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Diagnosis and Management of Pernicious Anemia

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Abstract Pernicious anemia is a macrocytic anemia due to cobalamin deficiency, which is the result of intrinsic factor deficiency. Pernicious anemia is associated with atrophic body gastritis, whose diagnostic criteria are based on the histologic evidence of gastric body atrophy associated with hypochlorhydria. Serological markers suggesting the presence of oxyntic mucosa damage are increased levels of fasting gastrin and decreased levels of Pepsinogen I. Without the now obsolete Schilling's test, intrinsic factor deficiency may not be proven, and gastric intrinsic factor output after pentagastric stimulation has been proposed. Intrinsic factor autoantibodies are useful surrogate markers of pernicious anemia. The management of patients with pernicious anemia should focus on the life-long replacement treatment with cobalamin and the monitoring to early diagnose an eventual onset of iron deficiency. Moreover, these patients should be advised about possible gastrointestinal long-term consequences, such as gastric cancer and carcinoids.

Keywords Pernicious anemia · Atrophic gastritis · Autoimmune gastritis · Intrinsic factor autoantibodies · Parietal cell autoantibodies · Vitamin B_{12} deficiency · Cobalamin deficiency · *Helicobacter pylori* infection · Gastric autoimmunity

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Introduction

Pernicious anemia (PA), an autoimmune disease, is the end-stage of atrophic body gastrits (ABG), likely as a consequence of long-standing *Helicobacter pylori* infection. The active infectious process is gradually replaced by an autoimmune disease terminating in a burned-out infection and the irreversible destruction of the gastric body mucosa [1, 2]. The autoimmune origin of PA is further supported by the presence of parietal cell and/or intrinsic factor autoantibodies and the frequent association with other autoimmune disorders, such as autoimmune thyroid disease, type I diabetes, and vitiligo [1, 3, 4]. HLA-DR genotypes suggest a role of genetic susceptibility in pernicious anemia [5]. By using blocking experiments with anti-DR and anti-DQ antibodies, DR has been shown to represent the HLA restriction element in autoimmune gastritis [6]. Recently, the genotypes HLA-DRB1*03 and DRB1*04 has been observed to be significantly associated with PA (OR 6.2 (95%CI 3.0–12.6) [7•], overlapping with those reported in other autoimmune diseases such as type I diabetes and autoimmune thyroid disease [8], thus suggesting a common immunological cluster and supporting the role of a genetic susceptibility for autoimmunity PA.

PA is a macrocytic anemia due to cobalamin (vitamin B_{12}) deficiency, which, in turn, is the result of deficiency of intrinsic factor, a protein that binds avidly to dietary vitamin B_{12} and promotes its transport to the terminal ileum for absorption. The deficiency of intrinsic factor is a consequence of the presence of atrophic body gastritis (ABG) resulting in the destruction of the oxyntic mucosa, and, thus, the loss of parietal cells, which normally produce chlorhydric acid as well as intrinsic factor [1, 9]. The term PA is sometimes used as synonym for cobalamin deficiency or for macrocytic anemia, but to avoid ambiguity, PA

should be reserved for conditions resulting from impaired secretion of intrinsic factor and atrophy of oxyntic mucosa. However, differential diagnosis may sometimes be challenging due to the limit of available diagnostic tools. The present review aimed to focus on diagnosis and management of PA patients from a gastroenterological point of view.

Clinical Presentation of Pernicious Anemia

The clinical presentation of PA is often insidious for various reasons. The onset is difficult to establish and progression of PA is very slow. As a consequence, often patients are not aware of their symptoms related to anemia, because over time they become accustomed to them. In many such cases, the underlying disease may not be suspected until a complete red blood count has been performed. However, patients with PA may seek medical advice due to unspecific symptoms related to the presence of anemia per se, such as weakness, asthenia, decreased mental concentration, headache, and, especially in elderly patients, cardiac symptoms such as palpitations and chest pain [1, 9]. Less frequently, PA may present with neurological symptoms, such as paresthesias, unsteady gait, clumsiness and in some cases spasticity. Indeed, vitamin B_{12} deficiency may cause peripheral neuropathy and lesions in the posterior and lateral columns of the spinal cord (sub acute combined degeneration) and in the cerebrum, and these lesions progress from demyelisation to axonal degeneration and eventual neuronal death. Moreover, there is a growing body of evidence on the relationship between cobalamin deficiency and dementia [10]. The early recognition of these symptoms is very important, because the neurological lesions may not be reversed after replacement therapy with vitamin B_{12} [9] and patients with PA generally respond favorably to supplemental B12 treatment, especially if PA is diagnosed early in the course of the disease [10].

Finally, PA may often be observed in patients under medical treatment for other autoimmune conditions frequently associated with PA, such as autoimmune thyroid disease, type I diabetes, and vitiligo, as part of the autoimmune polyendocrine syndromes [11].

Albeit the primum movens of PA is ABG, less frequently the disease is suspected due to symptoms of the gastrointestinal tract. The reason for the apparent paradox may lay in the fact that ABG is associated with hypochlorhydria, and symptoms of the upper gastrointestinal tract are often related to the presence of chlorhydric acid. However, hypochlorhydria itself may cause impaired gastric emptying, eventually leading to dyspeptic symptoms such as epigastric discomfort, postprandial bloating and fullness, and early satiety [12, 13]. Often the awareness and/or the concern about upper gastrointestinal symptoms and/or neurological symptoms are not sufficient enough to seek medical advice. For this reason, specific data about clinical presentation in PA are scarce. As shown in Table 1, in our experience of 177 consecutively diagnosed PA patients [14, 15], 27.7% complained of dyspeptic symptoms and neurological symptoms, such as paresthesias, were present in 18.6% of patients, suggesting that the presence of these symptoms should be related to the possible subclinical presence of PA.

As far as associated diseases, in our experience, 40.6% of our patients with PA had an associated autoimmune thyroid disease, 52.5% had positivity to thyroid peroxidase antibodies, and 10.2% presented other associated autoimmune disorders, such as vitiligo, psoriasis, and alopecia, well known for their association with PA as part of the autoimmune polyendocrine syndromes [11, 16].

In a recent work, we observed that ABG and ATD occur in a closely linked fashion with a prevalence of ATD in about 40% of atrophic body gastritis patients [4]. The diagnosis of a concomitant presence of autoimmune thyroiditis and PA may have an important clinical implication, in particular in those patients who require replacement therapy with thyroxine, because patients with an impaired acid secretion may present thyroxine malabsorption requiring an increased dose of the drug [29•], and in patients with PA, an associated hypochlorhydria is always present due to the loss of oxyntic mucosa [1, 2].

Epidemiological data may also be useful for determining who is affected by PA. PA is thought to be particularly common among individuals of Scandinavian, English, and

Table 1 Clinical features of a series of 177 patients with pernicious anemia (data on file)

Age, years, median (range)	60 (23–86)
Age groups, years	
<30	4
≥30 <40	10.2
≥40 <50	12.4
≥50 <60	24.3
≥60 <70	33.3
≥70 <80	13.6
≥80	2.2
Gender, females	51.4
Dyspeptic symptoms	27.7
Neurologic symptoms	18.6
Positivity to parietal cell antibodies	80.2
Positivity to intrinsic factor antibodies	38.9
Positivity to thyroid peroxidase antibodies	52.5
Autoimmune thyroid disease	40.6
Other autoimmune diseases	10.2
1st degree family history for gastric cancer	6.2

Data expressed as % of total number of patients

Irish ancestry, while it appears to be much less common in Caucasians of Italian or Greek origin [17]; but, more recently, the disease has been reported in African-American and Latin-American subjects [18, 19]. In the so-called high-risk groups, about 9 new cases are detected per 100,000 population per year, and about 0.13% of the population is affected [20]. The only more recent population survey reported that 1.9% of persons more than 60 years old has undiagnosed PA [18].

A female preponderance ranging from 1.7 to 2.0:1 has been reported in white subjects [9]. This gender distribution was confirmed in the more recent population survey of persons more than 60 years old conducted in California, in which the prevalence of PA was 2.7% in women and 1.4% in men [18]. Our data concerning an Italian population seem do not confirm the female preponderance described in older studies, because in our series of consecutive PA patients, half (51.4%) are female (Table 1).

Regarding age, PA is frequently described as a disease of adults >60 years of age [1, 18, 20]. Also in our series of PA patients, the median age was 60 years ranging from 23 to 86 years (Table 1). However, in this series of PA patients, about one half were under 60 years of age, in particular, 4% of patients were <30 years and 10.2% were between 30 and 40 years of age. These data challenge the common notion that PA is a disease of the elderly and suggest that in clinical practice, PA is probably underdiagnosed, not only in elderly but also in younger patients, as also reported in a recent paper [21].

Considering the clinical scenario, it's important to note that iron deficiency is a complication of achlorhydria and may precede the development of PA, [1] and that iron deficiency may be present in concomitance with PA [22]. Recently, it has been shown that stratification by age cohorts from younger than 20 years to older than 60 years of patients with AG identified by hypergastrinemia and positive parietal cell antibodies showed a regular and progressive increase in mean corpuscular volume and levels of ferritin and gastrin and a decrease in vitamin B_{12} levels, whereas the prevalence of *H. pylori* infection decreased from more than 80% at ages younger than 20 to 12.5% at ages older than 60 years [21]. These findings support the idea that PA seems to be a disease starting many years before the establishment of clinical vitamin B_{12} deficiency.

Diagnosis of Pernicious Anemia

PA is defined as the presence of a hemoglobin concentration <13 g/dL for men and <12 g/dL for women [23], mean corpuscular volume (MCV) ≥100 fL [9], low levels of cobalamin (vitamin B_{12}) [9], together with the concomitant presence of ABG and intrinsic factor deficiency (Fig. 1).

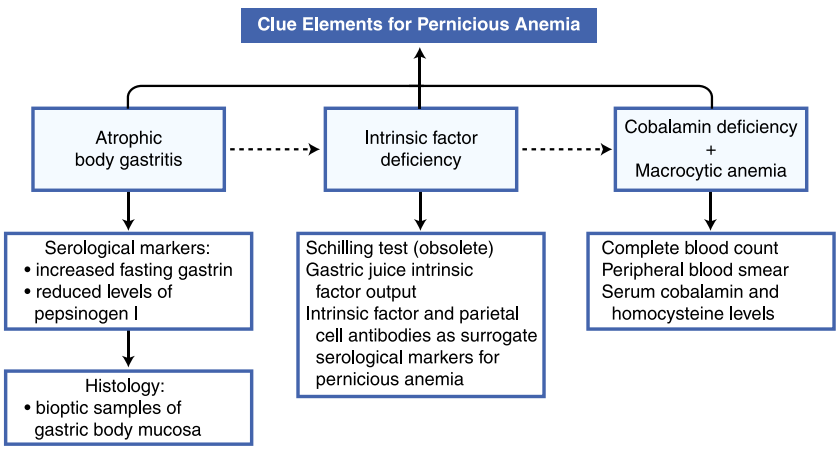

Fig. 1 The diagnosis of Pernicious anemia (PA) requires the concomitant presence of at least three hallmarks: macrocytic anemia with low cobalamin levels, atrophic body gastritis (ABG) and intrinsic factor deficiency. In clinical practice, the first two features of PA may be easily proven by performing a complete blood cell count and/or a peripheral blood smears together with serum cobalamin and homocysteine levels (and serum levels of folate in order to exclude macrocytic anemia due to folate deficiency) as well as a gastroscopy with multiple biopsies of the gastric antral and body mucosa and histological examination, possibly according to the updated Sydney System [46], in order to ascertain the presence of atrophic body gastritis. Serological markers such as hypergastrinemia, low Pepsinogen I levels and the positivity to intrinsic factor and parietal cell autoantibodies should be assessed to support the diagnosis of PA. In contrast, the presence of intrinsic factor deficiency may not always be proven in clinical practice, due to the vanishing availability of Schilling test. In alternative, the gastric intrinsic factor output after pentagastrin stimulation has been proposed. However, the presence of the other two diagnostic criteria, the eventual positivity to intrinsic factor and/or parietal cell autoantibodies as well as an accurate differential diagnosis in order to exclude other causes of cobalamin deficiency, should give a reliable diagnosis of PA in the vast majority of cases

Thus, by definition, PA is associated with ABG, and strict diagnostic criteria for ABG are based on the histological evidence of gastric body mucosal atrophy and ECL hyperplasia associated with hypochlorhydria to pentagastrin stimulation [24]. Increased levels of fasting gastrin and decreased levels of Pepsinogen I are well accepted serological markers suggesting the presence of oxyntic mucosa damage [25, 26], which should be confirmed, however, by appropriate histological sampling of gastric body mucosa to definitively diagnose ABG, according to the Updated Sydney System [27].

Regarding gastric mucosa histology, corpus-restricted atrophy with a spared antrum is a classical and indispensable feature required for the diagnosis of PA [1]. As reported in a previous review [28], in about 50% of PA patients antral mucosa is not spared, and in about 27% of PA patients a concomitant antral atrophic gastritis may be observed. These data strongly suggest that an extension of gastritis to the gastric antrum does not necessarily exclude the diagnosis of PA and the presence of gastric autoimmunity. Also the determination of ECL cells hyperplasia is considered helpful in the histological diagnosis of ABG associated with PA, because the presence of this histological change indirectly proves the presence of hypochlorhydria, which leads to hypergastrinemia that, in turn, is a trophic factor for ECL cells leading to their hyperplasia and eventually to the development of gastric carcinoids [29•].

In our consecutive series of 177 PA patients, the median value of fasting gastrin was 500 pg/mL ranging from 45 to 2,700 pg/mg (the reference value in our laboratory is <40 pg/mL). The values of hypergastrinemia in patients with PA are widely distributed. Indeed, in our series of PA patients, 15% had gastrin levels <200 pg/mL, but at the same time, 39% of patients had gastrin levels >600 pg/mL and, even 11.3% had gastrin levels >1,500 pg/mL. Thus, gastrin should always assessed together with Pepsinogen I levels, and the diagnosis of gastric mucosa atrophy should be confirmed by histological evaluation.

Intrinsic factor deficiency would be proven by the now obsolete Schilling test: in order to confirm that the cobalamin deficiency is the result of intestinal malabsorption due to intrinsic factor deficiency, urinary excretion of orally administered vitamin B_{12} is low, and is increased by administration of vitamin B_{12} together with intrinsic factor. Unfortunately, the availability of this test is vanishing due to problems related to its radioactive reagents. Alternatively, a gastric juice intrinsic factor assay has been proposed, which assesses the gastric intrinsic factor output after pentagastrin stimulation considering a value lower than 200 U/h as diagnostic for PA [30]. However, probably because gastric secretory testing requires the insertion of a nasogastric tube, its overall use is not widely popular.

Therefore, in clinical practice, the presence of intrinsic factor deficiency may not be definitively proven, and increasing reliance is placed on the detection of intrinsic factor antibodies for the diagnosis of PA, which are viewed as useful markers of this disease [31]. Earlier studies reported the positivity to intrinsic factor antibodies in 40% to 60% of patients with PA [32, 33], rising to 60% to 80% with increasing duration of disease [34]. More recently, we reassessed the diagnostic performance of intrinsic factor and parietal cell antibodies in patients with atrophic body gastritis with respect to cobalamin deficiency by using a novel ELISA assay [29•]: in PA patients, intrinsic factor antibodies achieved a sensitivity and a specificity of 37% and 100%, respectively, and parietal cell antibodies yielded a sensitivity and a specificity of 81.5% and 90.3%, respectively. The combined assessment of both autoantibodies significantly increased their diagnostic performance, yielding a 73% sensitivity for PA, while maintaining a 100% specificity. Thus, by combining the assessment of intrinsic factor and parietal cell autoantibodies, the diagnostic performance of these surrogate markers for PA may notably be improved. Further, beyond a specific hallmark of PA, the positivity to intrinsic factor and parietal cell antibodies may also be interpreted as an expression of oxyntic mucosa damage, because the increasing histological score of body mucosa atrophy correlated positively with the titer of both antibodies [12, 35].

Notwithstanding, an accurate differential diagnosis of other causes of cobalamin deficiency is mandatory. As previously reviewed [28], cobalamin deficiency may be caused by other triggers of impaired absorption in the stomach or in the intestine, such as gastrectomy, ileal disease or resection, or by decreased intake due to vegetarianism. Among maldigestion, there are very rare cases related to severe pancreatic insufficiency, but more interesting is the recent evidence of maldigestion of dietary cobalamin in patients with corpus predominant *H. pylori* gastritis leading to impaired acid secretion and consequent increased intragastric pH [36, 37]. In fact, dietary cobalamin is bound to salivary proteins, which need to be cleaved in presence of chlorhydric acid before it can be bound to intrinsic factor and be absorbed in the terminal ileum [28]. In these cases of dietary cobalamin maldigestion, Schilling test would be normal, indicating that cobalamin deficiency is not due to intrinsic factor deficiency. Without performing a Schilling test, it may be challenging to discriminate between the presence of PA and the presence of maldigestion of dietary cobalamin. However, from a practical point of view, the clinical management of these two groups of patients is similar. Further, an accurate differential diagnosis should also be carried out for macrocytic anemia, which may underlie other causes, such as folate deficiency and myelodysplasia [28], and the assessment of serum homocysteine levels is helpful. In this context, it should be kept in mind that in order to diagnose vitamin B_{12} deficiency, total vitamin B_{12} measurement is used cost effectively as the parameter of choice, but it

has limited sensitivity and specificity, especially in persons with vitamin B_{12} concentrations in the lower reference range (<400 pmol/L). Alternatively, modern biomarkers for early diagnosis of vitamin B_{12} deficiency, such as holotranscobalamin (holoTC), also known as active B_{12}, and methyl malonic acid as a functional B_{12} marker have been proposed [38]. Figure 1 shows the diagnostic clues for PA.

Management of Patients with Pernicious Anemia

The clinical management of patients with PA concerns two different aspects. First, the treatment of cobalamin deficiency and the monitoring of onset of iron deficiency. Second, the surveillance to early detection of long-term consequences of PA, such as gastric cancer and carcinoids.

Treatment of Cobalamin Deficiency and Monitoring of Iron Deficiency

The cobalamin replacement treatment is able to correct the anemia, whereas the neurological complications may be corrected only if the replacement treatment is given soon after their onset. The therapeutic recommendations of PA with regard to dosage and administration B_{12} substitution treatment are divergent [39]. In the USA, patients usually receive vitamin B_{12} injections of 1 mg daily in their first week of treatment; in the following month, they receive weekly injections and then monthly injections [40]. In Denmark, patients receive injections of 1 mg of cyanocobalamin weekly during the first month and every 3 months subsequently, or 1 mg hydroxycobalamin every other month [41]. According to our protocol, a higher dosage of cobalamin is successfully used to prevent early relapse of cobalamin deficiency. First, patients receive intramuscularly injection of 5 mg of cyanocobalamin daily for 5 days, replenishing the cobalamin body stores; then, vitamin B_{12} stores are maintained by an intramuscularly injection of 5 mg of cyanocobalamin every 3 months. In our experience, this protocol is appropriate for patients with anemia and macrocytosis relapse at long-term follow-up.

However, the practice of giving cobalamin as an intramuscular injection has several drawbacks, because injections can be painful, difficult to provide for the elderly or patients who live alone, and expensive if provided by health professionals. Thus, at least since the early'90s, the usefulness of oral cobalamin treatment in PA has been debated [42, 43]. According to a systematic review conducted by French hematologists [44], several prospective studies (n=4), prospective randomized studies (n=3) and a systematic review by the Cochrane group (n=1) provide evidence that oral cobalamin therapy may adequately treat cobalamin deficiency, particularly hematological abnormalities or manifestations. These studies suggest that at least 1,000 μg/day of oral cyanocobalmin are needed for pernicious anemia and a mean daily dose of 250 μg for food-cobalamin malabsorption, confirming the previously reported efficacy of oral cobalamin treatment in adult and elderly patients.

Furthermore, according to our protocol, PA patients are monitored at least by yearly biochemical controls of complete blood count, serum cobalamin and ferritin levels, in order to monitor the replacement treatment and to early detect the eventual onset of iron deficiency. Also patients with ABG with iron deficiency anemia or without hematological alterations should be monitored in the same way, in order to early detect the eventual onset of cobalamin deficiency. Finally, PA patients are monitored by at least one yearly clinical interview, in order to verify the onset of new symptoms suspicious of long-term consequences of PA, such as dysphagia, epigastric pain, dyspeptic symptoms, loss of body weight and/or iron-deficiency, requiring an immediate gastroscopic investigation.

Neoplastic Long-Term Consequences of PA

Albeit PA is substantially a benign disorder for a large part of patients, it is epidemiologically and biologically linked to the development of the intestinal-type gastric adenocarcinoma and gastric carcinoid type I [45, 46]. Hypergastrinemia, secondary to hypochlorhydria in PA patients, is a well-known risk factor for ECL cell hyperplasia and gastric carcinoids [47, 48], and it has been reported that one in 25 patients with PA develops gastric carcinoids [49]. In a recent long-term follow-up study of patients with atrophic body gastritis, half of them with PA, after 1,463 person-years, six patients developed gastric carcinoids with an annual incidence rate (person-year) of 0.4% showing that this neoplasia is a rare complication in patients with chronic atrophic gastritis [50].

Moreover, the crucial role of hypochlorhydria, as a consequence of atrophy of the oxyntic mucosa, in the development of gastric cancer, has been highlighted [51]. Hypochlorhydria leads to an overgrowth of nitrosamine-producing bacteria with potential carcinogen activity [52]. Also ascorbic acid, the main redox agent in the gastric juice with protective action against ROS, has been reported to be reduced in the presence of atrophy of the oxyntic mucosa [53].

In literature, annual incidence rates of gastric cancer in PA patients ranging from 0.1% to 0.5% are reported [47, 49, 54]. A recent follow-up study of patients with ABG, reported an annual incidence risk of 0.14% for developing gastric cancer during an observation period of 6.7 years [55, 56]. To date, the need and the cost-effectiveness of endoscopic-histological surveillance in patients with PA have not been definitively established. Considering the relatively benign nature of gastric carcinoids in patients with PA, 5-year follow-up intervals has been proposed

limited to patients with ECL hyperplasia; as for gastric cancer, the same authors further concluded that the first gastroscopic follow-up after a diagnosis of PA should be performed relatively soon, and that only PA patients with preneoplastic lesions and those with gastrointestinal symptoms should undergo endoscopic surveillance [49]. Another study concluded that follow-up should be performed at 3-year intervals only in PA patients younger than 60 years [47]. More recently, the first follow-up performed 4 years after the diagnosis has been reported to be safe and convenient for early detection of potentially neoplastic lesions [57]. Lacking prospective data on this item, and considering the low risk for developing neoplastic lesions over time in some PA patients, in our unit, PA patients aged <75 years are monitored regularly by gastroscopy with antral and corporal biopsies at 4-year intervals, and at onset of new upper GI symptoms as well as iron-deficiency anemia, immediate gastroscopy is performed.

Conclusions

The clinical presentation of PA is often insidious because the onset is difficult to establish and progression of PA is very slow. Patients with PA may seek medical advice due to aspecific symptoms such as weakness, asthenia, decreased mental concentration, headache, as well as for neurological symptoms, such as paresthesias, unsteady gait, clumsiness, and even dementia. Dyspeptic symptoms such as early satiation and postprandial fullness, even if often present, are generally not complaints voiced by patients. The cobalamin replacement treatment is able to correct the anemia, whereas the neurological complications may be corrected only if the replacement treatment is given soon after their onset making the early recognition of the neurological symptoms very important. The management of patients with pernicious anemia should focus on the life-long replacement treatment with cobalamin and the monitoring to diagnose an eventual onset of iron deficiency early. Moreover, these patients should be advised about possible gastrointestinal long-term consequences, such as gastric cancer and carcinoids.

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