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Review Article

Medication-Induced Small Bowel Enteropathy

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Abstract

In the past, over time, more and more medications were reported to cause diarrhea, weight loss and a small bowel enteropathy, sometimes similar to celiac disease. These failed to respond to gluten-free diet treatment; instead, removal of the offending medication often resolved the clinical disorder and the associated intestinal pathological changes. During the most recent decade, an increasing number of medications have been developed by the pharamaceutical industry, including drugs to treat common disorders, such as olmesartan for hypertension. Olmesartan was reported to sometimes cause a severe sprue-like enteropathy. Rarely, even a fatal outcome was described. New biological agents have also been developed for severe treatment-resistant inflammatory disorders along with advanced malignancies, including metastatic melanoma. In particular, attention has focused on monoclonal antibodies acting as checkpoint inhibitors (eg., ipilimumab) that may result in a superimposed and profound sprue-like small intestinal disease with marked diarrhea and weight loss.

Keywords: Sprue-Like Enteropathy; Drug-Induced Small Bowel Disease; Celiac Disease; Refractory Sprue

Introduction

A number of medications may induce diarrhea, weight loss and small intestinal mucosal inflammatory changes, including changes simulating the histopathological appearances of untreated adult celiac disease [1,2]. These sprue-like changes include architectural "flattening" or atrophy of the mucosa due to loss of villi as well as lengthening of crypts. Moreover, increased numbers of mucosal and intra-epithelial immune-type inflammatory cells, particularly lymphocytes are seen. Finally, some biopsies of the small bowel may exhibit collagen deposition as a sub-epithelial band of material histochemically trichrome-positive. Similarly, electron microscopic changes have been recorded showing banded fibres of collagen with the typical 640 Angstrom measurement. Finally, in some, but not all cases, similar associated pathological changes may occur in gastric and colorectal mucosa. Location of these different pathological features along the length of the gastrointestinal tract likely has a direct impact on the symptom type and their severity. The present discussion focuses on the small intestine *per se* and changes that may mimic other small intestinal mucosal disorders, particularly celiac disease, a clinical-pathological small intestinal disorder that responds to gluten restriction. Because of the possibility of a medication causing a similar pathological appearance in biopsies before treatment with a gluten-free diet, the importance of acquiring a precise medication history from the patient in this setting is emphasized.

Types of medications

Drug-induced small intestinal disease may be caused by different types or classes of medications. In the most recent decade, the rapid development and emergence of new biologics, including some monoclonal antibodies for treatment of immune-mediated inflammatory disorders and advanced malignancies is an important, but also concerning trend.

Pharmacological agents

One medication, *triparanol,* was used initially to experimentally induce an animal (i.e., rodent) model of celiac disease [3]. This drug was thought to increase the membrane lability of lysosomes leading to the intra-cellular release of destructive enzymes within epithelial cells. Later, other agents, including *alcohol*, were recognized to cause a direct mucosal toxic effect, either focally or diffusely [4]. An indirect effect was also hypothesized in chronic alcohol users via a folate depletion mechanism. Folate and vitamin B12 are important in the normal process of small intestinal epithelial cell renewal. Depletion may lead to megaloblastic precursor small intestinal epithelial cells visualized as so-called "nuclear-cytoplasmic asynchrony" similar to other rapidly renewing precursor cells, as in bone marrow. With reduction in renewal rates, epithelial cell mitotic figures may be reduced, villi shortened and the crypts become hypoplastic, rather than hyperplastic (as in untreated celiac disease). Similar effects may be observed with some *folate-depleting agents*, such as *methotrexate*, used as chemotherapeutic agents in malignancies or anti-inflammatory agents in treatment of some chronic liver diseases or chronic inflammatory forms of arthritis or ileo-colitis [5].

Some *antibiotics* may directly affect the small bowel mucosa. One of the best evaluated antibotics is *neomycin* including documentation of mucosal toxicity using both light and electron microscopy [6]. Alterations in epithelial cell structure were reported along with concomitant alterations in nutrient absorption [7]. Now, in spite of a increasing numbers of new anti-microbial agents, only limited small bowel studies have been conducted in prospective and blinded clinical trials.

Other medications also create small bowel epithelial cell changes. *Stathmokinetic drugs*, like *colchicine*, may lead to marked mucosal changes including "colchicine spindles" (due to arrested metaphase, particularly in the crypt regions) along with altered uptake of major nutrients, including carbohydrates, fat as well as other micronutrients (including vitamin B12) [8]. *Vincristine* and *vinblastine* may result in similar histological effects by disruption or assembly failure of the mitotic spindle [9].

Non-steroidal anti-inflammatory drugs (i.e., *NSAIDs*), such as *sulindac*, and *immunosuppressive agents* (e.g., *azathioprine*, *mycophenolate mofetil*) may also induce alterations in the small bowel mucosal architecture that fail to respond to gluten-free diet treatment [10,11].

Recent attention has focused on an intriguing group of pharmacologic agents for management of hypertension, specifically, *olmesartan*. This is an angiotensin II receptor antagonist popularly used to reduce cardiac and vascular risks related to increased blood pressure. In some, a sprue-like small intestinal disorder occurs with diarrhea, weight loss and the histopathological features of untreated celiac disease [12]. In some, but not all, patients treated with this medication, serologic studies for antibodies to tissue transglutaminase were negative and treatment with a gluten-free diet was not effective in resolution of the disorder. A number of patients became very ill, requiring hospitalization and other forms of treatment, including biological agents. After cessation of the drug, reversal of clinical and pathological changes also appeared to occur in some patients. A similar resolution of biopsy changes was also documented with the closely allied but rare small intestinal disorder, collagenous sprue, also induced by olmesartan. In at least one report [13], complete reversal occurred in the absence of any other form of treatment.

Biological Agents (i.e., Monoclonal Antibodies)

A further category of medications that may cause an enteropathy involving the small bowel (and sometimes the large bowel) may be categorized as biological agents since these are derived from a biological process rather than pharmacologically synthesized compound. To date, these are largely monoclonal antibodies mainly infused into patients with ongoing and severe inflammatory disorders along with treatment-resistant malignancies, such as malignant melanoma. One of the initial agents was ipilimumab [14], a humanized monoclonal antibody to limit the cytotoxic T-lymphocyte antigen 4, a critical negative feedback regulator of the T-cell anti-tumor response (anti-CTLA-4), also labeled as an immune checkpoint inhibitor. This monoclonal antibody agent has been used for treatment of different malignancies, including metastatic melanoma, metastatic prostate cancer and other extensive malignancies. About 40% develop adverse effects, including an immune-mediated enteritis. If severe, the effects may result in clinical deterioration, and ultimately, a fatal outcome. Endoscopic biopsies may show a diffuse enteritis with or without colitis, or sprue-like small intestinal mucosal changes similar to celiac disease. Treatment has

consisted of fluid replacement, parenteral nutrition, corticosteroids, and, in some, infliximab infusions have been used. Often, this small intestinal sprue-like small intestinal disorder is accompanied by negative serological studies (i.e., tissue transglutaminase) and fails to respond to a gluten-free diet. Other checkpoint inhibitors, including anti-PD-1, pembrolizumab and nivolumab, for treatment of metastatic malignancies have also been reported [15-19].

Vaccines (as biological agents) and post-vaccination immune-mediated disease

Recent studies have reported effects of SARS-Cov-2 infection in the gastrointestinal tract, especially with diarrhea [20,21]. Biopsy studies have shown that limited pathological changes may occur in the upper gastro-intestinal tract and colon, largely increased numbers of lymphocytes and plasma cells [22]. Additional studies have shown positive staining with viral host receptor, ACE2, in epithelial cell cytoplasm along with positive staining for viral nucleocapsid protein [22]. With this potential "pathological background" of inflammatory change, individuals receiving either a second Pfizer or a second Moderna vaccine demonstrated a transient intestinal inflammatory disease process [23]. Further studies are needed to explore the possible development of these post-vaccination changes.

Conclusion

To summarize, a number of medications may cause a small intestinal enteropathy, often labeled as sprue-like intestinal disease. However, these entities, while distinct, are usually serologically-negative without any celiac-related antibodies, including antibodies to tissue transglutaminase. Often, diagnosis is suspected following a failure to respond to a gluten-free diet (so called refractory disease). Thus, patients initially suspected to have celiac disease should have a detailed and extensive medication history obtained to ensure that medications are not playing a role in causing or prolonging the disorder. With the evolution and resulting emergence of novel pharmacologic and biological medications, it is likely that additional forms of sprue-like intestinal disease will appear in future.

Bibliography

1. Gujral N., *et al*. "Celiac disease: prevalence, diagnosis, pathogenesis and treatment". *World Journal of Gastroenterology* 18 (2012): 6036-6039.
2. Freeman HJ. "Pearls and pitfalls in the diagnosis of adult celiac disease". *Canadian Journal of Gastroenterology* 22 (2008): 273-280.
3. Robinson JW. "Intestinal malabsorption in the experimental animal". *Gut* 13 (1972): 938-945.
4. Wilson FA and Hoyumpa AM Jr. "Ethanol and small intestinal transport". *Gastroenterology* 76 (1979): 388-403.
5. Trier JS. "Morphologic alterations induced by methotrexate in the mucosa of the human proximal intestine. I. Serial observations by light microscopy". *Gastroenterology* 42 (1962): 295-305.
6. Longstreth GF and Newcomer AD. "Drug-induced malabsorption". *Mayo Clinic Proceedings* 50 (1975): 284-293.
7. Jacobson ED., *et al*. "Malabsorptive syndrome induced by neomycin: morphologic alterations in the jejunal mucosa". *Journal of Laboratory and Clinical Medicine* 56 (1960): 245-250.
8. Race TF., *et al*. "Intestinal malabsorption induced by oral colchicine. Comparison with neomycin and cathartic agents". *The American Journal of the Medical Sciences* 259 (1970): 32-41.
9. Wright N., *et al*. "The cell cycle time in flat (avillous) mucosa of the human small intestine". *Gut* 14 (1973): 603-606.
10. Freeman HJ. "Sulindac associated small bowel lesion". *Journal of Clinical Gastroenterology* 8 (1986): 569-571.
11. Ziegler TR., *et al*. "Severe villous atrophy and chronic malabsorption induced by azathioprine". *Gastroenterology* 124 (2003): 1950-1957.
12. Freeman HJ. "Olmesartan enteropathy". *International Journal of Celiac Disease* 4 (2016): 24-26.
13. Freeman HJ. "Olmesartan-induced collagenous sprue". *International Journal of Celiac Disease* 8 (2020): 32-34.
14. Gentile M., *et al*. "Association between ipilimumab and celiac disease". *Mayo Clinic Proceedings* 88 (2013): 414-417.
15. Freeman HJ. "Sprue-like intestinal disease induced by checkpoint inhibitor immunotherapy". *International Journal of Celiac Disease* 8 (2020): 28-31.

16. Duval L., *et al*. "Nivolumab induced celiac-like enteropathy in patient with metastatic renal cell carcinoma". *Clinical Case Reports* 7 (2019): 1689-1693.

17. Facchinetti F., *et al*. "Widespread nivolumab-induced enteropathy in long responder non-small cell lung cancer patient". *Clinical Lung Cancer* 19 (2018): e591-e596.

18. Arnouk J., *et al*. "A celiac disease phenotype after checkpoint inhibitor exposure: an example of immune dysregulation after immunotherapy". *ACG Case Reports Journal* 6 (2019): e00158.

19. Alsaadi D., *et al*. "A case of checkpoint inhibitor-induced celiac disease". *The Journal for ImmunoTherapy of Cancer* 7 (2019): 203.

20. Freeman HJ. "COVID-19 diarrhea". *International Journal of Celiac Disease* 8 (2020): 60-63.

21. Freeman HJ. "COVID-19 and celiac disease". *International Journal of Celiac Disease* 9 (2021): 3-5.

22. Xiao F., *et al*. "Evidence for gastrointestinal infection of SARS-Cov-2". *Gastroenterology* 158 (2020): 1831-1833.

23. Chey SW., *et al*. "Transient lymphocytic colitis after SARS-Cov-2 mRNA vaccine". *American Journal of Gastroenterology* 117 (2022): 685-687.