REGULAR ARTICLE

blood advances

Clinical heterogeneity and outcome of acquired PRCA: a multicenter European study

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Key Points

- PRCA shows marked diagnostic heterogeneity, where molecular data can help identify challenging secondary forms, such as MDS-associated cases.
- Early initiation of CyA improves ouctomes; mTORi are valuable second-line treatment. Infection related mortality remains non negligible.

Pure red cell aplasia (PRCA) is a rare single-lineage bone marrow (BM) failure characterized by anemia with profound reticulocytopenia and severe reduction of erythroid precursors. PRCA is heterogeneous, and diagnosis requires extensive evaluation to distinguish primary from secondary causes, such as thymoma, autoimmune diseases, T-cell large granular lymphocyte expansion, and myelodysplastic syndrome (MDS), the differential diagnosis of which is particularly challenging. Evidence guiding management remains limited because of the rarity of the disease and the lack of prospective studies. We analyzed 121 acquired adult PRCA (excluding Parvovirus B19-associated PRCA) cases across 14 European centers. Secondary forms accounted for 78% of diagnoses, mostly thymoma (23%) or MDS (21%). In a subset of patients, BM immunohistochemistry demonstrated significant depositions of C3, C4d, immunoglobulin M (IgM), and IgG, reducing after immunosuppression. Next-generation sequencing was performed in half of the patients, 36% of whom presented mutations predominantly related to clonal hematopoiesis, except in MDS-associated cases, which often carried multiple non-clonal hematopoiesis mutations. Immunosuppression represented the backbone of therapy: cyclosporine A (CyA) was the most effective agent, with 61% overall response rate (47% complete) and better outcomes when initiated earlier; mammalian target of rapamycin inhibitors (mTORi) showed promising activity as second-line therapy, with responses in 71% of the patients, including CyA-refractory cases. Mortality reached 30%, predominantly because of infectious complications, and was significantly higher in MDS-associated cases.

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All data are available within the manuscript, and further data may be available from the corresponding author, Bruno Fattizzo (bruno.fattizzo@unimi.it), on request.

The full-text version of this article contains a data supplement.

PRCA remains a diagnostically challenging and clinically heterogeneous disorder in which integration of molecular analyses may refine diagnostic accuracy and patient stratification. Immunosuppression remains the mainstay of treatment, with CyA being a reliable first-line treatment and mTORi emerging as encouraging rescue options.

Introduction

Pure red cell aplasia (PRCA) is a rare form of single-lineage bone marrow (BM) failure characterized by reticulocytopenic anemia resulting from the absence or marked depletion of BM erythroid precursors.[1,2] PRCA can be either constitutional, typically manifesting in childhood and associated with an underlying genetic defect (ie, Diamond-Blackfan anemia), or acquired.[3,4] The acquired form can be further subdivided into idiopathic or secondary, the latter arising in the context of diverse conditions, such as infections (eg, parvovirus B19–related aplastic crises), systemic autoimmune diseases, primary immunodeficiencies, and solid tumors, particularly thymoma. In addition, PRCA may occur in association with chronic lymphoproliferative disorders, including chronic lymphocytic leukemia and, more frequently, T-cell large granular lymphocyte (T-LGL) expansions. Finally, PRCA may also occur in the setting of an underlying myelodysplastic syndrome (MDS), where differential diagnosis is often particularly challenging.[5-8] In this context, a dual mechanism may be hypothesized, involving intrinsic erythroid defects within the MDS clone and immune-mediated erythroid suppression. However, with the exception of parvovirus B19–associated PRCA in immunodeficient patients, where IV immunoglobulins are generally effective, the pathogenesis and treatment of most acquired forms remain incompletely defined.[9,10] In secondary PRCA, treatment of the underlying condition is useful, whereas in idiopathic cases, frequent presence of marrow T-cell infiltrates and clinical efficacy of T-cell–targeting agents, such as cyclosporine A (CyA), strongly suggest an immune-mediated mechanism.[11] Owing to rarity, heterogeneity, and the absence of dedicated clinical trials, management is often individualized on a case-by-case basis. In this study, we evaluated the clinical and hematological features of patients with PRCA, with particular focus on common associations with T-LGL, subtle differences observed in MDS-associated cases, and treatment patterns and outcomes in terms of response and survival.

Materials and methods

This study included a retrospective cohort of 121 adult patients with PRCA followed up at 14 different centers from 6 countries across Europe from 2007 to 2025. PRCA was defined as anemia with severe reticulocytopenia associated with a reduction or complete absence of erythroid precursor on BM (<5% of total BM cellularity, with markedly increased myeloid-to-erythroid ratio). After accurate evaluation for thymoma, autoimmune screening, and testing for lymphoproliferative disorders or other hematological malignancies, PRCA was classified as primary (ie, idiopathic) or secondary if a concomitant condition was present. Congenital forms as well as parvovirus B19– or drug-related PRCA were excluded from analyses. T-LGL expansion was defined as the presence of BM T-LGL infiltration of >10%, with confirmed clonality by T-cell receptor analysis. Patients displaying such LGL clonal infiltrate by T-cell receptor analysis were considered as "PRCA associated with LGL clonal expansion" and therefore as "secondary forms." PRCA with associated MDS was considered in the presence of severe reticulocytopenia and absence of erythroid precursors in otherwise-diagnostic marrow for MDS according to World Health Organization 2022 criteria. BM trephines in a subset of patients were reevaluated locally by an expert hemopathologist, and immunohistochemistry analysis for complement fractions C3 and C4, immunoglobulin G (IgG) and IgM, and nuclear-cleaved caspases 3 deposits was performed in a subset of cases (supplemental Methods). Clinical and laboratory features at diagnosis, transfusion burden before and after therapy, iron parameters, therapy lines, and responses were retrospectively collected. Iron overload was defined as ferritin >800 mcg/L in association with transferrin saturation >60% in the absence of available T2* magnetic resonance imaging. Hypogammaglobulinemia was considered as IgG <400 mg/dL and/or IgA <70 mg/dL and IgM <40 mg/dL. Notably, in patients with low-to-normal endogenous erythropoietin levels, renal failure was excluded before inclusion in the study. Time to first treatment was recorded; response evaluation was made according to the treating physician, and time to first hemoglobin (Hb) response was systematically evaluated. All centers performed next-generation sequencing (NGS) analysis from DNA extracted from peripheral blood granulocytes on Illumina-based platforms. The targeted gene panel included coding exons and splice sites of genes involved in myeloid malignancies based on literature data. Variants were annotated as pathogenic, likely pathogenic, or variants of unknown significance based on available literature and query of publicly available databases (Catalogue of Somatic Mutations in Cancer). Mutations with variant allele frequencies (VAFs) as low as 2% were reported, and median coverage was 500. Mutations were further screened to evaluate their somatic nature and pathogenicity according to a stringent pipeline in use at the coordinating center (University of Milan). Complete response (CR) was defined as Hb >12 g/dL, whereas partial response (PR) was defined as achievement of transfusion independence in transfusion-dependent cases or an increase by 2 g/dL from baseline in non–transfusion-dependent ones whenever CR criteria were not met. Data on overall survival and causes of death were also systematically collected. A comparative analysis was carried out between primary and secondary PRCA, with particular focus on PRCA associated with T-LGL or MDS. Finally, we compared patients who responded vs those who did not respond to CyA and subsequently focused on individuals treated with mammalian target of rapamycin inhibitors (mTORi).

For statistical analyses, demographic and clinical variables were summarized using descriptive statistics. Exploratory analyses were performed for continuous variables via the Wilcoxon rank-sum test,

whereas categorical variables were analyzed using Pearson χ^2 test or the Fisher exact test, as appropriate. Survival analyses and Cox regression models were performed with RStudio (version 2025.05.1+513).

This study was conducted in accordance with the Declaration of Helsinki.

Results

Hematological features

Overall, 121 patients followed up for a median of 34 months (range, 5.1-403) were included in the analysis (Table 1; Figure 1A). Patients showed equal sex distribution and had a median age of 62 years (range, 21-93). PRCA was associated with another condition in 78% of the cases, most commonly thymoma (23%) or MDS (21%), followed by autoimmune diseases or T-LGL expansion (13% and 12%, respectively). At disease presentation, most patients had severe anemia (median Hb, 6.7 g/dL [range, 3.5-9.6]) with reticulocytopenia (median, 6 × 10^9/L [range, 1-44]); median platelets (255 × 10^9/L) and neutrophil counts (2.5 × 10^9/L) were within normal range. Vitamin B_{12} and folate levels were normal, and serum erythropoietin was increased in all but 3 patients tested (median, 908 mIU/mL [range, 29-3000]). Median number of red blood cell units transfused per month was 4 (range, 0-8). Of note, median ferritin levels were 752 µg/L (range, 43-6000), and median transferrin saturation was 73.6% (range, 9-107), with 35% of the patients displaying patterns of iron overload. Seven of the 40 (17%) patients tested had positive direct antiglobulin test results without signs of hemolysis, and 13 (11%) had concomitant hypogammaglobulinemia.

BM features

BM evaluation most frequently showed normal or increased total cellularity with severe reduction of erythroid precursors; lymphocyte infiltration was present in ~59% of the cases, median 15% of total cellularity, and mostly of the T cell phenotype (64%; Table 1). BM morphology was routinely evaluated in all cases, and diagnosis of associated MDS was supported by the presence of dysplastic changes (>10%), particularly in nonerythroid lineages. Cytogenetic analysis results were abnormal in 14 of the 92 patients tested (15%). In the 9 patients tested, significant deposition of C3, C4d, IgM, and IgG was detected using immunohistochemistry analysis on BM specimens. Supplemental Figure 1A presents a heat map illustrating the extent of deposition. Three of these patients had

Table 1. Baseline characteristics in the overall cohort and different PRCA subgroups

Characteristic	Overall (N = 121)	Primary (n = 27)	Secondary* (n = 94)	*P* value
Sex, n (%)				.7
Male	65 (54)	16 (59)	49 (52)	
Female	56 (46)	11 (41)	45 (48)	
Age, y	61.6 (21.4-93.3)	58.6 (21.4-79.9)	61.9 (27.4-93.3)	>.9
Follow-up duration, mo	34.3 (5.1-403.7)	44.1 (9.2-209)	33 (5.1-403.7)	.5
Hb, g/dL	6.7 (3.5-9.6)	5.9 (3.6-9.6)	6.8 (3.5-9.2)	.15
PLT, ×10^3/µL	255 (7-593)	338.5 (113-593)	215.0 (7-587)	**.004**
ANC, ×10^3/µL	2.5 (0.3-12.8)	3 (0.6-6.7)	2.5 (0.3-12.8)	.2
Reticulocyte count, %	6 (1-44)	4.6 (1-23)	7.7 (1-44)	**.013**
LDH, U/L	202 (92-389)	192 (139-336)	214 (92-389)	.12
Cellularity n (%)				**.057**
Reduced	25 (26)	2 (8.3)	23 (32)	
Normal	28 (29)	10 (42)	18 (25)	
Increased	44 (45)	12 (50)	32 (44)	
BM lymphocyte infiltrate, %	15 (5-91)	15 (10-20)	23 (5-91)	**.05**
Abnormal karyotype (n = 92),† n (%)	14 (15)	1 (1)	13 (14)	.3
Abnormal NGS findings (n = 60), n (%)	21 (36)	2 (3)	19 (32)	.09
Number of mutations	1 (1-6)	1 (1-2)	1 (1-6)	.68
Patients with >1 mutation, n (%)	10 (48)	1 (50)	9 (47)	.29
VAF, %	32.5 (4-51)	10 (5-31)	38 (3-51)	.25

Values are reported as median (range) unless otherwise indicated.
ANC, absolute neutrophil count; LDH, lactate dehydrogenase; PLT, platelets.
Boldface values indicate $P < .05$.
*Associated conditions:

- Primary, 27 (22%)
- Thymoma, 28 (23%)
- Autoimmune disease, 16 (13%)
- Other lymphoproliferative disorder, 10 (8.3%)
- T-LGL, 14 (12%)
- MDS, 26 (21%)

†Karyotype abnormalities were deletion chr(chromosome) Y (n = 5), deletion chr 5q (n = 2), trisomy chr 8, chr 1q gain, deletion chr 20q, CN LOH(Copy Number Loss of Heterozigosity) 22q, t(3;3), 45,XY,der(17)t(17;22)(p11;q11),-22, CN-LOH(1p36.33p32.3), gain(4q21.1q35.2), gain(5q35.3), del(9p24.2p24.1), and del(11q21q25).

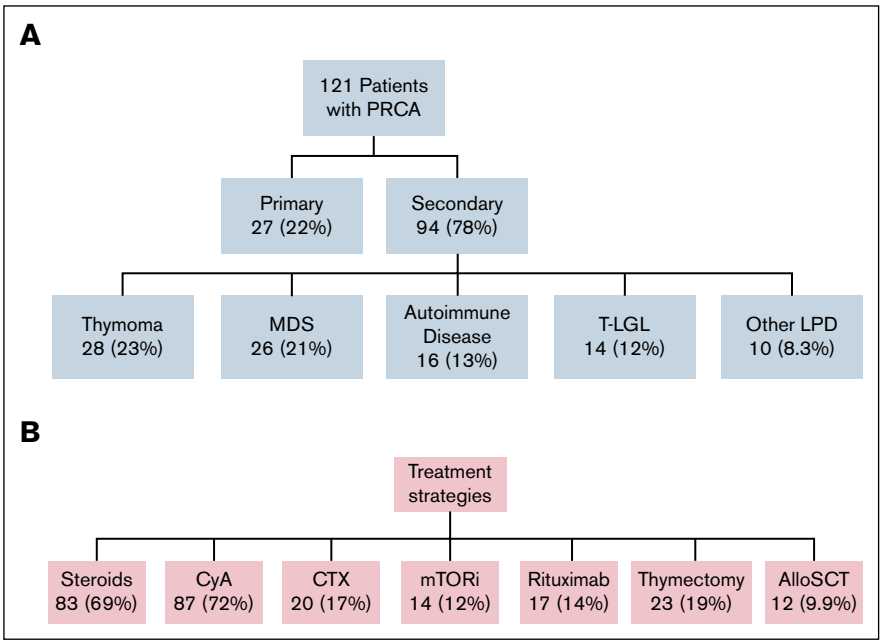

Figure 1. Consort Diagram showing diagnoses and treatment distribution. (A) Distribution of diagnoses across the overall patient cohort with PRCA. (B) Distribution of treatment strategies. AlloSCT, allogeneic stem cell transplant; CTX, cyclophosphamide; LPD, lymphoproliferative disorder.

primary PRCA, whereas 2 had an associated autoimmune disease (systemic lupus erythematosus); 2 of the 9 patients underwent treatment with rituximab and responded. Interestingly, patient 9 (with thymoma-associated PRCA) showed decreased immunological deposits after treatment with CyA (supplemental Figure 1B). As a marker of apoptosis, assessment of caspase-3 expression revealed 1 to 2 positive cells per high-power field in all cases during active disease. Conversely, in the specimen from patient 9 at clinical remission, no apoptotic cells were detected.

NGS analysis

NGS analysis was available for 60 patients (50%; Table 1), and the results were positive in 21 patients (36%). Median number of somatic mutations per patient was 1 (range, 1-6), with multiple mutations in 11 (48%); median VAF was 32.5% (range, 4-51). No difference in NGS positivity was observed in patients older or younger than 60 years (40% vs 29%; P = not significant [ns]). Most common mutations were in genes related to clonal hematopoiesis, such as *TET2* (7) and *DNMT3A* (6); other genes, such as *U2AF1* (3), *EZH2* (2), *ASXL1* (2), *RUNX1* (2), and NRAS (2), were mutated in the context of associated MDS. Mutations in the pathway were detected in 4 patients, whereas *TP53* was mutated in 2, 1 at low VAF and 1 in the context of multiple mutations. Finally, *STAT3* was mutated in 2 patients with associated T-LGL.

Subgroup comparisons

Subset analysis of primary and secondary PRCAs (Table 1) showed no significant differences in baseline characteristics, except for higher reticulocyte count (7.7×10^3 vs $4.6 \times 10^3/\mu L$; $P = .13$) and lower platelet count (215×10^3 vs $338 \times 10^3/\mu L$; $P = .004$) in secondary forms. Moreover, BM from secondary cases was more often hypocellular (32% vs 8%; $P = .05$) and showed a higher percentage of BM lymphocyte infiltration (23% vs 15%; $P = .05$). NGS mutations were mostly found in secondary PRCAs (41% vs 15%; P = ns) and at higher VAFs (38 vs 10; P = ns). Among secondary forms, we focused on MDS and T-LGL, which are common hematologic differentials of PRCA (supplemental Table 1). Patients with MDS presented with significantly lower median platelet counts (183×10^3 vs $267 \times 10^3/\mu L$; $P = .04$) and neutrophil counts (2.2×10^3 vs $2.9 \times 10^3/\mu L$; $P = .04$) as well as more frequent cytogenetic abnormalities (47% vs 31%; $P = .02$), including trisomy 8, del20q, and del5q. Somatic mutations were present in 47% of the patients at a median VAF of 40.5% (range, 4-49) and were more often multiple (71% vs 48%; $P = .001$). On the other hand, PRCA with associated T-LGL showed significantly higher Hb levels (7.6 g/dL vs 6.3 g/dL; $P = .04$) and reticulocyte counts (12×10^3 vs $5.8 \times 10^3/\mu L$; $P = .04$), consistently normal cytogenetics, and NGS positivity in 6 of the 10 evaluable patients ($P = .035$), 2 of which were in the STAT3 gene.

Management

Concerning management (Table 2; Figure 1B; supplemental Table 2), median time from presentation to treatment was 2 months (range, 1-204), and median number of therapy lines was 3 (range, 1-12).

Regarding specific therapies, 69% of the patients received steroids (median dose, 1 mg/kg per day of prednisone), with an overall response rate of 49%, of which 31% were complete. Median duration of treatment was 6.2 months (range, 0.3-99.6), and reasons for discontinuation included persistent response in 14% of the patients, no response (39%), relapse (14%), and toxicity (7%). CyA was used in 87 patients (72%). Median starting dose was 3 mg/kg per day, adjusted for attaining 100 to 150 ng/mL of blood levels in the first 2 months of therapy and for minimizing toxicity, resulting in a median dose over the treatment course of 200 mg/day (range, 75-800). CyA achieved a response in 61% of the cases, 47% of which were complete. Specifically,

Table 2. Treatment patterns and outcomes in the overall cohort

Treatment/outcome	Overall (N = 121)
Steroid, n (%)	83 (69)
NR	41 (51)
CR	25 (31)
PR	14 (18)
CyA, n (%)	87 (72)
NR	33 (39)
CR	40 (47)
PR	12 (14)
CTX, n (%)	20 (17)
NR	12 (63)
CR	2 (11)
PR	5 (26)
mTORi, n (%)	14 (12)
NR	4 (29)
CR	8 (57)
PR	2 (14)
Rituximab, n (%)	17 (14)
NR	12 (70)
CR	2 (12)
PR	3 (18)
Thymectomy, n (%)	23 (19)
NR	13 (62)
PR	5 (24)
Thymectomy before PRCA diagnosis	3 (14)
Thymus irradiation, n (%)	5 (4.1)
NR	1 (20)
PR	4 (80)
No. of therapies, median (range)	3.0 (1.0-12.0)
AlloSCT, n (%)	12 (9.9)
NR	8 (67)
CR	4 (33)
Deaths, n (%)	36 (30)

AlloSCT, allogeneic stem cell transplant; CTX, cyclophosphamide; NR, no response.

rate of CR progressively increased from 29% after 1 month of therapy to 70% at 12 months (Figure 2A), was significantly associated with lower absolute neutrophil counts at diagnosis ($P = .009$), and showed a trend toward higher response in younger patients ($P = .09$) and shorter time from presentation (1.9 in responders vs 2.8 months in nonresponders; $P = .08$). Notably, most patients receiving CyA also had a background of steroids, which were the initial treatment in most cases. Median time to first response was 3.8 months (range, 1.2-7.8), and median duration of treatment was 13 months, although extremely variable (range, 0.3-99.6). Of note, 20 of the 87 patients (23%) were able to discontinue therapy for persistent response after a median of 20 months (range, 8-60). Overall, ~29% of the patients relapsed during CyA tapering and required further therapy line; other reasons for discontinuation included no response (11%) and toxicity (11%). Other treatment strategies included oral cyclophosphamide in 20 patients (37% response; 11% complete) and rituximab in 16 (33% response); mTORi (sirolimus or everolimus) were used in 14 patients and induced response in 71% of the cases (57% complete). Overall, 12 patients (10%) underwent hematopoietic stem cell transplant, 8 of whom had associated MDS (31%; $P = .001$), one-third of whom responded. Concerning patients with thymoma, 23 of the 28 patients (82%) underwent thymectomy, obtaining a response in 42%, all partial; of these, all but 2 patients also received CyA, with a response in 15 of the 21 patients. Five patients also received thymus irradiation, 4 of whom exhibited PR. No major differences were found regarding management of primary and secondary PRCAs except for a trend in higher use of steroids in primary forms (85 vs 64%; $P = .06$). When considering patients with MDS, this difference became even more pronounced, with only 31% of the latter receiving steroid treatment ($P < .001$) and no patient receiving mTORi. Interestingly, reticulocyte dynamics (supplemental Table 3) showed progressive increase by week 8 onward in responding patients, which may be an early indicator of response to therapy.

Figure 2B depicts sequential treatment strategies for all patients. Steroids and CyA were most often the first treatment strategy, except for those who underwent thymectomy. mTORi or cyclophosphamide was used in later lines as well as allogenic hematopoietic stem cell transplantation. Figure 3 details treatment patterns in the 14 patients who received mTORi. Notably, most patients with previous response to CyA who switched to mTORi maintained CR; 1 patient who achieved PR with steroids and CyA attained CR with mTORi, whereas 1 patient who did not respond to either steroids or CyA finally achieved a response with mTORi. Of the 2 patients treated with frontline mTORi, 1 achieved PR.

Survival

Overall, 36 patients died (30%) at a median of 113 months from presentation. The major cause of mortality was infection (38% of the cases); 4 patients died because of progression of MDS to acute myeloid leukemia, whereas 2 died of transplant-related complications, and 1 patient died of metastatic thymic carcinoma. We observed a trend toward higher mortality in secondary PRCA and significantly increased mortality rate among patients with concomitant MDS (64%; $P < .001$), which had a shorter median overall survival of 39 months (vs 113 months; $P < .0001$). In multivariate Cox regression analysis, MDS remained an adverse prognostic factor for survival (hazard ratio, 2.73; 95% confidence interval, 1.21-6.17; $P = .01$; supplemental Table 4A-B; supplemental Figure 2). Notably, no differences in survival were observed according to response to therapy.

Discussion

In this large series of adult patients with acquired PRCA, we observed a very heterogeneous presentation. Primary PRCA accounted for 20% of the cases only, whereas most were secondary to thymoma (23%), autoimmune conditions, or hematological malignancies, such as MDS (21%) or T-LGL. As a matter of fact, PRCA remains primarily a morphological diagnosis and a diagnosis of exclusion, which is therefore highly influenced by the depth and accuracy of diagnostic workup. The broad clinical variability and heterogeneity of associated conditions frequently

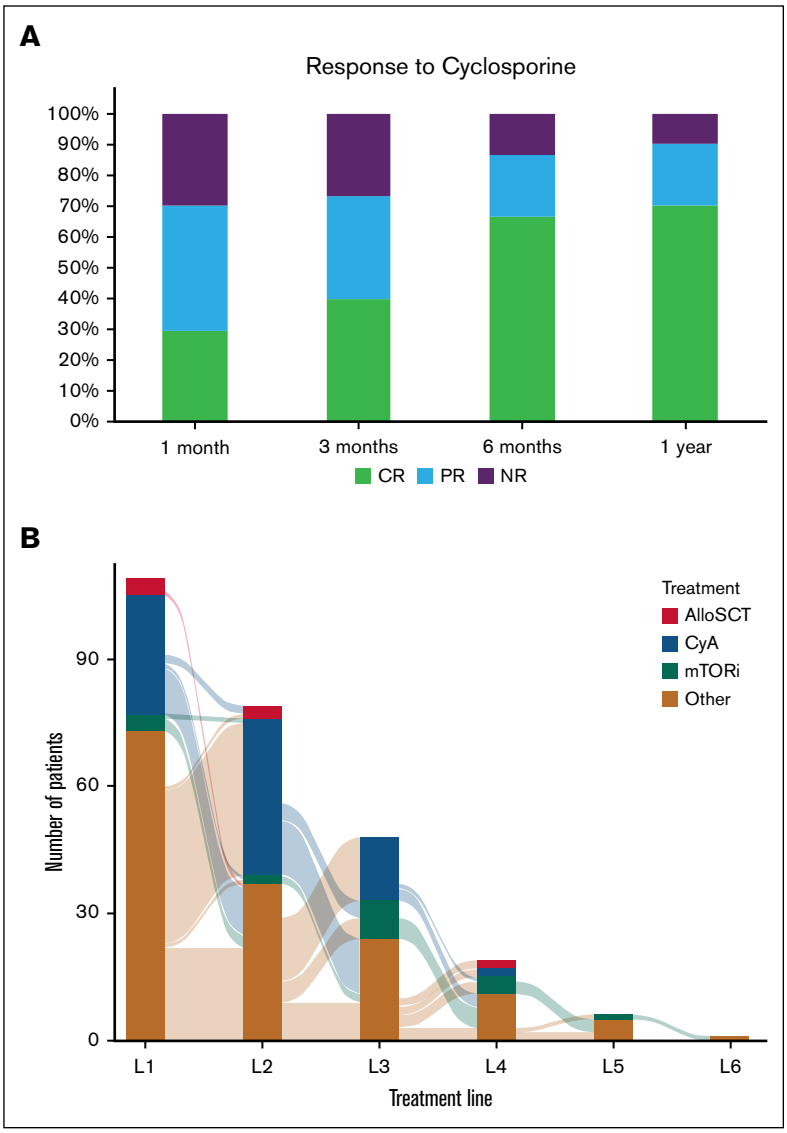

Figure 2. Response to cyclosporine and treatment sequencing. (A) Response rates to cyclosporine over time. (B) Alluvial plot for sequential treatment lines in the overall cohort. AlloSCT, allogeneic stem cell transplant; CTX, cyclophosphamide; mTORi, mTOR inhibitors; NR, no response; other, steroids.

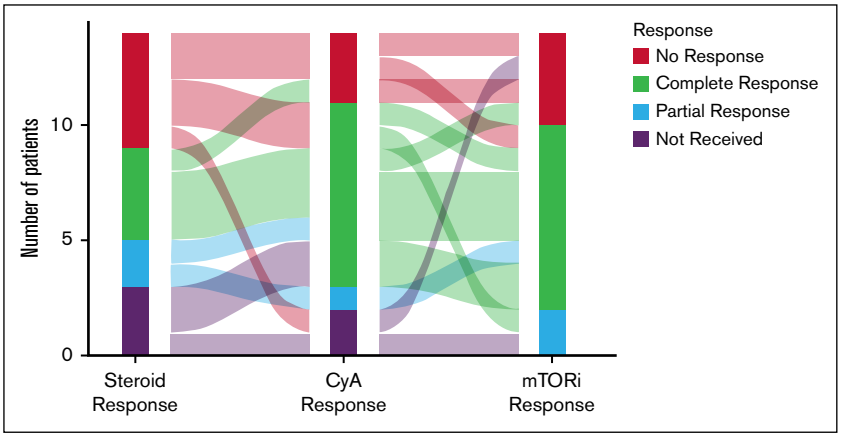

Figure 3. Alluvial plot for treatment pathway in mTORi treatment recipients.

led to delays in establishing diagnosis and, consequently, initiating appropriate treatment, ultimately reducing response rates. In our series, the median time to first treatment was 2 months, and a trend for worse response to CyA was noted in those delaying the start of treatment.

Although early immune trigger and specific antigenic target remain incompletely understood, the autoimmune nature of the pathogenesis is well established.[10] Immune attack can be mediated by cytotoxic T cells or driven by humoral mechanisms, as suggested by the prominent deposition of immunoglobulins and complement fractions on BM precursors observed by immunohistochemistry in our patients. The relative contribution of each pathway likely varies according to associated conditions and may aid in harnessing the choice of treatment (ie, CyA and mTORi in T-cell–mediated forms vs rituximab in humoral ones).

In this study, we first explored the molecular landscape of PRCA and found a heterogeneous profile marked by the presence of clonal hematopoiesis and mutations typical of the associated condition, such as STAT3 variants in T-LGL and canonical myeloid driver mutations in patients with MDS. The latter are often underrecognized, delaying proper treatment.[12,13] All in all, the integration of NGS analysis with clinical and hematologic features of patients with unexplained hyporegenerative anemia appears as an appealing tool to inform the differential diagnosis of secondary PRCA.[14,15]

Regarding management, immunosuppressive therapy remains the cornerstone of treatment, even in thymoma-associated PRCA, where thymectomy or thymic irradiation generally yielded suboptimal outcomes, with low CR rates and frequent relapses. In fact, although the response to thymectomy in our cohort was higher than in other published series, it must be noted that most patients were receiving concomitant CyA. Steroids were used in most patients, achieving CR in approximately one-third, and can be useful during the diagnostic phase, but long-term treatment is discouraged because of prominent side effects. Consistent with published evidence, CyA was the most frequently used first-line therapy and most effective in our cohort, administered at a median dose of 200 mg/d and yielding CR in about half of the treated patients, further supporting a central role for autoreactive T cells in PRCA pathogenesis.[16,17] The timing of response evaluation is pivotal in BM failures treated with immunosuppressive agents, and it is known that at least 3 months should be awaited in primary aplastic anemia. Although the median time to first response was similar for PRCA in our cohort (3.8 months), this is not standardized, and earlier responses were observed as early as 1.2 months of treatment. Similarly to acquired aplastic anemia, treatment should be continued for ~2 years. In our series, nearly one-fourth of patients were able to discontinue CyA after a median of 20 months, achieving treatment-free remission, thus minimizing long-term toxicity.

As for second-line options, mTORi emerged as a promising strategy, achieving CR in nearly 60% of the patients, most of whom had failed or relapsed after CyA.[18] Whether frontline treatment with mTORi may improve disease outcomes requires further investigation.

Mortality was nonnegligible, occurring in up to 30% of the patients at a median of 10 years from diagnosis. The leading cause of mortality was infectious complications, underscoring increased frailty associated with prolonged immunosuppressive therapy.

Finally, the separate analysis of patients with MDS with erythroid hypoplasia revealed that this group showed more severe cytopenias, though not in the range of MDS, with multiple cytogenetics and molecular abnormalities and higher mortality. However, this patient population showed a similar response to immunosuppression as compared to primary PRCA, thus deserving a diagnostic definition.

We acknowledge several limitations of this retrospective multicenter study. First, the diagnosis of PRCA is essentially morphological and remains largely a diagnosis of exclusion, and diagnostic interpretation may vary across centers, particularly regarding the thoroughness with which associated conditions are investigated. Moreover, center-specific differences in treatment approaches, together with the 18-year-long time span of the study, may have contributed to heterogeneity in management and clinical outcomes. Nonetheless, given the rarity of this condition, we believe that our cohort provides a valuable snapshot of real-world clinical practice and contributes meaningful insights into the management of this condition. In particular, PRCA should be promptly considered in patients presenting with hyporegenerative anemia. BM evaluation should not be deferred, and once diagnosis is confirmed, treatment with immunosuppressants should be initiated without delay.

In conclusion, PRCA is a rare disorder with highly heterogeneous presentations that may delay diagnosis. Future studies incorporating systematic molecular analyses will be essential in refining diagnostic accuracy and improving patient classification. Nonetheless, immunosuppressive therapy achieves good response rates independently of associated conditions, with CyA representing a reliable first-line option and mTORi emerging as an attractive rescue strategy.

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Authorship

Contribution: F.V., B.F., W.B., and A.K. were involved in conception and design; F.V., M. Michel, J.V., S.P-.P., R.T., S. Gandhi, S. Gogoi, M.W., O.R., M.T.L.-S., S. Giammarco, M.A.M., M. Memoli, A.G., G.M., Y.W.M., A.C., M.H., M.N., M.J.-J., F.A.B., A.P.-V., T.J.G.-L., C.C., M.B., G.L.P., F.P., W.B., A.K., and B.F. were involved in the provision of study materials or patients; G.A.C. was involved in provision of histopathological material and images; F.V., J.V., S. Gogoi, M.W., B.F., and A.K. were involved in collection and assembly of data; F.V., J.V., B.F., W.B., and A.K. were involved in data analysis and interpretation; and all authors wrote and revised the manuscript for important intellectual content and are thus accountable for all aspects of the work.

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