Adult pure red cell aplasia at Universitas Academic Hospital, Bloemfontein, South Africa: A 9-year review

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Background. Pure red cell aplasia (PRCA) is characterised by severe normochromic, normocytic anaemia and partial or complete absence of reticulocytes from the peripheral blood. With bone marrow of normal cellularity, an almost complete absence of erythroblasts but preservation of other cell lines is observed. It may be congenital or acquired, with the latter presenting as a primary haematological disorder or secondary to various contributing factors. Management focuses on treatment of the underlying cause and supportive transfusions. Occasionally, immunosuppression or intravenous immunoglobulin (IVIG) is required.
Objectives. To describe the clinical characteristics, treatment and outcomes of adult patients diagnosed with PRCA at Universitas Academic Hospital (UAH) in Bloemfontein, South Africa, from 2010 to 2018.
Methods. A retrospective descriptive file review was performed. All adult patients diagnosed with PRCA and treated in the Division of Clinical Haematology at UAH during the study period were included. Variables recorded included demographic information, clinical details of the PRCA diagnosis, classification of the PRCA, HIV and parvovirus B19 test results, results of special investigations, medical and drug history, treatment and response to treatment.
Results. Twenty-seven patients' files were included, with a female predominance (*n*=22; 81.5%). The median age at diagnosis was 35 years (range 20 - 62). The median number of days from onset of symptoms to date of diagnosis was 61 days (range 27 - 114). Approximately half (*n*=13; 48.2%) of the patients presented with a haemoglobin concentration of 1 - 3 g/dL. Most patients (*n*=26; 96.3%) were infected with HIV, with 76.9% (*n*=20) having a suppressed viral load. Parvovirus B19 infection accounted for 44.4% of cases (*n*=12), and all these patients were HIV positive. Lamivudine was a probable cause of PRCA in 18.5% of cases, although the true causal relationship was uncertain. Corticosteroids and IVIG were first-line therapy in 44.4% (*n*=12) and 37.0% (*n*=10) of cases, respectively. Thirteen patients (48.2%) achieved a complete response and 7 (25.9%) a partial response, while 2 (7.4%) showed no response, with continued transfusion dependence.
Conclusion. In this population, women were disproportionately affected by PRCA. HIV was the single most important cause of acquired PRCA, which was independent of virological control. Parvovirus B19 and drugs were also important causes of acquired PRCA and played a critical part in the evaluation and work-up of PRCA. Nearly half of the patients achieved a complete response to therapy, which was sustained over 24 months.

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Pure red cell aplasia (PRCA) is a medical condition characterised by severe normochromic, normocytic anaemia, partial or complete absence of reticulocytes from the peripheral blood, and the absence of erythroblasts from an otherwise normal bone marrow. It can present as an acute disease in childhood and as either an acute or a chronic disease in adults.[1] PRCA has no racial or geographical predilection, affects all age groups, and may be congenital or acquired. Acquired disease may present as a primary haematological disorder or secondary to several contributing factors and underlying conditions. A simplified classification of PRCA is presented in Fig. 1.[2,3]

Patients with PRCA mainly present with signs and symptoms of anaemia. Owing to the gradual decline in haemoglobin (Hb) secondary to impaired erythropoiesis, the patient's haemodynamic system is often able to compensate and symptoms may be less pronounced than expected. Patients with secondary PRCA may have

a relevant exposure history, manifest the additional symptoms, signs and laboratory features suggestive of a specific associated underlying condition, or have typical bone marrow features in the case of parvovirus B19 infection.[2,4] The work-up of a patient with PRCA concentrates on finding the underlying cause and its treatment, specifically in the setting of acquired secondary PRCA.[1] Despite the lack of a recommended standard therapy, apart from treating the underlying cause, remission can be achieved in the majority of patients.[5]

Limited information is available pertaining to the clinical characteristics, causes, treatment and outcomes of adult patients diagnosed with PRCA in the South African (SA) or sub-Saharan African setting. This project aimed to describe the clinical characteristics, treatment and outcomes of adult patients diagnosed with PRCA at Universitas Academic Hospital (UAH) in Bloemfontein,
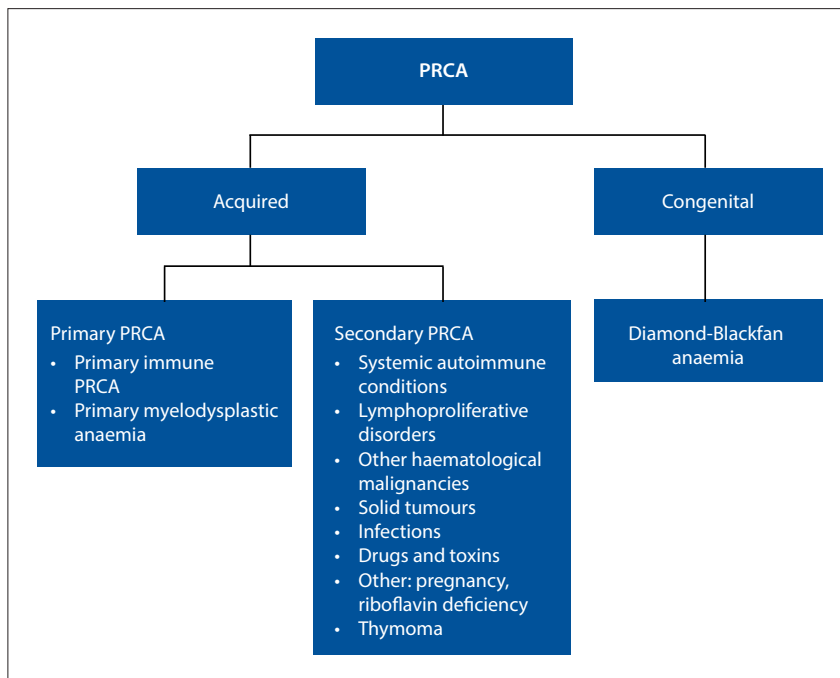
Fig. 1. Diagrammatic representation of the aetiology of PRCA. (PRCA = pure red cell aplasia.).

SA. Our objectives were to describe the association between PRCA and its known secondary causes and to determine patients' response to therapy.

Methods
Study design
A retrospective descriptive review of patient files was conducted.

Setting
The study was performed in the Division of Clinical Haematology, UAH. This tertiary hospital is a referral centre for adult haematology patients from Free State and Northern Cape provinces and Lesotho, and serves a population of ~7 million.

Sample
All adult patients (defined as ≥18 years of age) diagnosed with PRCA and referred to UAH between 1 January 2010 and 31 December 2018, for whom clinic files were available, were included in the study sample. These files were identified from the PRCA informal database at the Clinical Haematology Clinic. At the time of the study, the database contained the files of 51 patients diagnosed with PRCA.

Ethical considerations
Approval to perform this study was obtained from the Health Sciences Research Committee of the University of the Free State (UFS) (ref. no. UFS-HSD2019/0871/2611). The head of the Department of Internal Medicine,

School of Clinical Medicine, UFS, and the Free State Province Department of Health granted permission to conduct the research. No identifiable information was recorded, and each patient file was allocated a unique number to ensure confidentiality and protect the identity of the patients. Data were stored on a password-protected computer.

Measurement
Patient records were identified and obtained from the Clinical Haematology Clinic at UAH. Data were collected and managed using the Research Electronic Data Capture (REDCap) facility hosted by the UFS. REDCap is a secure, web-based software platform designed to support data capture for research studies.[6]

Information was collected on the following variables: the patient's age and gender, clinical details of their PRCA diagnosis, classification of the PRCA, HIV and parvovirus B19 test results, results of special laboratory investigations, medical and drug history, treatment administered, and the patient's response to the treatment.

Statistical analysis
All data were transferred from REDCap to an Excel spreadsheet, version 2016 (Microsoft Corp., USA) and given to the biostatistician for analysis. Results for categorical variables were summarised by frequencies and percentages, and percentiles were used for numerical variables. Data

analysis was performed by the Department of Biostatistics, UFS, using SAS version 9.4 (SAS Institute Inc., USA).

Results
Of the 51 files recorded in the Clinical Haematology Clinic informal database, 21 could not be traced. These files could not be found in the Haematology Clinic or in the Records Department of Universitas Hospital and were either misplaced or lost. The remaining 30 files were retrieved, of which 2 fell outside the study period and 1 patient was incorrectly placed on the PRCA database and had another cause of anaemia. In total, 27 patient files were included in the final analysis.

Demographic variables
The study comprised mostly female patients (n=22; 81.5%). The median age at diagnosis was 35.9 years, ranging between 20 and 62 years.

Presenting symptoms
The median (interquartile range) number of days from onset of symptoms to the date of diagnosis was 61 (27 - 114). All the patients presented with symptomatic anaemia.

Baseline haemoglobin level
A third (n=9; 33.3%) of the patients presented with an Hb concentration of 1 - 3 g/dL, 13 (48.2%) had an Hb concentration of 3.1 - 5 g/dL, and the remaining 5 (18.5%) had a concentration of 5.1 - 7 g/dL. No patient presented with an Hb concentration >7 g/dL.

Classification of causes
All the patients had acquired PRCA, and according to causality assessment, 20 (74.1%) of the cases had documented secondary causes. Although approximately one-quarter (n=6; 22.2%) were diagnosed as having primary (idiopathic) PRCA, 5 of these patients were HIV positive. In a single patient, the cause could not be established. In more than two-thirds of the female patients (n=15/22; 68.2%), secondary causes were established. No patients had underlying autoimmune conditions, lymphoproliferative disorders, solid tumours, haematological malignancies, thymomas or primary myelodysplasia at the time of diagnosis of PRCA. Table 1 summarises the causes of PRCA in the study population as recorded in the patients' files.

Thymoma
A chest X-ray (CXR) was performed on 10 patients (37.0%) to evaluate for a retrosternal

mass, although none had positive radiological findings. Only 1 of the 10 patients with a CXR was referred for thoracic computed tomography (CT) to further investigate for a thymoma, which was excluded on the CT scan. Seven patients (25.9%) underwent chest CT without a preceding CXR to investigate for a thymoma. One patient had CT features suggestive of a thymoma and was referred for thymectomy, with histological investigations showing normal thymus tissue.

HIV

HIV status and control
Almost all the patients (*n*=26; 96.3%) were HIV positive at baseline. Twenty (76.9%) of the HIV-positive patients had a suppressed HIV viral load, 3 (11.5%) had a non-suppressed viral load, and the remaining 3 patients' files did not contain information on the viral load.

Management of HIV
All HIV-positive patients were on combined antiretroviral therapy (cART). Approximately two-thirds (*n*=17; 65.4%) were on standard first-line therapy comprising a fixed-dose combination tablet consisting of tenofovir, emtricitabine and efavirenz. Table 2 summarises the cART regimens used by the HIV-positive patients in this cohort.

Drugs
Drugs were identified as the probable cause of PRCA in 5 cases (18.5%). Lamivudine was the probable offending agent in all of these patients. One patient, who did not use lamivudine, was being treated with dapsone for molluscum contagiosum of the left eyelid at the time of diagnosis of PRCA. However, PRCA was not attributed to dapsone in view of a positive parvovirus B19 polymerase chain reaction (PCR) result. This patient had a complete response to intravenous immunoglobulin (IVIG) despite continued dapsone therapy.

Parvovirus B19 infection
Parvovirus B19 immunoglobulin M (IgM) serology was determined

Table 1. Causes of PRCA in the study population as recorded in the patient files (*N*=27)

Cause	*n* (%)
Infections	
HIV	26 (96.3)
Parvovirus B19*	12 (44.4)
Drugs (lamivudine)	5 (18.5)
Pregnancy	3 (11.1)
Primary autoimmune PRCA	6 (22.2)

PRCA = pure red cell aplasia.
*All patients with parvovirus B19 were HIV positive.

Table 2. Patients on other antiretroviral therapy involving non-standard regimens* (*N*=9)

Non-standard antiretroviral regimen	*n* (%)
Abacavir + lamivudine + efavirenz	2 (22.2)
Lopinavir/ritonavir + efavirenz	1 (11.1)
Lamivudine + stavudine + lopinavir/ritonavir	1 (11.1)
Lamivudine + stavudine + efavirenz	1 (11.1)
Lamivudine + tenofovir + lopinavir/ritonavir	1 (11.1)
Lamivudine + tenofovir + efavirenz	3 (33.3)

*17/26 HIV-positive patients (65.4%) were treated with a fixed-dose combination tablet consisting of tenofovir, emtricitabine and efavirenz.

for 14 patients (51.9%), with all having a negative result. Parvovirus PCR was performed on 26 patients (96.3%), with a positivity rate of 38.5% (*n*=10). Two patients did not have a positive parvovirus PCR result or suggestive serology, but presented with typical bone marrow findings and were diagnosed as having parvovirus B19-associated PRCA. Parvovirus B19-associated PRCA contributed to 44.4% (*n*=12) of all PRCA cases. All cases of parvovirus B19 were seen in the setting of HIV infection. HIV and PCR-confirmed parvovirus B19 co-infection accounted for 40.0% (*n*=10/25) of cases in this study. The distribution of patients with parvovirus B19-associated PRCA with regard to PCR results, bone marrow findings and treatment is shown in Fig. 2.

Pregnancy
Of the 15 women with an identified secondary cause of PRCA, 3 (20.0%) were pregnant. All 3 pregnant patients were HIV positive with suppressed viral loads on first-line cART consisting of tenofovir, emtricitibine and efavirenz, and had negative parvovirus PCR results. These patients were treated with corticosteroids (CS) as part of their first-line therapy, with all having a complete response.

One of the pregnant patients in this series had a subsequent diagnosis of scleroderma 19 months after the initial PRCA diagnosis. She was treated with CS and achieved a complete response to therapy. The same patient was diagnosed with cold autoimmune haemolytic anaemia (AIHA) 3 years after the initial diagnosis of PRCA, for which she received CS as first-line therapy, followed by azathioprine 4 months later.

Comorbid conditions
The presence or absence of comorbidities was documented in 19 patients' files (70.4%), and of these patients 15 (78.9%) were identified with one or more comorbidities, as shown in Table 3.

A female patient with primary idiopathic PRCA was simultaneously diagnosed with severe polyarthritis with a low-titre (1:80) antinuclear antibody at the time of presentation. There were insufficient Systemic Lupus International Collaborating Clinics criteria[7] to make a diagnosis of systemic lupus erythematosus or any other autoimmune condition. She achieved a complete response to first-line CS therapy lasting >24 months.

Treatment of PRCA
Parvovirus B19-related PRCA
Eight of the 10 patients who had PCR-confirmed parvovirus B19 were treated with IVIG, with the remaining 2 attaining spontaneous remission on cART alone. Of the 2 PRCA cases with morphological bone marrow features of parvovirus B19, 1 was treated with IVIG and the other went into spontaneous remission on cART, as shown in Fig. 2.

Three HIV-positive patients, of whom 2 were PCR positive for parvovirus B19 and 1 had morphological bone marrow features of parvovirus B19-induced PRCA when diagnosed, had spontaneous remission of PRCA without treatment with IVIG, CS or adapting their antiretroviral therapy. Of the 9 patients treated with IVIG, 5 had a complete response to the first course of IVIG and 4 required a second course.

Drug-induced PRCA
Two of the 5 patients with PRCA attributed to lamivudine were managed by replacing it in the HIV treatment regimen with an alternative nucleoside reverse transcriptase inhibitor. Both patients were lost to follow-up, so their response to drug withdrawal was not recorded. The other 3 patients were managed with CS therapy. Owing
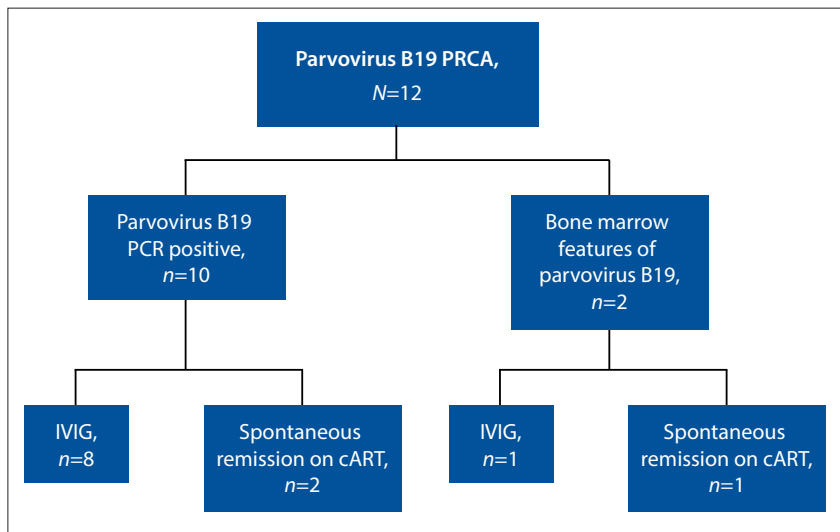
Fig. 2. Diagrammatic representation of patients with parvovirus B19-related PRCA, treatment and response to treatment. (PRCA = pure red cell aplasia; PCR = polymerase chain reaction; IVIG = intravenous immunoglobulin; cART = combined antiretroviral therapy.)

Table 3. Comorbid conditions in patients with PRCA at the time of diagnosis (N=19)*

Comorbid condition	n (%)
c-ANCA and p-ANCA positive	1 (5.3)
Current pulmonary tuberculosis on continuation therapy	1 (5.3)
Deep-vein thrombosis	1 (5.3)
Familial hypercholesterolaemia	1 (5.3)
Gastritis	1 (5.3)
High-output cardiac failure due to anaemia	1 (5.3)
Hypertension	3 (15.8)
Molluscum contagiosum	1 (5.3)
Pregnancy-induced hypertension	1 (5.3)
Previous pulmonary tuberculosis	5 (26.3)
Severe polyarthritis with a low-titre (1:80) antinuclear antibody	1 (5.3)
Stage 5 chronic kidney disease due to HIV-associated nephropathy	1 (5.3)
Subclinical hypothyroidism	1 (5.3)
Type 2 diabetes mellitus	1 (5.3)
Vitiligo	1 (5.3)

PRCA = pure red cell aplasia; c-ANCA = antineutrophil cytoplasmic antibody, cytoplasmic; p-ANCA = perinuclear antineutrophil cytoplasmic antibody.
*The total number of comorbidities was N=21, as two patients each had two comorbidities.

to the retrospective nature of our study, data in these patients' files were incomplete.

First-line therapy
Both IVIG and CS were used as first-line therapy, with the choice of agent guided by the underlying cause of PRCA.

Ten patients were managed with IVIG (400 mg/kg/d for 3 days according to our institutional protocol) as first-line therapy, with 6 receiving one dose, 2 receiving two doses and 2 receiving three or more doses of IVIG. Nine of these patients had parvovirus B19-associated PRCA (Fig. 2). One HIV-positive, virologically suppressed patient with no positive results for any parvovirus B19 tests also had no other clinical or laboratory information available to support the use of IVIG. Nevertheless, this particular patient was treated with IVIG as first-line therapy with a complete response.

Oral CS were used as first-line therapy in the remainder of the patients (n=12; 44.4%). All these patients received a starting dose of 1 mg/kg/d in line with unit guidelines. All pregnant patients with PRCA received CS as first-line therapy, with a 100% complete response rate. Three (60.0%) of the 5 patients on lamivudine were treated with CS as first-line therapy: 1 had complete response to therapy, 1 had a poor response to the initial dose and responded to an increased dose, and 1 had no response to CS alone.

Second-line therapy
Of the 22 patients treated with either IVIG (n=10) or CS (n=12) as first-line therapy,

7 did not respond to the first-line therapy and therefore required second-line therapy. Of these 7, 3 (42.9%) were treated with another course of CS and the other 4 received IVIG as second-line therapy. The patients treated with IVIG as second-line therapy all had parvovirus B19-associated PRCA and received IVIG as first-line therapy. Two of these received additional doses of IVIG for relapse after the initial administration of IVIG. The other 2 did not respond to the first course of IVIG, but responded to a second course. Of the 27 patients whose files we reviewed, none was treated with cyclosporine.

Third-line therapy
One patient, an HIV-positive woman with a suppressed HIV viral load and treated with emtricitabine, tenofovir and efavirenz, who did not have parvovirus B19-associated PRCA, received IVIG as third-line therapy. The patient was initially treated with CS, with a poor response. Second-line therapy included a higher dose of CS and the addition of cyclophosphamide, also with a poor response. She was then treated with IVIG 1 g/kg/d for 3 days, without a documented response. The patient was later followed up at the clinic and was found to be in remission. It is uncertain whether the cART regimen was changed at her base hospital. No patients with refractory PRCA were treated with cyclosporine.

Dose of IVIG
Of the patients who were managed with IVIG, 4 received a dose calculated at 400 mg/kg/d for 2 - 3 days. One of these 4 patients was subsequently put on a maintenance dose of 0.4 mg/kg/d, 1 day every 4 weeks. Three patients were managed with a dose of 1 g/kg/d for 2 - 3 days. The remainder of the patients managed with IVIG had insufficient data to determine the dose.

Response to first-line therapy
A complete response (defined as an increase in the Hb concentration to >10 g/dL) was achieved in 13 (48.2%) of the patients after receiving first-line therapy. Two patients (7.4%) showed a partial response (Hb <10 g/dL and transfusion independent), and 7 patients (25.9%) showed no response, with a continued dependence on transfusions and were subsequently transferred to second-line therapy.

Of the patients who achieved either a complete or a partial response, 88.9% (n=16/18) maintained their specific response for >24 months, while the remaining 2 patients maintained their response for 1 - 3 months.

One patient was diagnosed with PRCA secondary to a persistent parvovirus B19 infection. This patient was initially managed with IVIG with a poor response and subsequently placed on maintenance IVIG therapy. The patient was followed up at the referring centre, so no follow-up data were available in the file regarding the response to maintenance IVIG therapy.

Remission and relapse rates

Remission and relapse data were available for 25 patients, who all achieved at least a partial response. Eighteen patients (72.0%) achieved an Hb concentration of 12.0 g/dL with transfusion independence. In 5 patients (20.0%), the highest Hb concentrations ranged between 10.1 and 12.0 g/dL with transfusion independence, and the remaining 2 patients (8.0%) achieved a transfusion-independent Hb concentration of 7.1 - 10.0 g/dL. A complete response was therefore achieved in most patients (*n*=23/25; 92.0%).

Duration of response

Of the 18 patients who achieved a complete response (Hb >12 g/dL and transfusion independence), 2 (11.1%) maintained a complete response for <3 months. The remaining 16 patients (88.9%) maintained a complete response for >24 months.

Transfusion

Transfusion data were available in 24 patients' files. Eleven (45.8%) received <5 U of red cell concentrate (RCC), 7 (29.2%) received 6 - 10 U, 3 (12.5%) received 11 - 15 U and 3 received 16 - 20, 21 - 30 and >30 U (*n*=1/24; 4.2% each), respectively.

Discussion

This study investigated the clinical characteristics, treatment and outcomes of adults diagnosed with PRCA in a high HIV prevalence setting.[8,9] All but one of the patients in the cohort were HIV positive, most of whom had suppressed HIV viral loads at the time of presentation. Viral infections such as HIV and parvovirus B19 accounted for 65.0% of the secondary causes of PRCA, with 40.0% of patients having HIV and parvovirus B19 co-infection. Parvovirus B19-induced PRCA in HIV-positive adults has been well described.[10-13] Lamivudine used for the treatment of HIV was the probable cause of PRCA in 18.5% of cases. However, a clear association between lamivudine and its causality of PRCA in our study is uncertain owing to inadequate follow-up records.

HIV confers a multifaceted risk for PRCA on its host. Firstly, the HIV-infected host is susceptible to parvovirus B19, an independent cause of PRCA,[5] which has been demonstrated in our study. Secondly, many drugs used for the treatment of HIV and its associated opportunistic infections have been described as causing PRCA.[2,5,8] In our series, only lamivudine was identified as a probable cause. Thirdly, HIV is a risk factor for lymphoproliferative and other haematological malignancies that are known to cause PRCA.[2,14] These conditions were not noted in the study population. Finally, in our series, primary immune-mediated PRCA was the documented diagnosis in 6 patients (22.2%). However, 5 (83.3%) of these were HIV positive with a suppressed viral load at the time of diagnosis. It is debatable whether HIV was a trigger for the autoimmune process or the presence of HIV infection was coincidental.

A notable finding of this study was that the large number of HIV-positive patients had well-controlled HIV, as demonstrated by their suppressed viral loads at the time of PRCA diagnosis. This finding suggests that HIV as a risk factor for PRCA is not dependent on the effect of the viral load or viral pressure on the host.

Parvovirus B19 is a well-documented cause of secondary PRCA[2,5] in immunocompromised hosts, notably in HIV-infected individuals. These patients are unable to mount an adequate antibody response to parvovirus B19 owing to underlying immunosuppressive conditions.[5] The poor antibody response to parvovirus B19 in this population is also a cause of false-negative serology results. This association has been confirmed in our study, where all the parvovirus B19 IgM serological investigations that were performed yielded negative results, while parvovirus B19 PCR was positive in many of these cases. Furthermore, the two patients with morphological bone marrow features of parvovirus B19 both had negative IgM and PCR results. These cases could be associated with genotypes 2 and 3 of the virus, which account for ~25% of parvovirus cases in SA, and could have been missed on conventional PCR assays.[15] In a high HIV prevalence setting, the role of parvovirus IgM is therefore limited and PCR is the investigation of choice to diagnose parvovirus B19 infection as the cause of PRCA.

Our series confirmed that IVIG is an effective therapy for parvovirus B19-associated PRCA in the HIV-positive population, although some patients may require more than one course of IVIG or even maintenance therapy.

It has been assumed that in the three patients who achieved spontaneous remission of parvovirus B19-associated PRCA, adequate immune reconstitution on cART could have contributed to the outcome. Owing to the retrospective nature of this study, it was not possible to obtain further information on the duration of the patients' antiretroviral therapy, or timing of their virological suppression prior to achieving spontaneous remission.

Considering the fact that some patients do attain spontaneous remission with cART and the high cost of IVIG therapy, the exact timing of initiation of IVIG remains an important open question. A factor that may influence the decision whether to administer IVIG is the degree of underlying immunosuppression. Earlier initiation of IVIG in patients with lower CD4 counts may decrease transfusion-related risks and be more cost-effective.

Drugs are known to be an important cause of secondary PRCA and have previously been well described.[2,8,16,17] In the evaluation and work-up of PRCA, a thorough history of prescription and over-the-counter drugs used is therefore of paramount importance. It is imperative to establish a sequential relationship between the patient's drug history and the onset of symptoms. Lamivudine has been documented to be related to the development of secondary PRCA.[8,9] When evaluating an HIV-positive patient with PRCA, it is important to differentiate whether HIV itself or lamivudine, as part of the treatment regimen is the cause of the PRCA. Three HIV-positive patients in our cohort, assumed to have lamivudine-induced PRCA, were managed with CS therapy, which is not the standard approach for drug-induced PRCA. However, CS may have been instituted when the patients did not respond to drug withdrawal. These patients' response to immunosuppression can probably be attributed to immune-mediated rather than drug-induced PRCA. This temporal relationship highlights the important multifaceted causal link between HIV and PRCA.

Pregnancy as a cause of PRCA has been well described.[2,3] An early diagnosis of PRCA is important in this population, as anaemia may have detrimental effects on both mother and fetus as a result of increased physiological demands associated with pregnancy. Although this study was limited in terms of its small size, the pregnant patients, who all had well-controlled HIV, showed a satisfactory response to first-line therapy with CS, suggesting that in this study, PRCA was immune mediated.

Although the most common secondary causes of PRCA have been described as thymoma (10 - 13.21%) and parvovirus B19 (11.3%),[2,18]

no cases of PRCA were attributed to thymoma in this study. This finding suggested that in a high HIV prevalence setting, thymoma may not be an important cause of secondary PRCA compared with parvovirus B19, HIV and drugs.

Although none of the patients in this cohort had other autoimmune conditions at the time of diagnosis of PRCA, one of the pregnant patients, who was parvovirus B19 PCR negative, had a subsequent diagnosis of cold AIHA 3 years after the initial diagnosis of PRCA. The negative parvovirus B19 status was important in this case, as parvovirus B19 is known to cause a transient aplastic crisis in patients with chronic haemolysis.[19] A number of cases have been reported in the literature, and the association between PRCA and AIHA has been described.[20] A second patient had features suggestive of autoimmunity, and at the time of the study was still seen for follow-up consultations.

The finding that none of the patients eligible for evaluation in the series was treated with cyclosporine was unexpected. It is routine practice in the unit to use cyclosporine as second-line therapy for immune-mediated PRCA when no response is observed after 1 - 2 months on CS. Although an explanation for this finding would be speculative, it may reflect the small sample size, and hence the small number of immune-mediated PRCA cases. Response rates of >70% have been reported with the use of cyclosporine, which is generally recommended as standard first- or second-line therapy for immune-mediated PRCA.[21,22]

Supportive management

Most patients in this study received <5 U of RCC, while others received high volumes of blood products. The need for high volumes of blood could have been due to referral delays and prolonged supportive transfusion therapy at base hospitals or failure to respond to therapy. Timeous diagnosis and management of PRCA may have significant cost-saving advantages considering the relatively low cost of first-line therapy compared with transfusion. Apart from the cost of transfusion, blood is a scarce and precious resource, and blood banks in SA often struggle to maintain adequate levels of stock. Blood transfusion is also associated with both short- and long-term complications, with the risk of suffering complications increasing proportionately to the number of transfusions received.[23]

Study limitations

This study had some significant limitations. A major limitation was the large number of files that could not be retrieved, which compromised the representation of PRCA at the study centre. Only patients referred to the Division of Clinical Haematology were included in the study and they are therefore not representative of the population of the Free State Province, which could affect the generalisability of results. Owing to the retrospective nature of this study, not all files could be located, which may indicate poor record keeping at the institution that should be addressed. These two factors also contributed to the small sample size. Not all cases had a specific attributable cause documented and some patients had a number of possible causes of PRCA, for example HIV, drug-related causes and possible primary immune-mediated PRCA. These issues emphasise the often challenging clinical dilemma of determining the underlying cause of PRCA. Lastly, some patients were lost to follow-up and their follow-up data were therefore missing from the analysis.

Conclusion

HIV infection is the single most important aetiological factor for secondary PRCA in our setting, independent of virological response to treatment. HIV and parvovirus B19 co-infection contributed to a substantial number of cases, followed by drugs (specifically lamivudine) causing secondary PRCA. Thymoma was not an important secondary cause of PRCA in this study. The evaluation and work-up of a patient with PRCA should include a detailed medical and drug history, assessment of the HIV status and PCR testing, rather than serology, for parvovirus B19. Most cases of PRCA showed a sustained complete response to therapy. Patients who relapsed usually experienced this setback soon after completion of first-line therapy. Attention to effective and safe record keeping is strongly recommended to prevent potential files with potentially valuable information being lost or misplaced.

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