

# Pernicious Anemia Associated Autoimmune Diseases in a Sub Saharian African Internal Medicine Service

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## Abstract

**Introduction:** Pernicious anemia is an autoimmune disease. It is characterized by the presence of an autoimmune atrophic gastritis and various autoantibodies that lead to a vitamin B12 deficiency responsible for a macrocytic anemia. It is frequently associated with other specific or non-organ-specific autoimmune diseases. We report six patients with pernicious anemia associated with other autoimmune diseases. **Patients and Results:** There were six patients (4 females/2 males), mean age of 39.67 years. In all cases it was found macrocytic anemia. The average Hb was 6.08 g/dl and the average MCV: 110.67 fl. Bone marrow aspiration was performed in all patients. Megaloblastosis compatible with a lack of vitamin B12 or folic acid was constant. Determination of serum vitamin B12 was low in all cases while folic acid levels were within standards. Immunologically it was found in all patients, a positivity of anti-intrinsic factor antibody and/or anti-parietal cells antibody at rates up to 67 times over normal ranges. Pernicious anemia was associated with autoimmune thyroid dysfunction in 4 patients. It was two cases of Hashimoto thyroiditis at hypothyroidic phase (high TSHus, thyroperoxydase anti-antibody positive (over 10 N) in both cases and Graves' disease in the two other cases. Pernicious anemia was associated with a syndrome of primary antiphospholipid antibody in a case. Furthermore pernicious anemia was found in a patient autoimmune type 1 diabetes with strongly positive anti -GAD antibodies and rheumatoid arthritis by retaining it in the diagnosis of multiple autoimmune syndrome. **Conclusion:** These cases illustrate the existence of the association of pernicious anemia with other autoimmune diseases in our context. This should encourage practitioners to seek hidden autoimmune diseases when they consider the diagnosis of pernicious anemia.

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## Keywords

**Pernicious Anemia, Auto-Immune Diseases, Auto Immune Thyroid Dysfunction, Multiple Auto-Immune Syndrome**

### 1. Introduction

Pernicious anemia also known as Biermer disease is a complex disorder consisting of hematological, gastric and immunological alterations. Diagnosis of this disease relies on histologically proven atrophic body gastritis. The immunological mechanism of this disease is demonstrated by the presence of auto-antibodies anti-parietal cells and anti intrinsic factor. For a while it had been considered rare in Sub-Saharan African countries, but an increasing number of publications highlight the interest towards this disease whose prevalence is unknown in this area [1]-[4]. Its association with other auto-immune diseases is well known but poorly described in Black African people [1]-[4]. We studied diagnostic, therapeutic and evolutive aspects of Biermer disease associated with other auto-immune diseases through six new cases in the Internal medicine ward of University Teaching Hospital of Dakar.

### 2. Cases

We report six cases among a cohort of 80 persons followed for pernicious anemia in the internal medicine service of university teaching hospital Aristide le Dantec. Biermer disease diagnosis criteria were macrocytic anemia associated with megaloblastocytosis, low blood level of B12 vitamin, positivity of at least one of the following antibody: anti intrinsic factor or anti parietal cell; and or proven atrophic gastritis. The diagnosis was made when the patient met four or more criteria. We selected six patients who had in addition an organ or systemic dysfunction with specific immunological markers according to the defined diagnosis criteria of Hashimoto, Grave Basedow, systemic lupus erythematosus, rheumatoid arthritis, auto immune diabetes and anti-phospholipid syndrome.

There were six patients (4 females/2 males), mean age of 39.67 years. Macrocytic anemia was constant. The average Hb was 6.08 g/dl and the average MCV: 110.67 fl.

Bone marrow aspiration was performed in all patients revealing a constant megaloblastosis. Determination of serum vitamin B12 was low in all cases while folic acid levels were within standards. Immunologically it was found in all patients, a positivity of anti-intrinsic factor antibody and/or anti- parietal cells antibody.

Pernicious anemia was associated in 4 patients with autoimmune thyroid dysfunction consisting in two cases of Hashimoto thyroiditis at hypothyroidic phase (high TSHus, thyroperoxydase anti-antibody positive (over 10 N) in both cases and Graves' disease in the two other cases.

Pernicious anemia was associated with a syndrome of primary antiphospholipid antibody in one case. Furthermore pernicious anemia was found in a patient with multiple autoimmune syndrome associating autoimmune type 1 diabetes with strongly positive anti -GAD antibodies and rheumatoid arthritis.

Patients epidemiological, clinical, paraclinical, treatment, evolution at day eight characteristics are summarized in the **Table 1**.

### 3. Discussion

Our study report six new cases of pernicious anemia associated with other auto-immune diseases. It is the most important series of patients published in the Sub-Saharan african countries. In Senegal, respectively three and one case had been previously reported [1] [2]. In Cote d'Ivoire Lokrou [4] reported one association of pernicious anemia and type I diabete. Our cases were predominantly female like in the other studies [2] [5] [6] that seem to be related to the global female predominance of auto-immune diseases. Pernicious anemia can precede, succeed or occur simultaneously with the associated auto-immune disease. These diseases were dominated by thyroid dysfunction Hashimoto thyroiditis as previously reported [5]-[7] or Grave Basedow disease. In a population of pernicious anemia patients associated with other auto-immune diseases, Zulfiqar [5]-[7] noticed a thyroid dysfunction in 77% of cases and 61% of them were Hashimoto thyroiditis. Such findings have not been reported yet in sub saharian countries.

Table 1. Diagnostic, epidemiologic and evolutive characteristics of patients.

N	Age	sex	Autoimmune associated disease	Biology	Biochemistry	Medullogram	Immunology	Endoscopy -Histology	Treatment	Evolution: D8
1	48 ans	F	Grave Basedow	Hb: 5.4 g/dl ↓ MGV: 110 fl ↑ WBC: 2300/mm <sup>3</sup> ↓ Plat: 67,000/mm <sup>3</sup> ↓ Ret: 6700/mm <sup>3</sup> ↓	Vit B12: 98 pmol/l ↓ Folic acid: ND TSHus: 4 UI/ml T4L: 12 ng/l	Mégalo blastocytosis	Anti PC negative Anti IF: 215 AU/ml ↑ Anti TSHR: 8 UI/L	Atrophic fundic gastritis without metaplasia nor HP infection	Vit B12*  Carbimazole	Hb: 7.8 g/dl ↓ MGV: 98 fl WBC: 3300/mm <sup>3</sup> Plat: 97,000/mm <sup>3</sup> ↓ Ret: 126,000/mm <sup>3</sup>
2	32 ans	F	Hashimoto thyroiditis	Hb: 3.7 g/dl ↓ MGV: 115 fl ↑ WB: 3100/mm <sup>3</sup> Plat: 95,000/mm <sup>3</sup> ↓ Ret: 2000/mm <sup>3</sup> ↓	Vit B12: 22 pmol/l ↓ Folic acid: ND TSHus: 72 µU/ml ↑ T4L: 2 ng/l ↓ Cortisolemie: 72 µg/l	Mégalo blastocytosis	Anti PC: negative Anti IF: 118 AU/ml ↑ Anti TPO: 333 KU/l ↑	Normal Histology: fundic atrophic gastritis No HP	Vit B12**  Lévothyroxine	Hb: 6.1 g/dl ↓ MGV: 101 fl ↑ WBC: 4200/mm <sup>3</sup> Plat: 134,000/mm <sup>3</sup> Ret: 75,000
3	41 ans	F	Hashimoto thyroiditis	Hb: 6.4 g/dl ↓ MGV: 100 fl ↑ WBC: 3100/mm <sup>3</sup> Plat: 52,000/mm <sup>3</sup> ↓ Ret: 70,000/mm <sup>3</sup> ↓	Vit B12: 100 pmol/l Folic acid: 20 ng/ml TSHus: 8.2 µU/ml ↑ T4L: ND	Mégalo blastocytosis	Anti PC: 320 AU/ml ↑ Anti IF: 103 AU/ml ↑ Anti TPO: >600 KU/l ↑	Endoscopy: ND	Vit B12*  Lévothyroxine	Hb: 8.2 g/dl ↓ MGV: 92 fl GB: 3870/mm <sup>3</sup> Plat: 98,000/mm <sup>3</sup> ↓ Ret: 250,000/mm <sup>3</sup>
4	55 ans	F	Grave- Basedow disease	Hb: 6.9 g/dl ↓ MGV: 122 fl ↑ WBC: 3000 Plat: 70,000 ↓ Ret: 42,000 ↓	Vit B12: 84 pmol/l ↓ Ac Folique: 12 µg/l TSHus: 2 µU/ml T4L: 15 ng/l	Mégalo blastocytosis	Anti PC: negative Anti IF: 100 AU/ml ↑ Anti TSHR: 6 UI/l	Atrophic gastritis Intestinal metaplasia No HP infection	Vit B12*  Carbimazole	Hb: 9.9 g/dl ↓ MGV: 98 fl WBC: 4200/mm <sup>3</sup> Plat: 121,000/mm <sup>3</sup> Ret: 162,000/mm <sup>3</sup>
5	24 ans	M	Antiphospholipid syndrome	Hb: 9 g/dl ↓ MGV: 102 fl ↑ WBC: 1770 ↓ Plat: 58,000 ↓ Ret: 59,000 ↓	Vit B12: 37 pmol/l ↓ Folic acid: 9 µg/l Bil T: 47 mg/l ↑ Bil F: 39.5 mg/l ↑ Homocysteine: 67 µmol/l	Mégalo blastocytosis	Anti PC: 80 AU/mlAnti ↑ IF: 240 AU/ml ↑ B2GPI: IgM (32 MAU/ml) ↑ IgG (15 GAU/ml) ↑ Coombs test: négative	Cesophagal varices Atrophic gastritis No HP infection	Vit B12*  Anticoagulant Corticosteroids	Hb: 11.6 g/dl MGV: 86 fl WBC: 3240/mm <sup>3</sup> Plat: 11,000/mm <sup>3</sup> ↓ Ret: 334,000/mm <sup>3</sup>
6	38 ans	M	Type I diabetes Rheumatoid arthritis	Hb: 5.1 g/dl ↓ MGV: 115 fl ↑ WBC: 4200/mm <sup>3</sup> Plat: 115,000/mm <sup>3</sup> ↓ Ret: 56,000/mm <sup>3</sup> ↓	Vit B12 (pmol/l): 100 ↓ Hb A1c: 11.5% ↑ Blood glucose: 5.2 g/l ↓	Mégalo blastocytosis	Anti PC: negative Anti IF 15 N Anti GAD: 198 UI/L Rheum fact: negative Anti CCP: NF	FOGD: ND	Vit B12* Insulin Corticosteroids Hydroxy-chloroquine	Hb: 8.4 g/dl ↓ MGV: 100fl WBC: 5100/mm <sup>3</sup> Plat: 147,000/mm <sup>3</sup> Ret: 148,000/mm <sup>3</sup>

**LEGEND F:** female; **H:** male; **Hb:** hemoglobin; **MGV:** mean globular volume; **WBC:** white blood cells; **Plat:** Platelets; **Vit B12:** vitamin B12; **Anti PC:** anti parietal cells antibodies; **Anti IF:** anti intrinsic factor antibodies; **Anti TSH:** anti-TSH receptors antibodies; **B2GPI:** type I beta 2 glycoprotein; **Anti GAD:** anti gliadine antibodies; **RF:** rheumatoid factor; **Ret:** reticulocytes count; **Anti CCP:** anti cyclic citrullinated peptides antibodies; **FT4:** free thyroxin, **TSHus:** thyroxine Stimulin hormon ultra sensible; **Bil T:** total bilirubin, **Bil F:** free bilirubin, **HP:** *Helicobacter pylori*; **HbA1c:** glycated hemoglobin; **ND:** not done, **D8:** eighth day of treatment, **Vit B12\*:** Cyanocobalamin 2000 µg orally every day during 1 week, than every week than each month, **Vit B12\*\*:** Cyanocobalamin 1000 µg intramuscular route every day during 1 week, than every week than each month.

The association of pernicious anemia and diabetes was reported in our geographical area [5]-[7] and is well known. But the association with anti-phospholipid syndrome is less frequent. It was reported by Zulfiqar but not found in Sub-Saharan Africa. The diagnosis of this first known case in Africa was made while researching thrombophilia suggested by atypical location of thrombo-embolic manifestations. This case was particular because of the co-existence of a hyperhomocysteinemia which is another thrombophilic risk factor. The lack of recurrence after acute thrombo embolic phase with only vitamin B12 therapy suggest a participation of hyperhomocysteinemia in the occurrence of thrombo-embolic manifestations in this case.

In one case there was a multiple auto-immune syndrome associating pernicious anemia, rheumatoid arthritis and auto-immune type I diabetes. These complex cases were classified by Humbert in three types [8] but some cases don't match this classification and remain unclassified.

Symptoms revealing pernicious anemias associated with other auto-immune diseases are numerous and non specific. Anemia was quasi constant in our cases like in those reported in Black African patients [1]-[4], acquired diffuse melanoderma which is a particularity of pernicious anemia in Black population and found in 80% of cases reported by Diop [1], was noticed in only one case in our series. Same for sensitive neuropathy and glossitis. These symptoms were found respectively in near half of the cases reported by Diop and in 23% of those reported by Ndiaye [2]. We haven't noticed diarrhea, constipation or gastric pain in our series but the size of our population study did not allow us any interpretation. Biological characteristics of our population are similar to those previously published in Subsaharian Africa. Macrocytic anemia was almost constant coexisting with other cytopenia realizing a bicytopenia. or pancytopenia [2] [4]. Medullar megaloblastocytosis was frequently associated with haemolysis. In this context of dysimmunity an auto-immune hemolytic anemia must be evoked, but in all our cases Coombs test was negative. Low blood level of vitamin B12 was noticed in all our cases like in other publications [1] [6].

Positivity of auto-immune markers like anti intrinsic factor and anti parietal cells antibodies with a respective specificity of 95% and 50% [6] is a major diagnostic criteria for diagnosing Biermer disease. Anti intrinsic factor were more frequently found (6 cases). Body gastric atrophy is another diagnosis criteria reported in 86% of cases by N'diaye F.S. It was constantly found in subjects who did have and digestive endoscopic examination in our serie. Histologically atrophic gastritis can be associated with an intestinal type metaplasia that can lead to gastric cancer. Gastric endoscopy must be regularly performed to detect as earlier as possible the malignant transformation in case of isolated pernicious anemia and when there is another autoimmune disease associated [9].

Treatment of pernicious anemia alone or associated with another auto-immune disease is based upon lifetime parenteral administration of vitamin B12. But high doses of vitamin B12 given orally are effective and very useful in patients with thrombopenia and when health care facilities are poor [6]. Treatment of the associated disease were corticosteroids or immunomodulators such hydroxychloroquine associated with specific measures like insulin, levothyroxine or carbimazole.

#### 4. Conclusion

Pernicious anemia associated with other auto-immune diseases is not frequent in a Black African population. Physicians should pay attention to this association because of the lack of specificity of clinical symptoms. Macrocytic anemia is constant and haemogram is a convenient diagnostic tool in case of suspicion of a pernicious anemia or an auto-immune disease.

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