Journal of Clinical Immunology (2019) 39:7–10
https://doi.org/10.1007/s10875-018-0585-9

LETTER TO EDITOR

Monoclonal Gammopathy of Unclear Significance in a Child with Wiskott-Aldrich Syndrome: a Rare Occurrence

Rashmi Rikhi[1] · Sagar Bhattad[2] · Ankur Jindal[1] · Biman Saikia[3] · Ravinder Garg[1] · Amit Rawat[1] · Deepti Suri[1] · Surjit Singh[1]

Received: 20 September 2018 / Accepted: 19 December 2018 / Published online: 3 January 2019

To the Editor,

The presence of anomalously high monoclonal immunoglobulins or paraproteins in serum is seldom encountered in patients with abnormal proliferation of B cells. In these conditions, elevated levels of light chains, heavy chains, or whole immunoglobulins (hypergammaglobulinemia) may be detected in serum. Wiskott Aldrich Syndrome (WAS), a rare combined primary immunodeficiency disorder, is characterized by eczema, thrombocytopenia, and susceptibility to infections. Immunoglobulin levels in patients with WAS conventionally reveal normal to high IgG and IgA, normal to low IgM and high IgE levels, though these can be extremely variable. Monoclonal gammopathy has been rarely described in patients with WAS. Chronic antigenic stimulation due to frequent infections coupled with ineffective specific antibody production results in a coincidental increase in amount of non-specific antibodies and paraproteins. We report a child with WAS who was found to have monoclonal gammopathy of unclear significance (MGUS).

A 5-year-old boy was diagnosed to have WAS when he presented with recurrent life-threatening pneumonia, eczema, and persistent micro-thrombocytopenia. There was no history suggestive of X-linked disorder in the family. Laboratory investigation at the time of diagnosis revealed low IgM (25 mg/dL), high IgA (233 mg/dL), and normal IgG levels. However, Wiskott Aldrich syndrome protein (WASp) expression was low and a splice-site mutation was found in intron 1 of *WAS* gene (c.931+1G>A), which confirmed the diagnosis. Due to lack of availability of matched sibling or unrelated donor, hematopoietic stem cell transplant could not be performed. He was advised cotrimoxazole prophylaxis along with replacement intravenous immunoglobulin (IVIG) 400 mg/kg every month. He was doing well clinically and did not have any major illness. Serial trough levels of IgG however showed consistent hypergammaglobulinemia over the next 2 years, IgG levels ranging from 13.6 to 41.40 g/L (normal range, 6.13–15.12 g/L) so replacement IVIG was transiently discontinued. However, IgG levels continued to be high. Serum electrophoresis was performed which showed M band in γ region (Fig. 1) which was further characterized by immunofixation that showed the presence of IgG and κ chain. A clinical possibility of underlying lymphoproliferative disorder was thought of but bone marrow examination showed non-specific reactive changes with mild excess of lymphocytes and no evidence of malignancy. His

✉ Deepti Suri
surideepti@gmail.com

Rashmi Rikhi
rashmirikhi@gmail.com

Sagar Bhattad
drsagarbhattad@gmail.com

Ankur Jindal
ankurjindal11@gmail.com

Biman Saikia
bimansaikia@hotmail.com

Ravinder Garg
ravindergarg1410@gmail.com

Amit Rawat
rawatamit@yahoo.com

Surjit Singh
surjitsinghpgi@rediffmail.com

[1] Allergy and Immunology Unit, Department of Pediatrics, Advanced Pediatric Centre, Postgraduate Institute of Medical Education and Research, Chandigarh 160012, India

[2] Pediatric Immunology and Rheumatology, Aster CMI Hospital, Bengaluru, Karnataka 550092, India

[3] Department of Immunopathology, Postgraduate Institute of Medical Education and Research, Chandigarh 160012, India

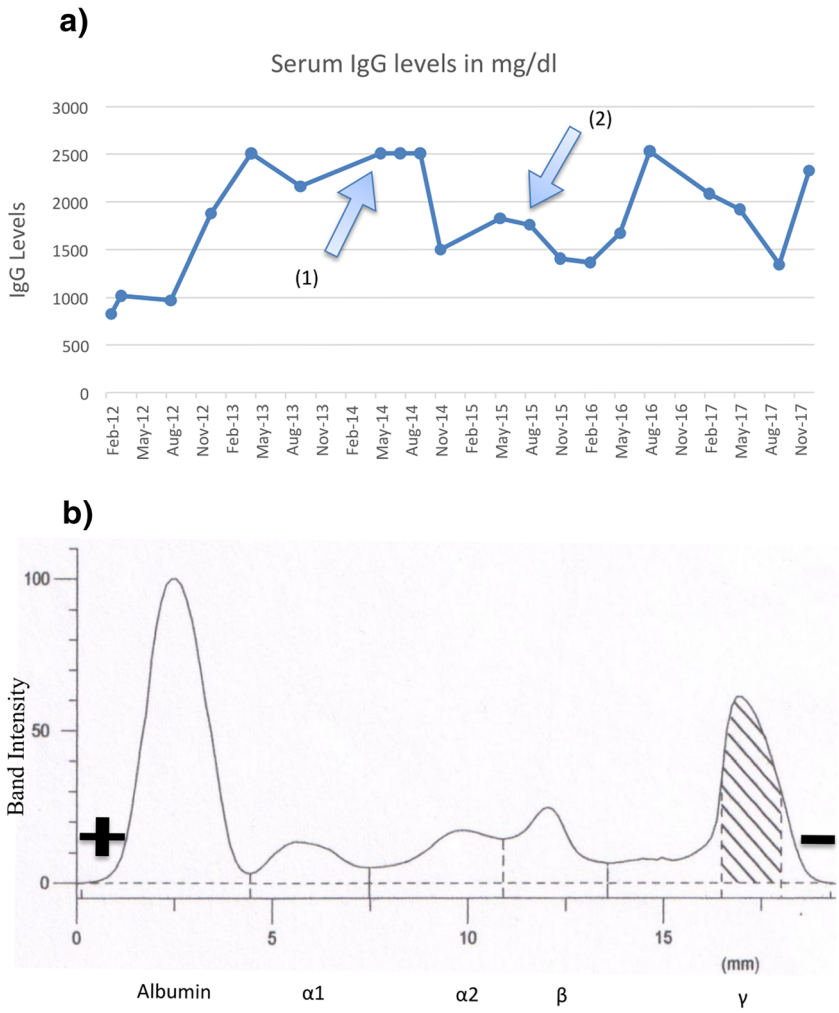

Fig. 1 **a** Graph showing persistent high levels of IgG levels in patient. Arrow 1 indicates time of discontinuation of IVIG and arrow 2 is time of reinitiation of IVIG. **b** Result of serum gel-electrophoresis, band intensity represented in the form of graph, showing M-spike in γ region

Epstein-Barr virus (EBV) DNA PCR and IgM EBV viral capsid antigen (VCA) serology was negative. He was being managed conservatively with only cotrimoxazole prophylaxis. However, recurrence of pyogenic meningitis on discontinuation of IVIG prompted reinitiation of replacement IVIG. During the last 5 years of follow-up, he has had one episode of *Burkholderia cepacia* pneumonia requiring respiratory support, few episodes of epistaxis, and frequent respiratory infections. He continues to have high IgG with persistent M band without any overt evidences of malignancy. The patient is being closely followed up with regular clinical examinations, blood counts every 3 months and abdominal ultrasonographic scans performed every 6 months. He underwent a repeat bone marrow examination 2 years back. The latest IgG values were 13.45 g/L (Sept. 2017), 24.33 g/L (Dec. 2017), and 15.55 g/L (April 2018). He still awaits hematopoietic stem cell transplant due to financial constraint and non-availability of matched donor.

Monoclonal gammopathy in children is a rare disorder that is defined as a monoclonal B cell proliferative disorder accompanied by an electrophoretically homogeneous immunoglobulin component of a single isotype, allotype, and idiotype in the serum. Benign monoclonal or polyclonal gammopathies have been described in lymphoproliferative diseases, malignancies, autoimmune diseases, and aplastic anemia. It is important to differentiate monoclonal from polyclonal hypergammaglobulinemia, which is assessed using protein electrophoresis and immunofixation. Monoclonal gammopathy is characterized by the presence of sharp well-defined band with a single heavy chain and a similar band with a kappa or lambda light chain. A broad diffuse band with one or more heavy chains and kappa and lambda light chains characterizes a polyclonal gammopathy [1]. Monoclonal gammopathies are distinctly more common in adults. They have been rarely reported in children with primary or secondary immunodeficiencies especially in severe combined immunodeficiency, ataxia telangiectasia, and after renal or hematopoietic stem cell transplantation. A retrospective study for the presence of monoclonal and oligoclonal gammopathies in Caucasian population from 0 to 21 years using serum immunofixation electrophoresis

Table 1 Summary of the monoclonal gammopathies ever reported with Wiskott-Aldrich syndrome

S. no.	Author name, year, and country	Number of cases	Age of paraprotein detection and gender	Type of gammopathy	Comments
1.	Dalloz J. C., 1965; France [3]	1	5 months/M	IgG	Paraprotein disappeared after initial detection
2.	Rádl J., 1967; Czechoslovakia [4]	1	12 years/M	M band	Bleeding manifestations and serious infections (including conjunctivitis and herpes zoster)
3.	Blaese R M, 1971; USA [5]	1	3 years*/M	IgG λ	Paraproteins completely disappeared from patients serum after several months
4.	Danon F., 1973; France [6]	1	10 years/M	IgG λ	Never observed increase in the level of the monoclonal Ig after initial detection
5.	Bruce R. M., 1974; USA [7]	3	3 years*, 7 years/M	IgG λ and IgG κ	The IgG λ paraprotein present at the age of 3 completely disappeared from his serum several months later. A second monoclonal protein appeared in his serum at age 7. This protein, which is also an IgG, has κ-light chains and migrates with no evidence of the previously detected cathodal IgG λ paraprotein
			1 years/M	IgG λ	Died of pneumonia and autopsy suggested reticulum-cell sarcoma
			5 months/M	IgG λ	Died of internal bleeding and no evidence of malignancy
6.	Rádl J., 1976; Netherlands [8]	3	20 months/M (observed levels 3 times in 24 months)	IgG λ IgM κ, IgG κ, IgG λ IgG λ, IgG κ	Paraproteins were transient, patient died of gastrointestinal bleeding
			13 months/M (observed levels 3 times in 18 months)	IgM λ, IgG λ IgG λ, IgG κ IgG λ	Paraproteins were transient, patient died of uncontrollable mucosal bleeding
			11 months/M (observed levels once in 12 months)	IgM λ, IgG λ	Paraproteins were transient, patient was live until reporting
7.	Yoshida K., 1997; Japan [9]	1	1 year/M	IgA κ chain	EBV-associated malignant lymphoma developed at an early age and was accompanied by macroamylasemia
8.	Index case	1	9 year/M	IgG κ	Persistent paraprotein with no malignancy; live

*Patient discussed in both the article is the same and at the age; in the other article, it was evaluated again

from 2005 to 2011 identified a gammopathy in 83 out of 695 patients (11%) and the most common associated diagnosis was ataxia telangiectasia (22%) [2].

Primary immunodeficiencies associated with hypergammaglobulinemia include chronic granulomatous disease, immunoglobulin subclass deficiency, autoimmune lymphoproliferative disorders, and WAS; however, there are no definite guidelines to suspect or investigate for under lying monoclonal gammopathy in these patients. The index patient was investigated for monoclonal gammopathy because he had extremely high IgG levels while on replacement IVIgG and which persisted despite discontinuation of IVIg replacement therapy.

Paraproteinemia in association with WAS was first reported in 1965 [3]. Table 1 summarizes the patients of WAS with gammopathy described in the literature to date. Bruce et.al. described three children with WAS and one of these three patients was identified to have reticulum-cell sarcoma at autopsy while no malignancy was identified in the other two [7]. Localized reticular lymphosarcoma of the duodenal mucosa in association with dys-γ-globulinemia and IgA κ chain gammopathy in a child with WAS who died of EBV-associated lymphoma has also been reported [4, 9] The index patient was evaluated for underlying malignancy as well as for EBV infection but no overt cause was found. Moreover, he has remain asymptomatic over the last 5 years.

Varied paraproteins have been reported, though the commonest has been IgG λ type. Different paraproteins have been also detected in the same patient on single or multiple occasions. In the index patient, we found IgG κ type of M protein. The nature of light chains has not been implicated to have any clinical correlation or a suggestion to an underlying pathogenesis.

Monoclonal or oligoclonal gammopathies of unclear significance are thought to be secondary to monoclonal B cell proliferation and plasma cell conversion, as a consequence of an abnormal regulatory T cell function. Lack of effective

immune responses in the presence of chronic antigenic stimulation may lead to increase in paraproteins or a specific immunoglobulin in serum.

Follow-up analysis in previously reported patients revealed that most of these monoclonal gammopathies were transient [10]. However, the same paraprotein has persisted in the index child for more than 5 years without any symptoms and development of malignancy. Patients with benign monoclonal gammopathy, however, need prolonged follow-up. The presence of organ dysfunction (renal involvement, central nervous involvement, bone involvement, and hypocalcemia), bone marrow showing increased plasma cells, and the presence of J chains may suggest progression to malignant disease [11, 12]. There are no definite recommendations for screening in these patients.

There is paucity of recent literature on this aspect and this could be attributed to early HSCTs being performed in children with WAS in most of the developed countries. In developing countries, however, availability, accessibility, and affordability of HSCT are still limited. Children continue to have repeated infections despite replacement immunoglobulins and prophylactic antimicrobials.

This report highlights the natural course of these children and a need for more scientific explanation for occurrence of this phenomenon in patients with WAS.

Authors' Contributions (Rashmi Rikhi: RR; Sagar Bhattad: SB; Ankur Kumar Jindal: AK; Biman Saikia BS; Ravinder Garg: RG; Amit Rawat: AR; Deepti Suri: DS; Surjit Singh: SS)

DS, AR, SB, AK, and RR conceptualized; AK, SB, and RR did data collection; SS, DS, AR, SB, AJ, BS, and RR analyzed; RG performed electrophoresis for paraprotein determination; DS, RR, and AJ drafted the manuscript; and DS and AR critically analyzed the manuscript. SS, DS, AR, and RR are responsible for the overall content as guarantors.

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

Ethical Approval Department Review Board (DRB), Advanced Pediatrics Centre, Post Graduate Institute of Medical Education and Research Chandigarh, has approved the study.

Informed Consent Informed consent was obtained from the parents of the child.

Publisher's Note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

References

1. O'connell TX, Horita TJ, Kasravi B. Understanding and interpreting serum protein electrophoresis the pattern of serum protein electrophoresis results depends on the fractions of two major types of protein: albumin and globulins. 2005.
2. Karafin MS, Humphrey RL, Detrick B. Evaluation of monoclonal and oligoclonal gammopathies in a pediatric population in a major urban center. Am J Clin Pathol. 2014;141:482–7.
3. Dalloz JC, Castaing N, Nezelof C, Seligmann M. Paraproteinémie transitoire de type gamma. Presse Med. 1965;73:1541–6.
4. Rádl J, Masopust J, Houštěk J, Hrodek O. Paraproteinaemia and unusual dys-γ-globulinaemia in a case of Wiskott-Aldrich syndrome. An immunochemical study. Arch Dis Child. 1967;42:608–14.
5. Blaese RM, Strober W, Levy AL, Waldmann TA. Hypercatabolism of IgG, IgA, IgM, and albumin in the Wiskott-Aldrich syndrome. J Clin Invest. 1971;50:2331–8.
6. Danon F, Seligmann M. Serum monoclonal immunoglobulins in childhood. Arch Dis Child. 1973;48:207–11.
7. Bruce RM, Blaese RM. Monoclonal gammopathy in the Wiskott-Aldrich syndrome. J Pediatr. 1974;85:204–7.
8. Radl J, Dooren LJ, Morell A, Skvaril F, Vossen JMJJ, Uittenbogaart CH. Immunoglobulins and transient paraproteins in sera of patients with the Wiskott-Aldrich syndrome: a follow-up study. Clin Exp Immunol. 1976;25:256–63.
9. Yoshida K, Minegishi Y, Okawa H, Yata J, Tokoi S, Kitagawa T, et al. Epstein-Barr virus-associated malignant lymphoma with macroamylasemia and monoclonal gammopathy in a patient with Wiskott-Aldrich syndrome. Pediatr Hematol Oncol. 1997;14:85–9.
10. Simão I, Cordeiro AI, Borrego LM, Martins C, Neves C, Neves JF. Monoclonal IgG kappa gammopathy previous to hematopoietic stem cell transplantation in an infant with severe combined immunodeficiency. Clin Immunol. 2012;145:133–5.
11. Atkin C, Richter A, Sapey E. What is the significance of monoclonal gammopathy of undetermined significance? Clin. Med. (Northfield. Il. 2018.
12. Bast EJEG, Van Camp B, Boom SE, Jaspers FCA. Differentiation between benign and malignant monoclonal gammopathy by the presence of the J chain. Clin Exp Immunol. 1981;44:375–82.