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Aplastic Anemia in the Hematology Department of the University Hospital of Brazzaville: Epidemiological, Diagnostic and Therapeutic Aspects

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Abstract

Aplastic anemia (AA) is a rare, life-threatening disease characterized by pancytopenia and bone marrow failure. However, since the introduction of immunosuppressive therapy and allogeneic stem cell transplantation, outcomes have improved considerably, with 5-year survival reported to be 70% - 90%. In Congo, contemporary data on survival are lacking. We performed a retrospective study to describe the epidemiological, diagnostic, and therapeutic characteristics of patients with AA diagnosed in the clinical hematology department of the University Hospital of Brazzaville from 2017 to 2023. Chemically induced aplasia was excluded from the study. The CAMITTA criteria were used to classify the severity of AA. In total, 45 confirmed cases were identified, and 35 files provided sufficient data for the descriptive study. The median age was 26 years (range: 1 - 50). Adults made up 75% of the study population. The sex ratio was 1.05 (0.5 in children and 1.17 in adults). One case of AA was secondary to treatment with imatinib mesylate; the other cases (97.1%) were idiopathic. Pancytopenia was present in all patients. Moderate, severe, and very severe AA represented 11.4%, 74.3%, and 14.3% of cases, respectively. Severe and very severe forms were more frequent in adults (77.4% vs. 22.6%) and in men. Nine patients (26%) received cyclosporine monotherapy. Only one received treatment regularly and obtained the only favorable response. No patient received ATG or eltrombopag. Hemorrhagic syndrome was the most common cause of death (4 out of 6 cases) due to the unavailability of platelet concentrates. Eighteen patients (51.4% of cases) were lost to follow-up. The median follow-up was 28.7 (1 - 96) months. In conclusion, the

prognosis of AA remains poor and could be improved with affordable immunosuppressive treatments, availability of platelet concentrates, and implementation of allogeneic bone marrow transplantation.

Keywords

Aplastic Anemia, Blood Transfusion, Bone Marrow Transplantation, Cyclosporin, Corticosteroids, Immunosuppressive Therapy

1. Introduction

Aplastic anemia (AA) is a bone marrow failure characterized by the partial or complete disappearance of hematopoietic tissue without abnormal cell proliferation. It is a rare disease, with an incidence of fewer than ten cases per million per year. Most cases of AA are acquired and idiopathic, with data indicating an autoimmune cause in the majority of instances. About 15% to 20% are inherited forms, often found in children and associated with genetic defects. Some cases are linked to exposure to toxic agents or drugs (1% to 2%). The severity of AA varies [1] [2]. The cessation of hematopoietic stem cell production results in a global failure of hematopoiesis, leading to cytopenias detected in blood counts and exposing the patient to anemic, infectious, and hemorrhagic complications that could be life-threatening. In high-income countries, survival has improved significantly over the past four decades due to advances in allogeneic bone marrow transplantation and immunosuppressive therapy. Allogeneic bone marrow transplantation, performed on eligible patients with a compatible donor, is currently the only curative treatment, with over 80% of cases being cured. For patients lacking a matched family donor or those over 40 years old, the combination of horse antithymocyte globulin (ATG), cyclosporin, and eltrombopag, an analog of thrombopoietin, is the treatment of choice. This combination achieves transfusion independence with global hematological response rates approaching 90%, almost 40% complete responses, and an excellent overall five-year survival rate of about 85% [2]-[6]. Nevertheless, symptomatic treatments, including transfusions of red blood cells and platelet concentrates, are important in management as they aim to correct the complications of pancytopenia [2] [3]. In sub-Saharan Africa, there is little literature on AA. Usually, late diagnosis and mainly symptomatic treatment explain a survival rate rarely exceeding six months [7]-[11]. In the Republic of the Congo, a 2016 study reported that three-quarters of AAs were severe forms, and the majority of patients (91%) had received only symptomatic treatment, marked by inconsistent availability of blood products. The mortality rate was 95% after a mean follow-up of 9 weeks [12]. In recent years, the National Blood Transfusion Center has taken steps to increase blood donations to meet its annual needs. The supply of labile blood products has nearly doubled, from 45,000 to 86,000 units in 2022 [13]. In addition, although allogeneic bone marrow transplantation is still not feasible, cyclosporin is available at the pharmacy. This study aimed to provide an

overview of the disease, including its epidemiological, clinical, and biological characteristics, and report the management challenges in the clinical hematology department of the University Hospital of Brazzaville from 2017 to 2023. UHB is the largest department in the country dedicated to diagnosing and managing blood diseases.

2. Methodology

The study was cross-sectional and descriptive with retrospective data collection. Case records of patients with a confirmed diagnosis of AA (verified by bone marrow biopsy) over a period of 7 years and 6 months, from January 1, 2017, to June 30, 2023, were reviewed. Patients undergoing chemotherapy for malignant haemopathies with chemo-induced aplasia were excluded. Therefore, the sample size was not calculated. All patients meeting the inclusion criteria were selected. Information extracted for each patient included epidemiological characteristics (age, sex, mechanism of AA), clinical characteristics (symptoms and diagnostic delay), biological characteristics (number of cytopenias at diagnosis and severity of AA), and therapeutic characteristics (symptomatic and specific treatments received and response to treatment). The severity of AA was defined according to the widely accepted criteria described by Camitta [14] [15]. Severe disease was defined by two of the following three blood counts: an absolute neutrophil count $<0.5 \times 10^9$/L, platelet count $<20 \times 10^9$/L, and reticulocytes <1%. Extreme neutropenia (absolute neutrophil count $<0.2 \times 10^9$/L) is defined as very severe aplastic anemia. All other cases were defined as moderate. Diagnostic delay refers to the interval between the onset of the first signs of the disease and the first consultation with a hematology specialist. Efficacy of specific treatment was defined as an absolute neutrophil count $>1 \times 10^9$/L, platelet count $>100 \times 10^9$/L, and hemoglobin rate >10 g/dL, correlated with transfusion independence according to the criteria of the National Institute of Health [1]. Data was entered using an input mask from the KoboToolbox online software. Microsoft Excel was used for processing statistical charts and tables. Qualitative variables were presented in absolute and percentage values, while quantitative variables were presented as median, minimum, and maximum.

3. Results

3.1. Epidemiological Characteristics

A total of 45 patients were diagnosed with AA over a 7.5-year period, giving an annual incidence of 6 cases per year. Thirty-five patients had complete analyzable data. The age range of the patients was 1 to 50 years (median 26 years). Adults (age 18 and older) constituted 74.3% of the study population (26/35 patients). The male-to-female ratio was 1.05:1; it was 0.5:1 in children and 1.17:1 in adults. Etiologically, AA was considered idiopathic in 34 of 35 patients (97.1% of cases) due to the absence of obvious environmental or medicinal factors, negative HIV and hepatitis B and C serologies, and absence of physical abnormalities. A karyotype

study to exclude congenital AA was performed in only one patient, a 12-month-old infant, and the result was normal. One case of AA was secondary to treatment with imatinib mesylate in a 28-year-old man. The patient was treated for chronic myeloid leukemia for 5 months before the onset of pancytopenia, which led to the diagnosis of AA.

Table 1 shows the distribution of patients with AA in the clinical hematology department of UHB from 2017 to 2023 by age group.

Table 1. Distribution of patients with AA in the clinical hematology department of UHB from 2017 to 2023 by age group.

Age group	Number of patients (n)	Frequency (%)
0 - 10	5	14.3
11 - 20	6	17.1
21 - 30	12	34.3
31 - 40	6	17.1
41 - 50	6	17.1
Total	**35**	**100**

3.2. Clinical and Biological Characteristics

On their first visit to our department, most patients (68.5%) presented with anemic, hemorrhagic, and infectious syndromes. Additionally, 34 patients (97.1% of the cases) already had pancytopenia. In one case, a woman developed global AA during acquired idiopathic amegakaryocytosis. She initially had bicytopenia, specifically thrombocytopenia and regenerative anemia. After a myelogram and bone marrow biopsy, the initial diagnosis was amegakaryocytosis complicated by anemia due to blood loss from a severe hemorrhagic syndrome. Symptomatology progressed to pancytopenia within 2 months of the diagnosis of amegakaryocytosis.

For hemorrhagic syndrome, purpura was found in all patients. The mucous hemorrhages observed included gingivorrhagia, epistaxis, subconjunctival hemorrhage, digestive hemorrhage, hematuria, and menometrorrhagia in women. The most frequent infection sites were the skin, followed by the ear, nose, and throat system, lungs, and digestive tract. Most often, patients had a fever without any identifiable focus (60% of cases). No patient had comorbidities.

The diagnosis of AA was made within an average time of 8 months, ranging from 1 to 24 months: 7.44 months [1 month; 20 months] in children and 8.85 months [1 month; 24 months] in adults.

Regarding the severity of AA, moderate, severe, and very severe forms accounted for 11.4%, 74.3%, and 14.3% of cases, respectively. All the men had severe and very severe forms. Among the women, 4 had moderate forms. Severe and very severe forms were more frequent in adults (77.4% vs. 22.6%).

Table 2 shows the distribution of patients with AA in the clinical hematology

department of the UHB from 2017 to 2023, categorized by the severity of AA in children and adults.

Table 2. Distribution of AA patients in the clinical hematology department of the UHB from 2017 to 2023 by severity in children and adults.

	Moderate AA		Severe AA		Very severe AA		Total	
	n = 4 (11.4%)		n = 26 (74.3%)		n = 5 (14.3%)		35 (100%)	
Children	2	50.0%	5	19.2%	2	40.0%	9	25.7%
Adults	2	50.0%	21	80.8%	3	60.0%	26	74.3%

3.3. Therapeutic Characteristics

Before their first consultation in our department, 26 patients (74.3% of cases) had already been transfused at least once in other hospitals: 25 had received red blood cell concentrates, and 1 had received both red blood cell and platelet concentrates. The number of transfusions ranged from 1 to 7, with an average of 3. For 9 patients, the first blood transfusion was conducted in our service. From admission to the department, 34 out of 35 patients received at least one red blood cell concentrate (97.1% of cases), 23 out of 35 (65.7% of cases) received platelet concentrates, and 33 out of 35 received curative antibiotic therapy (94.3% of cases). Delivery times for red blood cell concentrates ranged from one to two days and for platelet concentrates from one to eight days, due to their inconsistent availability at the blood bank.

Disease outcome was favorable after the discontinuation of imatinib in a patient with chronic myeloid leukemia. Cyclosporine was the only specific treatment validated by expert groups that patients with idiopathic AA received. No patients received ATG or eltrombopag.

Table 3 shows the distribution of patients with AA in the clinical hematology department of the UHB from 2017 to 2023 according to the type of specific treatment received.

Table 3. Distribution of patients with idiopathic AA in the clinical hematology department of the UHB from 2017 to 2023 by type of specific treatment received.

Specific treatment	Effective (n)	Frequency (%)
None	1	3
Corticosteroid*	24	70.5
Cyclosporin	9	26.5
Total	**34**	**100**

*High doses of methylprednisolone for 5 days with per-os prednisone relay (progressive decrease over 3 weeks).

Cyclosporin treatment was irregular in 8 out of 9 patients due to insufficient financial means of the patients and/or their families to buy the drug. Transfusion

independence was achieved after 3 months of treatment in a 5-year-old girl who regularly took cyclosporin. She is currently alive and in the 12th month of treatment. The treatment was ineffective in all other patients. At the end of our study, 6 patients (17.14% of cases) had died (2 from severe anemia without hemorrhagic syndrome and 4 from hemorrhagic syndrome), 18 (51.43% of cases) were lost to follow-up, and 11 (31.43% of cases) were alive, with one showing a therapeutic response. The median follow-up time was 28.7 weeks, ranging from 1 to 96 weeks.

4. Discussion

4.1. Epidemiological Characteristics

AA is a rare disease with an incidence of less than 10 cases per million annually, about 2 cases per million annually in Europe and North America [1]. The disease is two to three times more prevalent in Asia, particularly among the elderly. In a national, multicenter Thai study of adults, the incidence was 4.8 cases per million per year, peaking at 14.4 cases per million per year in patients aged 80 to 89 [16]. Li in Taiwan Region reported an overall incidence of 5.67 cases per million inhabitants per year with a biphasic distribution: the highest incidence was observed starting at age 70 (19.83 cases per million inhabitants per year) and another peak at ages 2 - 9 years (5.26 cases per million inhabitants per year) [17]. Frequent environmental exposures to agricultural pesticides or genetic factors were cited as explanations for these figures [16]. Series of patients with AA in sub-Saharan Africa are generally hospital-based, probably due to the absence of national registries. Tolo in Ivory Coast reported 36 cases in 14 years, giving an annual incidence of 2.6 cases per year [10], and Arewa in Nigeria reported 25 cases in 15 years, giving an annual incidence of 1.7 cases per year [7]. More recently in Tanzania, Ally reported one of the largest series: 30 cases in a year [15].

The 21 - 30 age group was most represented, with young adults most affected [12]. This result is similar to those reported by Arewa in Nigeria (mean age 28.7 years, median 22 years) and Ally in Tanzania [7] [15]. In Western countries and Asia, the incidence of AA shows a bimodal curve, with a first peak in young individuals and another above 50 years [1] [16] [17]. The sex ratio, close to 1 in our study, differs from one series to another.

Idiopathic acquired AAs are the most frequent, but this diagnosis is one of exclusion. It should be considered only after ruling out secondary and especially constitutional forms through an exhaustive paraclinical review [6]. The number of idiopathic AA in our department may have been overestimated, as the etiological assessment was limited by insufficient technical resources. Specialized examinations, such as testing for paroxysmal nocturnal hemoglobinuria clones, lymphocyte karyotyping with chromosomal break tests, screening for telomeropathy (which should be systematic before age 18), and searching for mutations by studying a panel of genes involved in constitutional bone marrow insufficiencies (systematic before age 10), are not feasible. In addition, when patient samples are sent to countries with specialized laboratories, the cost is usually beyond the reach of

families. That is why, in our series, only a karyotype study was possible for one child.

4.2. Clinical and Biological Characteristics

During the course of the disease, bone marrow failure often initially affects one or two blood cell lines, leading to bicytopenia. Pancytopenia gradually appears within a few weeks, resulting in complete bone marrow failure. The initial deep pancytopenia observed in most patients (34/35), associated with global medullary insufficiency syndrome in two-thirds of them, indicates late admission, the causes of which need to be identified.

AA was most often reported as severe and very severe in the literature [16].

4.3. Therapeutic Characteristics

The therapeutic management of severe acquired idiopathic AA (or moderate cases requiring repeated transfusions) is an emergency because treatment delays impact prognosis. Any patient under 40 should be typed, along with their siblings, once the diagnosis is established. The three validated treatments are gene-identical bone marrow allograft, immunosuppressive therapy, and more recently, eltrombopag. The choice depends on the patient's age, comorbidities, and donor availability. In the absence of an intrafamilial donor or if the patient is over 40 years old, the combination of ATG (horse ATG is preferred to rabbit ATG for its better efficacy) and cyclosporin has long been the standard treatment. Now, the combination of ATG, cyclosporin, and eltrombopag is effective in 80% of patients, with an overall response rate of 68% at 6 months [18].

There is no allogeneic bone marrow transplantation unit in our country. Additionally, ATG is not available at public pharmacies and must be ordered through private pharmacies, but its cost limits accessibility. Cyclosporin, available in some drugstores in the country, has seen an increase in administration: only 9% of patients had received it previously [12] *versus* 26% in this study. However, its cost limits accessibility, with only one patient receiving regular treatment. For example, a monthly treatment for a 110 lb subject costs around US$550, while the minimum wage in Congo is US$150. This high cost explains the limited use of the product and its premature discontinuation by most patients. In our series, cyclosporin monotherapy and high doses of methylprednisolone are often the main therapeutic options in resource-limited countries. The results of cyclosporin are modest, with an overall response often less than 50% [19] [20]. Methylprednisolone does not achieve transfusion independence [7] [10]. According to several recent publications, corticosteroids, used alone or in high doses to treat severe AA, are ineffective and cause significant infectious and bone toxicity [6] [21]. Therefore, they should only be combined with treatment to prevent the side effects of ATG. Their ineffectiveness is illustrated by the high case-fatality rates reported in the African series cited: 96% with a median survival of 6.5 weeks in Nigeria, and 94.73% with a maximum survival of 11 months in Congo. In Ivory Coast, 1-year

survival was 51.58%, but nearly a quarter of patients were lost to follow-up. The high number of patients lost to follow-up in our department may reflect the fatigue of patients and their families, linked to the socio-economic burden of the disease. The healthcare system in Congo lacks social security for public sector employees, the unemployed, and some private sector workers. The cost of all medicines, including blood products, as well as paraclinical examinations and hospitalization, is entirely borne by the patient. As a result, the financial burden of this serious, chronic disease quickly becomes significant, leading to irregularity or absence of certain treatments. These concerns are described by several authors on the continent [7] [10] [15].

In high-resource countries, these concerns are generally absent. Validated therapies are available, and social security and health insurance allow optimal patient management. Infectious complications can be managed in sterile units, and labile blood products are more available than in low-income countries. Gene-identical allogeneic bone marrow transplantation and immunosuppressive treatment currently allow a 5-year survival rate of 90% [6] [22]-[24]. The addition of eltrombopag to standard immunosuppressive therapy improved the rate, speed, and strength of hematologic response among previously untreated patients with severe AA, without additional toxic effects. The combination of horse ATG, cyclosporin, and eltrombopag is effective in 80% of patients, with an overall response rate of 68% at 6 months [15] [18]. Age over 40, a very severe form, cyclosporin monotherapy, and lack of specific treatment are risk factors for lower survival [17] [22].

One limitation of our study is that we obtained follow-up information from clinical records. Consequently, the retrospective nature of the study and the high proportion of lost follow-up cases limit the assessment of survival and its associated factors. In short, the management of patients with AA in Brazzaville remains primarily symptomatic. Despite efforts by the National Blood Transfusion Center in recent years to increase blood donations and meet the country's annual needs, and the supply nearly doubled in 2022 [13], availability of labile blood products remains a major problem. This is justified by the insufficient number of donors. Platelet concentrates are prepared "on demand", meaning only with a medical prescription, and their delivery time is usually several days. Similar findings are observed in Nigeria. Hemorrhagic syndrome accounts for the majority of causes of death in Africa [7] [11] [12].

5. Conclusion

The prognosis of AA is poor and could be improved by the availability and affordable cost of ATG, cyclosporine, eltrombopag, and bone marrow transplantation. Policies must be implemented by public authorities. Equipping public laboratories is also important to improve etiological research on AA. The National Blood Transfusion Center should raise awareness among the population about the importance of blood donation to make labile blood products more available. Finally, healthcare practitioners should quickly refer people with bone marrow failure

syndrome to specialized hematology services to reduce diagnostic delays.

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Data Availability

The data used to support the findings of this study are included within the article.

Disclosure of Interest

The authors declare that they have no conflicts of interest concerning this article.

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