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Agranulocytosis following intravenous immunoglobulin administration in a patient with Guillain-Barré Syndrome triggered by COVID-19: A case report

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Abstract

Neutropenia during recovery after coronavirus disease 2019 (COVID-19), as well as neutropenia after intravenous immunoglobulin (IVIG) administration are very rare hematological abnormalities. We report the first case of agranulocytosis following IVIG administration in patients with Guillain-Barre syndrome (GBS) triggered by COVID-19. A 62-year-old female patient was admitted to the Emergency Department due to progressive limb weakness and sensory disturbances that began two weeks before admission. Five weeks before admission she was treated for COVID-19 and has fully recovered. She was diagnosed with Guillain-Barre syndrome (GBS), and treatment with IVIG was started. Twenty hours after the first dose of IVIG, blood analysis showed neutropenia and thrombocytopenia, and after the fifth dose she developed agranulocytosis followed by mild increase in body temperature. Granulocyte colony-stimulating factor (G-CSF) was administered and after 12 hours the leukocyte lineage recovered. According to the previous findings, neutropenia after IVIG administration might be related to CD11b, and COVID-19 is associated with an increase in immature neutrophil populations in the later stages of the disease defined by their expression of CD11b. Meanwhile, some finding suggests that corticosteroid pretreatment prevent neutropenia after IVIG administration, which might be important because many patients with post-COVID GBS have been treated with corticosteroids for COVID-19.

Keywords: COVID-19, Guillain-Barre syndrome, neutropenia, agranulocytosis, intravenous immunoglobulin, case report

INTRODUCTION

Neutropenia during recovery after coronavirus disease 2019 (COVID-19), as well as neutropenia after intravenous immunoglobulin (IVIG) administration are very rare hematological abnormalities.[1-8] We report the first case of agranulocytosis following IVIG administration in patients with Guillain-Barre syndrome (GBS) triggered by COVID-19.

CASE REPORT

A 62-year-old female was admitted to the Emergency Department due to progressive walking difficulties, muscle pain and paresthesias in the lower limbs that began two weeks before admission. In her previous medical history, she had well-controlled hypertension. Five weeks before her current hospitalization, she was diagnosed with COVID-19, and she fully recovered after two weeks.

At admission, muscle strength was globally reduced (proximal upper limbs, MRC scale grade 4/5; proximal lower limbs, 4/5; distal upper limbs, 4/5;distal lower limbs, 4/5); reflexes on the upper and lower extremities were absent; muscle tone was preserved; she had dysesthesia and allodynia in her soles and palms; gait was slightly slow. Functional disability measured by GBS Disability Scale (GDS) was 3. The systemic finding was normal.

Initial laboratory values, including blood count, sedimentation, biochemical blood analysis, vitamin B12, folate, screening for hemostasis and thyroid hormonal status, were normal. Tumor markers (AFP, Ca 125, Ca 15-3, Ca 19-9, Ca 72-4, CEA, CYFRA, and NSE) were all in the reference range. There was no Bence Johnson proteins in

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urine. Serological test showed the absence of IgM antibodies against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), while IgG antibodies were present. Virological (HIV, cytomegalovirus, Epstein-Barr virus, hepatitis B and C) and immunological (ANA, ANCA) serum analyzes were in the reference range. Serum and urine protein electrophoresis and immunofixation were normal. Throat and nose swabs, urine culture and blood culture repeated during hospitalization were sterile. Lung X-ray and abdominal ultrasound were normal. Nerve conduction study showed the presence of symmetrical, predominantly motor, axonal-demyelinating polyneuropathy (Table 1).

On the day of admission, treatment with IVIG at a dose of 0.4 mg/kg/daily was started. Twenty hours after the first dose of IVIG, blood analysis showed neutropenia and thrombocytopenia, and after the fifth dose she developed agranulocytosis followed by subfebrility (Table 2). Hematologist was consulted, granulocyte colony-stimulating factor (G-CSF) was administered and after 12 hours the leukocyte recovered (Table 2). A bone marrow aspirate was not performed because the patient refused the procedure. After eight days of hospitalization, patient was discharged. On neurological examination she still had mild globally reduced muscle strength at proximal and distal lower limbs and parestesia, GDS 2. Two month later she was without subjective complaints, while neurological examination except for the reduced reflexes, was normal, GDS 0. Informed consent was obtained from patient to use anonymous data in scientific publications.

DISCUSSION

Our patient with a clinical presentation of GBS after COVID-19 developed agranulocytosis as a rare complication following IVIG administration.

Only a few cases of neutropenia have been reported in patients during recovery after COVID-19.[1-5,8] Currently, it is unknown what are the possible mechanisms of COVID-19 associated

Table 1: Nerve conduction study of the patient (22nd day of illness)

Nerve	CMAP latency (ms)	CMAP amplitude (mV)	MCV (m/s)	Sensory onset latency (ms)	SNAP amplitude (μV)	SCV (m/s)	Mean F-latency (ms)
Right median							
Wrist	4.1*	1.9*		2.6	23.0	51.9	31.4
Elbow	8.3*	1.9*	57.1				
Right ulnar							
Wrist	3.0	5.8					30.3
Below elbow	7.1	4.6	54.2				
Above elbow	8.5	4.4	51.9				
Fourth finger				2.4	11.0	50.0	
Right peroneal							
Ankle	3.9	2.8*					NR
Fibula Head	14.2	0.4*	32.0*				
Knee	15.2	1.2*	66.7				
Left peroneal							
Ankle	3.9	3.4*					NR
Fibula Head	10.6	0.2*	51.1*				
Knee	13.2	0.9*	38.5*				
Right tibial							
Ankle	5.7	2.5*					NR
Knee	15.8	1.6*	34.0*				
Left tibial							
Ankle	5.3	3.1*					NR
Knee	14.9	1.3*	37.0*				
Right sural				2.6	15.4	52.8	
Left sural				2.9	11.1	48.3	

CMAP= compound muscle action potential; MCV= motor conduction velocity; SNAP= sensory nerve action potential; SCV= sensory conduction velocity; NR= no response; *abnormal values

Table 2: Laboratory parameters by day of IVIG

	WBC, n x 10^9/L (3.4-9.7)†	Ne, n x 10^9/L (2.1 - 6.5)†	Ly, n x10^9/L (1.2 - 3.4)†	RBC, n x 10^{12}/L (3.86 - 5.08)†	PLT, n x 10^9/L (158.0 - 424.0)†
Five weeks before admission (SRAS-CoV-2 positive)	**2.5**	**1.3**	**0.8**	4.2	**120**
Three weeks before admission	6.3	4.0	1.7	4.69	251
Admission day (first day of IVIG)	6.1	3.3	2.1	4.67	180
Day 2	**3.3**	**1.6**	1.3	4.04	**110**
Day 3	**2.6**	**0.8**	1.4	4.3	**124**
Day 4	**2.5**	**0.8**	1.3	4.45	**121**
Day 5 (fifth day of IVIG)	**1.9**	**0.5**	**1.0**	4.3	**109**
Day 6 (G-CSF administration)	**1.9**	**0.4**	**1.0**	4.39	**99**
Day 7	6.6	4.8	1.3	4.48	**92**
Day 8 (discharge)	16.6	12.7	1.8	4.38	**110**

WBC-white blood cell count; Ne- neutrophils; Ly- lymphocytes; RBC- red blood cells; PLT-platelets; SRAS-CoV-2-severe acute respiratory syndrome coronavirus 2
Values are presented as absolute counts; † range of normal values

neutropenia. Given the significant time latency from the first respiratory problems considering that the patient was already without symptoms related to COVID-19, with negative IgM and positive IgG antibodies, it is unlikely that direct effect of SARS-CoV-2 is primary cause of neutropenia. Immune-mediated neutropenia is also unlikely given a rapid and stable response to a single dose of G-CSF. It should be emphasized that no other infection was identified, as well as other immune or paraneoplastic disorders. Although bone marrow aspiration was not performed, as white cell recovery was rapid and stable over time only after a single dose of G-CSF, the primary disorder at the hematopoietic level was unlikely. The question remains about the possible combined effect of COVID-19 and the actions of IVIG.

The exact mechanism for the development of neutropenia after IVIG has not been fully clarified. According to some authors, neutrophils migrate into the vascular wall after complement activation, and the other mechanism would be neutropenia induced by antibodies contained in IVIG preparations.[6,7,9] Matsuda *et al*. reported that neutropenia after IVIG administration might be related to CD11b, as they found decreased CD11b expression in parallel with a decrease in white blood cells and neutrophils in these patients.[6] They concluded that CD11b could be involved in the adherence of circulating neutrophils to the vascular wall.[6] Meanwhile, COVID-19 is associated with an increase in immature neutrophil populations at later stages of the disease, among others, by their expression of CD11b.[10] Furthermore, one previously published study showed a downregulation of neutrophil CD11b during acute COVID-19, with its upregulation 28 days after COVID-19.[11] Matsuda *et al*. also noted the protective value of corticosteroid pretreatment in preventing neutropenia after IVIG administration,[6] which might be important because many patients with post-COVID GBS have been previously treated with corticosteroids for COVID-19. However, our patient had a mild COVID-19 and was not treated with corticosteroids. Mild thrombocytopenia after IVIG administration observed in our patients has also been described in immune-mediated neurological diseases.[6]

The reasons for the introduction of G-CSF in our case were neutrophils less than $0.5x10^9$, mild increase in body temperature, to shorten the period of severe neutropenia and preventing possible bacterial infections. Our patient had rapid and stable response after a single dose of G-CSF. Nevertheless, some researchers question the necessity of G-CSF use since the recovery of neutrophils (especially after the administration of

IVIG) is usually fast and without complications[6], thus clinician should weight benefit and cost of such therapy.

In conclusion, our patient with a clinical presentation of GBS after COVID-19 developed agranulocytosis as a rare complication following IVIG administration. Observations from further studies is needed to clarify to what extent IVIG and COVID-19 contribute to the development of neutropenia or whether it is a combined effect.

DISCLOSURE

Availability of data and material: Additional data that support the findings of this study are available on request from the corresponding author.

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