acquired mutations. No neutrophil-associated antibodies were identified. Duffy antigen phenotype was not tested given the patient's European ancestry.

IVIG-mediated neutropenia was suspected, and the ANC was monitored serially over a 6-month period (the final 6 months of the 15-year IVIG treatment). ANC trend showed a cyclical pattern, with a median ANC pre-IVIG of 1.1×103/μL (range 0.7–1.6), dropping to a median of 0.4×103/μL (range 0.4–0.8) by 24 h after IVIG infusion (Figure 1A), nadiring at 0.3×103/μL over the first week (Figure 1B), and recovering to a pre-IVIG baseline by the next infusion. Despite cyclical dips to ANC<0.5×103/μL every 3 weeks, he experienced no oral ulcers or unusual infections. During the SARS-CoV2 pandemic, he had an uncomplicated coronavirus disease 2019 infection, with an ANC rise to 2.4×103/μL.

Given the absence of infectious complications and a demonstrated ability to mobilize neutrophil response during an infection, we did not recommend granulocyte colony-stimulating factor or antimicrobial prophylaxis. The patient was advised to seek immediate medical care in the event of a fever or acute illness. The patient elected to continue his current IVIG regimen, prioritizing the good control of neurologic symptoms.

While IVIG is generally well tolerated, adverse reactions are estimated to affect 20%–50% of patients and 5–15% of all IVIG infusions [9, 10]. Most IVIG-induced adverse events are mild and include immediate and delayed systemic infusion reactions resolving with appropriate treatment [11]. In 1992, one of the earliest reports of IVIG-associated neutropenia described a patient receiving IVIG for systemic lupus erythematosus who developed neutropenia after IVIG [6]. The suspected etiology has been attributed to the presence of anti-leukocyte antibodies within the pooled plasma product from over 8000 volunteer blood donors [6]. In the PRIMA clinical trial, which evaluated Privigen 1 g/kg every 3-week dosing, two patients with mild Privigen-related leukopenia (WBC 2.3–3.7×103/μL) were reported [11]. Reduced neutrophil count was also identified as a common adverse reaction in postmarketing experience [12].

Several single-institution studies have investigated IVIG-induced neutropenia. In a previous report of a patient with MMN receiving one cycle of IVIG treatment, neutropenia developed with an ANC nadir $<0.5 \times 10^3/\mu L$, but neutrophil levels returned to normal after 2 weeks and whether neutropenia recurred or became chronic or more severe as a consequence of repeated IVIG cycles was not investigated [13]. In a study of 14 pediatric immune thrombocytopenia (ITP) patients, four (29%) developed ANC<1.5×103/μL after IVIG, resolving within 36–48 h, with no recurrence after subsequent IVIG courses [5]. The baseline ANC of these four patients was not statistically different from the 10 patients who did not develop post-IVIG neutropenia. In another study, comparing the incidence of neutropenia in 64 ITP patients receiving IVIG to 46 ITP patients receiving anti-D immunoglobulin [4], 28% of IVIG-treated children developed neutropenia, with 4.7% having ANC<0.5×103/μL, while no cases occurred with anti-D immunoglobulin. Pre-treatment ANCs were not significantly different between treatment groups, and there were no cases of neutropenia recurrence in patients who required more than one course of IVIG. In patients with neuro-immunologic diseases, the effects of high-dose IVIG on neutrophil counts were studied in 16 patients receiving 22 IVIG cycles. Most experienced a drop in neutrophils, but only two had ANC nadir $<1 \times 10^3/\mu L$ [3]. Although baseline ANC values were not formally compared, consistent with other reports, patients who developed neutropenia had similar baseline ANCs to those who did not. Further, none of the patients in this study developed ANC$<0.5 \times 10^3/\mu L$ or experienced infectious complications.

In contrast, infections were more common in patients receiving IVIG for cutaneous autoimmune disorders [2]. Of 106 IVIG cycles among 17 patients, seven cycles (6.6%) in four patients were associated with bacterial infections, with over half preceded by moderate neutropenia (ANC<1×103/μL). None of these patients had ANC<0.5×103/μL, with a higher rate of bacterial infections in this cohort likely reflecting a higher-risk cohort on concurrent immunosuppressant therapy with possible cutaneous routes of infection and longer follow-up.

The mechanism of IVIG-associated neutropenia has been proposed to occur by direct clearance of neutrophils by anti-neutrophil antibodies present in the pooled donor immunoglobulins [6] and through increased endothelial adhesion via immune-complex aggregates [3]. These mechanisms may act in combination and may differ between patients who exhibit single

episodes of IVIG-associated neutropenia (more likely associated with transient causes or specific preparations of IVIG), as compared to recurrent IVIG-associated neutropenia, which may represent neutrophil margination or non-specific antibody-based clearance. The role of baseline ANC in the development of IVIG-related neutropenia is not entirely clear and likely depends on the underlying mechanism. Although previous studies suggest there is not a strong correlation between baseline ANC and the risk of neutropenia, documenting a pre-IVIG baseline ANC and monitoring ANC levels over the first one or two treatment cycles could be clinically useful. Such monitoring would help identify patients at risk of developing neutropenia and assess dose-dependent IVIG-induced neutropenia. In our case, more significant neutropenia emerged after escalating the IVIG dose and shortening the interval between treatments, suggesting a dose-dependent effect. Additionally, repeated doses at short intervals likely contributed to the failure to recover neutrophil counts fully before each subsequent cycle.

Our case highlights the clinical presentation of IVIG-induced neutropenia, which should be considered in neutropenic patients on IVIG. Our case underscores the importance of obtaining a complete blood count with differential before starting IVIG and with dose escalations. In most cases, IVIG-induced neutropenia has a benign clinical course with a low rate of infectious complications. Subcutaneous preparations of immunoglobulins may have a lower rate of IVIG-induced neutropenia and should be explored in future studies [14].

Author Contributions

Shannon Ugarte and Daria V. Babushok analyzed the clinical data and wrote the manuscript. Talia Gebhard analyzed clinical data, performed a literature review, and revised the manuscript. David R. Cornblath and Steven S. Scherer critically reviewed and edited the manuscript. All authors approved the final manuscript.

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Conflicts of Interest

David R. Cornblath: Consultant for Grifols S.A., Octapharma AG, Pfizer Inc. Data Safety Monitoring Board for Sanofi. The rest of the authors declare no conflicts of interest.

Data Availability Statement

All of the relevant data are included within the case description.

Ethics Statement

Not applicable.

Informed Consent

Informed consent with a signed consent-to-disclose form was obtained from the patient in this case report. Permission has been granted to include all relevant clinical details in the manuscript.

Clinical Trial Registration

Not applicable.

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