Immunoglobulin-Induced Aseptic Meningitis in Juvenile Dermatomyositis: A Case Report

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Aseptic meningitis is a known but unusual serious adverse effect of intravenous immunoglobulin (IVIG). It usually resembles infectious meningitis, which makes its diagnosis challenging. In this report, we present the case of a five-and-a-half-year-old Chinese girl with juvenile dermatomyositis (JDM) who presented with signs of meningismus 21 hours after the initiation of IVIG infusion. Her blood work at diagnosis showed neutrophilia and lymphopenia. The cerebrospinal fluid (CSF) analysis demonstrated neutrophilic pleocytosis, hyperproteinorrachia, and normoglycorrhachia. All microbiological tests were negative. The child fully recovered within 72 hours without neurological sequelae. IVIG-induced aseptic meningitis remains a diagnosis of exclusion. Although it is rare, pediatricians should be aware of this complication and avoid unnecessary investigations or treatment.

Introduction

Aseptic meningitis is a known severe adverse effect of immunoglobulin. It is rare and usually resembles infectious meningitis, which makes its diagnosis challenging. Its causes are either infectious or non-infectious (also called aseptic), consisting of autoimmune, neoplasia, and iatrogenic etiologies [1].

Intravenous immunoglobulin (IVIG) is widely used for a broad range of diseases, including immunodeficiencies, neuromuscular diseases, and autoimmune diseases. The treatment of juvenile dermatomyositis (JDM) with IVIG is generally considered effective as a second-line option, particularly for steroid-resistant patients or those with predominant skin activity [2-4]. A retrospective JDM cohort in 2011 demonstrated IVIG efficacy in controlling disease activity [5]. We discuss the case of a five-and-a-half-year-old girl with JDM, who experienced no adverse events with initial IVIG (Intragam P) administration, but subsequently developed aseptic meningitis after switching to another formulary IVIG (Privigen). The possible risk factors for developing aseptic meningitis are also discussed.

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Case Presentation

Our patient was a Chinese girl who initially presented with proximal muscle weakness and limping gait at four years of age. She also demonstrated dermatological features including heliotrope rash over the facial region and Gottron papules over her metacarpophalangeal and interphalangeal joints with cutaneous ulcerations. She had raised serum creatine kinase up to 3900 IU/L, and her MRI showed features of myositis over her bilateral shoulders, arms, and thigh muscles. She was given the diagnosis of JDM. Her Childhood Myositis Assessment Scale (CMAS) score (see the CMAS score sheet, Figure 1, in appendices) was 5/52 points (Table 1).
Maneuver | Patient score
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1. Head elevation (neck flexion) | 1: 1–9 seconds
2. Leg raise/touch object | 0: unable to lift the leg off the table
3. Straight leg lift/duration | 0: unable
4. Supine to prone | 1: turns onto the side fairly easily, but cannot fully free arms and is not able to fully assume a prone position
5. Sit-ups | 0: unable
6. Supine to sit | 0: unable
7. Arm raise/straighten | 1: can raise wrists at least up to the level of the acromioclavicular joint but not above the top of the head
8. Arm raise/duration | 1: 1–9 seconds
9. Floor sit | 0: unable, afraid to even try
10. All-fours maneuver | 0: unable to go from a prone to an all-fours position
11. Floor rise | 0: unable, even if allowed to use a chair for support
12. Chair rises | 0: unable to rise from the chair, even if allowed to place hands on sides of the chair
13. Stool step | 1: much difficulty. Able, but needs to place one hand on the exam table
14. Pick-up | 0: unable to bend over and pick up a pencil off the floor

**TABLE 1: Childhood Myositis Assessment Scale (CMAS) score**

The patient was initially treated with intravenous methylprednisolone, subcutaneous methotrexate, and six doses of monthly IVIG (Intragam P) at presentation. The IVIG was administered at a dosage of 1 gram/kg (total of 15 grams in the volume of 250 ml) over nine hours each day for two consecutive days. She had no adverse reaction to the medication. She responded well to treatment and her muscle power improved with a CMAS of 45 out of 52 four months later. Her steroid was gradually tapered down, but she developed worsening vasculitis with necrotic lesions and chondritis over both ears. Her skin condition remained refractory despite increasing the steroid and methotrexate dosage, as well as adding oral cyclosporin A. Cyclosporin A was subsequently switched to oral cyclophosphamide. Two days after the switch, IVIG was given additionally to optimize the control of her skin activity at the age of five-and-a-half years. Due to a change in our hospital drug formulary, the patient received Privigen instead. She was given 2 grams/kg (total of 32.5 grams in the volume of 325 ml), which was infused over 11 hours.

She was asymptomatic during the infusion but developed a high fever with a temperature of 40 ºC, headache, and repeated vomiting 10 hours after the completion of the injection. She also complained of neck pain and photophobia. There was no seizure, altered state of consciousness, or abnormal behavior. Physical examination demonstrated meningismus with neck stiffness and positive Kernig sign. There was no other focal neurological deficit.

Her blood tests (Table 2) showed an elevated white cell count at 24 x 10^9/L with neutrophilia (absolute neutrophil count: 17.5 x 10^9/L), but normal C-reactive protein (<0.7 mg/L) and serum procalcitonin level (0.14 ng/ml). The CT of the brain was normal. The cerebrospinal fluid (CSF) was clear and colorless. Its analysis demonstrated neutrophilic pleocytosis with 2188 cells/mm³ (87% neutrophils) without eosinophils, hyperproteinorrachia (0.66 g/L), and normoglycorrhachia (2.9 mmol/L in CSF and 4.7 mmol/L in plasma). She was initially treated with an intravenous meningitic dose of meropenem and acyclovir. Meropenem was chosen because of the abundance of extended-spectrum beta-lactamase-producing Enterobacteriaceae (ESBL-E) in the Hong Kong community [6]. The cultures from her blood sample and CSF did not isolate any causative organisms.
A lumbar puncture was repeated on day six and CSF analysis revealed a white cell count of 11 cells/mm$^3$ with 9% polymorphs, normal protein (0.19 g/L), and normal glucose levels (3.6 mmol/L in CSF and 5.3 mmol/L in plasma) (Table 2). The patient completed a 14-day course of meropenem. Based on the temporal relation between IVIG administration and the symptoms onset, sterile cultures, as well as the normal C-reactive protein and procalcitonin levels, a diagnosis of aseptic meningitis was made.

Her symptoms and fever subsided on day two of admission, and she recovered completely without any neurological sequelae.

### Discussion

IVIG-induced aseptic meningitis is a rare complication, with an estimated incidence of 0.6-1% [7]. Apart from being used in the treatment of immune thrombocytopenia (ITP), IVIGs are also being given to patients as a treatment for various autoimmune and inflammatory diseases such as Kawasaki disease, Guillain-Barre syndrome, and chronic inflammatory demyelinating polyneuropathy. The exact pathophysiology of IVIG-induced aseptic meningitis remains unclear, with postulated mechanisms including direct toxic effect and immunological hypersensitive reaction [8].
Our patient did have the typical features of IVIG-associated aseptic meningitis described in the literature (Table 3) [7,9]. Firstly, there was a temporal relationship between the onset of the symptoms of aseptic meningitis and high-dose IVIG therapy. Secondly, the symptoms and signs of meningismus quickly resolved within 48 hours in our patient. Thirdly, although the initial bloodwork revealed leukocytosis and neutrophilia, and the CSF analysis showed neutrophilic pleocytosis, all cultures were negative. All these fit into the picture of aseptic meningitis induced by IVIG as described by Bharath et al. and Kemmotsu et al.

| Symptoms | IVG-induced aseptic meningitis |
|----------|--------------------------------|
| Headache, vomiting, photophobia, and fever | Headache, vomiting, photophobia, and fever |
| Nuchal rigidity, positive Kernig sign without focal neurological sign | Nuchal rigidity, positive Kernig sign without focal neurological sign |

**CSF Leukocytes/mm³**

- 500–10,000
- 100–2000

**Main leukocyte type**

- Neutrophils

**Other criteria**

- Bacteria in CSF
- Sterile CSF; temporal relationship with IVIG infusion

**Management**

- Antibiotics
- Drug discontinuation; symptomatic treatment

**Time to regression**

- 7–21 days
- Within 2–3 days

Evidence concerning both patient and IVIG-related risk factors remains controversial. It has been suggested that a history of migraines, female sex, and underlying connective tissue disease such as systemic lupus erythematosus could be potential risk factors for developing aseptic meningitis following IVIG administration [10-12]. Further evidence is needed to evaluate whether JDM could also be a risk factor.

It is important to note that this was not the first time our patient had received IVIG. She developed aseptic meningitis after IVIG therapy was given at a higher dose (2 grams/kg) and faster rate (over 11 hours). Besides, our patient received a different brand of IVIG (Privigen) from her previous IVIG infusions (Intragam P) prior to the incidence of aseptic meningitis. Regarding IVIG-related risk factors, fast infusion rate and high initial dosage of IVIGs are thought to be risk factors for developing aseptic meningitis, but it is not always the case (Table 4). There is no concrete evidence as to whether different IVIG brands have various potentials in causing aseptic meningitis. It was thought that IgA concentration might be related. The administration of IVIG containing IgA may cause dramatic clinical reactions in patients with serum anti-IgA [1,13]. The IgA contents in both Privigen and Intragam were not specified, with Privigen stating a maximum of 0.025 mg/ml and Intragam P reporting <0.025 mg/ml (Table 5). Although 50% of patients developed aseptic meningitis after Privigen infusion in Bharath et al.’s retrospective study, due to the small number of patients, the brands of IVIG or varying commercial preparations have not been identified as risk factors.

**TABLE 3: Typical symptoms and signs of IVIG-induced aseptic meningitis**

| Source                     | Number of patients | Diagnosis                        | Age (years) | IVIG dose | IVIG duration (hours) | Brand           | Onset                   | WBC × 10⁹/L, CSF | CSF cytosis | Treatment                              | Time to recovery |
|----------------------------|--------------------|----------------------------------|-------------|-----------|-----------------------|----------------|-------------------------|----------------|-------------|----------------------------------------|------------------|
| Rao et al. [14]            | 1                  | Idiopathic thrombocytopenic purpura | 9           | 0.4 g/kg  | 4                     | Sandoglobulin  | 12 hours after the last dose | 2.5           | 98%         | Prednisone 2 mg/kg for 4 days          | 48 hours         |
| Mitterer et al. [15]       | 1                  | Idiopathic thrombocytopenic purpura | 4           | 0.4 g/kg  | Non-specified         | Sandoglobulin  | Second day               | 2             | 67%         | Self-limiting                          | 2 days           |
| Chaabane et al. [16]       | 1                  | Idiopathic thrombocytopenic purpura | 14          | 0.4 g/kg  | Non-specified         | Non-specified  | 2 days after the last infusion | 0.14          | 70%         | Floctafenine                           | 3 days           |
| Casteel-Van et al. [17]    | 1                  | Idiopathic thrombocytopenic purpura | 7           | 0.4 g/kg  | 11                    | Sandoglobulin  | Third day                | Non-specified  | Non-specified | Non-specified Non-specified Non-specified  | Non-specified  |
| Sekul et al.               | 1                  | Dystrophy                        | 7           | 2 g/kg    | Non-specified         | Non-specified  | Within 24 hours           | 0.22          | 85%         | Narcotic analgesics and                 | 3–5 days         |

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| No. | Author(s) [Ref] | Disease | Age/Weight | Treatment | Duration | Course | Meds and Dose | Outcome | Notes |
|-----|----------------|---------|------------|-----------|----------|--------|---------------|---------|-------|
| 6   | Kato et al. [19] | Idiopathic thrombocytopenic purpura | 2 | 0.4 g/kg/day for 5 days | Non-specified | Prepared with PEG | 7 days after therapy | 0.45 | 9% | Self-limiting | 1 day |
| 7   | Casteels-Van et al. [20] | Idiopathic thrombocytopenic purpura | 7 | 0.4 g/kg for 5 days | 11 | Sandoglobulin | 1 hour after the completion of the second dose | 2.45 | 89% | Self-limiting | 1 day |
| 8   | Casteels-Van et al. [20] | Idiopathic thrombocytopenic purpura | 10 | 1 g/kg | 6 | Sandoglobulin | At the beginning of the second dose | 2.86 | 97% | Cefotaxime for 72 hours | 2 days |
| 9   | Otando et al. [22] | Idiopathic thrombocytopenic purpura | 6–10 | 1 g/kg/day for 2 days | 8–12 | Pategoma | 10–12 hours after the second infusion | 0.85–7.44 | 60–98% | Cefotaxime for <48 hours, analgesics | 24–48 hours |
| 10  | Boyer and Spesman [23] | Kawasaki syndrome | 9 | 2 g/kg | 14 | Polypam | 10 hours after the last infusion | 1.515 | 99% | Cefotaxime for 72 hours | 5 days |
| 11  | Peinger-Stapko et al. [24] | Acquired immune neutropenia | 2 | 1 g/kg/day for 4 days | Non-specified | Sandoglobulin | During the second infusion | 3.5 | 90% | Self-limiting | 24 hours |
| 12  | Kesselbach et al. [25] | Idiopathic thrombocytopenic purpura | 7–8 | 0.4 g/kg/day | Non-specified | Sandoglobulin | 12 hours after the second infusion; during the third infusion | 0.867–1.62 | 92–95% | Self-limiting | Within a few hours |
| 13  | Kammoula et al. [26] | Kawasaki disease | 1–10 | 1–2 g/kg | Non-specified | Sulfasalazine/Peg-infered | Within 25–40 hours from the start of the infusion | 0.021–1.248 | 13–69% | Methylprednisolone 15 mg/kg in 2 children, self-limiting in 2 children | 1–2 days |
| 14  | Kaithagaya and Bank [27] | Common variable immunodeficiency | 10 | 0.4 g/kg | Non-specified | Non-specified | 10 days after the last infusion | 0.223 | Non-specified | Ticarcillin/clavulanate and ofloxacin | Within 1 week |
| 15  | Jain et al. [28] | Guillain-Barre syndrome | 14 | 0.4 g/kg/day for 5 days | Non-specified | Non-specified | Fourth day | 0.0080018 | 15% | Hydration, analgesics | 2 days |
| 16  | Vassafi et al. [29] | Acute Epstein-Barr virus infection | 4 | 0.4 g/kg | Non-specified | Non-specified | 6 hours after the second infusion | 2.983 | 84% | Cefotaxime, dexamethasone | 36 hours |
| 17  | Kattnera et al. [30] | Idiopathic thrombocytopenic purpura | 8–11 | 1 g/kg/day for 2 days | Non-specified | Venoglobulin | Non-specified | 0.625–2.227 | 64–91% | Non-specified | Non-specified |

**TABLE 4: Documented cases of IVIG-related aseptic meningitis**

IVIG: intravenous immunoglobulin; WBC: white blood cell; CSF: cerebrospinal fluid; PEG: polyethylene glycol
Supportive measures such as analgesics and antiemetics seem to be sufficient in these cases [30]. Corticosteroids do not seem to be effective in treating IVIG-induced aseptic meningitis [9,10,31]. Stiehm suggested that steroids or anti-TNF could be used in severe cases of aseptic meningitis [32]. However, in Kemmotsu et al.’s study, there were no differences in the clinical courses between patients who received no medical treatment and those treated with intravenous methylprednisolone [9]. Re-infusions are not contraindicated [7,27]. In case our patient requires IVIG in the future, Privigen will be avoided. Switching to subcutaneous preparation could potentially be an effective strategy in attenuating adverse effects [33]. Subcutaneous immunoglobulin (SCIG) was associated with lower rates of aseptic meningitis [10]. Several studies have shown that SCIG can be used in treating various diseases including immunodeficiency diseases, myasthenia gravis, chronic inflammatory demyelinating polyneuropathy, etc. Further research is needed to determine its efficiency as an immunomodulatory therapy. Preventive measures including infusing at a slow rate, pre-hydration, and adequate fluid intake throughout infusion, as well as premedication with acetaminophen and antihistamine, could be considered [31].

Milder cases of aseptic meningitis might not necessarily be recognized, given that aseptic meningitis is such a rare complication of IVIG. On the other hand, post-IVIG headache is common. The true incidence of IVIG-induced aseptic meningitis could be under-reported. Although there is increasing evidence on the self-limitedness of IVIG-induced aseptic meningitis and its temporal profile, the necessity for lumbar puncture and antibiotics remains controversial [7,34]. Given that our patient had been treated with several immunomodulatory medications and her increased risks for opportunistic infections, she was treated with intravenous antibiotics.

Conclusions

IVIG-induced aseptic meningitis remains a diagnosis of exclusion. Although it is rare, pediatricians should be aware of this complication and avoid unnecessary investigations or treatment. Supportive measures seem to be sufficient in these patients. Children usually recover without neurological sequelae.

Appendices
FIGURE 1: Childhood Myositis Assessment Scale (CMAS) scoring sheet

1. Lovell DJ, Lindsey CB, Rennebohm RM, et al.: Development of validated disease activity and damage indices for the juvenile idiopathic inflammatory myopathies. II. The Childhood Myositis Assessment Scale (CMAS): a quantitative tool for the evaluation of muscle function. The Juvenile Dermatomyositis Disease Activity Collaborative Study Group. Arthritis Rheum. 1999, 42:2213-2219. 10.1002/1529-0131(199910)42:10<2213::Aid-ansr2>3.0.Co;2-8

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Additional Information

Disclosures

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