Acta Biomed 2018; Vol. 89, Supplement 8: 100-103 DOI: 10.23750/abm.v89i8-S.7919

Review

Autoimmune diseases in autoimmune atrophic gastritis

Kryssia Isabel Rodriguez-Castro[1], Marilisa Franceschi[1], Chiara Miraglia[1], Michele Russo[1], Antonio Nouvenne[1], Gioacchino Leandro[3], Tiziana Meschi[1], Gian Luigi de' Angelis[1], Francesco Di Mario[1]

[1] Endoscopy Unit, Department of Surgery, ULSS7-Pedemontana, Santorso Hospital, Santorso (VI), Italy; [2] Department of Medicine and Surgery, University of Parma, Parma, Italy; [3] National Institute of Gastroenterology "S. De Bellis" Research Hospital, Castellana Grotte, Italy

Summary. Autoimmune diseases, characterized by an alteration of the immune system which results in a loss of tolerance to self antigens often coexist in the same patient. Autoimmune atrophic gastritis, characterized by the development of antibodies agains parietal cells and against intrinsic factor, leads to mucosal destruction that affects primarily the corpus and fundus of the stomach. Autoimmune atrophic gastritis is frequently found in association with thyroid disease, including Hashimoto's thyroiditis, and with type 1 diabetes mellitus, Other autoimmune conditions that have been described in association with autoimmune atrophic gastritis are Addison's disease, chronic spontaneous urticaria, myasthenia gravis, vitiligo, and perioral cutaneous autoimmune conditions, especially erosive oral lichen planus. Interestingly, however, celiac disease, another frequent autoimmune condition, seems to play a protective role for autoimmune atrophic gastritis. The elevated prevalence of autoimmune disease clustering should prompt the clinicial to exclude concomitant autoimmune conditions upon diagnosis of any autoimmune disease. (www.actabiomedica.it)

Key words: autoimmune atrophic gastritis, Hashimoto's thyroiditis, diabetes mellitus, celiac disease

Autoimmune diseases, characterized by dysregulation of the immune system which results in a loss of tolerance to self-antigens, tend to cluster, often coexisting in the same patient. While the exact etiology of the majority of these diseases is unclear, a complex combination of host and environmental factors seem to play a pivotal role. Moreover, sequential or simultaneous development of two or more autoimmune disorders, causing deficiencies in the function of several endocrine organs, is termed autoimmune polyglandular syndrome (1).

Autoimmune atrophic gastritis (AAG) is a chronic disease that affects the corpus-fundus of the stomach, and is characterized by the development two types of auto-antibodies: anti-parietal cells antibodies and anti-intrinsic factor antibodies. A strong association between autoimmune atrophic gastritis and other autoimmune disorders has been well documented. The hypergastrinemia that ensues as a consequence of gastric cell destruction and hypochlorhydria increase the risk of adenocarcinoma and neuroendocrine tumors; an early diagnosis and an appropriate follow-up are therefore warranted. AG is usually diagnosed using a combination of APCA positivity and histological criteria. However, the latter is an invasive and costly method, and lacks an evaluation of gastric function.

The unraveling of the pathophysiology leading to autoimmune atrophic gastritis is somewhat challenging due to the following reasons: 1) the prevalence of autoimmune atrophic gastritis is relatively low, possibly due at least in part to underdiagnosis, 2) in many cases there is a concurrent *Helicobacter pylori*-induced gastritis, and 3) early stages of disease lack clinical manifestations. Alike other autoimmune disorders, autoimmune atrophic gastritis more commonly affects females than males, with a 3:1 ratio.

Although mechanisms of disease development are yet to be established, disease evolution appears to fol-

low through a sequence that commences with infiltration of the oxyntic mucosa by lymphocytes and plasma cells. At this initial stage, endoscopic appearance of islets is due to the uneven destruction of parietal cells with preserved islands of relatively normal oxyntic mucosa. Subsequently, loss of oxyntic mucosa as well as disruption of maturation of parietal cells (2) lead to hypochlorydria. Thereafter, loss of negative feedback from parietal cells induces G-cell hyperplasia and increased gastric secretion in the antrum, which, in turn, leads to parietal cell pseudohypertrophy and proliferation of enterochromaffin-like (ECL) cells. Progression of ECL cell hyperplasia to neoplastic subtype can ultimately result in carcinoid tumor formation. Metaplasia develops primarily within corpus and fundus, leading to "oxyntic antralization", with appearance of mucus-secreting cells which phenotypically resemble antral mucous cells in oxyntic regions of the stomach (3).

Aside from the fact that most cases of micro- as well as macrocytic anemia are treated with iron, folic acid and vitamin B12 without a complete workup that excludes the presence of autoimmune atrophic gastritis, anemia might be attributed to concomitant autoimmune disorders. Thus, if unsuspected and not specifically sought for, autoimmune atrophic gastritis easily goes undiagnosed.

The fact that patients with autoimmune atrophic gastritis are more prone to developing other concomitant autoimmune diseases began to be a consistent observation upon initial recognition and description of cases of autoimmune atrophic gastritis. In a series of 34 patients with pernicious anemia, in whom parietal cell antibodies (PCA) were detected in 97% of patients, and intrinsic factor blocking antibody (IFBA) was found in 52%, 32 patients had concomitant autoimmune or immunologic diseases (4). Autoimmune thyroid disease is frequent in patients with autoimmune atrophic gastritis, and in turn, patients with autoimmune thyroid disease are also frequently affected by autoimmune atrophic gastritis. Other autoimmune conditions that have been described in association with autoimmune atrophic gastritis include Addison's disease (5), chronic spontaneous urticaria (6), type 1 diabetes mellitus (7), myasthenia gravis (8), vitiligo (9) (10), and perioral cutaneous autoimmune conditions (especially erosive oral lichen planus). In a small case series reporting on 8 patients with marked pangastric atrophy, associated systemic autoimmune and/or connective tissue diseases included inflammatory bowel disease, systemic lupus erythematosus, and autoimmune hemolytic anemia (11).

It has long been recognized that AAG, as well as other autoimmune disorders, tend to cluster in families, which could reinforce the genetic component of disease. Using mouse models, it has been possible to discover AAG susceptibility genes (Gasa 1, 2, 3, and 4) on chromosomes 4 and 6 and H2 region, three of which are located on the same locus as non-obese diabetic mouse diabetes mellitus susceptibility genes (12, 13) The prevalence of AAG is increased 3- to 5-fold in patients with type 1 diabetes mellitus (14), reportedly reaching 5% to 10% and 2.6% to 4%, for autoimmune atrophic gastritis and for pernicious anemia, respectively (7). In a study conducted at Washington University Diabetes Center analyzing over 1200 patients with type 1 Diabetes Mellitus, incidence and prevalence of concomitant autoimmune disorders increased with age, and female gender strongly predicted the development of concomitant autoimmune disorders. Aside from thyroid disease and collagen vascular diseases, pernicious anemia was one of the most frequent autoimmune comorbidities in patients with type 1 diabetes (15).

Approximately 10-40% of patients with Hashimoto's thyroiditis, the most frequent thyroid disease, have associated gastric disorders. Similarly, Hashimoto's thyroiditis is present in nearly 40% of patients with AAG. In a recently published study analyzing 320 patients with autoimmune atrophic gastritis, an associated autoimmune disorder was present in 53.4%; the most common concurrent disease was autoimmune thyroiditis, found in 116 (36.2%) patients. Interestingly, authors found that serum levels of gastrin, chromogranin A, as well as the presence of ECL hyperplasia, correlated significantly with the coexistence of an autoimmune disease (16).

In a study analyzing (17) 115 patients with Hashimoto's thyroiditis, enterochromafin-like cells were found in 11.3%; nevertheless, normal levels of gastrin and chromogranin were found in a fraction of these patients. Conversely, elevated gastrin levels with concomitant low vitamin B12 levels constituted the

most specific combined parameters associated with a 96.1% specificity for the presence of enterochromafin-like cells. Thus, the authors conclude that elevated gastrin levels have a high diagnostic accuracy for enterochromafin-like cell hyperplasia identification in patients with Hashimoto's thyroiditis, and that the concomitance of low levels of Vitamin B12 are highly specific for the former. The authors acknowledge, however, that gastrin levels may be normal in the presence of enterochromafin-like cell hyperplasia, which is why monitoring is needed in time, and further examinations may be required.

The association between chronic AAG and autoimmune thyroid disease, first described in the early 1960s, was initially termed "thyrogastric syndrome". In recent times, this association has been encompassed in polyglandular autoimmune syndrome type IIIb, in which autoimmune thyroiditis is the principal disease (18).

Anti-thyroid antibody titers are a frequent finding in patients with pernicious anemia, and an important group of this subset of patients will go on to develop overt autoimmune thyroid disease. Anti-thyroid autoimmunity was found in 44% of patients with pernicious anemia in a study by Chan and coworkers (19); interestingly, thyroid disease was more frequent in females. Atrophic gastritis has been reported in 35% of patients with autoimmune thyroid disease, with the presence of pernicious anemia in 16% of patients, in a study by Centanni and collaborators (24), while the prevalence was similar (40%) in a later study by Lahner and coworkers (25). In a study exploring the association between pernicious anemia and type 1 diabetes coexisting with autoimmune thyroid disease, Perros and collaborators found that 6.3% of patients were affected by the three conditions at the same time, the risk being particularly elevated in women (8.5%) (26).

Vitamin B12 deficiency is frequent in autoimmune thyroid disease, primarily represented by patients with hypothyroidism and Graves disease, with studies reporting rates as high as 28%-55% (20, 21). Importantly, symptoms of vitamin B12 deficiency may be poorly expressed and/or attributed to the underlying thyroid disease. The presence of neurophyschiatric disturbances including lethargy, weakness, motor alterations, memory loss and paresthesis, especially if persistent after adequate L-thyroxine replacement, warrant determination of levels of Vitamin B12. Paresthesis, dysphagia and numbness are more frequently reported in hypothyroid patients with vitamin B12 deficiency with respect to patients with normal vitamin levels (22).

It is advisable to screen for Vitamin B12 deficiency (with or without chronic atrophic gastritis) upon initial diagnosis of an autoimmune disorder, and levels should be assessed periodically every 3 to 5 years, independently from the stability of the primary autoimmune disease (23). Low levels of Vitamin B12 should prompt determination of serum gastrin levels; however, although performing upper endoscopy to exclude chronic atrophic gastritis as an examination following elevated levels of Vitamin B12 and gastrin is debatable, determination of the complete Gastropanel test (including pepsinogen I and II, as well as Gastrin and anti-H. pylori antibodies) is certainly useful to identify patients in whom endoscopic evaluation is warranted.

For reasons that must still be clarified, no patient with celiac disease, another frequent autoimmune disorder, has been reported to be affected by autoimmune atrophic gastritis. In a study analyzing a cohort of 107 patients with polyglandular syndrome type 3, Hashimoto's thyroiditis coexisted with only celiac disease, and no patient with celiac disease was affected by another non-thyroid autoimmune disorder (27).

Conclusion

In practical terms, it is advisable to screen for concomitant autoimmune disease in all patients with chronic AAG. Conversely, a high-degree of suspicion must be maintained to look out for atrophic gastritis in patients with other autoimmune diseases. Although the gold-standard remains histological demonstration of atrophy of the gastric corpus and fundus, together with determination of positivity for anti-parietal cell antibodies, the elevated sensitivity and specificity of serologic assessment of gastric function (Gastropanel) render this non-invasive test an important tool for the clinician to aid in the identification of patients who should undergo endoscopic evaluation.

References

1. A. Rojas-Villarraga, J. Amaya-Amaya, A. Rodriguez-Rodriguez, R. D. Mantilla, and J. M. Anaya, "Introducing polyautoimmunity: Secondary autoimmune diseases no longer exist," Autoimmune Diseases. 2012.
2. L. M. Judd, P. A. Gleeson, B. H. Toh, and I. R. van Driel, "AAG results in disruption of gastric epithelial cell development.," Am. J. Physiol., vol. 277, no. 1 Pt 1, pp. G209-18, Jul. 1999.
3. A. Minalyan, J. N. Benhammou, A. Artashesyan, M. S. Lewis, and J. R. Pisegna, "Autoimmune atrophic gastritis: current perspectives.," Clin. Exp. Gastroenterol., vol. 10, pp. 19–27, 2017.
4. J. W. Hughes et al., "High-risk gastric pathology and prevalent autoimmune diseases in patients with pernicious anemia," Endocr. Pract., vol. 23, no. 11, pp. 1297–1303, Nov. 2017.
5. P. M. J. Zelissen, E. J. E. G. Bast, and R. J. M. Croughs, "Associated Autoimmunity in Addison's Disease," J. Autoimmun., vol. 8, no. 1, pp. 121–130, Feb. 1995.
6. P. Kolkhir, E. Borzova, C. Grattan, R. Asero, D. Pogorelov, and M. Maurer, "Autoimmune comorbidity in chronic spontaneous urticaria: A systematic review," Autoimmun. Rev., vol. 16, no. 12, pp. 1196–1208, Dec. 2017.
7. G. J. Kahaly and M. P. Hansen, "Type 1 diabetes associated autoimmunity," Autoimmun. Rev., vol. 15, no. 7, pp. 644–648, Jul. 2016.
8. K.-H. Chang, R.-K. Lyu, L.-S. Ro, Y.-R. Wu, and C.-M. Chen, "Coexistence of Pernicious Anemia and Myasthenia Gravis—A Rare Combination of Autoimmune Diseases in Taiwan," J. Formos. Med. Assoc., vol. 105, no. 11, pp. 946–949, Nov. 2006.
9. P. Amerio et al., "Vitiligo associated with other autoimmune diseases: polyglandular autoimmune syndrome types 3B + C and 4," Clin. Exp. Dermatol., vol. 31, no. 5, pp. 746–749, Sep. 2006.
10. A. M. Dahir and S. F. Thomsen, "Comorbidities in vitiligo: comprehensive review," Int. J. Dermatol., vol. 57, no. 10, pp. 1157–1164, Oct. 2018.
11. D. Jevremovic, M. Torbenson, J. A. Murray, L. J. Burgart, and S. C. Abraham, "Atrophic autoimmune pangastritis: A distinctive form of antral and fundic gastritis associated with systemic autoimmune disease.," Am. J. Surg. Pathol., vol. 30, no. 11, pp. 1412–9, Nov. 2006.
12. P. A. Silveira et al., "Identification of the Gasa3 and Gasa4 AAG susceptibility genes using congenic mice and partitioned, segregative and interaction analyses," Immunogenetics, vol. 53, no. 9, pp. 741–750, Dec. 2001.
13. A. G. Baxter, M. A. Jordan, P. A. Silveira, W. E. Wilson, and I. R. Van Driel, "Genetic Control of Susceptibility to AAG," Int. Rev. Immunol., vol. 24, no. 1–2, pp. 55–62, Jan. 2005.
14. C. E. M. De Block, I. H. De Leeuw, and L. F. Van Gaal, "AAG in Type 1 Diabetes: A Clinically Oriented Review," J. Clin. Endocrinol. Metab., vol. 93, no. 2, pp. 363–371, Feb. 2008.
15. J. W. Hughes et al., "Late-Onset T1DM and Older Age Predict Risk of Additional Autoimmune Disease," Diabetes Care, p. dc181157, Oct. 2018.
16. D. Kalkan and I. Soykan, "Polyautoimmunity in AAG," Eur. J. Intern. Med., 2016.
17. A. Nicolaou, D. Thomas, K. I. Alexandraki, S. Sougioultzis, A. V. Tsolakis, and G. Kaltsas, "Predictive value of gastrin levels for the diagnosis of gastric enterochromaffin-like cell hyperplasia in patients with hashimoto's thyroiditis," Neuroendocrinology, 2014.
18. M. Cellini et al., "Hashimoto's thyroiditis and AAG," Frontiers in Endocrinology. 2017.
19. J. C. W. Chan et al., "Pattern of thyroid autoimmunity in Chinese patients with pernicious anemia," Am. J. Med. Sci., 2009.
20. C. Das, P. K. Sahana, N. Sengupta, D. Giri, M. Roy, and P. Mukhopadhyay, "Etiology of anemia in primary hypothyroid subjects in a tertiary care center in Eastern India.," Indian J. Endocrinol. Metab., 2012.
21. Y. P. Wang, H. P. Lin, H. M. Chen, Y. S. Kuo, M. J. Lang, and A. Sun, "Hemoglobin, iron, and vitamin B12 deficiencies and high blood homocysteine levels in patients with anti-thyroid autoantibodies," J. Formos. Med. Assoc., 2014.
22. A. Jabbar et al., "Vitamin B12deficiency common in primary hypothyroidism," J. Pak. Med. Assoc., 2008.
23. R. Ness-Abramof et al., "Prevalence and evaluation of B12 deficiency in patients with autoimmune thyroid disease," Am. J. Med. Sci., 2006.
24. M. Centanni et al., "Atrophic body gastritis in patients with autoimmune thyroid disease: An underdiagnosed association," Arch. Intern. Med., 1999.
25. E. Lahner et al., "Occurrence and Risk Factors for Autoimmune Thyroid Disease in Patients with Atrophic Body Gastritis," Am. J. Med., 2008.
26. P. Perros, R. K. Singh, C. A. Ludlam, and B. M. Frier, "Prevalence of pernicious anaemia in patients with type 1 diabetes mellitus and autoimmune thyroid disease," Diabet. Med., 2000.
27. R. Vita et al., "Serum Thyroid Hormone Antibodies Are Frequent in Patients with Polyglandular Autoimmune Syndrome Type 3, Particularly in Those Who Require Thyroxine Treatment.," Front. Endocrinol. (Lausanne)., vol. 8, p. 212, 2017.

Correspondence:
Kryssia Isabel Rodriguez-Castro
Endoscopy Unit, Department of Surgery,
ULSS7-Pedemontana, Santorso Hospital, Santorso (VI), Italy
E-mail: kryssia.rodriguez@aulss7.veneto.it