Appendices

Appendix 1: Differential diagnosis for enteropathies with villous atrophy and negative coeliac serology - inspired by "Nomenclature and diagnosis of seronegative coeliac disease and chronic non-coeliac enteropathies in adults: the Paris consensus" by Annalisa Schiepatti et al. [5].

- Seronegative coeliac disease including coeliac disease associated with IgA deficiency and coeliac disease associated with CIVD
- Auto-immune enteropathy
- Drug induced enteropathy (angiotensin II receptor blockers particularly olmesartan, azathioprine, micophenolate mophetile, methotrexate and chemotherapy)
- Enteropathy associated T-cell lymphom
- CIVD
- Tropical Sprue
- Giardiasis
- Indolent CD4 T cell lymphoma
- Transplanted small intestine
- Radiotherapy and graft-versus-host disease.
- Crohn's disease
- HIV enteropathy
- Eosinophilic enterititis
- Idiopathic villous atrophy

Appendix 2: Comparison between Olmesartan-induced enteropathy and coeliac disease

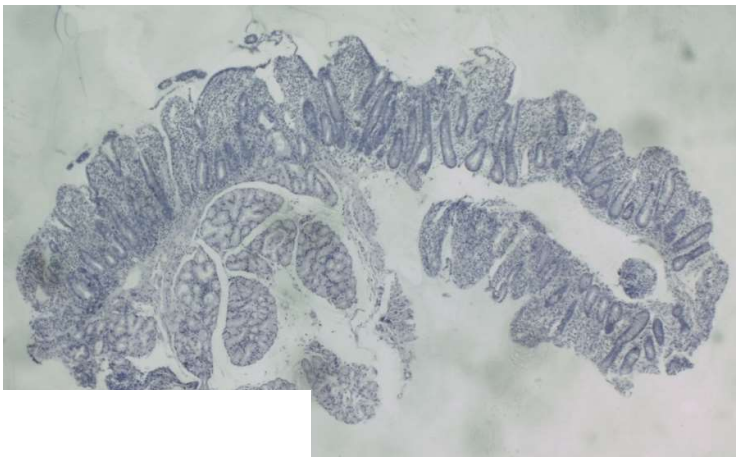
	Olmesartan-induced enteropathy [3,5]	**Coeliac Disease [6,14]**
Epidemiology	Very rare occurrence (<1/10000). Sur-risk < 1/10000 patients treated for exposure durations of more than 2 years. 1,1 to 4,9 cases per million patients exposed per year.	1% of the world's population and growing in recent years. Significant geographical disparities. 13 new cases/100,000 inhabitants per year
Population	Men = Women (45-55%). Average age: 68.	Male/female ratio 1:2 - all ages (70% >20y). White ethnicity. Most often diagnosed in childhood.
Clinic	Acute or chronic diarrhoea Weight loss (average 18kg) Nausea +/- vomiting Abdominal pain Bloating Fatigue	*Digestive symptoms:* chronic diarrhoea, weight loss, bloating, constipation. *Atypical symptoms:* dermatitis herpetiformis, ataxia, recurrent mouth ulcers, depression. *Aspecific symptoms:* chronic fatigue, headache, abdominal pain, osteoporosis. *Biological manifestations:* anemia +/- iron, B9 or B12 deficiency. Elevated liver enzymes.
Diagnosis	**Exclusion diagnosis.** **Taking Olmesartan + duodenal biopsies with villous atrophy +/- intraepithelial lymphocytosis + negative**	**Positive celiac serology:** anti-Tg IgA + in the absence of total IgA deficiency (Sensitivities of 90-9% and negative predictive values

	celiac serology. Typically, months to years after initiation of medication (3 years).	of 99-6%) **+ Duodenal biopsies with villous atrophy +/- intraepithelial lymphocytosis.** *In children, if anti-Tg Ac>10N AND symptoms, biopsy not necessary for diagnosis.* Requires gluten ingestion! Possibility of gluten challenge (3g/D, >14D). *In case of intermediate value, IgA EMA assay (anti-endomysial Ac).* *In case of IgA deficiency: anti-DGP IgG, anti-Tg IgG, EMA IgG assay.* *In case of doubt: HLA DQ2/DQ8 typing to exclude CD (99% VPN).*
Biopsies	**Total or partial villous blunting** (92%) **Increased intraepithelial lymphocytes** (IELs) ranging from 25 to more than 100 lymphocytes per 100 enterocytes (61%) **Subepithelial collagen thickening** (22%) Variable degrees of lamina propria chronic inflammation, acute inflammation, and increased eosinophils may be present	• **Increased intraepithelial T-lymphocytes:** >25 T-lymphocytes/100 enterocytes • **Crypt hyperplasia** : extension of the regenerative epithelial crypts associated with presence of more than 1 mitosis per crypt. • **Villous atrophy:** decrease in villous height, alteration of normal crypt/villous ratio (3:1) until total disappearance of villi. Marsh classification (4 duodenal biopsies +1 bulb biopsy).
Genetic Predisposition	No genetic predisposition, but HLA-DQ2/DQ8 prevalence higher in patients developing enteropathy on Olmesartan than in the general population (60-80% according to case studies vs. 30%).	**HLA DQ2/DQ8 in 100% of patients** 90% are HLA DQ2 +, 10% HLA DQ8 + (including even heterozygotes!)
Complications	Dehydration with or without renal failure Electrolyte disorders including hypokalemia Metabolic acidosis undernutrition No death reported. Unknown oncological risk	Osteoporosis Dermatitis herpetiformis T lymphoma of the digestive tract Non-Hodgkin's lymphoma Digestive cancer (mainly small bowel and liver) Can lead to death.
Treatment	**Drug discontinuation.** Management of complications. Clinical improvement in days/weeks. Biopsies and serologies normalized.	**Gluten-free diet (GFD)** Clinical improvement in days/weeks. Subsequent normalization of biopsies and serologies. Improves mortality and complications (T and non-Hodkgkin's lymphoma, other neoplasia).

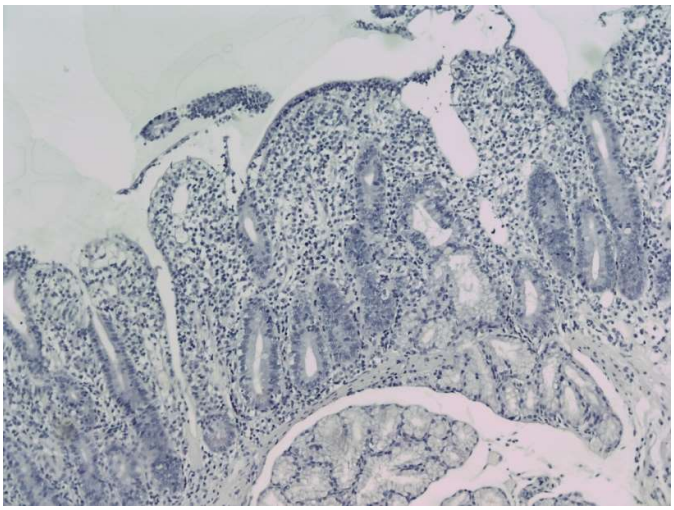
CD, celiac disease; EGD, esophagogastroduodenoscopy; GFD, gluten-free diet; HLA, human leukocyte antigen; tTG, tissue transglutaminase; VA, villous atrophy.

Appendix 3: Anatomopathogy features of the patient.

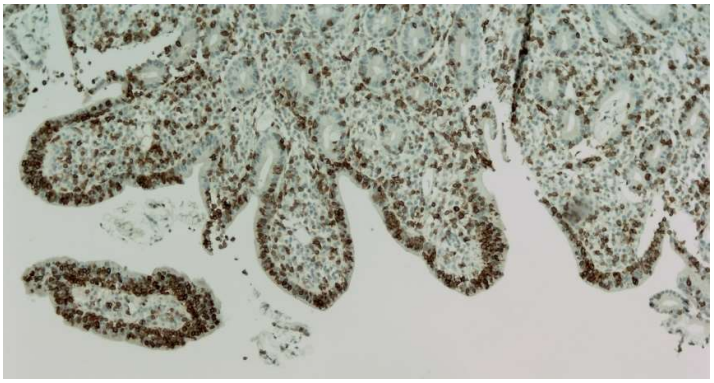
1. Fragment of duodenal mucosa with moderate to severe villous atrophy.



2. Inflammation in the lamina propria, as well as the increased number of intra-epithelial lymphocytes.



3. CD3 immunohistochemistry marks the lymphocytes. Almost 100 lymphocytes per 100 epithelial cells.



4. Normal duodenal mucosa; villous/crypt ratio over 3:1; number of T lymphocytes <25 x 100 epithelial cells. **(A)** H&E x 10, **(B)** CD3 immunostain x10. Extract from Villanacci V, Vanoli A, Leoncini G, Arpa G, Salviato T, Bonetti LR, Baronchelli C, Saragoni L, Parente P. Celiac disease: histology-differential diagnosis-complications. A practical approach. Pathologica. 2020 Sep;112(3):186-196.