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Etiological profile of hemolytic anemia

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Abstract

Introduction: The discovery of hemolytic anemia must lead to a precise etiological assessment guided by clinical and biological data. The aim of our study is to describe the etiological profile of hemolytic anemia cases diagnosed in the hematology laboratory of the Hassan II University Hospital in FEZ.

Material and Methods: We conducted a retrospective and descriptive study of hemolytic anemia cases diagnosed between January 2017 and July 2019 and based on epidemiological and clinical data collected from computerized reports and laboratory investigations.

Results: The analysis of clinicobiological records identified 100 cases of hemolytic anemias. The mean age of our patients was 36 years , with a sex ratio (F /H) of 1.5. Anemia was symptomatic in the majority of patients. The etiologies found were : neoplasia in 32 patients, systemic lupus erythematosus in 10 patients , sickle cell disease in 10 patients, immunological thrombocytopenic purpura in 7 patients, glucose-6-phosphate dehydrogenase deficiency in 7 patients, alloimmunization in 5 patients, hemolytic uremic syndrome in 5 patients, hyperthyroidism in 5 patients, thalassemia in 4 patients, microspherocytosis in 4 patients, hypersplenism in 4 patients, paroxysmal nocturnal hemoglobinuria in 1 patient , pyruvate kinase deficiency in 1 patient, Gaucher disease in 1 patient, and the use of alpha-methyl Dopa in only one patient.

Conclusion: Hemolytic anemia constitute a real diagnostic challenge. Neoplasia predominate in elderly subjects while autoimmune pathologies are more frequent in young subjects.

Keywords: Hemolytic anemia; Etiological profile; Blood smear; Direct antiglobulin test

1 Introduction

Hemolytic anemia is a major public health issue and a common reason for hospitalization. Hemolytic anemias are a clinically heterogeneous group of disorders that can be classified into hemoglobinopathies, membranopathies, enzymopathies, immune-mediated anemias, and extrinsic non-immune causes. Extrinsic non-immune causes include the thrombotic microangiopathies, infections, systemic diseases, oxidative insults and medications. A precise etiological assessment is crucial in the management of hemolytic anemia. The underlying cause of the anemia will determine the appropriate treatment and management strategies. The aim of our study is to describe the etiological profile of hemolytic anemia cases diagnosed in the hematology department of the Hassan II University Hospital of Fez.

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2 Material and methods

We conducted a retrospective and descriptive study of hemolytic anemias cases diagnosed between January 2017 and July 2019 at the hematology department of the HASSAN II University Hospital of Fez.

Epidemiological data (age, sex), clinical data (personal and family history , dyspnea, hemolytic triad (pallor, jaundice, splenomegaly), acute or chronic character, an infection or use of medication are collected from computerized reports and the following laboratory investigations : complete blood count with reticulocyte counts, peripheral blood smear, chemistry (including lactate dehydrogenase (LDH) and bilirubin test) ,serum haptoglobin , plasma hemoglobin, direct antiglobulin test (DAT) , osmotic fragility test (OFT) and Hemoglobin electrophoresis results.

All patients with anemia and biological evidence of hemolysis were included. Hemolysis was defined as anemia with reticulocytosis. (>150 × 109/L), associated with at least two of the following three signs of hemolysis: low serum haptoglobin, hyperbilirubinemia, and higher LDH levels. In auto-immune hemolytic anemia, serological evidence of an autoantibody is provided by positive direct antiglobulin test (DAT).

The exploration of erythrocyte enzymes deficiencies : glucose-6-phosphate dehydrogenase (G6PD) and pyruvate kinase (PK)was based on a low enzyme assay for G6PD or PK and a negative DAT.

A compatible hemogram and positive hemoglobin electrophoresis were consistent with a diagnosis of thalassemia or sickle cell anemia.

A negative DAT and a positive osmotic fragility test supported the diagnosis of hereditary spherocytosis

All analyses were performed using Epi Info and SPSS version 17.0.

All the patients who did not meet the inclusion criteria or for whom insufficient data were available, were excluded from the study.

3 Results

The analysis of the clinicobiological records allowed us to identify 100 cases of hemolytic anemias. The average age of our patients was 36 years [Day 1 of life - 66 years]. Women were the most affected with a sex ratio (F/H) of 1.5.

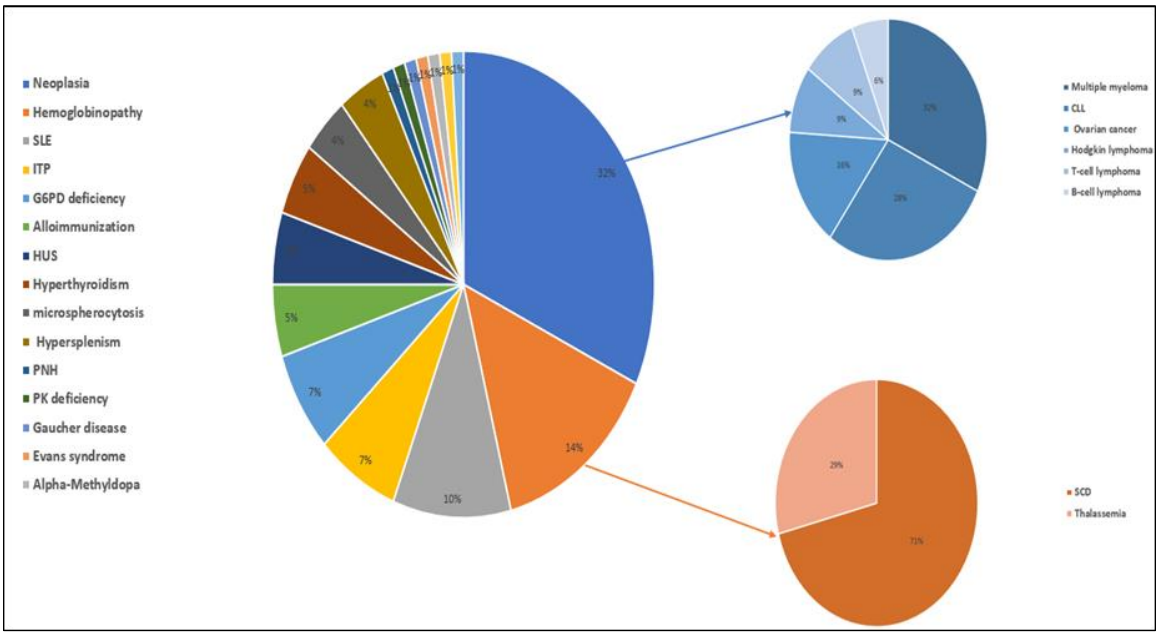
Anemia was symptomatic in the majority of patients. The mean hemoglobin level was was 6.85 g/dl [2.8-11]. Pancytopenia was observed in 42 patients. The mean reticulocyte count was 200,000/mm3. The mean lactate dehydrogenase level was 880 IU/l. The mean serum total bilirubin was 38 mg/l. The haptoglobin level was decreased in 35% of cases.

The direct antiglobulin test was negative in 39 patients, positive in 44 patients and wasn't performed in 23 patients. The presence of schistocytes on a peripheral blood smear was found in 17 patients. The osmotic fragility test was positive in 10 patients. Hemoglobin electrophoresis was positive in 14 patients.

Hemolytic anemia was indicative of an underlying pathology in 2 patients (Pernicious anemia and ulcerative colitis (UC)). Evans syndrome was found in only one patient.

The etiologies found were: neoplasia in 32 patients, systemic lupus erythematosus in 10 patients, sickle cell disease in 10 patients, Immune thrombocytopenic purpura (ITP) in 7 patients , G6PD deficiency in 7 patients, alloimmunization in 5 patients , hemolytic uremic syndrome (HUS) in 5 patients, hyperthyroidism in 5 patients, thalassemia in 4 patients, microspherocytosis in 4 patients, hypersplenism in 4 patients, Paroxysmal nocturnal hemoglobinuria (PNH) in 1 patient , pyruvate kinase deficiency in 1 patient, Gaucher disease in 1 patient and the use of alpha-methyl Dopa in only one patient.

The neoplasia found in our study were: multiple myeloma in 10 patients, chronic lymphocytic leukemia in 9 patients, ovarian cancer in 5 patients, Hodgkin's lymphoma, T-cell lymphoma in 3 patients and B-cell lymphoma in 2 patients. **(Figure 1)**



Abbreviations :SLE: Systemic lupus erythematosus, ITP: Immune thrombocytopenic purpura, HUS: Hemolytic uremic syndrome, PNH: Paroxysmal nocturnal hemoglobinuria, PK: Pyruvate kinase, UC: Ulcerative colitis, CLL: Chronic lymphocytic leukemia, SCD: Sickle cell disease

Figure 1 : Hemolytic anemia etiologies

4 Discussion

The results of our study showed a considerable presence of hemoglobinopathies, which is 14%, with a predominance of sickle cell disease (71.42 % of all hemoglobinopathies). The anemic syndrome was the most frequent reason for consultation. Sickle cell disease is the major hemoglobin abnormality in Morocco and a real public health issue. Our result was similar to the study of Dahmani et al, which was carried out in the north-east of Morocco, and reported a predominance of sickle cell disease, contrary to the study of Marzouki et al which was carried out in the south of Morocco and revealed a predominance of beta-thalassemia [1,2].

Neoplasia (32% of cases)and systemic lupus erythematosus (10% of cases) were the leading causes of auto-immune hemolytic anemia (AIHA) in our study, these findings were consistent with a study conducted in Tunisia by M. Mama [3].

The frequency of lymphoid hemopathies is about 20% in different series of AIHA. The prevalence of AIHA is important in angio- immunoblastic T lymphoma (13%) and chronic lymphocytic leukemia (CLL) (10 to 35%). The latter were found respectively in 3% and 9% of our sample. However, AIHA is estimated to be less than 5% in Non-Hodgkin Lymphoma (NHL) [4-8].

CLL is the leading cause of secondary AIHA. However, the prevalence of AIHA in CLL has been decreasing according to recent studies. The diagnosis of AIHA may precede the diagnosis of hemopathy by more than 5 years in the majority of cases of AIHA caused by warm autoantibodies [5,9,10,11].

The search for Lymphoproliferative disorders in the case of AIHA caused by warm autoantibodies requires a CT Chest, Abdomen and Pelvic scan and protein electrophoresis with immunofixation to look for monoclonal peaks or hypogammaglobulinemia. Factors that predict underlying hemopathy at the time of diagnosis of AIHA or its subsequent occurrence are : age over 60 years, the presence of hypogammaglobulinemia or monoclonal gammopathy and the existence of other auto-immune manifestations [5,12].

Studies have shown that auto-immune hemolysis may be more commonly associated with solid tumors and ovarian tumors in particular. Indeed a remission of AIHA after surgical removal of an ovarian cyst has been demonstrated, suggesting the presence of a cross-reaction between erythrocyte Ag, the cyst and the local production of autoantibodies by intracystic B lymphocytes [13]. In some cases, AIHA may be the first manifestation of lupus disease and may precede other symptoms by several years. Although it represents only 15% of the causes of anemia in this pathology. AIHA is significantly associated with the presence of antiphospholipids, but also with thrombocytopenia and risk of thrombosis.

According to some studies, AIHA is a risk factor for thrombotic complications related to antiphospholipids independently of lupus [14-17].

Hemolytic anemia was indicative of two pathologies in our study: ulcerative colitis (UC) and biermer's disease. The association of UC with auto-immune hemolytic anemia (AIHA) is rare, occurring in 0.2 to 1.7% of UC cases. It may be explained by the production of anti-erythrocyte antibodies by the diseased colon [18,19].

The association of Biermer's disease with AIHA was found in only one patient in our study. It makes us discuss the hypothesis of an immune disorder common to both types of affections. Indeed, when AHAI precedes pernicious anemia the diagnosis of macrocytosis suggests a deficiency due to excessive consumption of folic acid and vitamin B12.

On the other hand, the development of AIHA in a patient with pernicious anemia may suggest an underlying viral infection that triggered the autoimmune response, or it may indicate the presence of a lymphoproliferative disorder, which can cause AIHA as an early sign [20,21].

Alloimmunization hemolytic anemias can occur due to a variety of reasons, including mix-ups in blood transfusions or as a result of rhesus immunization during pregnancy. Auto-immune hemolytic anemia (AIHA) with cold agglutinins is most often post-infectious. The association of dysthyroidism with AIHA was found in 5 patients of our study compared to a Tunisian study conducted by Ben Ahmed et al where the association was noted in only one case. The frequency of autoimmune diseases seems to be more important in patients with dysthyroidism than in the general population [22].

Evans syndrome was found in only one patient compared to 7 cases found in a Tunisian study by R. Klii. This rare chronic hematological disorder combines autoimmune hemolytic anemia, immunologic thrombocytopenic purpura (ITP) and/or autoimmune neutropenia occurring in isolation or in association with another auto-immune disease. Its incidence and prevalence remain unknown. However, Evans syndrome represents 0.3 to 2% of autoimmune thrombocytopenia/ AIHA in adults [23,24].

The existence of drug-induced autoimmune hemolytic anemia, including alpha-methyldopa has been the subject of several studies. It is thought to cause IgG hemolysis without complement fixation in 84% of cases with a high level of free antibodies in the serum. Baier JE et al. suggested that the mechanism of autoantibody formation involves an increase in the production of interferon-gamma (IFN-gamma) after stimulation of T cells. The interferon gamma has been shown to increase the expression of human leukocyte antigens (HLA) class I and II molecules. The development of hemolysis in drug-induced autoimmune hemolytic anemia typically occurs after several weeks of treatment and progressively regresses when the drug is stopped [25].

5 Conclusion

The appropriate treatment for anemia will always vary depending on the underlying cause. Immediate interventions, including blood transfusions, plasmapheresis or diuresis, may need to be performed depending on the cause of hemolytic anemia and the severity of illness.

Blood transfusions can be an important and life-saving treatment for people with severe anemia. Neoplasia predominate in elderly subjects while autoimmune pathologies are more frequent in young subjects.

Compliance with ethical standards

Disclosure of conflict of interest

No conflict of interest.

Statement of informed consent

Informed consent was obtained from all individual participants included in the study.

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