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Review

Diagnosis and classification of pernicious anemia

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ABSTRACT

Pernicious anemia (PA) is a complex disorder consisting of hematological, gastric and immunological alterations. Diagnosis of PA relies on histologically proven atrophic body gastritis, peripheral blood examination showing megaloblastic anemia with hypersegmented neutrophils, cobalamin deficiency and antibodies to intrinsic factor and to gastric parietal cells. Anti-parietal cell antibodies are found in 90% of patients with PA, but have low specificity and are seen in atrophic gastritis without megaloblastic anemia as well as in various autoimmune disorders. Anti-intrinsic factor antibodies are less sensitive, being found in only 60% of patients with PA, but are considered highly specific for PA. The incidence of PA increases with age and is rare in persons younger than 30 years of age. The highest prevalence is seen in Northern Europeans, especially those in the United Kingdom and Scandinavia, although PA has been reported in virtually every ethnic group. Because of the complexity of the diagnosis, PA prevalence is probably underestimated and no reliable data are available on the risk of gastric cancer as the end-stage evolution of atrophic gastritis in these patients.

Contents

1. Introduction

Pernicious anemia (PA) is a disease of autoimmune origin in which atrophy of the gastric mucosa which involves the body and fundus of the stomach, reduces the number of parietal cells that produce the intrinsic factor necessary for absorption of vitamin B_{12}, which, in turn, is indispensible for erythropoiesis and myelin synthesis. This condition is progressive over a span of years, from a mild chronic inflammation of the stomach body to an advanced state associated with a lack of vitamin B_{12}.

The symptomatology is dominated by a profound megaloblastic-type anemia and, in the most serious cases, by neurological alterations, which can precede the diagnosis of gastric atrophy by several decades.

The autoimmune nature of the process that brings on gastric atrophy and PA is documented by the presence of autoantibodies against intrinsic factor secreted by the stomach and the gastric parietal cells, and by the frequent coexistence in these patients of other disorders of autoimmune origin. Recent epidemiological studies support the evidence that autoimmune gastritis and PA are found across all continents [1,2] and probably are underdiagnosed [3,4], given that most patients with

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microcytic or macrocytic anemia are treated with iron, folates, and cobalamin, without any more thorough investigation into the cause of the anemia; a biopsy of the gastric mucosa in many cases is not undertaken; even if a biopsy is performed, the pathologists often describe a generic histological pattern of chronic gastritis with intestinal metaplasia [5,6].

2. Historical notes

1860: Austin Flint, connects observations made by Thomas Addison in 1849, describing an important form of anemia associated with a degenerative disease of the tubular glands of the stomach.

1872: Anton Biermer designates this condition 'pernicious anemia'.

1900: Faber and Bloch document for the first time in a patient with PA the presence of a histological pattern of gastric atrophy.

1953: William B. Castle demonstrates that anemia is caused by a concomitant lack of an 'extrinsic factor' metabolized in the liver (cobalamin or vitamin B_{12}) and of an 'intrinsic factor' present in the gastric juice necessary for absorption of cobalamin at the intestinal level.

1960: Michael Schwartz demonstrates the presence in patients with PA of autoantibodies against the intrinsic factor.

1962: James Irvine identifies in patients with PA the presence of another autoantibody against parietal cells of the gastric mucosa [7].

3. Genetics

A genetic susceptibility for PA is suggested by a specific HLA-DR pattern and by blocking experiments with anti-DR and anti-DQ antibodies that have shown that DR antigen represents the HLA restriction element in atrophic body gastritis [8]. By using a DNA-based, sequence-specific oligonucleotide technology, it has been observed that the genotypes HLA-DRB1*03 and DRB1*04, which are known to be associated with other autoimmune disease (such as type1 diabetes and autoimmune thyroid disease) [9], were significantly associated with PA, which further supports the concept that autoimmunity may play a role in PA [10].

4. Clinical features

Pernicious anemia usually manifests itself in persons over age 30 and strikes both sexes equally. It is particularly frequent in northern Europeans, especially Scandinavians. Nevertheless, it is present in other populations but is relatively infrequent in subjects of the oriental races.

Patients usually exhibit symptoms of anemia with pallor, fatigue, lightheadedness, or tachycardia. Often the anemia is of such insidious onset that the severity is not suspected clinically. Inhibition of DNA synthesis due to vitamin B_{12} deficiency causes megaloblastic changes not only in bone marrow but also in other rapidly dividing cells, such as gastrointestinal epithelium. Involvement of small-bowel epithelium may result in malabsorption and diarrhea with weight loss. Anorexia is an additional common complaint. Glossitis is a frequent sign of megaloblastic anemia, with the patient displaying a painful, smooth, red tongue. The elevation in bilirubin levels, caused by ineffective erythropoiesis, manifests as jaundice.

Neurologic abnormalities are seen in PA as a result of vitamin B_{12} deficiency. Demyelination is the initial finding, which progresses to axonal degeneration and neuronal death if left untreated. Peripheral numbness and paresthesias are the initial symptoms, with subsequent development of weakness and ataxia. The appearance of motor symptoms is indicative of subacute combined degeneration involving the dorsal and lateral spinal columns. Mental disturbances may be present, ranging from forgetfulness to psychosis.

In the general population, the prevalence increases with age, from 2.5% to 12% [11] and is, overall, more frequent in carriers of other diseases of immunological pathogenesis, especially endocrine disorders such as Graves' disease, myxedema, thyroiditis, idiopathic adrenal insufficiency, hypoparathyroidism, type 1 diabetes, Addison's disease, inflammatory bowel diseases, acquired agammaglobulinemia, and vitiligo. Anti-thyroid antibodies are present in more than 50% of the subjects with PA and are common in their relatives. Patients with PA may also be at a higher risk for developing gastric cancer as an end-stage evolution of atrophic gastritis.

5. Autoantibodies

Patients with PA have been shown to have two types of antibodies, one to parietal cells (PCA) and the other to intrinsic factor (IFA) or its binding site in the small bowel.

5.1. Parietal cell autoantibodies

The gastric enzyme H^+/K^+-ATPase is the target antigen recognized by PCA [12,13]. This proton pump is responsible for acid secretion in the stomach and is the major protein of the secretory canaliculi of gastric parietal cells. It produces acid by secreting H^+ ions in exchange with K^+ [13,14]. The gastric H^+/K^+-ATPase is formed by a catalytic 100 kDa α subunit and a 60–90 kDa β subunit. The highly conserved catalytic α subunit is phosphorylated during its reaction cycles; the β subunit comprises a heavily glycosylated 35 kDa core protein. The atrophic gastritis is caused by the action of lymphocyte cluster of differentiation T-helper cell-1 inflammatory cells, directed against this enzyme [15]. The β subunit is considered the causal antigen and the source of the autoimmune response responsible for the damage to the gastric mucosa.

PCA are present at a high frequency in PA (80%–90%), especially in early stages of the disease [16] and bind to both α and β subunits of gastric H^+/K^+-ATPase. Antibody reactivity to the α catalytic subunit includes epitopes on the cytosolic side of the secretory membrane. Antibody reactivity to the β subunit requires the antigen to be in a disulfide-bond and glycosylated, suggesting that autoepitopes are located in the luminal domain of the glycoprotein [14,17]. The localization of these molecules may explain why the pathogenetic role of PCA in vivo remains elusive [18]. Circulating PCA belong to IgG, IgA and IgM isotypes. In gastric juice the antibody isotypes are predominantly IgA and IgG [14].

In the later stages of the disease, the incidence of PCA decreases due to the progression of autoimmune gastritis and a loss of gastric parietal cell mass, as a result of the decrease in antigenic rate. In recent studies, an average incidence of 55% of PCA was documented in patients with advanced PA [19]. PCA are, however, not specific as they can be found at low frequency in other autoimmune diseases (e.g., Hashimoto's thyroiditis or type 1 diabetes) or in elderly subjects, even those free of any atrophic gastritis.

5.2. Intrinsic factor autoantibodies

Human intrinsic factor (IF) is a 60 kDa glycoprotein secreted by gastric parietal cells. Its action is high affinity binding and transport of vitamin B_{12}. The complex IF-vitamin B_{12} reaches terminal ileum where it is absorbed after binding to specific receptors in the membranes of cells of ileal lumen. IFA interferes with absorption of intrinsic factor-vitamin B_{12} complex in the terminal ileum.

IFA are considered specific markers for diagnosing PA [20] and are present both in blood serum and in gastric juices. In serum, two specific types of IFA, both of the IgG class, have been described: type 1 (blocking antibody) reacts with the vitamin B_{12} binding site and type 2 (binding o precipitating antibody) recognizes a site away from this binding site and impedes the binding of IF to receptors in the ileal mucosa. Recent studies have reported positivity for IFA in 40%–60% of patients with PA [21,22], which rises to 60%–80% with increasing duration of disease [23]. Autoantibodies directed against the binding site (type I) are found in 70% of patients; autoantibodies directed to

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