Chapter

Current View on Autoimmune Gastritis

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Abstract

Autoimmune gastritis (AIG) is a chronic inflammatory disease of the gastric corpus and fundus. Although still unclear, genetic and environmental factors, antigenic mimicry or cross-reactivity are proposed pathogenic mechanisms. Parietal cells destruction results in loss of intrinsic factor and increased gastric pH due to hypochlorhydria and G-cell proliferation. Furthermore, atrophy, intestinal, pancreatic and spasmolytic polypeptide-expressing metaplasia are observed. AIG is underdiagnosed, however, proper diagnostic approach, including endoscopic, serological and histopathological assessment, is required. Gastroscopy with corpus and fundus biopsies is a gold standard. A serological combination of anti-parietal cell antibodies, intrinsic factor antibody, anti-Helicobacter pylori IgG, gastrin, pepsinogen I and pepsinogen I/II ratio improves the diagnostic sensitivity and specificity and allows atrophy level prediction. AIG might manifest with multifactorial iron deficiency anemia, vitamin B12 deficiency (pernicious anemia), neurological and neuropsychiatric conditions, small intestinal bacterial overgrowth and gastrointestinal infections. AIG association with other autoimmune diseases is well-established. Gastric cancer and gastric carcinoid are neoplastic transformations of a continuous chronic inflammation. Patients with AIG should be carefully monitored as no specific AIG therapy is available and disease complication could be fatal.

Keywords: autoimmune gastritis, parietal cells, atrophy, metaplasia, pernicious anemia

1. Introduction

First reported by Thomas Addison (1849) as an atrophic gastritis with autoimmune etiology and co-existing distinctive type of anemia, the autoimmune gastritis (AIG) represents a chronic gastric inflammation with progression to mucosal atrophy, occurring in up to 8% of the general population. Since parietal cells antibodies (PCA) and anti-intrinsic factor antibodies (AIFA) have been first reported by Schwartz (1960) and Irvine (1962), the autoimmune conception of this type of gastritis is recognized. The autoimmune reaction with CD4+ T cells leads to destruction of parietal cells, which are unique cells in the corpus and fundus glands. Therefore, AIG is located in stomach corpus and fundus, which distinguish AIG from other diseases, leading to gastric atrophy (*H. pylori* infection, drugs etc.).

Based on Sydney System, pyloric or intestinal glands replace the oxyntic glands. The consequences of the loss of parietal cells are hypochlorhydria, gastric pH increasement and decreased production of intrinsic factor with concomitant megaloblastic pernicious anemia in the end-stage due to vitamin B12 malabsorption. Patients might suffer from iron deficiency anemia due to hypochlorhydria and inadequate iron uptake. Gastrointestinal symptoms are rarely reported. AIG is often presented with other autoimmune co-morbidities (thyroid autoimmune disease, type 1 diabetes, etc.). Although gastrointestinal symptoms are rarely reported, a malignant transformations, namely intestinal-type gastric cancer and type I gastric carcinoid are observed in respectively 5.3% and ca. 9% of AIG patients [1–3].

2. Epidemiology

Nowadays the prevalence of AIG is difficult to obtain, as the disease occurs asymptomatic in early stages, remains undiagnosed for a long period as symptoms arise with atrophy and mucosal dysplasia progression. Further explanations for the underdiagnosed AIG are the inadequate and not from the right location biopsy sampling and the poor identification of the etiology of anemia, which is one of the AIG manifestations. Estimated incidence is ca. 2% in younger and up to 12% in elderly patients. Studies demonstrate increased prevalence of AIG with advancing age and in patients with *H. pylori* infection (Zhang et al.). Females are more often affected than males (3:1 ratio), although this has not been consistently observed. Cabreta et al. in their randomized study find no age difference. The reported prevalence of pernicious anemia, which is one of the most typical AIG manifestations, is about 0.1% in the general population and about 2% in elderly (older than 60 years). The prevalence of pernicious anemia does not differ between populations (white, African American and non-white Hispanic). A study of Carmel and Johnson elucidate that African American women develop pernicious anemia at significantly younger age. Association with other autoimmune diseases (autoimmune thyroid diseases - Hashimoto's thyroiditis and Graves' disease, type 1 diabetes, vitiligo, Addison's disease etc.) is documented to additionally increase the prevalence to up to 35%. This consequence determines a multiple autoimmune diseases (MAS) type 3B and 4. Pernicious anemia is present in patients with Graves' disease, Hashimoto's thyroiditis, type 1 diabetes, autoimmune thyroid disease, Addison's disease, primary hypoparathyroidism and vitiligo in 2, 4–12%, up to 4, 2–12, 6, 9 and 3–8%, respectively. Recent data direct the attention to the possible association between *H. pylori* infection and AIG development in respect to molecular mimicry between *H. pylori* antigens and the gastric H+/K+ adenosine-triphosphate enzyme (ATPase). Few studies evaluate the incidence of AIG (using histology, PCA positive levels) in patients with iron deficiency anemia (IDA) of unknown etiology. The estimated prevalence varies between 15 and 27%. The profile of patients with IDA and positive PCA are younger females with lower hemoglobin and ferritin levels and who suffer more often from restless legs syndrome [1, 2, 4–14].

3. Pathogenesis

AIG is a chronic inflammation, localized in the gastric corpus and fundus. The inflammatory processes start with lymphocytes and plasma cells infiltration in lamina propria with involvement of deep layers, leading to parietal cells destruction. Because of preservation of relatively normal oxyntic mucosa, a gastric pseudopolyposis appears (also known as "islands in the sea"). The loss of parietal cells results in hypochlorhydria and further in G-cell hyperplasia due to missing

negative feedback, leading to higher gastrin secretion in the antrum. A further consequence of the increased gastric pH is the parietal cell pseudohypertrophy. The higher gastrin secretion leads to direct stimulation of enterochromaffin-like (ECL) cells and their proliferation in hyperplastic, dysplastic and neoplastic subtypes that might onset a carcinoid tumor. Pseudopyloric metaplasia ("oxyntic antralization", spasmolytic polypeptide-expressing metaplasia (SPEM)), intestinal metaplasia (IM) and pancreatic metaplasia can be observed. SPEM can be transformed into IM, which represents the replacement of gastric mucosa with intestinal epithelium (small intestinal and colonic). AIG results in microcytic iron deficiency anemia and megalocytic pernicious anemia due to vitamin B12 deficiency [2, 4].

3.1 Immunogenetic factors

AIG and PCA are observed in 20–30% of the family members of patients with pernicious anemia. However, a genetic predisposition has been proposed. Although the association between pernicious anemia and particular HLA haplo/genotypes is weak, studies evaluate HLA DR4, with DR2 and DR5 haplotypes. A genetic heterogeneity is observed in respect to DR3/DR4 genotype, which is found in patients with pernicious anemia and concomitant endocrinopathy. Using murine models, 4 distinct genetic regions of susceptibility genes for AIG were identified (Gasa1, 2, 3 and 4) on chromosomes 4 and 6 and H2 region. Interestingly, three of these genes are nonmajor histocompatibility complex genes and are located on the same locus with those of type 1 diabetes, which could explain the strong concordance between AIG and type 1 diabetes [2, 15–18].

3.2 Cell-mediated autoimmunity

Cell-mediated autoimmunity has a key role for the AIG development. The main trigger of autoimmunity are the 100-kd catalytic α-subunit and the 60- to 90-kd glycoprotein β-subunit of the gastric H+/K + -ATPase, which membrane protein is a proton pump. PCA and AIFA are found in both serum and gastric juice. The higher the PCA titer is, the more severe the corpus atrophy is and the lower the parietal cells concentration is. The loss of parietal cells is a consequence of mainly CD4+ CD25– Th1 resting lymphocyte effectors initiated perforin-mediated cytotoxicity (perforin/granzyme B pathway) or Fas–FasL apoptosis. CD4+ CD25– Th1 resting lymphocyte effectors produce IFN-γ and TNF-α. Submucosa, lamina propria and gastric glands are infiltrated by CD4 + CD25– T-cells, together with macrophages and B lymphocytes, leading to loss of parietal (CD4+ T cells react to H+/K+-ATPase α chain and marginally to the β chain), principal and P/D1 ghrelin-producing cells [2, 5, 15, 19–21].

3.3 Humoral autoimmunity

Two types of antibodies are produced by B cells from activated CD4+ T cells in patients with AIG, namely PCA (antibody to the parietal cells) and AIFA (antibody to the produced by the parietal cells a 60-kDa glycoprotein intrinsic factor). PCA are found in the serum and gastric juice in up to 90% and AIFA in 30–50% of AIG patients. A catalytic and β subunits of gastric H+/K + -ATPase are bound by PCA. In end-stages of AIG the PCA titer decreases because of parietal cells loss. Researchers have found two types of AIFA from IgG class. Type 1 is present in 70% of patients and acts as a blocking antibody that reacts with the binding site for vitamin B12. Type 2 AIFA is present in 30% of patients and is a precipitating antibody that binds other binding sites from vitamin B12 and impedes binding of intrinsic factor-vitamin B12 to the receptors in the ileal mucosa [5, 22–24].

3.4 Association with *H. pylori*

H. pylori, which is well-established etiological factor for atrophic gastritis development, may induce AIG through mechanisms of molecular mimicry at the T-cell level (autoreactive T cells against gastric proton pump), bystander activation and / or epitope spreading. This hypothesis is supported by recent studies as some patients may have AIG with co-existing *H. pylori* infection (20–50%). *H. pylori* leads to development of various antibodies, including PCA and anticanalicular antibodies against the H+/K+ ATPase, which are in fact most frequent. Studies show a high homology between the β subunit of *H. pylori* urease and the subunit β of gastric proton pump, which is a precondition for cross-reactivity against parietal cells and IFN-γ production, resulting in killing or apoptotic suicide. Some patients with PCA and/or AIFA, who underwent *H. pylori* eradication, demonstrated loss of antigastric antibodies. However, the correlation between AIG and *H. pylori* still remains controversial. AIG patients with observed gastric atrophy or IM in the course of *H. pylori* infection do not decrease their risk for gastric cancer development even after *H. pylori* eradication [2, 5, 25–30].

3.5 Endocrine factors

AIG is frequently associated with other autoimmune diseases. Emphasized is the link to type 1 diabetes and autoimmune thyroid disease (Hashimoto's thyroiditis and Graves' disease). Reported risk factors for patients with AIG and type 1 diabetes are persistent positive islet cell antibody and positive glutamic acid decarboxylase-65 antibody, which is found in the thyroid gland and stomach except in pancreas and brain. Studies demonstrate that type 1 diabetes itself and not hereditary might be a risk factor for AIG development. Positive thyroid peroxidase autoantibody are reported in up to 50%of AIG patients due to possible cross-reaction. As PCA are verified in up to 40% of patients with autoimmune thyroid diseases, screening the patients of this population for AIG should be recommended. Other reported co-existing autoimmune conditions are polyglandular autoimmune syndromes (mainly type 3B), Addison's disease, vitiligo, perioral cutaneous autoimmune diseases (mainly erosive oral lichen) and myasthenia gravis [2, 4, 7, 31–34].

4. Diagnostic approach

4.1 Serological tests

The evaluation of AIG-associated autoantibodies (PCA and AIFA), anti-*H. pylori* antibodies (anti-HP-IgG) and markers for gastric atrophy (gastrin and pepsinogen levels) is used for serological noninvasive diagnosis of AIG ("serological biopsy", the so-called GastroPanel test (ELISA test, Biohit, Helsinki, Finland)). AIG-associated autoantibodies are widely used for screening and diagnosis of AIG. They differ according to their sensitivity and specificity as PCA is higher sensitive (80% compared to 50% sensitivity for AIFA) but less specific for pernicious anemia detection. Studies are controversial whether PCA levels correlate with AIG severity or not. Due to low gastric acid output and G-cells stimulation and elevated gastrin secretion in patients with atrophic autoimmune gastritis, it is crucial to evaluate gastrin levels (usually gastrin 17) as gastrin correlates strong with gastric atrophy based on histopathology. Other useful atrophy markers are the produced by the chief cells of oxyntic mucosa of stomach corpus and fundus pepsinogen I and the secreted by the chief cells and mucous neck cells of the whole stomach mucosa

pepsinogen II. In patients with atrophic autoimmune gastritis are demonstrated significant decrease of pepsinogen I (low pepsinogen II levels are not commonly observed) and low Pepsinogen I/Pepsinogen II ratio (<3). In respect to diagnosis of pernicious anemia, a panel of vitamin B12, homocysteine and methylmalonic acid measurement is required. In those patients may be observed thrombocytopenia, increased levels of LDH and bilirubin, and rarely schistocytes in the peripheral smear. Iron deficiency anemia, which is often present in patients with AIG, should be identified by levels of hemoglobin, mean corpuscular volume (MCV), serum iron, ferritin, total iron-binding capacity (TIBS) and serum transferrin receptor (TfR). In patients with suspected carcinoid tumor transformation the measurement of chromogranin A, which is secreted by the ECL cells, can be useful, although it shows low specificity (23%) and false-positive results in patients with inflammatory bowel disease, renal insufficiency and other conditions [4, 23, 35–45].

4.2 Endoscopy

Of a great importance for AIG diagnosis is the performance of gastroscopy with separately collected biopsies - two from the corpus, two from the antrum and one from the incisura angularis (updated Sydney System recommendations). New endoscopic techniques (magnifying endoscopy, autofluorescence and narrow-band imaging) improve the diagnostic accuracy as they provide information for minimal gastric atrophic changes. A number of endoscopic appearances can be present: polyps (hyperplastic or adenomatous), pseudopolyps, flattened rugal folds, visible submucosal vessels, loss of subepithelial capillary network resembling honeycomb, collecting venules in regular shape and appearance and vascular pattern and swelling of areae gastricae. A combination of them improves the sensitivity and specificity of the procedure. In early AIG stages with minimal or no endoscopical and histological changes, gastric acid production is increased due to hypo- or achlorhydria. Thus, gastric acid measurement (simple intragastric pH measurement or volume of acid secretion) might be useful for early AIG diagnosis [1, 4, 46–52].

4.3 Histopathology

Histopathological assessment of biopsies form gastric corpus and fundus remains gold standard for AIG diagnosis even in early stages of the disease. The correct site of biopsy is of great importance for the proper AIG diagnosis, which could be tested by immunohistochemical staining of G cells (gastrin). Histological characteristics change with disease progression. Typical but non-specific for AIG are lymphoplasmacytic infiltration in lamina propria, which is mainly multifocal with accentuation in the deeper; glandular portion in early stage and diffuse lymphoplasmacytic infiltration of the lamina propria in end-stage; focal to profound atrophy of oxyntic mucosa with disease progression. End-stage AIG is further characterized by distinct reduction or total loss of oxyntic glands with pseudohypertrophy of parietal cells due to fragmentary oxyntic glands destruction in end-stage of AIG; SPEM presence; pancreatic or intestinal metaplasia; ECL cells hyperplasia with additional samples immunohistochemical testing with chromogranin A and synaptophysin [1, 4, 11, 53–57].

5. Clinical presentation

Symptoms vary during the course of AIG as patients at early stages are most often asymptomatic, which makes the diagnostic approach only on clinical

presentation challenging. With disease progression a wide spectrum of gastrointestinal, hematological and neurological signs and symptoms arises [1, 3, 4].

5.1 Gastrointestinal manifestations

Gastrointestinal symptoms are not the leading presentation of patients with AIG. Carabotti et al. report in their recent study frequency of one or more gastrointestinal symptoms in 56.7% of AIG patients. Female gender, younger age (<55 years) and non-smoking are independent risk factors for gastrointestinal symptoms manifestation. More than half of the patients had upper gastrointestinal complains as most frequent one was vague dyspepsia in respect to post-prandial fullness and/or early satiation. Furthermore, as achlorhydria is a major pathogenetic consequence of AIG, patients may suffer from bloating, delayed gastric emptying, small intestinal bacterial overgrowth, and gastrointestinal infections such as *Clostridium difficile*. Pain and peptic or duodenic ulcers are not reported. Atrophic glossitis due to vitamin B12 deficiency is an early stage AIG manifestation. Interestingly, heartburn (24%) and acid regurgitation (12%) are presented in a study of Miceli et al., which could develop from nonacidic refluxes. Data exist to support the observation that gastroesophageal reflux disease and its complications like Barrett's esophagus may develop even in AIG patients [1–4, 6, 58–69].

5.2 Hematological manifestations

Typical hematological manifestations of AIG are iron deficiency anemia (IDA) in the early stages and pernicious anemia in the end-stage of the disease.

IDA is the leading hematological manifestation, occurring in 50% of AIG patients as reported by Hershko et al. Several epidemiological studies demonstrate IDA in younger patients prior to pernicious anemia development. Iron metabolism, which is regulated by an uptake, is impaired in AIG mainly due to the presence of achlorhydria. Different mechanisms of IDA with AIG etiology are observed. For the necessary reduction of the ferric form of inorganic iron (the iron type in food) to ferrous as well as for releasing the ferric/ferrous iron from its protein-complex in order to precede to an iron uptake, gastric acid is needed. Another cause for IDA in AIG is the decreased iron absorption due to lack of ascorbic acid, destroyed in AIG. IDA symptoms vary as the commonly reported are fatigue, brittle nails, hair loss, restless legs syndrome, immune dysfunction, ineffective wound healing, while due to anemia itself tachycardia, shortness of breath, dizziness, lightheadedness and cognitive and physical dysfunction may develop. Pregnant women are at risk of early birth and underweight newborns. Of great importance is that IDA with AIG etiology is refractory to iron therapy [1, 4, 6, 13, 20, 58–60, 70–75].

Pernicious anemia is usually caused by vitamin B12 deficiency due to loss of intrinsic factor and insufficient releasing of vitamin B12 from the food due to low levels of gastric acid. Vitamin B12 is a key regulator of DNA synthesis. Mostly affected are patients at advanced age due to age-related reduced absorption and minimal turnover with further large stores of vitamin B12. The clinical manifestations vary widely; therefore pernicious anemia is so-called "great pretender". Reported symptoms of pernicious anemia are fatigue, lightheadedness, palpitations, angina pectoris and congestive heart failure and mental disturbances. Patients are at increased risk of endovascular dysfunction and myocardial infarction and pulmonary embolism due to hyperhomocysteinemia and the related thrombosis. Therefore, untreated pernicious anemia may lead to lethal exit [1, 4, 6, 20, 58–61, 76–80].

5.3 Neurological manifestations

Neuronal death due to demyelination and axonal damage leads to the typical neurological manifestation of vitamin B12, which might be present even in patients with no hematological changes. The loss of vibratory and position sensations together with distal paresthesias develop from damages in the lateral and posterior columns of the cervical and upper thoracic segments of the spinal cord. This syndrome is called a subacute combined degeneration and is very specific for pernicious anemia. Other vitamin B12 deficiency presentations are peripheral neuropathy (paresthesia and numbness of the lower extremities), optic neuropathy and neuropsychiatric conditions (dementia, mania, depression, psychosis, obsessive–compulsive disorder, etc.). Proper diagnosis and early vitamin B12 substitution are mandatory to delay progression and for better outcome [1, 4, 81–89].

6. Neoplastic transformations

Patients with AIG are at increased risk of gastric cancer development. The estimated prevalence is about 5.3% as recent studies suggest even higher incidence - 14.2 per 1000 person-years with patients with AIG having risk of gastric cancer development 3 to 6-fold higher than the general population. Recent meta-analysis demonstrates 0.27% per person-year with an overall relative risk of 6.8 (95% CI 2.6–18.1) for gastric cancer development. Elderly people, chronic inflammation due to *H. pylori* infection, achlorhydria, presence of dysplasia and intestinal metaplasia are significantly risk factors for gastric tumorogenesis [1, 57, 90].

6.1 Gastric carcinoid

Gastric carcinoids are verified in 4–9% of patients with AIG and pernicious anemia. 50–85% of all gastric carcinoids develop in patients with AIG. Three types of gastric carcinoids are established, of which type I is found in patients with AIG, type II is associated with Zollinger-Ellison syndrome and multiple endocrine neoplasia I and type III carcinoid is the most aggressive type. Achlorhydria is a key factor for the development of gastric carcinoids in AIG patients. As described, achlorhydria leads to loss of negative feedback and G-cells stimulation in antrum, followed by hypergastrinemia (typical for type I and II carcinoids). The high gastrin levels demonstrate trophic effects on ECL cells hyperplasia, which further may result in dysplasia and transformation into gastric carcinoid. Gastric carcinoids are quite benign lesions with low metastatic potential (less than 10%). Patients with gastric carcinoids are usually asymptomatic. However, they may complain of dyspepsia, abdominal pain, flushing, diarrhea and symptoms of anemia. Classical carcinoid syndrome is seen very rare. Carcinoids are usually diagnosed incidentally during endoscopy in patients with anemia. Gastroscopy with biopsy sampling with further immunostaining for chromogranin A and/or neuron-specific enolase is the best diagnostic approach. The presence of polyps in the stomach body in patients with AIG is significantly associated with type I carcinoid. As long as polyps might be underdiagnosed during endoscopy, serum chromogranin A levels are more accurate for carcinoids diagnosis. Chromogranin A levels correlate strong with gastrin levels and ECL cell density in the corpus and fundus mucosa, representing high specificity (59%) and sensitivity (100%). According to the algorithm of Gilligan et al. based on size and number, gastric carcinoids in AIG patients, which size is <1 cm and the number is 3–5, should be removed endoscopically, and those >1 cm and/or > 5 should be followed by antrectomy. Surveillance at every 6-month

is proposed. Another therapeutic option is the administration of octreotide, which leads to lower gastrin levels, improved ECL status and even spontaneous regression (Ferraro et al.) [1, 2, 4, 45, 90–110].

6.2 Gastric cancer

The chronic inflammation, which is an integral part of the pathogenesis of AIG, increases significantly the risk of malignant transformations. Achlorhydria, high dietary salt intake and bacterial overgrowth are proposed risk factors. Furthermore, the concomitant *H. pylori* infection additionally increases the risk of precancerous lesions. Current studies suggest that cancer stem cells, which might be exposed on mutations, have an important role in cancerogenesis. This concept is assumed as stem cells are well-known for their longevity and inherent capacity for self-renewal. As a consequence of chronic inflammation, stem cells level and proliferation potential increase, which favors their intestinal metaplasia (possible phenotype of stem cells abnormality) and dysplasia. In 1988, Correa and Piazuelo proposed the so-called "Correa hypothesis/cascade" for gastric cancer development in patients with *H. pylori* infection: unknown genetic and epigenetic factors lead stepwise to 1. chronic inflammation; 2. atrophy gastritis; 3. intestinal metaplasia; 4. low to high grade dysplasia, which finally results in gastric cancer in some patients. *H. pylori* factors, associated with higher malignancy potential are CagA-positive strains, VacA gene and s1 m1 [1, 4, 5, 111–120].

An attention is paid at the role of tumor-associated autoantigens in immunogenicity and immunodiagnosis, which may detect cancer at early stage. Usually these autoantigens are cellular proteins, which can be ectopically expressed or a result from genetic mutations and rearrangements. Additional mutations in the tumor-associated autoantigens lead to new antigenic epitopes and finally increased immunogenicity. According to a current concept of the immunological response of cancer tissue, tumor-associated antigens lead to autoantibodies production. Autoantibodies with potential clinical usefulness are anti-carcinoembryonic antigen (CEA), anti-p53, anti-survivin, anti-mucin, and anti-livin autoantibodies. The autoantibodies are missing in healthy people and non-cancer diseases. Thus, autoantibodies against tumor antigens can serve as biomarkers and may have the potential to verify an early stage cancer, which may significantly improve patients diagnosis and outcome as the majority of patients with gastric cancer are diagnosed late, when are symptomatic and the management is rather palliative. Studies show significant lower levels of biomarkers after radical tumor resection, which suggest their prominent role in patient monitoring [5, 121–125].

The estimated frequency of detection of anti-carcinoembryonic antigen (CEA) anti-survivin, anti-mucin, and anti-livin autoantibodies is 46–56, 40, 75 and 50%, respectively, as anti-CEA is found in 10% of healthy people. They are present in the early stage of gastric cancer and demonstrate a good prognostic value for survival and postoperative monitoring, especially in patients without anti-p53 antibodies [123, 126–131].

p53 is a key factor in carcinogenesis. In 46% of patients with p53-positive gastric cancer are found increased anti-p53 antibodies levels. Anti-p53 antibodies, which are first reported in patients with breast cancer, correlate significantly with the tumor suppressor gene p53 protein expression, demonstrating about 96% specificity for neoplastic detection. In contrast to anti-carcinoembryonic antigen (CEA) anti-survivin, anti-mucin, and anti-livin autoantibodies, anti-p53 antibodies are not appropriate markers for early diagnosis and prognosis as they are detected in advanced gastric tumors with regional lymph node involvement [123, 126, 132–134].

Extracellular protein kinase A (ECPKA) is a cAMP-dependent intracellular enzyme. Anti- ECPKA antibodies are significantly increased in patients with gastric cancer and other malignancies. They have the potential to be future universal screening method for tumors of different origin as their sensitivity and specificity are very high - 90 and 87%, respectively [135].

The presence of substantial number heterogeneous autoantibodies varies widely and demonstrates high specificity but low diagnostic sensitivity. To improve their sensitivity in order to enable their application in clinical practice for screening and diagnosis of gastric cancer; it is reasonable to promote a combination of serological AIG- and tumor biomarkers, microRNAs and/or glycosylation signatures. Using a combination of 5 biomarkers (MAGEA4, CTAG1, TP53, ERBB2_C, and SDCCAG8), Werner et al. demonstrated 32% sensitivity and 87% specificity for diagnosis of early stage gastric adenocarcinoma. In a study of Zhou et al. a combination of 7 markers, namely p53, Koc, p62, c-myc, IMP1, survivin and p16, identified gastric cancer with sensitivity and specificity of 64% and 87%, respectively. Wang et al. verified a panel of 8 biomarkers (IMP1, p62, Koc, p53, c-myc, cyclin B1, survivin and p16), able to detect gastric cancer with 56.1% sensitivity and 86.2% specificity [136–144].

7. Treatment

Up-to-date there is no consensus on whom to screen for AIG and how often. The treatment management of AIG with avoiding further complications requires according to the present symptoms, serological results and imaging data proper follow-up. A proper monitoring with testing once a year complete blood count, gastrin, iron and vitamin B12 levels seems to be beneficial. Therapy depends on the stage of AIG*, H. pylori* infection, current nutrient deficiencies, concomitant autoimmune conditions and (pre)malignant transformation. As described above, *H. pylori* infection may play a crucial role in AIG pathogenesis. However, screening for *H. pylori* (serological anti-HP-Ig G and Ig M, fecal HP-antigen, breath tests, histological and cultural methods) in patients with AIG, gastric atrophy, intestinal metaplasia/dysplasia, and hypo- or achlorhydria should be performed. If positive for *H. pylori*, patients need subsequent treatment and eradication. Studies support *H. pylori* treatment as *H. pylori* eradication was associated with decreased levels of PCA and AIFA and AIG early stages healing. Oral supplementation with vitamin B12, iron and folic acid is recommended in early stages of AIG. With neurological symptoms occurring, parenteral vitamin B12 should be applied. As long as various autoimmune diseases are recognized as AIG co-morbidities, attention should be paid at their screening and following treatment. Researchers recommend the routine screening for type 1 diabetes and autoimmune thyroid diseases. On the other hand, in patients, who are diagnosed with type 1 diabetic (positive glutamate decarboxylase-65 antibodies) and autoimmune thyroiditis (positive thyroid peroxidase antibodies), PCA should be investigated at the disease's onset and thereafter yearly for 3 years and later on a longer intervals if there is no AIG clinical signs. Screening for AIG in those patients' populations might avoid the development of IDA and pernicious anemia with their above mentioned serious complications. As long as gastric carcinoid is curative, proper diagnosis and radical treatment are essential. According to size, number and location of gastric cancer / carcinoid, polypectomy, antrectomy (gastrin-producing part), surgical eradication of a gastric tumor, with resection of adjacent lymph nodes or medicamentous treatment with further surveillance is performed. Somatostatin analogs are used as they can reduce gastrin and chromogranin A levels in patients with neuroendocrine

tumor (carcinoid). Promising therapeutic option is the gastrin receptor antagonist Netazepide, leading to decreased chromogranin A levels together with cancer size and number. A new technique for carcinoid tumors treatment is the peptide receptor radiotherapy, which would be worth to be tested in AIG patients. Whether to perform surveillance program with regular endoscopic and histological examination in patients with AIG or not remains controversial and guidelines according to AIG surveillance are missing. If mild to moderate dysplasia or ECL cell hyperplasia are observed, an endoscopic surveillance every 5 years is proposed. In contrast to the rare and with far better prognosis carcinoids, gastric cancer development might be fatal. According to the American Society for Gastrointestinal Endoscopy recommendations (2006) for monitoring of patients with *H. pylori* atrophic gastritis, depending on the primary endoscopic finding the follow-up should be in intervals of 3–5 years (patients with simple, linear/micronodular hyperplasia); every 3 years (patients with extensive atrophy/IM) or every year (patients with adenomas/low-grade dysplasia) [1, 2, 11, 90, 103, 109, 113, 145–153].

8. Discussion

Although *H. pylori* is a leading cause for gastritis, AIG frequency is increasing in elderly people and in those with other autoimmune pathology. As AIG is commonly underdiagnosed, AIG should be considered in the differential diagnosis of patients with anemia, dyspepsia and especially in those with concomitant autoimmune thyroid disease and type 1 diabetes and with relatives with gastric neoplasia. *H. pylori* presence does not exclude AIG in the pathogenesis of an underlying gastritis. Screening of patients with a panel of serological markers pepsinogen I and II, gastrin, and/or *H. pylori* antibodies as well as the antibodies PCA and AIFA directs to the need of gastroscopy. However, gastroscopy with separately collected biopsies and histopathological assessment of specimens form gastric corpus and fundus remain the gold standard for AIG diagnosis. Asymptomatic in the early stages of the disease, AIG is not recognized in guidelines as an etiological factor for iron deficiency. However, AIG is often leading to iron deficiency anemia, which requires a different treatment strategy. Untreated pernicious anemia, which is a later manifestation of AIG, could cause both neurological complications and letal cardiovascular events. AIG is a precancerosis for the development of gastric cancer and neuroendocrine tumors. An effort is required to identify a biomarker panel with high sensitivity for early-stage gastric malignancy diagnosis. The treatment of AIG still remains challenging due to asymptomatic early stage and complex pathogenesis of the disease.

9. Conclusion

Proper and early diagnostic approach and prevention, followed by patients' carefully lifelong monitoring at yearly intervals is mandatory to improve the prognosis and outcome of AIG. New therapeutic strategies are needed to delay disease progression and influence the gastric atrophy, making it a reversible entity. Guidelines of AIG surveillance are awaited.

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Conflict of interest

There is no conflict.

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