

Aseptic meningitis induced by intravenous immunoglobulins in a child with acute Epstein-Barr virus infection and thrombocytopenia

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SUMMARY

Drug-induced aseptic meningitis (DIAM) represents a diagnostic challenge since clinical and cerebrospinal fluid (CSF) findings may be indistinguishable from a bacterial meningitis. Intravenous immunoglobulin (IVIg) are commonly used in a variety of diseases, including inflammatory and autoimmune disorders. Although usually well-tolerated, various adverse effects have been

reported. DIAM is a serious neurological side effect of IVIg therapy: albeit rare (0.067% of all IVIg infusions), the condition represents an important diagnostic challenge and should be considered by physicians. Here we report a case of an aseptic meningitis induced by IVIg therapy in a child with acute Epstein-Barr virus (EBV) infection and thrombocytopenia.

INTRODUCTION

Intravenous immunoglobulin is a blood product used in a variety of diseases, such as immunodeficiency disorders, autoimmune and inflammatory diseases [1-3]. IgG is the main component of IVIg, but it also contains small amounts of others Ig classes (most IgA), albumin, sugars, salts and trace of non active polymers, which may contribute to tolerability difficulties [4].

Although IVIg therapy is considered safe, adverse effects do occur. Most of these are mild and alleviated after infusion withdrawal, but some side effects could be serious and life threatening, such as hemolytic anemia, anaphylaxis, thrombosis and renal failure [5]. Aseptic meningitis is a serious neurological side effect: although rare (0.067% of

all infusions), this condition should be considered by physician, representing a diagnostic challenge because clinical and CSF findings may be indistinguishable from an infective meningitis [6].

Here we report a case of a child with EBV-related thrombocytopenia who developed aseptic meningitis following intravenous immunoglobulin infusion.

CASE REPORT

A 4-year-old previously healthy boy was admitted to Infectious Diseases Unit because of seven days of fever (T_{max} 39°C) and sore throat. A diagnosis of acute EBV infection was made based on clinical symptoms and results of serological testing (VCA-IgM positive, VCA-IgG negative, EBNA-IgG negative). He also showed low platelet count (47.000/mm³) and therapy with betamethasone 0.2 mg/kg was started. After 4 days he was discharged in good general condition and a platelet count of 124.000/mm³.

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Ten days after discharge the patient showed low platelet count (34.000/mm³) and EBV-DNA copies of 453/mL. He was admitted to our department starting treatment with IVIg 400 mg/kg. Six hours after the second dose of IVIg he developed fever (38.5°C), headache and vomiting. He was treated by the physician on duty with single dose of ceftriaxone 1 g/die.

Twelve hours after the beginning of symptoms, the physical examination revealed nuchal rigidity, and lumbar puncture (LP) was performed. CSF analysis showed an elevated white blood cell count of 2,993/mm³ with a neutrophil predominance (84%), glucose (75 mg/dL) and proteins concentration (300 mg/L) were unremarkable. IVIg therapy was withdraw, while he continued ceftriaxone, and dexamethasone treatment was started. Film-array for neurotropic viruses and bacteria, gram stain and cultures of CSF were negative. Brain MR was unremarkable. Twenty-four hours after LP the clinical picture of meningitis completely resolved.

■ DISCUSSION

We report the first case of a child with Epstein-Barr virus (EBV)-related thrombocytopenia who developed aseptic meningitis following IVIg infusion.

Due to temporal relation to IVIg administration and symptoms, this case can be considered as a DIAM IVIg-induced. This entity represents a di-

agnostic challenge since clinical and CSF findings may be indistinguishable from a bacterial meningitis; in particular this case, due to the administration of antibiotic therapy before LP, may lead to different interpretations.

Therapy with IVIg was introduced in 1982 for patients with antibody immunodeficiency; subsequently, it was developed for treatment of inflammatory diseases (thrombocytopenic purpura, Kawasaki disease, immunomediated neurologic disorders) and for treatment and prevention of some infectious disease including Tetanus, Hepatitis B, Varicella, CMV and EBV [3, 7-12].

Although considered safe, IVIg therapy adverse event do occur. Struff et al. reported among 1,705 immunodeficient patients given 15,548 infusions at the same IVIg product, only 0.6% had an adverse systemic reaction with an overall rate per infusion of 0.064% [13]. Higher rates of systemic reactions are reported in other groups, such as children, or patients affected by multiple myeloma, chronic inflammatory polyneuropathy, asthma and multiple sclerosis [14-18].

Adverse effect associated with IVIg can be local (at the infusion site) or systemic. Adverse systemic reactions are immediate (within 6 hours from infusion, 60% of reactions), delayed, occurring 6 hours to 1 week after infusion (40%), or late occurring greater than 1 week after infusion in less than 1% of reactions (Table 1).

Aseptic meningitis is a rare severe side effect of IVIg therapy occurring in 0.6-1% of patients [6,

Table 1 - Drug related reactions to IVIg infusion (adapted from Stiehm [29]).

<i>Immediate reactions (within 6 hours)</i>	<i>Delayed reactions (6 hours to 1 week)</i>	<i>Late reactions (more than 1 week)</i>
<ul style="list-style-type: none"> • Anaphylactic reaction • Hypo/hypertension, tachycardia • Fever, flushing • Headache, arthralgia • Anxiety, fatigue • Nausea, vomiting • Pain, swelling and erythema at infusion site 	<ul style="list-style-type: none"> • Aseptic meningitis • Hemolytic anemia • Arthritis • Hyponatremia • Neutropenia • Thrombosis/Embolism¹ • Colitis² • Dermatologic complications³ • Pulmonary complications⁴ • Impaired renal functioning 	<ul style="list-style-type: none"> • Interference with immunodiagnosis⁵ • Blood borne infectious diseases⁶ • Interference with vaccine effectiveness

1: arterial 80%, venous 20%.

2: Necrotizing enterocolitis in premature infants.

3: eczema, alopecia, erythema multiforme, dyshidrosis, baboon syndrome.

4: embolism, edema, pleural effusion, transfusion-related lung injury, leukocyte aggregation in lung.

5: particularly live virus.

6: Parvovirus B19, Prion diseases only theoretically, no cases of HCV transmission since 1996.

Table 2 - Characteristic of IVIg induced aseptic meningitis compared to main infectious meningitis.

	<i>Appearance</i>	<i>Leukocytes/mcL and main type</i>	<i>Protein level mg/L</i>	<i>Glucose level</i>	<i>Microbiological and virological findings</i>
Physiological condition	Clear	<5 lymphocytes	80-450	2/3 of blood level	Sterile
Drug induced aseptic meningitis	Clear	100-2,000 neutrophils	Increased	2/3 of blood level	Sterile
Bacterial meningitis	Cloudy	500-10,000 neutrophils	Highly increased	Decreased	Culture/PCR positive
Viral meningitis	Clear	500-1000 lymphocytes	Normal or slightly increased	2/3 of blood level	PCR positive

19]. The onset is usually 6 to 24 hours after the infusion, and clinical features include headache (96%), fever (92%), meningeal signs (89%), nausea and vomiting (86%) [20, 21]. Cerebral spinal fluid analysis usually shows a pleocytosis of a hundred to several thousand cells per microliter (mean 300/mcL), with a polymorphonuclear predominance, elevated proteins level and normal glucose concentration [22, 23]. Neuroimaging is usually non-informative and bacterial culture and viral PCR are negative. It is usually self-limiting in few days after discontinuation of IVIg administration; treatment only consist analgesic therapy [24]. Table 2 summarizes the main criteria suggesting IVIg induced meningitis compared to the main infectious meningitis categories.

Since clinical and CSF findings may be indistinguishable from a bacterial meningitis, aseptic meningitis IVIg induced represents a diagnostic challenge for physicians. In this case, due to temporal relation to IVIg administration and symptoms, DIAM IVIg-induced can be considered, although antibiotic administration before LP may lead to different interpretations. For this reasons, although various authors suggest discontinuing antibiotics therapy once diagnosis of IVIg-related aseptic meningitis is accepted, in this case we had considered reasonable to continue empiric therapy for bacterial meningitis [21].

Several mechanisms have been proposed as pathophysiology of DIAM IVIg-induced, such as hypersensitivity reaction due to direct entry of IVIg into CSF compartment, or immunological mechanisms leading to activation of monocyte or neutrophil pathways. IgA has also been proposed as cofactor [25-28].

Finally, we cannot exclude that EBV infection acts as trigger of immunological reaction to IVIg.

In summary, the initial presentation of IVIg associated meningitis is indistinguishable from an infectious meningitis. Considering this is a very rare condition, DIAM IVIg-induced remains a great diagnostic challenge for physician. Further evidences are needed to evaluate the possible relation between EBV infection and IVIg reaction; in the meanwhile, we suggest being cautious when administering IVIg during EBV acute infection.

■ REFERENCES

- [1] Albinn S., Cunningham-Rundles C. An update on the use of immunoglobulin for the treatment of immunodeficiency disorders. *Immunotherapy*. 6, 1113-1126, 2014.
- [2] Chen S., Dong Y., Yin Y., Krucoff M.W. Intravenous immunoglobulin plus corticosteroid to prevent coronary artery abnormalities in Kawasaki disease: a meta-analysis. *Heart*. 13, 99, 76-82, 2013.
- [3] Feasby T., Banwell B., Benstead T., et al. Guidelines on the use of intravenous immune globulin for neurologic conditions. *Transfus. Med. Rev.* 21, 2, (Suppl. 1), S57-S107, 2007.
- [4] Prins C., Gelfand E.W., French L.E. Intravenous immunoglobulin: properties, mode of action and practical use in dermatology. *Acta Derm. Venereol.* 87, 206-218, 2007.
- [5] Guo Y., Tian X., Wang X., Xiao Z. Adverse effects of immunoglobulin. *Therapy Front Immunol.* 9, 1299. eCollection 2018.
- [6] Bharath V., Eckbert K., Kang M., Chin-Yee I., Hsia C. Incidence and natural history of intravenous immunoglobulin - induced aseptic meningitis: a retrospective review at a single tertiary care center. *Transfusion*. 55, 2597-2605, 2015.
- [7] Ammann A.J., Ashman R.F., Buckley R.H., et al. Use

- of intravenous gamma globulin in antibody immunodeficiency. Results of a multicenter controlled trial. *Clin. Immunol. Immunopathol.* 22, 60-67, 1982.
- [8] Imbach P., Barandun S., d'Apuzzo V., et al. High dose intravenous gammaglobulin for idiopathic thrombocytopenic purpura in childhood. *Lancet.* 1, 1228-1231, 1981.
- [9] Furusho K., Sato K., Soeda T., et al. High-dose intravenous gammaglobulin for Kawasaki disease. *Lancet.* 2, 1359, 1983.
- [10] Fibl M.M. History of immunoglobulin replacement. *Immunol. Allergy Clin. North Am.* 28, 737-64, 2008.
- [11] Grossi P., Mohacs P., Szabolcs Z., Potena L. Cytomegalovirus immunoglobulin after thoracic transplantation: an overview. *Transplantation.* 100 (Suppl. 3), S1-S4, 2016.
- [12] Trappe R., Riess H., Anagnostopoulos I., et al. Efficiency of antiviral therapy plus IVIG in a case of primary EBV infection associated PTLD refractory to rituximab, chemotherapy, and antiviral therapy alone. *Ann. Hematol.* 88, 167-172, 2009.
- [13] Struff W.G., Klasser M., Eckert V., Dietrich R.L. Safety monitoring of a polyvalent immunoglobulin preparation: documentation of 15,548 administrations. *Int. J. Clin. Pharmacol. Ther.* 43, 420-428, 2005.
- [14] Singh-Grewal D., Kemp A., Wong M. A prospective study of the immediate and delayed adverse events following intravenous immunoglobulin infusions. *Arch. Dis. Child.* 91, 651-654, 2006.
- [15] Chapel H.M., Lee M., Hargreaves R., Pamphilon D.H., Prentice A.G. Randomised trial of intravenous immunoglobulin as prophylaxis against infection in plateau-phase multiple myeloma. The UK Group for immunoglobulin replacement therapy in multiple myeloma. *Lancet.* 343, 1059-1063, 1994.
- [16] Donofrio P.D., Bril V., Dalakas M.C., et al. Safety and tolerability of immune globulin intravenous in chronic inflammatory demyelinating polyradiculoneuropathy. *Arch. Neurol.* 67, 1082-1088, 2010.
- [17] Kishiyama J.L., Valacer D., Cunningham-Rundles C., et al. Multicenter, randomized, double-blind, placebo-controlled trial of high-dose intravenous immunoglobulin for oral corticosteroid-dependent asthma. *Clin. Immunol.* 91, 126-133, 1999.
- [18] Hommes O.R., Sorensen P.S., Fazekas F., et al. Intravenous immunoglobulin in secondary progressive multiple sclerosis: randomized placebo-controlled trial. *Lancet.* 364, 1149-1156, 2004.
- [19] Kemmotsu Y., Nakayama T., Matsuura H., Saji T. Clinical characteristics of aseptic meningitis induced by intravenous immunoglobulin in patients with Kawasaki disease. *Pediatr. Rheumatol. Online J.* 9, 28, 2011.
- [20] Scribner C.L., Kapit R.M., Phillips E.T., Rickles N.M. Aseptic meningitis and intravenous immunoglobulin therapy. *Ann. Intern. Med.* 121, 305-306, 1995.
- [21] Patel A., Potu K.C., Sturm T. A Case of IVIG induced aseptic chemical meningitis. *S. D. Med.* 70, 119-121, 2017.
- [22] Yelehe-Okouma M., Czml-Garon J., Pape E., Petitpain N., Gillet P. Drug-induced aseptic meningitis: a mini-review. *Fundam. Clin. Pharmacol.* 32, 252-260, 2018.
- [23] Kepa L., Oczko-Grzesik B., Stolarz W., Sobala-Szczygiel B. Drug-induced aseptic meningitis in suspected central nervous system infections. *J. Clin. Neurosci.* 12, 562-564, 2005.
- [24] Moris G., Garcia-Monco J. The challenge of drug-induced aseptic meningitis revisited. *JAMA Intern. Med.* 174, 1511-1512, 2014.
- [25] Orbach H., Katz U., Sherer Y., Shoenfeld Y. Intravenous immunoglobulin: adverse effects and safe administration. *Clin. Rev. Allergy Immunol.* 29, 173-184, 2005.
- [26] Asano T., Koizumi S., Mishina-Ikegami K., Hatori T., Miyasho T., Fujino O. Increased levels of monocyte chemoattractant Protein-1 in cerebrospinal fluid with gamma globulin induced meningitis. *Acta Paediatr.* 99, 164-165, 2010.
- [27] Jarius S., Eichhorn P., Albert M.H., et al. Intravenous immunoglobulins contain naturally occurring antibodies that mimic antineutrophil cytoplasmic antibodies and activate neutrophils in a TNF α -dependent and Fc-receptor-independent way. *Blood.* 109, 4376-4382, 2007.
- [28] Dashti-Khavidaki S., Aghamohammadi A., Farshadi F., et al. Adverse reactions of prophylactic intravenous immunoglobulin; a 13-year experience with 3004 infusions in Iranian patients with primary immunodeficiency diseases. *J. Investig. Allergol. Clin. Immunol.* 19, 139-145, 2009.
- [29] Stiehm E.R. Adverse effects of human immunoglobulin therapy. *Transfus. Med. Rev.* 27, 171-178, 2013.