Blood Cells, Molecules and Diseases 91 (2021) 102595

Contents lists available at ScienceDirect

Blood Cells, Molecules and Diseases

journal homepage: www.elsevier.com/locate/bcmd

Letter to the Editor

Monoclonal IgM gammopathy in adult acquired pure red cell aplasia: culprit or innocent bystander?

ARTICLE INFO

Editor: Mohandas Narla
Keywords
Pure red cell aplasia
MGUS
Waldenström's macroglobulinemia
IgM
Bone marrow failure syndromes

To the Editor

Acquired pure red cell aplasia (aPRCA) is characterized by severe anemia and disappearance of bone marrow (BM) erythroid precursors likely due to diverse etiologies. However, the most common form of the disease is idiopathic and attributed to both cellular-mediated and humoral immune mechanisms [1]. This notion is supported by the paucity of other mechanistic clues, the variety of clinical observations and most importantly the responsiveness to immunosuppressive therapies. Inherent to its orphan nature, only few systematic trials have been conducted and therapeutic decisions often rely on analysis of co-associated conditions providing helpful clues as to the rational choice of treatment modalities [1].

This letter is inspired by the recent evaluation of a patient with aPRCA associated to the presence of monoclonal IgM gammopathy and low grade BM involvement by Waldenström's macroglobulinemia (WM). aPRCA has been previously described in the context of B-cell dyscrasia (*i.e.* monoclonal gammopathy of undetermined significance, MGUS) and anecdotally in B-cell lymphoplasmocytic disorders (WM) [2,3]. The largest study on MGUS and aPRCA association reported a frequency of 24%, similar to that of our recent series, with all cases being of IgG subtype [1,3,4]. We then systematically searched for the presence of IgM gammopathy among 74 patients diagnosed with aPRCA at our institution between 2000 and 2020, identifying additional 4 cases. Clinical, laboratory and molecular data were abstracted in accordance to approval of the Cleveland Clinic Internal Review Board (Supplementary Appendix).

Overall, all 5 patients were male with a median age at diagnosis of

Table 1
Patients' characteristics at presentation.

UPN	Gender	Age	WBC ($\times 10^9$/L)	ANC ($\times 10^9$/L)	Hb (g/dL)	PLT ($\times 10^9$/L)	Reticulocytes (M/uL)	LGL	WM[a]	IgM (mg/dL)	M-protein	EPO (U/L)	M:E ratio	PB19 active infection[b]	Cytogenetics
1	M	72	4	1.33	3.4	229	0.004	Yes	No	464	IgM kappa	11,560	62	Negative	Normal
2	M	63	7.23	4.93	10.1	461	0.009	Yes	Yes	341	IgM kappa	981	11	Negative	Normal
3	M	47	7.22	4.92	7.5	422	0.010	No	No	1345	IgM kappa	172	12	Negative	Normal
4	M	46	5.52	4.24	10.3	410	0.006	No	Yes	350	IgM lambda	1692	12	Negative	Normal
5	M	69	4.39	2.07	8.3	258	<0.004	Yes	No	147	IgM kappa	841	25	Negative	Normal

M: male; WBC: white blood cells; Hb: hemoglobin; ANC: absolute neutrophils count; PLT: platelets; LGL: Large granular lymphocytic leukemia; WM: Waldenström's macroglobulinemia; IgM: Immunoglobulin M; M-protein: Monoclonal paraprotein; EPO: erythropoietin; M:E ratio: Myeloid:Erythroid ratio; PB19: parvovirs B19. Normal ranges were considered according to the followings: WBC, 3.70–11.00 $\times$ 10^9/L; neutrophil count, 1.45–7.50 $\times$ 10^9/L; platelet count 150–400 $\times$ 10^9/L; Hb 11.5–15.5 g/dL; reticulocytes count 0.0180–0.1000 M/μL; IgG 717–1411 mg/dL, IgA 78–391 mg/dL, IgM 53–334 mg/dL.

[a] Waldenström's macroglobulinemia/Lymphoplasmacytic lymphoma diagnosis was established because of low grade bone marrow infiltration (>10% of clonal lymphoplasmacytic cells by flow cytometry; see also Supplemental Methods) and presence of an IgM monoclonal gammopathy according to standard established criteria defined elsewhere (see also Supplementary Appendix).

[b] Detected by positive IgM serology and/or viral DNA by PCR on peripheral blood.

https://doi.org/10.1016/j.bcmd.2021.102595
Received 30 June 2021; Accepted 9 July 2021
Available online 14 July 2021

Table 2
Somatic mutations in our internal cohort of aPRCA patients ($N = 52$).

UPN[a]	Genetic alterations (VAF %)[b]	Protein change
1	STAT3 (12.7)	p.D661Y
2	Negative	–
3	Negative	–
4	Negative	–
5	Negative	–
6	BCOR (9)	p.1252_1253del
7	ASXL1 (33.3)/RUNX1(21.6)	p.R693X/p.G336fs
8	JAK2 (3.1)/STAT3 (9.9)	p.V617F/p.D661V
9	STAT3 (21)	p.D661Y
10	STAT3 (8)	p.S614R
11	TET2 (4.3)	p.N275Ifs*18
12	SF3B1 (18.2)	p.K666N
13	BCORL (8.2)	p.L179fs

[a] UPN 1–5 correspond to UPN 1–5 of Table 1. Negative cases (UPN 14–52) are not reported.
[b] Somatic variants are reported at the time of collection of bone marrow specimens and diagnosis of pure red cell aplasia.

63 years (Table 1). Majority of cases had an IgM kappa light chain MGUS (4/5) with two fulfilling a diagnosis of WM. aPRCA was the reason for seeking medical attention in 4 out of 5 cases while one patient was already followed for a previous diagnosis of T-cell large granular lymphocyte leukemia (T-LGL). Molecular characterization (Tables 2 & S1) revealed a *STAT3*^{D661Y} mutation in one patient (UPN1) with T-LGL at a variant allele frequency (VAF) of 12.7% while none carried *MYD88*^{L265P} mutation. When focusing on BM histopathological characteristics, these patients had a myeloid-to-erythroid ratio >10, normal karyotype and, of note, presence of atypically stained clonal plasma cells (PC). Despite representing a low bulk as expected in patients with MGUS, a subset of PC appeared to have an atypical "balloon-shape" stained with CD138, kappa/lambda light chains and CD71 immunostaining (Fig. 1). All patients were poorly responsive to standard immunosuppression and had a median of 3 previous lines of treatment. A specific bortezomib-based therapeutic approach was used in 4 cases with half obtaining a normalization of hemoglobin levels and the remaining patients becoming transfusion-independent. All WM cases also received rituximab (Supplementary Appendix).

IgM-MGUS and WM have been only anecdotally reported in the literature in association with aPRCA and ours is the largest monocentric case series described so far (Table S2). In line with Korde et al. [3], the overall prevalence of MGUS in our internal cohort of aPRCA patients was 26% with the majority of cases being of IgG type (60%). However, when looking at subtype distribution, we found a substantial amount of IgM-MGUS (33%), which were not present in the aforementioned study [3] and had a frequency twice higher than expected for non-PRCA MGUS population [5] (Fig. 1). Moreover, in our cohort of aPRCA patients with MGUS we did not register an increased BM fibrosis and/or eosinophilia (median eosinophil 4%, range 0–7%) as described by Korde et al. [3]. When looking at treatment data, patients with MGUS were poorly responsive to 1st line immunosuppressive treatment as suggested by the higher number of treatment lines received, irrespective of the paraprotein subtype (4 *vs.* 2 in non-MGUS carriers, $p = 0.0002$). Of note, a unique gender distribution was found in patients with IgM gammopathy with the totality of cases being male (as also confirmed by previously reported cases, Table S2) *vs.* only 40% in non-IgM cases ($p = 0.044$).

When looking at sequencing data ($n = 52$ out of 74 aPRCA patients), clonal somatic mutations were rarely (17%) found with *STAT3* as the most commonly mutated gene (Table 2). The enrichment in *STAT3* lesions is explained by the concomitant presence of a T-LGL diagnosis in about 23% of aPRCA cases as previously shown [1,4,6]. While *MYD88*^{L265P} somatic mutations are typically found in virtually all patients with WM and in a good fraction of those with IgM-MGUS [7], their

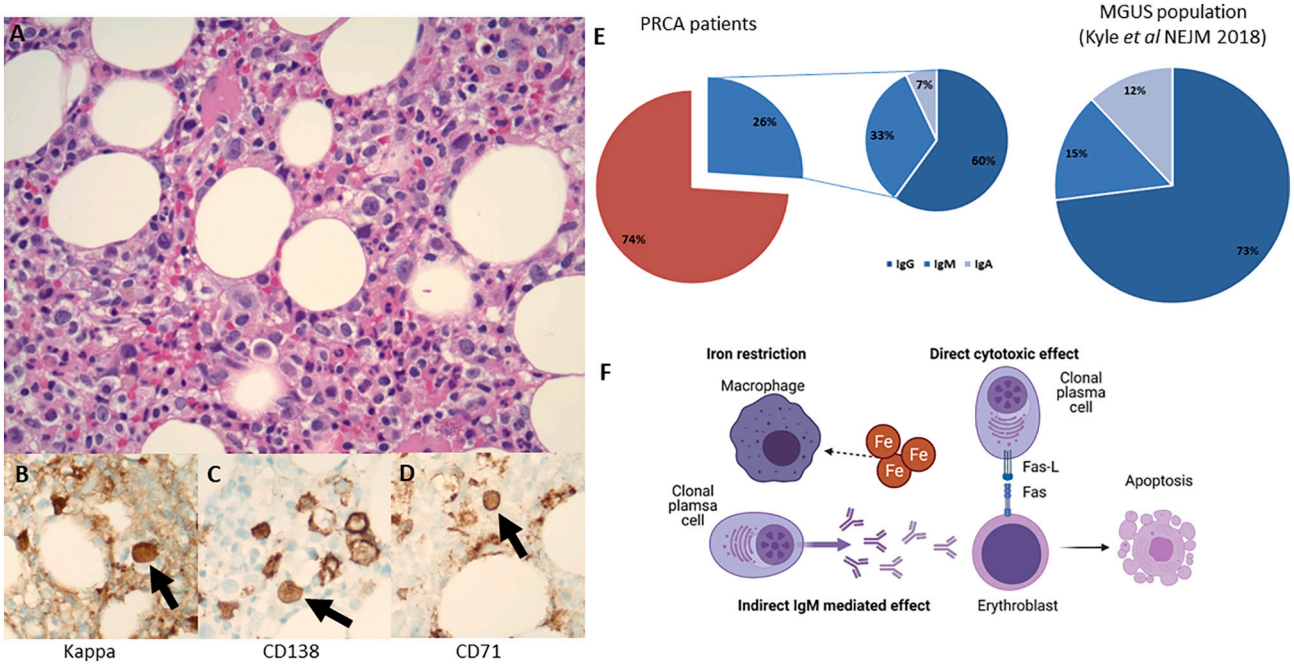

Fig. 1. IgM-related acquired pure red cell aplasia. On the left, bone marrow evaluation of a representative patient (UPN 5). Hematoxylin-eosin stain on the core biopsy (panel A) showing paucity of erythroid precursors. Immunostains with kappa light chain (panel B), CD138 (panel C) and CD71 (Panel D) of the same patient depicting a subset of plasma cell (arrows) characterized by atypical balloon-shape staining, in addition to normal staining pattern of plasma cells and erythroid precursors. Pie charts (panel E) showing our aPRCA cohort ($N = 74$) in relation to the presence and the subtype distribution of MGUS (on the left) and comparison with MGUS population [5] (on the right). Panel F shows the putative pathogenic mechanisms underlying aPRCA associated with IgM monoclonal protein. A direct cytotoxic effect *via* Fas/Fas-ligand and an indirect IgM inhibitory effect are invoked to explain the suppression of BM erythropoiesis in such patients. Another mechanism is also represented by the deprivation of iron operated by macrophages, which prevents its availability for erythropoiesis [9,10]. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

absence in our case series may underlie a different pathogenic route and also explain the presentation with low/absent lymphoma-specific features.

The identification of atypically stained PC in the BM specimens of our patients together with the increased frequency of IgM paraprotein in our internal aPRCA cohort suggest that this peculiar clinical combination may not be coincidental, but rather represents another of the polymorphous presentations of aPRCA. B-cell dyscrasias with low tumor bulk such as MGUS have been associated with aPRCA, suggesting that the presence of a paraprotein may be a sufficient condition to perturb BM erythropoiesis irrespectively of the percentage of PC [2]. Indeed, anemia is usually present in B-cell dyscrasias even when the bulk of BM disease is low and the inhibition of erythropoiesis is supposed to be mediated by the abnormal immunoglobulins produced by clonal PC and or clonal lymphoplasmacytic cells [8]. Malignant PC can be responsible for erythroblast apoptosis *via* abnormal up-regulation of Fas ligand and tumor necrosis factor-related apoptosis-inducing ligand (TRAIL) or *via* a mechanism of iron restriction as shown by multiple myeloma mouse models [9,10]. This latter mechanism may play an important role in aPRCA with IgM paraprotein as the identification of clonal $CD71^{+}$ PC (Fig. 1) together with increased iron accumulation in BM macrophages (Fig. S1) has been registered already at aPRCA onset prior to any possible transfusions overload [9].

In conclusion, IgM-MGUS identified by specific bone marrow PC features and aPRCA appears to be another of the multifaceted version of this fascinating and rare disorder. Whether coincidental or not, this peculiar subentity is characterized by a preferential male predominance possibly reflection of the gender predisposition of the underlying condition, and poor responsiveness to standard immunosuppressive treatment. In this context, aPRCA may represent a paraneoplastic syndrome or inversely upstage otherwise typical IgM-MGUS. The *ex juvantibus* responses registered with bortezomib-based therapies may suggest an inherent mechanistic link between these two conditions.

Declarations

Ethics approval and patients' consent to participate to the study was approved by The Institutional Review Board of the Cleveland Clinic Foundation. All procedures were carried out in accordance with guidelines set forth by the Declaration of Helsinki.

Consent for publication

Written informed consent was obtained from all patients.

Declaration of competing interest

The authors declare no competing financial interests.

Acknowledgements

We thank the HENRY & MARILYN TAUB FOUNDATION, grant R35HL135795 (to J.P.M), AA&MDSIF, VeloSano Pilot Award, and Vera and Joseph Dresner Foundation–MDS (to V.V.). G.C. was supported by the American-Italian Cancer Foundation Post-Doctoral Research Fellowship.

Authors' contributions

C.G. and J.P.M generated and conceived the study design, figures, tables and manuscript; C.G. and H.J.R., reviewed histopathology data. S. P., H.A., M.Z., B.J.P., V.V. and J.V. reviewed the clinical data, took part in patients selection and helped edited the manuscript. All authors participated in data interpretation and critical review of the final paper and submission.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bcmd.2021.102595.

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Carmelo Gurnari[a,b,*], Simona Pagliuca[a,c], Hassan Awada[a], Misam Zawit[a], Bhumika J. Patel[a,d], Valeria Visconte[a], Jason Valent[a,d], Heesun J. Rogers[e], Jaroslaw P. Maciejewski[a,d]

[a] *Translational Hematology and Oncology Research Department, Taussig Cancer Center, Cleveland Clinic, USA*
[b] *Department of Biomedicine and Prevention, PhD in Immunology, Molecular Medicine and Applied Biotechnology, University of Rome Tor Vergata, Rome, Italy*
[c] *Université de Paris, Paris, France*
[d] *Department of Hematology and Oncology, Taussig Cancer Institute, Cleveland Clinic, Cleveland, OH, USA*
[e] *Department of Laboratory Medicine, Cleveland Clinic, USA*

[*] Corresponding author at: Department of Translational Hematology and Oncology Research, Taussig Cancer Institute, 9620 Carnegie Ave, Building NE6-250, Cleveland, OH 44106, USA.
E-mail address: carmelogurnari31@gmail.com (C. Gurnari).