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BIERMER's Disease: About 4 Cases Diagnosed at Regional University Hospital of Ouahigouya (Chur/Ohg) and Literature Review

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Abstract

Megaloblastic pernicious anemia is an autoimmune disorder, considered rare in African context. The objective of this study was to report four clinical cases collected at the CHUR/OHG, and to review the literature. The study population consisted of two men and two women. The clinical manifestations were mainly neurological and hematological. The neurological signs were mainly paresthesia. One patient presented memory problems. On the biological level, macrocytic anemia and vitamin B12 deficiency were reported in two cases prior to treatment while the other two without serological assay of vitamin B12 were put on trial treatment. Anti-intrinsic factor antibodies were positive in three patients. The Schilling test was not used. Upper gastrointestinal endoscopy revealed atrophic fundic gastritis in all four patients who received treatment through intramuscular injection of hydroxocobalamin (vitamin B12). The evolution was favorable after one month of treatment in all cases. The literature review is dominated by clinical case reports, the largest cohorts of which are from the Maghreb.

Keywords

Anemia, Pernicious, Megaloblastic, Vitamin B12

1. Introduction

BIERMER's disease was first discovered in 1849 by Thomas Addison, who described it as a remarkable form of general anemia; and, its fatal course caused it to be described as "pernicious" [1]. It is an autoimmune disease with the presence of

autoantibodies leading to chronic atrophic gastritis and vitamin B12 malabsorption [2] [3]. The reduction in gastric acid secretion and that of intrinsic factor are linked to a reduction in the number of parietal cells leading to fundic glandular atrophy [4]. The lack of specificity of its clinical signs as well as clinical and biological polymorphism help to explain delays and difficulties in the diagnosis. The eventual neurological and hematological complications add to the seriousness of the pathology [5]-[7]. The aim of this study was to report four clinical cases encountered in our daily practice and to review the literature.

2. Observation 1

A 68-year-old patient (born in 1955), a retired secretary, had been followed since March 2010 for hypotension upon awakening, dizziness, and numbness of the right hemibody which had been evolving for a year, requiring several consultations without success. Her medical history included asthma, staged degenerative spondylodiscopathy with L4 - L5 protrusive disc disease, polyarthritis, cerebral protuberant cavernoma. As cardiovascular risk factors, she combined morbid obesity (weight = 113 kg; height = 1.62 m; BMI = 43.06 kg/m^2), a sedentary lifestyle and asymptomatic hyperglycemia.

She was referred to the gastroenterologist in 2020 for the evaluation of chronic anemia that had been evolving insidiously for approximately nine years.

The biological assessment noted mild anemia (Hb = 11.2 g/dl), macrocytic MCV (100 fl); Leukocytes and platelets were normal at 7920 elements/ml and 371000 elements/ml respectively; HBcAb was positive; HBsAg negative; HBsAb positive with a level of 21 mIU/ml; intrinsic factor Ab was positive with a level greater than 480 IU; the serum vitamin B12 dosage was lowered to 109 picomol/l (148 ng/l).

Upper digestive endoscopy revealed atrophic corporeal gastritis, erosive pangastritis with hiatal hernia, peptic esophagitis and bile reflux. Histology revealed an atrophic appearance, suggesting Biermer's disease is associated with numerous *Helicobacter pylori* without dysplasia.

Abdominopelvic ultrasound revealed hepatic steatosis and colonoscopy of colonic diverticula (3 of the ascending colon).

She had benefited from treatment consisting of vitamin B12 injections of 1000 ug intramuscularly per day for 15 days, then per week for a month, then every month. Eradication of *Helicobacter pylori* was associated.

Biological monitoring after 1 month of treatment normalized vitamin B12 (192 pmol/l) and reduced clinical signs. She is regularly followed with monthly injections of vitamin B12.

3. Observation 2

A 64-year-old patient (born in 1958), a state midwife, consulted in July 2020 for headache, dizziness, hyperpigmentation of the palms and macrocytic anemia; everything had been evolving for several months. She had a history of high blood

pressure, a heart rhythm disorder such as ventriculars extra-systoles, type 2 diabetes, an allergy to calcium channel blockers, a multinodular goiter, cervical spondylosis, recurrent inflammation of the oral mucosa and throat. The clinical history found this glossitis two years before the appearance of anemia and memory problems.

Clinical examination at entry revealed conjunctival pallor and epigastric tenderness.

In biology, we noted severe anemia (hemoglobin level of 8.8 g/dl); macrocytic (VGM = 116 fl), normal platelet and leukocyte levels at 270,000/mm^3 and 5500/mm^3.

Serum vitamin B12 dosage was lowered <74 pmol/L, intrinsic factor Ab was high at 332.04 IU/l.

Furthermore, hypertriglyceridemia and hypercholesterolemia were noted.

The initial upper digestive endoscopy revealed grade I peptic esophagitis, a large hiatal hernia, atrophic corporal gastritis, and nodular antral gastritis.

She benefited from a treatment consisting of intramuscular injection of vitamin B12 at a dose of 1000 ug daily for a week, then weekly for a month.

The evolution was marked at one month by the normalization of the hemoglobin level (12.5 g/dl), the rise in the level of vitamin B12 to 1476 pmol/L, which motivated to stop vitamin B12 injections. A check after 6 months showed that this level returned to 235 pmol/L (*i.e.*, a loss of 177 pmol/month). The reintroduction of vitamin B12 injections at the rate of 1000 ug per month made it possible to normalize the vitamin B12 level.

The symptoms have disappeared and she is followed regularly with check-ups. The upper digestive endoscopy in March 2024 found atrophic fundal gastritis and the pathological results suggest a histological appearance of non-active chronic gastritis, without *Helicobacter pylori* with moderate atrophy, moderate intestinal metaplasia and low-grade dysplasia. A monitoring program was proposed to the patient with a view to preventing carcinomatous degeneration.

4. Observation 3

A 79-year-old male patient (born in 1945), a farmer, was hospitalized at the end of October 2023 for dyspnea, dizziness, asthenia, paresthesia which had been on for several weeks. Clinical examination revealed poor general condition, pale conjunctiva without jaundice and melanoderma of the palms of the hands and soles of the feet. The physical examination revealed a syndrome of global heart failure consisting of an edema-ascetic syndrome, turgor of the jugular veins, and hepatojugular reflux. Biology found a hemoglobin level of 4.1 g/dl, MCV: 120 fl, CCMH: 36.3 g/dl, reticulocyte level of 28,000/ml. The blood smear found the presence of poikilocytes and anisocytes. Cardiac ultrasound revealed bi-atrial dilatation and moderate PAH. Treatment for heart disease was initiated. Trial treatment of regenerative macrocytic anemia by injection of vitamin B12 was also initiated in the absence of serum determination of vitamin B12 levels. The evolution after one

week of treatment was favorable, with an Hb level of 6.3 g/dl, an MCV of 111 fl, and the reticulocyte level of 157,000/ml. Basing on this favorable development, treatment with hydrocobalamin was initiated with one injection per week for one month then one injection per month for life. At the appointment 3 months after hospitalization, the blood test found an Hb level of 10.2 g/dl with an MCV of 85 fl. The upper digestive endoscopy requested as part of the follow-up revealed a hiatal hernia, atrophic pangastritis with abnormal visibility of the submucosal vascular network and antral erosions. The anatomopathological results concluded the presence of severe, follicular, mild, not very active, congestive chronic gastritis caused by *Helicobacter pylori*. There was also moderate gastric atrophy, mild intestinal metaplasia and the absence of dysplasia. Regular follow-up is offered to the patient in order to monitor the evolution of gastric lesions.

5. Observation 4

A 57-year-old male patient (born in 1967), a farmer, was seen in an outpatient gastroenterology consultation for the management of macrocytic anemia. Faced with the lack of diagnostic means, the patient was put on trial treatment with hydroxocobalamin in a peripheral health facility before being referred to the higher level for further treatment. The symptoms presented by the patient were paresthesias. The dizziness, asthenia and palpitations had improved. Hemodynamic constants were normal. The blood test found a hemoglobin level of 12 g/dl, a normal MCV of 88.3 fl. The dosage of intrinsic factor antibodies was positive with 166 U/ml (positivity threshold greater than 10). Upper digestive endoscopy revealed a small hiatal hernia, an antral ulcer and atrophic fundic gastritis with abnormal visibility of the submucosal vessels. The pathological examination suggested active, moderate chronic atrophic gastritis, associated with numerous *Helicobacter pylori*. Treatment consisted of maintaining monthly vitamin B12 injections. Endoscopic monitoring of gastric lesions has also been implemented thanks to endoscopy every two or three years.

6. Discussion

In this work, we have reported a series of four cases of BIERMER's disease. The average age of patients was 67 years with an equitable distribution of both sexes. BIERMER's disease is in fact, a disease of people aged over 60 [8]. One of the limitations of clinical case reports is that prevalence cannot be described using this type of studies. The literature review on PubMed with the keywords "megaloblastic anemia", "pernicious anemia", "BIERMER disease" and "Africa" over the last 10 years revealed 5 publications in Africa, including three (3) from subsaharan countries and two (2) from the Maghreb on this pathology [2] [9]-[12] while the same search without the keyword "Africa" presented over the last 10 years 219 works as of July 3, 2024. This scarcity of scientific publications in Africa probably hides the diagnostic difficulties in this context, and above all, reflects an underreporting of the pathology.

Macrocytic anemia was the mode of revelation in all cases. The delay between the onset of clinical manifestations (particularly haematological) and consultation with hepato-gastroenterology was more than one year in our series. This is reported by several authors [2] [11] [13]. Observation 1 had the longest delay in etiological diagnosis of anemia, approximately 10 years. Furthermore, clinical presentations are very variable and constitute a practical challenge for clinicians [6], especially since the numerous medical histories of patients associated with comorbidities are also confounding factors, as in our observations 1, 2 and 3. Iron deficiencies, very common in Africa [14]-[16], make the biological profile of patients with BIERMER's disease even more complex in whom macrocytosis was reported in 54.5%, microcytosis in 14.5% and average globular volume normal in 30% [17].

The clinical manifestations of our patients were essentially neurological with paresthesias and memory disorders. These neurological disorders are in fact often reported and sometimes seem irreversible, thus constituting formidable complications [5] [10] [18]-[20]. The dermatological manifestations were mainly melanoderma of the palms and soles found in a patient. Coulibaly *et al.* in Burkina also reported a case of melanoderma [8]. BIERMER disease is frequently associated with other signs of autoimmunity [21]. A case of multinodular goiter was found in our series as well as a case of glossitis. Youssra *et al.* in Morocco found 37% cases of Hunter glossitis in their series [12].

On a biological level, other tests useful for diagnosis apart from the blood count are not available in our laboratories. Blood measurement of vitamin B12 and intrinsic factor antibodies and parietal cell antibodies requires sending samples to developed countries. The differential diagnosis of anemia due to vitamin B12 deficiency is not commonly done in the literature. The Schilling test which allows vitamin B12 deficiency to be linked to an ileal disease is not commonly requested [2] [9] [11] [12] [20] and is not feasible in Burkina Faso. We found intrinsic factor antibodies in 3 of our patients. Parietal cell antibodies were not measured. These two antibodies are not found in all cases. Morawiec *et al.* reported a prevalence of 61.3% in a series of 124 patients [2]. However, according to the algorithm of Rojas *et al.*, the presence of intrinsic factor antibodies combined with a drop in serum vitamin B12 levels of less than 200 pcmol/ml is sufficient to make the diagnosis of pernicious anaemia [1]. Furthermore, patients with BIERMER disease do not have more autoantibodies compared to a control group of patients with specific autoimmune conditions such as celiac disease and connective tissue disease [2].

Anemia is often called megaloblastic without myelogram in African studies. Studies using myelograms are quite rare [22].

Upper digestive endoscopy revealed atrophic fundic gastritis in all cases, very suggestive of BIERMER's disease. This is frequently reported in the literature [23]-[25]. However, the overall prevalence of chronic atrophic and autoimmune gastritis is low, varying between 0.3% and 2.7% in the general population [9].

Helicobacter pylori infection was found in 3 out of 4 patients. The prevalence

of *Hp* infection is indeed very high in Africa [10]. This infection is the main cause of atrophic gastritis, but its role is not clearly established in the occurrence of pernicious anemia [9].

The treatment is fairly well codified. Initially, vitamin B12 reserves were replenished by frequent injections then more spaced ones. The duration of treatment is lifelong. Some works propose oral treatment [11]. Although these works are the outcome of serious studies, they remain marginalized and most practitioners are still doing parenteral treatment [12] [13] [18]-[20] [23] [24] [26]. In our study, the treatment of both cases consisted of the intramuscular injection of hydroxocobalamin, which allowed the disappearance of clinical signs in all our patients, as well as the normalization of the hemoglobin level. This is reported by several authors.

Surveillance after screening for BIERMER disease is mandatory due to the risk of malignant degeneration [9] [25]. The Odds ratio for gastric adenocarcinoma is estimated at 2.18 CI 95%: [1.94 - 2.45] and for gastric neuroendocrine tumors, the annual incidence is estimated at 1.4% with an OR of 11.43, CI 95% [8.9 - 14.69] [25]. In our series, no malignant lesion has been detected, but one patient had low-grade dysplasia which we continue to monitor with endoscopic examinations every two years.

7. Conclusion

BIERMER's disease is a reality in our context. The number of cases collected in our study does not reflect reality, because it is unknown and underdiagnosed. Its clinical manifestation is polymorphic, and the most frequent biological manifestation is macrocytic anemia despite. It is, therefore, advisable to think about it in the event of any macrocytic anemia in order to avoid diagnostic delay.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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