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CASE REPORT

IVIG-induced Aseptic Meningitis in an Adult Patient With Acute Inflammatory Demyelinating Polyneuropathy: A Case Report and Literature Review

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Abstract

Intravenous immunoglobulins (IVIG) therapy is used to treat various autoimmune, immunodeficiency, and inflammatory conditions. One of the rare, but serious, side effects is aseptic meningitis. In this case report, we present a 55-year-old female who experienced IVIG-induced aseptic meningitis for treatment of acute inflammatory demyelinating polyneuropathy (AIDP).

Keywords: Intravenous immunoglobulins (IVIG), Aseptic meningitis, Acute inflammatory demyelinating polyneuropathy (AIDP)

1. Introduction

Intravenous immunoglobulins (IVIG) are a composite blood product of serum proteins from human donors which consists mainly of IgG, but also contains IgM, IgA, and albumins.[1] It is used to treat various autoimmune, immunodeficiency, and inflammatory conditions, often acting as a replacement in a deficient patient or an immunomodulator for conditions such as acute inflammatory demyelinating polyneuropathy (AIDP), chronic inflammatory demyelinating polyneuropathy (CIDP), thrombocytopenic purpura (ITP), systemic lupus erythematosus (SLE), and many others.

Adverse effects of IVIG are generally mild and transient, occurring in as many as 81% of IVIG infusions, however there is significant variability in the reports of the incidence of adverse effects with most noting occurrence in about 40%.[1,16] Immediate adverse effects include fever, headache, chills, flushing, nausea, vomiting, diarrhea, myalgia, back pain, chest tightness, dyspnea, tachycardia, and anaphylaxis, which generally is associated with IgA-deficient patients.[3] Fever and headache are generally the most common.[1] Delayed adverse effects, which occur between 6 h and 1 week, are generally more severe.[1] These include renal failure, thromboembolic events, autoimmune hemolytic anemia, neutropenia, skin reactions, arthritis, and aseptic meningitis.[1,3] The rate of infusion can contribute to increased risk of adverse effects and slowing the rate of the infusion may provide treatment in some cases.[1,3] Adverse effects may require only symptomatic treatment with agents such as non-steroidal anti-inflammatory drugs, antihistamines, or glucocorticoids, however in some cases, such as cases of aseptic meningitis, discontinuation of the infusion may be required.[3]

Drug-induced aseptic meningitis is a known but unusual complication of intravenous immunoglobulin (IVIG) therapy. This adverse reaction to IVIG therapy was first reported in 1988.[8] As Kretowska-Grunwald et al. noted in April 2022, only 44 cases of IVIG-induced aseptic meningitis had been

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documented in the English-language literature,[1] among which only 2 cases were in the setting of inflammatory demyelinating polyneuropathy.

2. Case presentation

We present a 55-year-old female with a past medical history of chronic low back pain, depression, gastric bypass, and nephrolithiasis, who presented to the emergency department with a chief complaint of acute bilateral lower extremity weakness. She endorsed 2 days of bilateral lower extremity ascending paresthesia and tingling, followed by bilateral lower extremity weakness, noted to be worse in the left leg than the right. She also endorsed chronic low back pain radiating up to the thoracic area which she described as intermittent and aching for over 6 months and significantly worsened over the past few days prior to presentation. Additionally, she reported sore throat and intermittent fever in the last few weeks prior to presentation, however she denied headache and neck stiffness. She denied any history of illicit drug use, recent sick contact or vaccination, previous similar episodes, and any autoimmune or neurological conditions. Her family history was positive for lupus in her sister and niece. Physical examination showed tenderness overlying the T8 vertebra and extending caudally, 3/5 strength in the left lower extremity, 4/5 strength in the right lower extremity, persevered strength in the bilateral upper extremities, diminished sensation of the entire left lower extremity, diminished sensation of the right lower extremity to the knee, and absent patellar and Achilles reflexes bilaterally.

Initial work up consisted of a comprehensive metabolic panel, complete blood count with differential, erythrocyte sedimentation rate, C-reactive protein, thyroid stimulating hormone, and viral panel including COVID-19 and Influenza testing, which all returned within normal limits. The patient underwent MRI with and without contrast of the entire spine which revealed multilevel moderate to severe degenerative disc changes but no evidence of spinal cord compression or enhancement. A lumbar puncture was performed with 4 vials of clear cerebrospinal fluid collected and sent for analysis, which included culture, cell count with differential, glucose, protein, and West Nile virus PCR. Cerebrospinal fluid results showed 0 to 0 total nucleated cells with 8 to 1 RBCs from vial 1 to 4, respectively. Glucose and protein were within normal limits as well at 57 mg/dl and 32 mg/dl, respectively. West Nile PCR, Gram stain and culture all returned negative.

Given the constellation of the patient's symptoms, neurology consultation was prompted with high concerns of AIDP. Therefore, treatment with IVIG was recommended. The patient completed 4 days of treatment with IVIG. On day 4 of treatment, the patient was noted to have headache, neck stiffness, and chills. After neurology assessment, there was concern for aseptic meningitis from IVIG. Therefore, the treatment was stopped, and a repeat lumbar puncture was performed revealing 129/mm^3 total nucleated cells with 77% lymphocytes, 56/mm^3 RBCs, glucose 52 mg/dl, and protein 35 mg/dl. Pathology review revealed small mature lymphocytes. An extensive infectious workup was performed including CSF PCR for *Escherichia coli* K1, *Haemophilus influenzae*, *Listeria monocytogenes*, *Neisseria meningitidis*, *Streptococcus agalactiae*, *Streptococcus pneumoniae*, Cytomegalovirus, Enterovirus, Herpes simplex virus 1 and 2, Human Herpesvirus 6, Varicella Zoster virus, and *Cryptococcus neoformans*/gattii, which all returned negative. In addition, Gram stain and culture, and Lyme (*Borrelia burgdorferi*) serologies were negative. With the return of the above findings, a diagnosis of aseptic meningitis induced by IVIG was made with the collaboration of a multidisciplinary team which included neurology and infectious diseases. In addition to IVIG discontinuation, supportive care was started with adequate hydration and symptomatic management with improvement of her symptoms over the following days and she was subsequently discharged to a rehabilitation facility.

3. Discussion

In this case report we describe a patient who developed aseptic meningitis due to IVIG infusion. Although this is a known complication of treatment with IVIG, the incidence remains uncommon, generally between 0 and 1% with one single study noting incidence up to 11% with high dose administration,[4,10] and timely identification is of utmost importance as the clinical presentation of aseptic meningitis is very similar to other types of meningitis and require immediate cessation of the offending agent. Patients generally present with complaints including fever, headache, neck stiffness, and altered mentation. Diagnosis requires lumbar puncture with cerebrospinal fluid analysis to rule out infectious etiologies.

A notable temporal relationship existed in this case between IVIG administration and onset of symptoms. Typically, the onset of symptoms occurs between 6 and 48 h, however in this case were observed at about 4 days after the initial infusion.[5]

While many cases of aseptic meningitis are reported to occur within 48 h of IVIG administration, Kubota et al. noted that the median occurrence of adverse effects with IVIG administration was 3 days in their study of pediatric patients.[9] Similarly, Ventura et al. noted a case of a 26-year-old female treated with IVIG for recalcitrant pemphigus vulgaris who developed aseptic meningitis on day 3 of therapy.[6]

A comparison of the various cases of IVIG-induced aseptic meningitis is shown in Table 1. In this comparison it is evident that while most cases of aseptic meningitis are diagnosed within 48 h of IVIG

Table 1. Comparison of reported cases of IVIG-induced aseptic meningitis.

Case	Age (in years)	Gender	IVIG Indication	Time of symptom onset after initiation of IVIG
1[a]	55	F	AIDP	4 days
2[1]	6	M	ITP	10 h after last dose
3[1,6]	9	M	ITP	12 h after last dose
4[1]	4	M	ITP	2nd day
5[1]	4	M	ITP	2nd day
6[1]	25	F	ITP	Evening of 3rd day
7[1]	26	F	ITP	3rd day
8[1]	26	F	Recalcitrant pemphigus vulgaris	3rd day
9[1,5]	14	F	ITP	2 days after last infusion
10[1]	7	M	ITP	3rd day
11[1,10]	40	M	Polymyositis	Within 24 h after infusion
12[1,10]	7	M	Dystrophy	Within 24 h after infusion
13[1,10]	37	M	Multifocal motor neuropathy with conduction block	Within 24 h after infusion
14[1,10]	61	F	Paraproteinemic polyneuropathy	Within 24 h after infusion
15[1,10]	48	F	Dermatomyositis	Within 24 h after infusion
16[1]	27	F	ITP	3rd day
17[1,8]	2	F	ITP	7 days
18[1]	7	M	ITP	1 h after 2nd dose
19[1]	10	M	ITP	At the beginning of the 2nd dose
20[1]	62	F	CIDP	5th day
21[1]	44	F	ITP	2nd day
22[1]	10	F	ITP	10 h after 2nd infusion
23[1]	6	F	ITP	12 h after 2nd infusion
24[1]	9	M	Kawasaki syndrome	10 h after last infusion
25[1]	2		Acquired immune neutropenia	During 2nd infusion
26[1]	7	M	ITP	12 h after 2nd infusion
27[1]	8	M	ITP	During 3rd infusion
28[1]	42	F	SLE with renal failure	2 days
29[1,18]	6	F	Kawasaki disease	Within 40 h of infusion
30[1,18]	7	F	Kawasaki disease	Within 25 h of infusion
31[1,18]	10	F	Kawasaki disease	Within 31 h of infusion
32[1,18]	1	M	Kawasaki disease	Within 33 h of infusion
33[1]	10	M	CVID	10 days after last infusion
34[1,13]	14	M	GBS	4th day
35[1,4]	77	F	ITP	1st day
36[1,4]	35	F	ITP	1st day
37[1,4]	4	M	ITP	Within 2 h of infusion
38[1,4]	49	M	CIDP	1 day after 3rd dose
39[1,4]	20	M	WAIHA	1st day
40[1,4]	80	F	ITP	1st day
41[1,4]	25	F	Primary immune deficiency	3 days after last infusion
42[1,4]	18	F	Myasthenia gravis	Within 1–2 days of infusion
43[1]	31	M	ESKD	<24 h after last infusion
44[1]	46	F	SLE	36 h after 1st infusion
45[1]	4	M	Acute EBV infection	6 h after 2nd infusion
46[4]	40	M	ITP	2 h
47[19]	47	F	Dermatomyositis	<48 h after last dose

F = female, M = male, ITP = immune thrombocytopenia, CIDP = chronic inflammatory demyelinating polyneuropathy, WAIHA = warm autoimmune hemolytic anemia, CVID = common variable immunodeficiency, GBS = Guillain-Barre syndrome, SLE = systemic lupus erythematosus, ESKD = end-stage kidney disease.

[a] The patient in this case report.

Table 2. Comparison of reported cases of IVIG-induced aseptic meningitis in patients treated for AIDP.

Case	Age (in years)	Gender	IVIG Indication	Symptoms	CSF WBC count (/mm^3)	CSF cytosis	Time of symptom onset after initiation of IVIG	Treatment
1[a]	55	F	AIDP	Headache, neck stiffness, chills	129	77% lymphocytes	4th day	Hydration and symptomatic care
2[13]	14	M	GBS	Headache, neck pain, vomiting	1800	85% lymphocytes	4th day	Hydration and analgesics

[a] The patient in this case report.

administration, cases can present even up to 5–7 days later. It is also important to note that acute onset of aseptic meningitis can present even in patients who have previously received IVIG without complications or adverse reactions.

A comparison of the 2 cases of AIDP in the prior table is shown in Table 2. While the patients were quite different in terms of age and gender, their presentation was very similar in terms of symptoms and time of onset, with both occurring 4 days after IVIG administration. As well, they were treated identically with only hydration and symptomatic care.

Remission of symptoms generally occurs 48–72 h after discontinuation of IVIG.[1,5,13] Multiple different CSF analyses have been reported in IVIG-induced aseptic meningitis. CSF analysis generally demonstrates neutrophil-predominant (60–80%) leukocytosis (50–2500 leukocytes/mm3), however lymphocyte-predominant leukocytosis or eosinophilia may be seen.[1,7,14,18] The risk of developing aseptic meningitis is potentially increased with higher dosing, increased speed of administration, dehydration, and elevated total proteins. Kubota et al. found a significant relation between total serum protein above 6.7 g/dl and the incidence of aseptic meningitis with IVIG infusion.[9] IVIG has been shown to cause an elevation of serum protein which is thought to cause hyper viscosity of the blood and could be considered an additional risk factor for development of aseptic meningitis with IVIG therapy.[1,9,12,17] As Scribner et al. report that a history of migraines also appears to increase risk of developing aseptic meningitis with IVIG.[10] There are multiple mechanisms that have been theorized to explain the pathophysiology of IVIG-induced aseptic meningitis. Immune-complex mediated and cell-mediated, or type III and type IV respectively, hypersensitivity reactions, and cerebrovascular sensitivity or irritation either directly by the drug or indirectly via cytokine release have all been speculated as possible mechanisms.[1,10,13,15] Asano et al. showed an increased level of monocyte chemoattractant protein-1 (MCP-1) present in patients diagnosed with IVIG-induced aseptic meningitis suggesting activation of monocytes is involved.[11]

Treatment involves discontinuation of IVIG treatment and supportive therapy. Generally, it is recommended that patients maintain adequate hydration, which may be beneficial both prophylactically and therapeutically given evidence of increased total protein with IVIG administration.[16] In some cases, NSAIDs, steroids or antihistamines may be considered, given the postulation that symptoms are a result of a hypersensitivity reaction.

Patients that have experienced IVIG-induced aseptic meningitis are at risk for recurrence if exposed again, however adequate hydration status, slower infusion rate, changing of the IVIG formulation, or subcutaneous administration which prolongs absorption time may possibly prevent or minimize this risk.[1-3] Generally, the prognosis of patients that experience aseptic meningitis is very good, however a significant portion of patients may have prolonged neuropsychological symptoms. These symptoms can include mental fatigue due to decreased psychomotor speed and impaired executive and visuoconstructive functions.[20,21]

4. Conclusion

In summary, IVIG-induced aseptic meningitis is a known, but relatively rare, adverse effect that must be included in the differential diagnosis if a patient develops symptoms consistent with meningitis during or after treatment. The investigations should include lumbar puncture to rule out infectious etiology first and foremost. CSF analysis generally shows a neutrophil-predominance however this is not sensitive nor specific. Clinicians should have a high index of suspicion for such a complication as identification may warrant immediate discontinuation of IVIG treatment. In most cases, the prognosis is very good, and the symptoms are self-limited with conservative treatment.

Disclaimers

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Conflict of interest

None.

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