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UNMASKING PERNICIOUS ANEMIA: CLINICAL DIVERSITY AND AUTOIMMUNE OVERLAP IN A NORTH AFRICAN POPULATION

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ABSTRACT

Background: Pernicious anemia (PA) is a complex autoimmune disorder caused by chronic atrophic gastritis leading to intrinsic factor deficiency and then to vitamin B12 deficiency. By the huge heterogenicity of symptoms, PA can be misdiagnosed. This pathology is also challenging by her association with many other auto-immune diseases. **Methods:** We conducted a retrospective observational study including 46 patients diagnosed with PA between 2018 and 2024 at a Moroccan university center. Was included patient with confirm PA diagnosis. This diagnosis was established based on: clinical manifestations, biochemical evidence of vitamin B12 deficiency, positive serological markers (anti-parietal cell and/or anti-intrinsic factor antibodies), and essentially endoscopic/histological confirmation of gastric atrophy. **Results**: The 46 patients had a mean age of 56.2 ± 12.3 years, with a female predominance (F/M ratio = 1.8). Anemia was present in all cases, with macrocytic morphology in 37%, microcytic in 27%, and normocytic in 29%. Neurological manifestations occurred in 19.6% of patients, most frequently peripheral neuropathy (17%). Autoimmune comorbidities were identified in 32.6%, mainly autoimmune thyroiditis (33% of cases) and primary biliary cholangitis (20%). Vitamin B12 supplementation achieved hematological normalization in 95% of patients, although two developed neoplastic complications during follow-up. **Conclusion:** diagnosing PA can by extremely complexed, our study highlight the importance of evaluation beyond classical macrocytic anemia to bring the right diagnostic. Systematic screening seems to by indispensable since PA comes with high prevalence of associated autoimmune disorders. Our findings align with recent international literature while providing unique insights from a North African population.

KEYWORDS: Pernicious anemia, vitamin B12, autoimmune gastritis, primary biliary cholangitis

INTRODUCTION

Pernicious anemia (PA), first described in the 19th century, represents the hematological manifestation of autoimmune metaplastic atrophic gastritis, resulting in vitamin B12 malabsorption due to intrinsic factor deficiency.[1] Despite extensive knowledge of its pathophysiology, PA remains a diagnostic and therapeutic challenge because of its heterogeneous clinical presentation.[2,3] Recent epidemiological studies estimate the prevalence of PA at approximately 0.1% in the general population, rising to 1.9% in individuals over 60 years of age.[4,5,6] Emerging evidence indicates a comparable prevalence across diverse ethnic populations, challenging the earlier view that PA predominantly affects northern Europeans.[7,8] PA shows a female predominance, with a female-to-male ratio of 2:1, and is frequently associated with other autoimmune disorders, observed in 20–40% of cases.[9] In this study, we provide a comprehensive analysis of a Moroccan PA cohort. Our findings contribute to the growing understanding of PA in non-European populations and highlight the need for awareness of this condition across diverse demographic settings.

Methods

Study Design and Population

We conducted a retrospective observational study of 46 patients with a confirmed PA diagnosis, evaluated at our institution between January 2018 and March 2024.

Diagnostic Criteria

PA diagnosis was based on major criteria

1. Clinical evidence of vitamin B12 deficiency (anemia and/or neurological symptoms)
2. Biochemical confirmation (serum B12 <200 pg/mL or elevated MMA/homocysteine)
3. Serological evidence (anti-parietal cell and/or anti-intrinsic factor antibodies)
4. Endoscopic evidence of corpus-predominant atrophy

Data Collection
We extracted:

- Demographic characteristics
- Clinical manifestations
- Laboratory parameters (hemoglobin, B12, iron studies)
- Serological profiles
- Endoscopic and histological findings
- Treatment regimens and outcomes

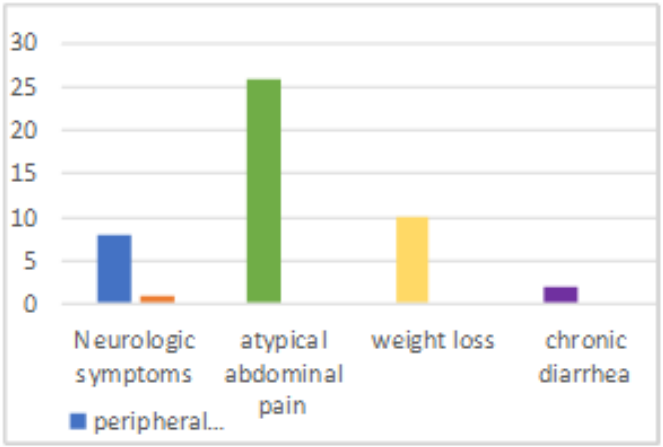
Statistical Analysis
Continuous variables were expressed as mean ± SD or median (IQR). Categorical variables were reported as frequencies (%). Comparisons were made using Student's t-test or χ^2 test as appropriate. Statistical significance was set at $p<0.05$.

RESULTS
1. Demographic Characteristics
The study included 46 patients with a mean age of 56.17 years (±12.3 years), ranging from 29 to 85 years. There was a clear female predominance, with 30 female patients (65.2%) and only 16 males (34.8%) with a sex ratio: F/M=1.8. Despite the gender disparity Statistical analysis didn't find a significant age difference between genders (p=0.34).

Sexe	Âge moyen	Écart-type	Min-Max
Femmes	56.5	±11.2	29-85
Hommes	55.8	±14.1	32-83

2. Clinical Presentation
All 46 patients (100%) presented with anemia. However, the morphological patterns varied significantly: macrocytic anemia was observed in 14 patients (37%), microcytic anemia in 10 patients (27%), and normocytic anemia in 11 patients (29%). This distribution highlights the importance of considering PA even with the absence of classic macrocytosis.

Neurologic symptoms were documented in 9 patients (19.6%), with peripheral neuropathy was the most present manifestation (8 patients, 17%). one patient (2%) presented with ataxia. These findings underscore that neurologic manifestations could be at the first plan and constitute the main complications in PA.

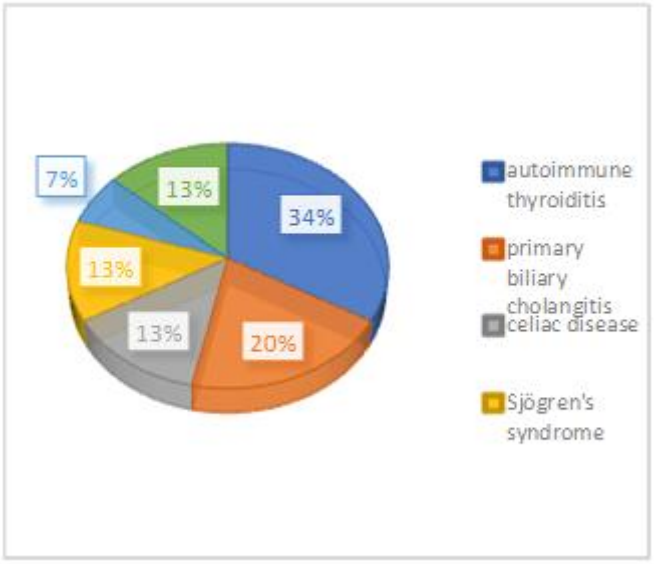


Gastrointestinal symptoms were prevalent, with atypical abdominal pain reported by 26 patients (56%). Significant weight loss was noted in 10 patients (21%), chronic diarrhea affected 2 patients (4%) and upper gastrointestinal bleeding in one patient (2%). Reflecting the atrophic gastritis characteristic in PA.

3. Laboratory Findings
The mean hemoglobin level across the cohort was 9.2 ± 1.8 g/dL. Vitamin B12 levels were markedly deficient, with a median value of 158.5 pg/mL (IQR 120-190). These biochemical results confirm the vitamin B12 deficiency in PA despite some patients having borderline serum B12 levels.

4. Serological Profiles
Autoantibody testing was performed in 28 patients and revealed anti-parietal cell antibodies in 10 patients (35%) and anti-intrinsic factor antibodies in 8 patients (28%). 6 patients (21%) were positive for both antibodies, while 4 patients (14%) were seronegative. This seronegative subgroup shows the limitations of antibody testing for confirming PA diagnosis and the necessity for a global diagnostic approaches.

5. Associated Autoimmune Conditions
Autoimmune comorbidities were identified in 15 patients (32.6%). The most frequent association was autoimmune thyroiditis (5 patients, 33% of comorbid cases), followed by primary biliary cholangitis (3 patients, 20%), Sjögren's syndrome in 13% of them (2 patients), celiac disease in 13% of them (2 patients), chronic inflammatory bowel disease in 13% of cases (2 patients), and ankylosing spondylitis 6% patients (1 patient). By its autoimmune nature PA is frequently associated with other autoimmune diseases, and our finding aligns with this statement.



6. Treatment Outcomes

All patients received vitamin B12 supplementation as treatment, of course specific treatment were administrated for the associated autoimmune disease. response was excellent, achieved in 44 patients (95%)., (clinical improvement and progressive correction of anemia). However,1 patient developed a paraneoplastic syndrome. And 1 patient developed a neuroendocrine tumor type 1.

DISCUSSION

Our study provides several important and unique insights from a North African population the modern understanding of PA:

1. Hematological Heterogeneity

The finding that 56% of our patients presented with non-macrocytic anemia don't aligns the classical teaching of PA who admit that it can exclusively causing macrocytosis. Our work aligns with recent researchers reports[10,11], who emphasize that concurrent iron deficiency can mask macrocytosis.

2. Diagnostic Challenges

The limitations of antibody testing is quite known in literature and the 14% seronegative rate in our cohort goes along with it.[12,6] In such cases, endoscopic takes a prime, with all seronegative patients showing characteristic corpus atrophy. This statements comfort the recent AGA guidelines recommending endoscopic screening in uncertain PA.[4]

3. Autoimmune Associations

In our study we found the prevalence of associated autoimmunity is 32%. Showing PA can be interred in autoimmune polyendocrine syndromes as found in.[9] Our work also find a high rate of autoimmune thyroiditis (33%) parallels reports from Italian cohorts.[6] However the 20% prevalence of primary biliary cholangitis exceeds European averages, reflecting probably a genetic regional factors.

4. Treatment Considerations

Our work demonstrated the excellent response to B12 supplementation (95%) confirms treatment efficacy reported in recent meta-analyses.[13] However, our followed up discovered 2 neoplastic complication. This result goes to show how crucial it is to monitor patients with PA closely.[14]

Study Limitations

Our study didn't test for genetic causes that might explain PA developing condition. And 1 in 7 patients needed endoscopy because blood tests were normal. Showing the importance of endoscopy in patients with vitamin B12 deficiency.

CONCLUSION

This Moroccan cohort study highlights the marked clinical and hematological heterogeneity of pernicious anemia, with over half of the cases presenting without the classic macrocytic anemia, and a significant proportion (14%) showing seronegative disease requiring multimodal diagnostic confirmation. The high prevalence of autoimmune comorbidities—particularly autoimmune thyroiditis and an unexpectedly elevated rate of primary biliary cholangitis compared to European series—underscores the need for systematic screening for associated autoimmune disorders in all PA patients. Our findings not only support current international recommendations but also provide novel epidemiological insights from a North African population, which may have distinct genetic or environmental determinants. Clinicians should maintain a high index of suspicion for PA even in atypical hematologic presentations, and ensure close follow-up for the early detection of neoplastic complications.[14] Future multicentric prospective studies in the Maghreb are warranted to better define regional specificities and optimize patient management.

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