Celiachia e malattia linfoproliferativa del tratto digestivo

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Disclosures Dr Carla Felice

None

Celiac disease and intestinal lymphoma

Celiac disease (CD)

Chronic multi-organ immune disorder due to sensitivity to dietary gluten and its proteins (glutenin and gliadin)

Enteropathy-associated T cell Lymphoma (EATL)

- Numbers
- Link between CD and EATL
- Diagnosis
- Treatment

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CD: prevalence and incidence

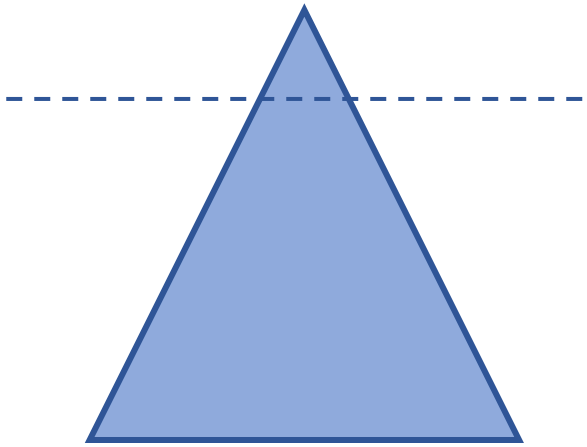
CD prevalence increased over the last 50 years

Western countries: 0.6% histologically confirmed and 1% serological screening

70% diagnosed >20 years

Female:male 1:3 to 1.5:1

Increased risk in first-degree relatives and in other autommune disorders



Ludvigsson & Murray Gastroenterol Clin N Am 2018

EATL: prevalence and incidence

RARE

<1% non-Hodgkin lymphomas

Diagnosis > 60 years

Same geographical prevalence of CD

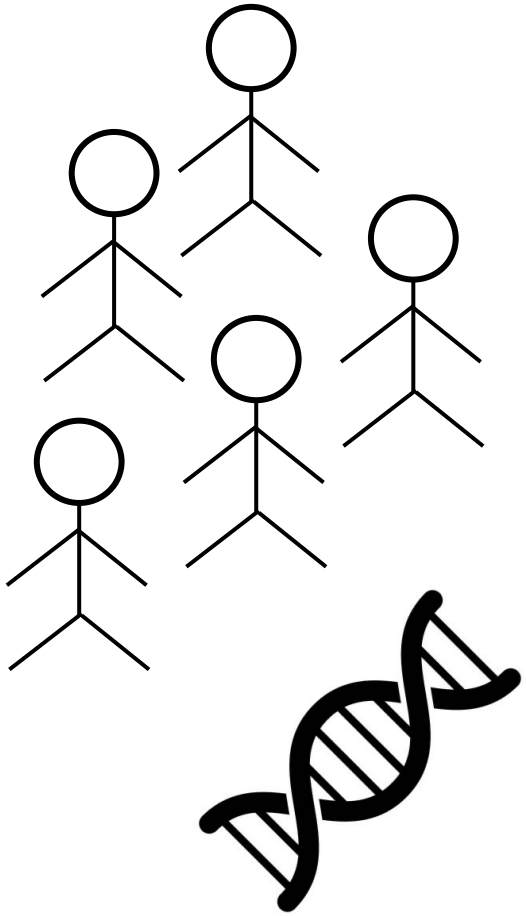
Negative prognosis

Prevention

Zettl A et al. Am J Clin Pathol 2007
Cellier C et al. Lancet 2000
Swerdlow SH et al. Blood 2016

- Numbers
- Link between CD and EATL
- Diagnosis
- Treatment

Celiac disease



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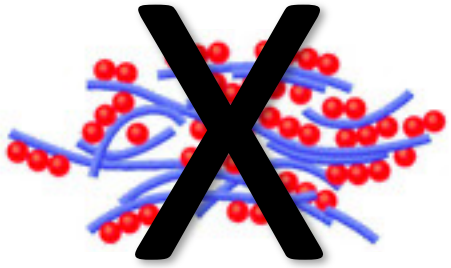


GLUTEN

=

Innate and adaptive inflammatory reaction and tissue damage

Celiac disease

Diagnosis in adults: positive serology (IgA –TTG) + duodenal histology

Panel 1: Terminology describing patients with coeliac disease (adapted from Ludvigsson and colleagues, 2013)[70]

Potential
Positive serological tests and normal intestinal biopsy

Asymptomatic
Absence of symptoms despite specific questioning regarding symptoms

Symptomatic
Presence of either intestinal or extra-intestinal symptoms

Classic
Diarrhoea, signs and symptoms of malabsorption, or both

Non-classic
Lack of malabsorption symptoms, but other symptoms present (eg, anaemia, osteoporosis)

Refractory
Persistent symptoms and villous atrophy despite adherence to a gluten-free diet

Panel 2: National Institute for Health and Care Excellence guidelines[71] on the indications that should prompt testing for coeliac disease

Coeliac testing recommended

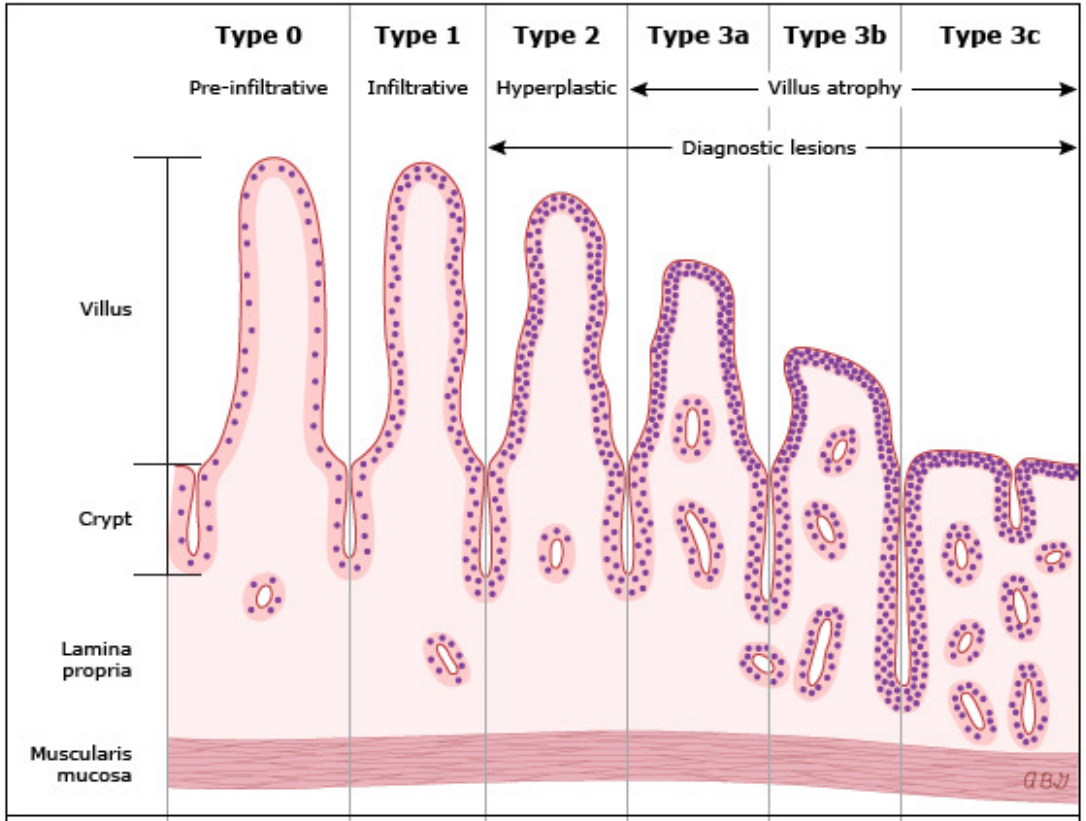
- Persistent unexplained abdominal or gastrointestinal symptoms
- Faltering growth
- Prolonged fatigue
- Unexpected weight loss
- Severe or persistent mouth ulcers
- Unexplained iron, vitamin B12, or folate deficiency
- Type 1 diabetes
- Autoimmune thyroid disease
- Irritable bowel syndrome
- First degree relatives of people with coeliac disease

Coeliac testing should be considered

- Metabolic bone disorders (reduced bone mineral density or osteomalacia)
- Unexplained neurological symptoms (particularly peripheral neuropathy or ataxia)
- Unexplained subfertility or recurrent miscarriage
- Persistently increased concentrations of liver enzymes with unknown cause
- Dental enamel defects
- Down's syndrome
- Turner syndrome

Lebwohl et al. Lancet 2019

Marsh-Oberhuber Classification



Villus	Normal	Normal	Normal	Mild atrophy	Moderate atrophy	Severe atrophy
Crypt	Normal	Normal	Hyperplasia	Hyperplasia	Hyperplasia	Hyperplasia
Ratio, villus height: crypt depth	3:1	3:1	<3:1	<2:1	1:1	<1:1
IEL/ 100 EC	<40	>40	>40	>40	>40	>40

Oberhuber G et al. Eur J Gastroenterol Hepatol. 1999

Celiac disease

Panel 3: Causes of non-responsive coeliac disease

Incorrect initial diagnosis
- Non-coeliac gluten sensitivity
- Seronegative villous atrophy

Inadvertent gluten exposure

Additional conditions
- Irritable bowel syndrome
- Small intestinal bacterial overgrowth
- Food intolerance (eg, to lactose or fructose)
- Pancreatic exocrine insufficiency
- Microscopic colitis

Refractory coeliac disease

Mortality risk
EATL risk

Referral to a specialist centre for treatment and monitoring

Lebwohl et al. Lancet 2019

Refractory celiac disease (RCD)

Persistent symptoms and villous atrophy despite gluten-free diet for > 12 months

Flow cytometry
Immunohistochemistry
PCR for TCR rearrangements

Type I (RCD-I)

No IEL atypia
<20% aberrant T cells
No ulcers

Type II (RCD-II)

No IEL atypia
>20% aberrant T cells
Clonal TCR rearrangement
Ulcerative jejunitis

Pre-EATL

IL-15 (anti-apoptotic)

IEL stimulated by IL-2, IL-21, TNF produced by gluten-specific CD4+

5-year survival 44-58%
5-year EATL 33-52%

Al-Toma et al. UEG Journal 2019 , Lebwohl et al. Lancet 2019, Nijeboer et al. UEG Journal 2016, Al-Toma et al. Gut 2007

Risk of NHL

Disorder*	No. of studies	Prevalence†		Pooled relative risk	
		All NHL: ever/never (%)	Controls: ever/never (%)	OR (95% CI)‡	Study heterogeneity *P*§
Rheumatoid arthritis	12	504/11735 (4.3)	556/15222 (3.7)	1.06 (0.87-1.29)‖	<.01
Psoriasis	7	278/7460 (3.7)	279/10122 (2.8)	1.16 (0.98-1.38)	.82
Ulcerative colitis	9	125/9775 (1.3)	138/12148 (1.1)	1.02 (0.79-1.31)	.84
Type 1 diabetes	9	32/10289 (0.3)	58/13613 (0.4)	0.76 (0.49-1.19)	.79
Sarcoidosis	6	19/7607 (0.2)	27/8856 (0.3)	0.73 (0.40-1.32)	.70
Pernicious anemia	5	13/3410 (0.4)	16/5865 (0.3)	1.08 (0.51-2.30)	.25
Crohn disease	7	23/9230 (0.2)	27/10614 (0.3)	0.89 (0.50-1.56)	.74
Celiac disease	7	33/9343 (0.4)	25/10424 (0.2)	1.50 (0.89-2.54)	.72
Hemolytic anemia	5	21/3242 (0.6)	13/5585 (0.2)	2.57 (1.27-5.21)	.57
Systemic lupus erythematosus	11	57/12034 (0.5)	26/15237 (0.2)	2.69 (1.68-4.30)	.39
Multiple sclerosis	10	15/9666 (0.2)	18/12341 (0.1)	0.96 (0.48-1.92)	.89
Sjögren syndrome	8	52/8178 (0.6)	8/10543 (0.1)	6.56 (3.10-13.9)	.72
Primary Sjögren syndrome	8	23/8176 (0.3)	5/10543 (0.0)	4.75 (1.79-12.6)	.93
Secondary Sjögren syndrome	8	29/8178 (0.4)	3/10542 (0.0)	9.57 (2.90-31.6)	ND
Scleroderma	7	4/7616 (0.1)	7/10093 (0.1)	0.69 (0.20-2.40)	.81
Immune thrombocytopenia	5	4/4095 (0.1)	3/6529 (0.0)	2.13 (0.47-9.73)	.54
Myasthenia gravis	6	4/6385 (0.1)	3/7413 (0.0)	1.45 (0.31-6.82)	.53
Polymyositis/dermatomyositis	5	6/6662 (0.1)	0/7947 (0.0)	ND	ND

Smedby et al. Blood 2008

Risk of NHL by cell lineage

Disorder*	Controls: Ever/never	Cases					
		B cell† (n = 10,723)		T cell‡ (n = 745)		Unknown cell lineage (n = 1514)	
		Ever/never	OR (95% CI)§	Ever/never	OR (95% CI)§	Ever/never	OR (95% CI)†
Psoriasis	279/10 122	231/5971	1.11 (0.92-1.33)	22/351	1.63 (1.03-2.57)	25/1138	1.30 (0.83-2.03)
Ulcerative colitis	138/12 148	96/7996	1.04 (0.79-1.37)	8/504	1.53 (0.73-3.21)	21/1275	0.96 (0.59-1.56)
Type 1 diabetes	58/13 613	29/8430	0.85 (0.53-1.35)	0/564	ND	3/1295	0.56 (0.17-1.86)
Sarcoidosis	27/8856	14/6627	0.61 (0.32-1.18)	4/465	2.49 (0.85-0.27)	1/515	0.66 (0.08-0.17)
Pernicious anemia	16/5865	13/2719	1.32 (0.61-2.84)	0/153	ND	0/538	ND
Crohn disease	27/10 614	17/7726	0.79 (0.421-.47)	2/494	1.47 (0.34-6.35)	4/1010	1.58 (0.52-0.78)
Celiac disease	25/10 424	22/7916	1.16 (0.652-.08)	9/554	6.21 (2.82-13.6)	2/873	1.66 (0.36-7.62)
Hemolytic anemia	13/5585	17/2466	2.62 (1.25-5.52)	1/176	2.08 (0.24-17.7)	3/600	2.32 (0.63-8.53)
Systemic lupus erythematosus	26/15 237	45/9886	2.44 (1.49-3.99)	3/669	2.43 (0.72-8.24)	9/1479	4.53 (2.00-10.3)
Multiple sclerosis	18/12 341	14/8172	1.06 (0.52-2.16)	0/594	ND	1/900	0.80 (0.10-6.33)
Sjögren syndrome	8/10 543	45/6800	6.52 (3.061-3.93)	1/505	2.03 (0.25-16.6)	6/873	16.3 (4.70-56.4)
Primary Sjögren syndrome	5/10 543	21/6798	4.97 (1.86-13.29)	0/505	ND	2/873	5.54 (0.87-35.5)
Secondary Sjögren syndrome	3/10 542	24/6800	9.11 (2.72-30.46)	1/505	5.13 (0.51-51.8)	4/873	37.7 (7.38-192)

Smedby et al. Blood 2008

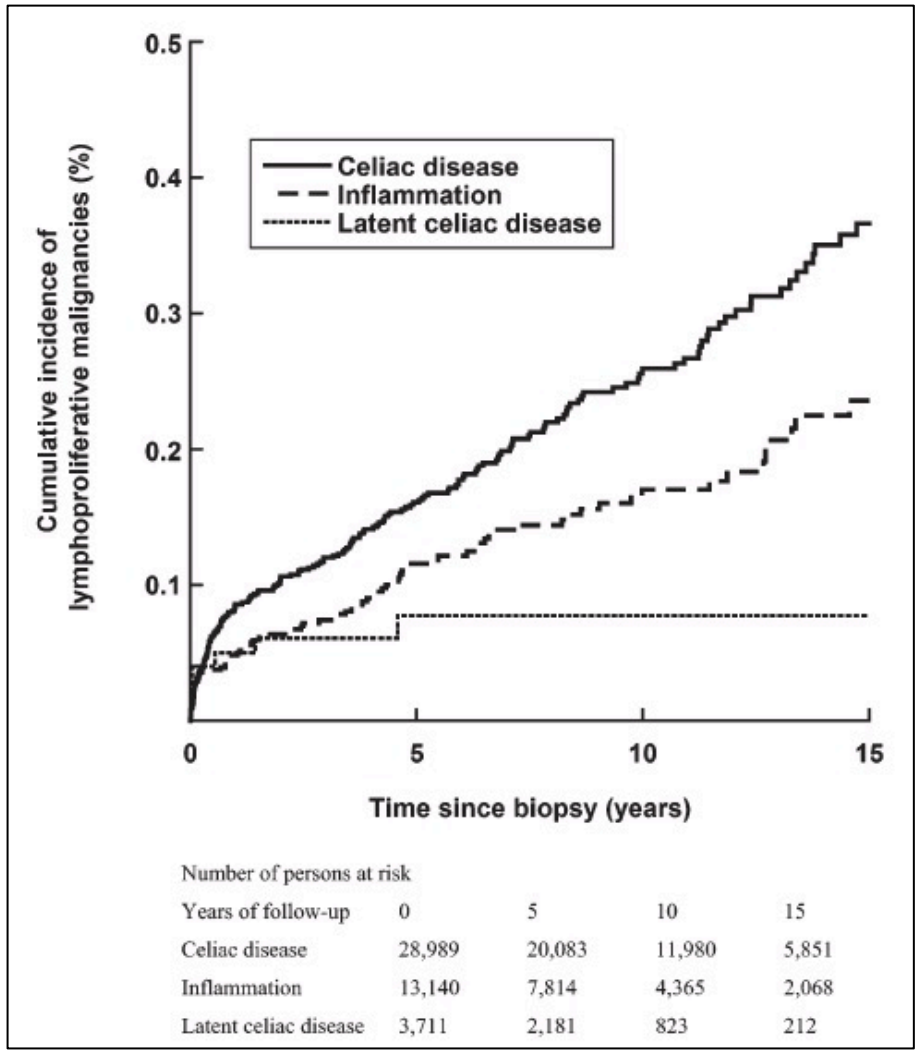
Risk of NHL and disease duration

	Never			2-5 years			6-10 years			More than 10 years		
Disorder*	**Cases**	**Controls**	**OR (95% CI)†**	**Cases**	**Controls**	**OR (95% CI)†**	**Cases**	**Controls**	**OR (95% CI)†**	**Cases**	**Controls**	**OR (95% CI)†**
Psoriasis	7460	10 122	1.00 (referent)	41	40	1.35 (0.86-2.10)	31	47	0.81 (0.51-1.28)	200	188	1.19 (0.97-1.47)
Ulcerative colitis	9775	12 148	1.00 (referent)	12	19	0.83 (0.39-1.75)	9	13	0.73 (0.30-0.75)	86	90	1.08 (0.80-1.47)
Type 1 diabetes	10 289	13 613	1.00 (referent)	1	3	1.08 (0.11-10.4)	1	3	0.66 (0.07-6.55)	30	52	0.76 (0.48-1.20)
Sarcoidosis	7607	8856	1.00 (refer						0.34 (0.03-3.28)	11	15	0.78 (0.35-1.71)
Pernicious anemia	3410	5865	1.00 (refer						ND	4	6	1.13 (0.31-4.08)
Crohn disease	9230	10 614	1.00 (refer						1.91 (0.41-8.85)	12	16	0.73 (0.34-1.57)
Celiac disease	9343	10 424	1.00 (refer						0.69 (0.16-2.93)	20	13	1.82 (0.89-3.69)
Hemolytic anemia	3242	5585	1.00 (refer						2.13 (0.29-15.8)	15	9	2.50 (1.08-5.83)
Systemic lupus erythematosus	12 034	15 237	1.00 (refer						2.46 (0.90-6.75)	26	16	1.89 (1.00-3.55)
Multiple sclerosis	9666	12 341	1.00 (refer						ND	6	11	0.61 (0.22-1.68)
Sjögren syndrome	8178	10 543	1.00 (referent)	15	3	4.54 (1.31-15.8)	13	1	15.7 (2.04-121)	20	4	5.07 (1.72-14.9)
Primary Sjögren syndrome	8176	10 543	1.00 (referent)	6	2	2.84 (0.57-14.2)	2	1	2.64 (0.23-30.3)	12	2	6.37 (1.42-28.6)
Secondary Sjögren syndrome	8178	10 542	1.00 (referent)	9	1	7.92 (1.00-62.8)	11	0	ND	8	2	3.78 (0.79-18.1)

Increased risk (2 fold) in patients diagnosed with CD at age > 33 years

Smedby et al. Blood 2008

Risk of NHL



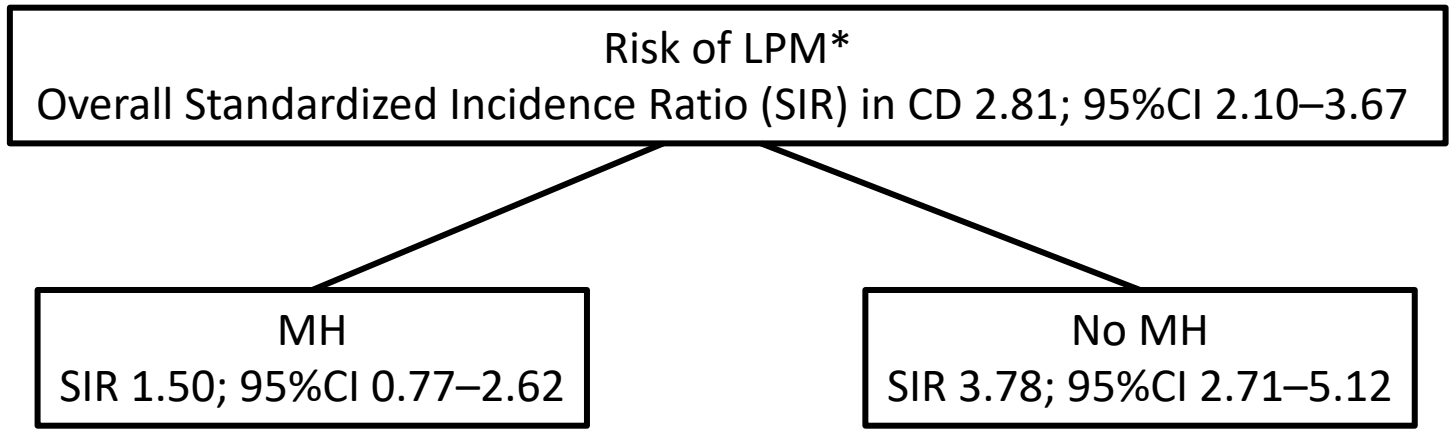
Marsh 3 | Marsh 1-2 | Marsh 0

Outcome	Celiac disease (n = 28989) No. of events	HR (95% CI)	P	Inflammation (n = 13140) No. of events	HR (95% CI)	P	Latent celiac disease (n = 3711) No. of events	HR (95% CI)	P
Lymphoproliferative malignancy (any type)	193	2.82 (2.36 to 3.37)	<.001	89	1.81 (1.42 to 2.31)	<.001	7	0.97 (0.44 to 2.14)	0.95
Non-Hodgkin lymphoma	138†	4.26 (3.39 to 5.36)	<.001	47	1.86 (1.32 to 2.60)	<.001	5	1.27 (0.49 to 3.32	0.62
Non-Hodgkin lymphoma T-cell	28	48.0 (15.8 to 145)	<.001	1	1.36 (0.16 to 11.8	0.78	0	0.00 (0.00 to ∞)	1.0
Non-Hodgkin lymphoma B-cell	40	1.90 (1.32 to 2.73)	<.001	28	2.05 (1.32 to 3.18)	0.001	2	0.58 (0.14 to 2.53)	0.47
Non-Hodgkin lymphoma not specified	70	6.72 (4.61 to 9.81)	<.001	18	1.66 (0.96 to 2.86)	0.07	3	4.47 (1.19 to 16.8)	0.03
Other types of lymphoma	16	5.34 (2.62 to 10.9)	<.001	5	3.26 (1.13 to 9.44)	0.03	1	1.83 (0.19 to 17.8)	0.60
Hodgkin lymphoma	10	2.73 (1.26 to 5.93)	.01	2	0.94 (0.21 to 4.21)	0.93	0	0.00 (0.00 to ∞)	1.0
Chronic lymphocytic leukemia	7	0.63 (0.29 to 1.39)	0.25	13	1.50 (0.80 to 2.81)	0.20	0	0.00 (0.00 to ∞)	1.0
Myeloma	16	1.14 (0.66 to 1.98)	.64	18	1.82 (1.06 to 3.12)	0.03	1	0.91 (0.12 to 7.18)	0.93
Acute lymphocytic leukemia	7	2.06 (0.84 to 5.04)	0.11	3	1.36 (0.35 to 5.26)	0.65	0	0.00 (0.00 to ∞)	1.0
Unspecified lymphoid leukemia	3	8.79 (0.73 to 105)	0.09	1	6.15 (0.35 to 109)	0.21	0	0.00 (0.00 to ∞)	1.0

Elfstrom et al. JNCI 2011

Risk of NHL

- Population-based cohort study (Sweden)
- CD with a follow-up biopsy **(n=7625)** minimum 6 months up to 5 years after the diagnosis
- Mucosal healing (MH) = resolution of villous atrophy **57% of cases**



*LPM lymphoprolipherative malignancy

Lebwohl et al. Ann Int Med 2013

Risk factors for EATL in CD

- ✓ Age at diagnosis
- ✓ Gluten ingestion
- ✓ Villous atrophy
- ✓ No mucosal healing
- ✓ Refractory CD

- Numbers
- Link between CD and EATL
- Diagnosis
- Treatment

EATL: clinical presentation

62 EATL

Symptoms	
Abdominal pain	88% (30)
Fatigue	38% (13)
Anorexia	38% (13)
Infection	23% (8)
Adenopathy	15% (5)
Hepatomegaly	6% (2)
Splenomegaly	6% (2)
Pruritus	3% (1)

Stage	
IE	10% (6)
IIE	21% (13)
IIIE	5% (3)
IV	64% (39)
B symptoms	
No	37% (23)
Yes	63% (39)
Largest mass	
< 5 cm	37% (17)
≥ 5 cm	63% (29)
Bone marrow involvement	
No	97% (60)
Yes	3% (2)
Elevated LDH	
No	65% (37)
Yes	35% (20)

Acute presentation with
bowel perforation or bleeding

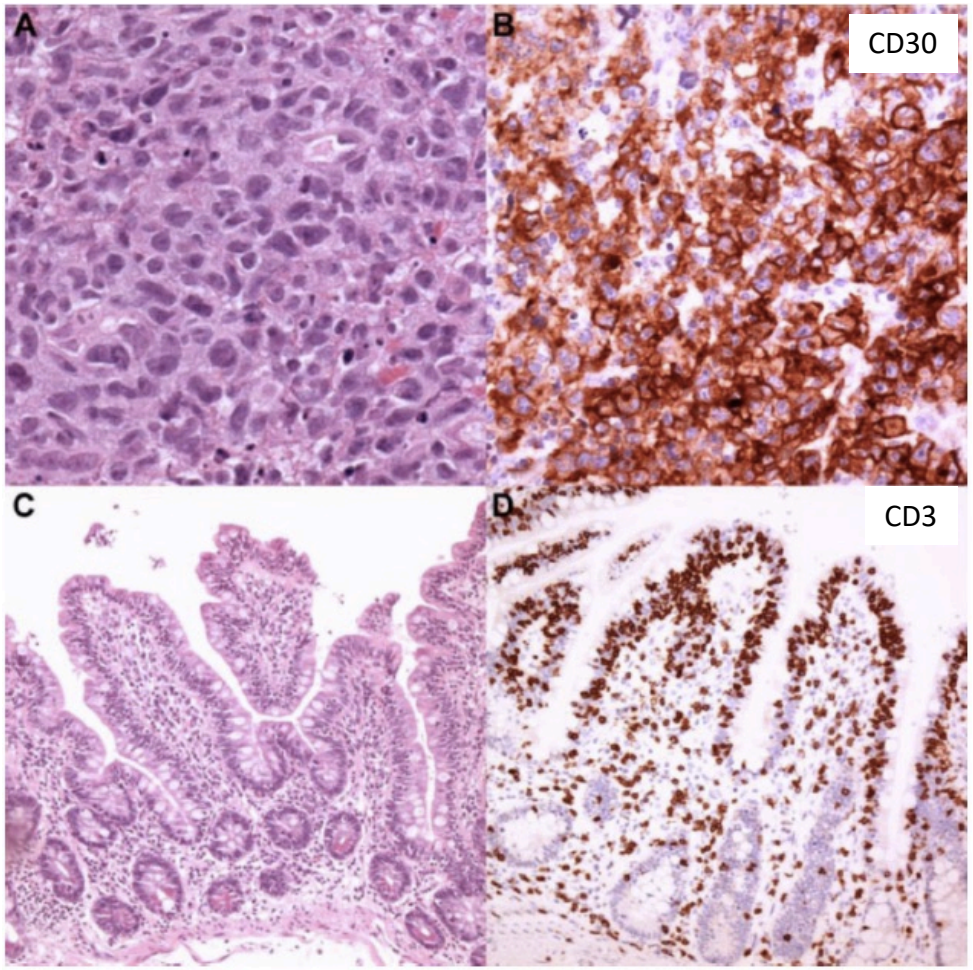
Delabie et al. Blood 2011

Histology

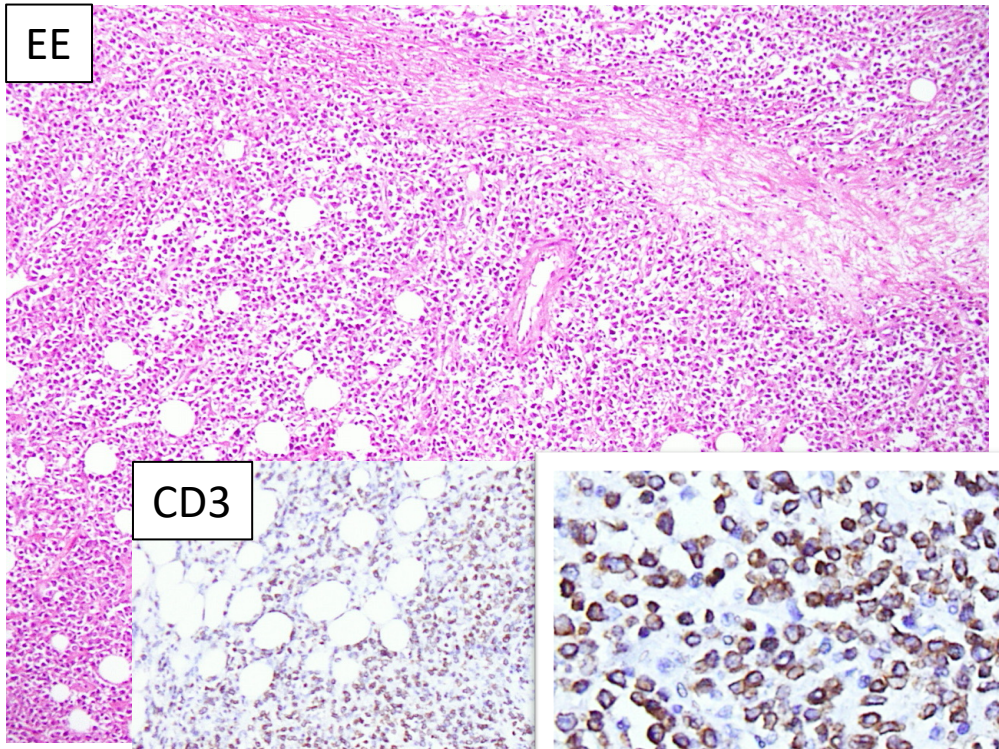
Aggressive infiltrate of variable size cells

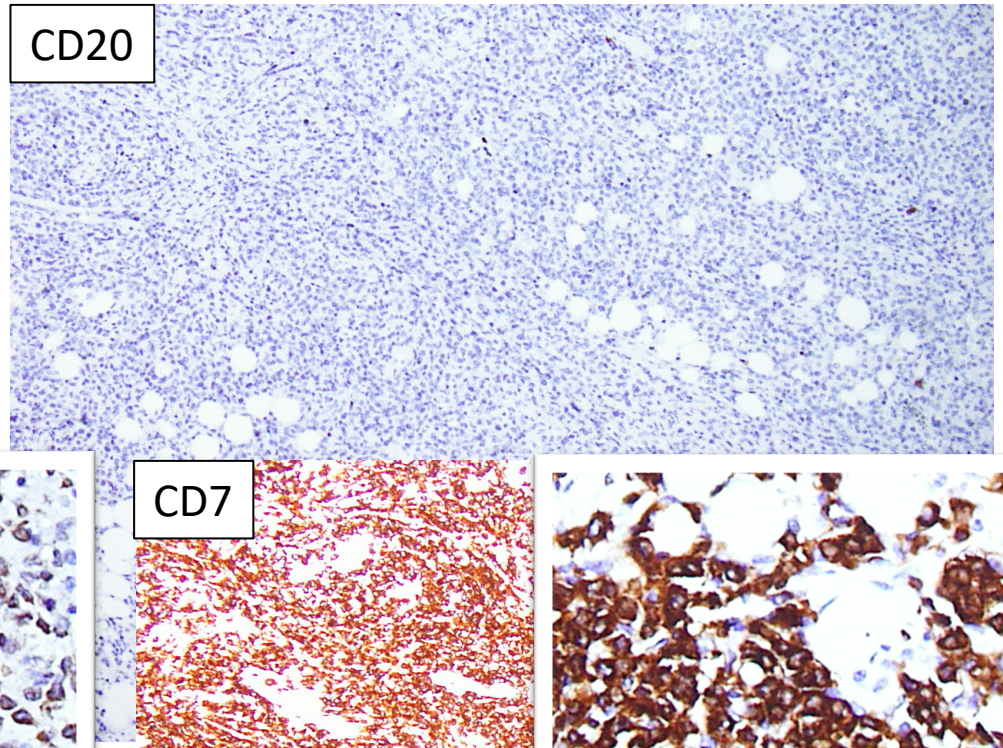
	EATL type 1
CD3e	89%
CD2	43%
CD5	17%
CD4	11%
CD8	43%
CD30	37.5%
CD56	30%

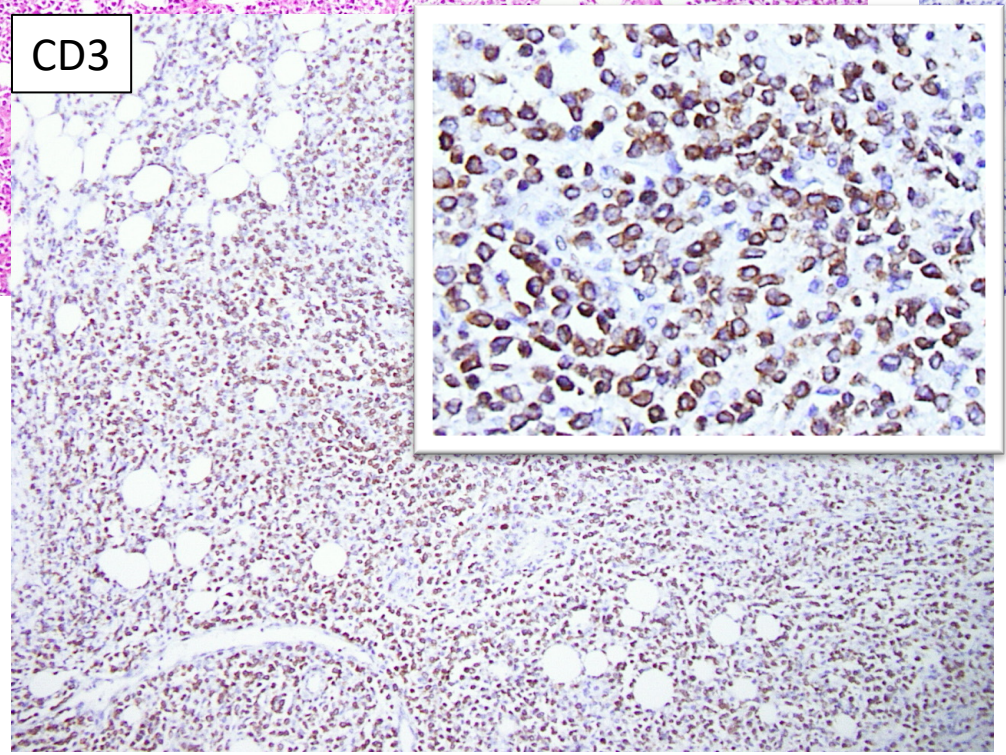
CD7+
CD103+
T cell protein (Granzym B, TIA-1, Perforin)

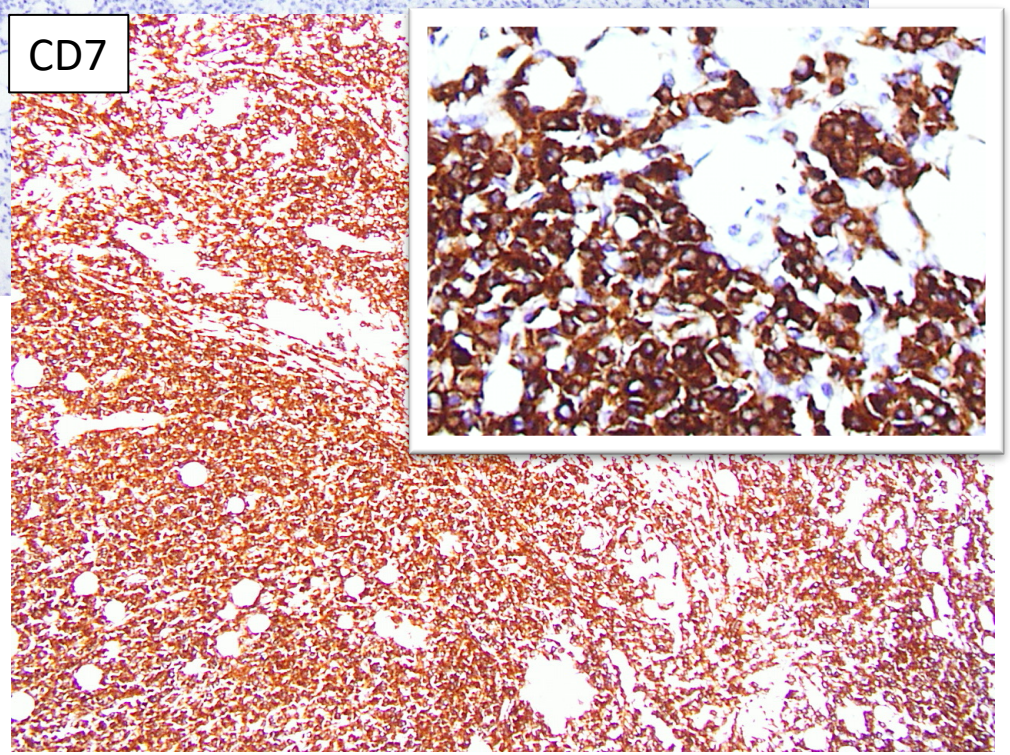


Murray et al Am J Pathol 1995
Delabie et al. Blood 2011









Female 61 ys
CD3+
CD30-
CD8-
CD56-
CD5-
CD4+
CD7+
CD20-
Ki67 80%

Thanks to Dr Ivana Cataldo, Pathology Unit, Ca' Foncello Hospital, Treviso

Genetics

DQA1*0501 or DQB1*0201 HLA haplotype

Rearrangement of TCR **β** and **γ**

50-60% complex segmental amplifications of the 9q31.3-qter region

Mutations of the JAK/STAT pathway

Differential diagnoses

- RCD
- Monomorphic epitheliotropic intestinal T cell lymphoma
- Indolent T cell lymphoproliferative disease
- Extranodal NK/T cell lymphoma
- Gamma-delta T cell lymphoma
- Anaplastic large cell lymphoma
- B cell lymphomas

- Numbers
- Link between CD and EATL
- Diagnosis
- Treatment

Refractory celiac disease (RCD)

RCD-I:

- Steroids
- Thiopurines
- Infliximab

RCD-II:

- Steroids
- Cladribine
- Chemotherapy (CHOP) + autologous stem-cell transplantation (ASCT)
- Anti-IL-15 (AMG-714)
- Surgery for complications

Gluten-free diet
Nutritional support
Infection prevention

EATL

Surgery
Chemotherapy + autologous stem-cell transplantation (ASCT)

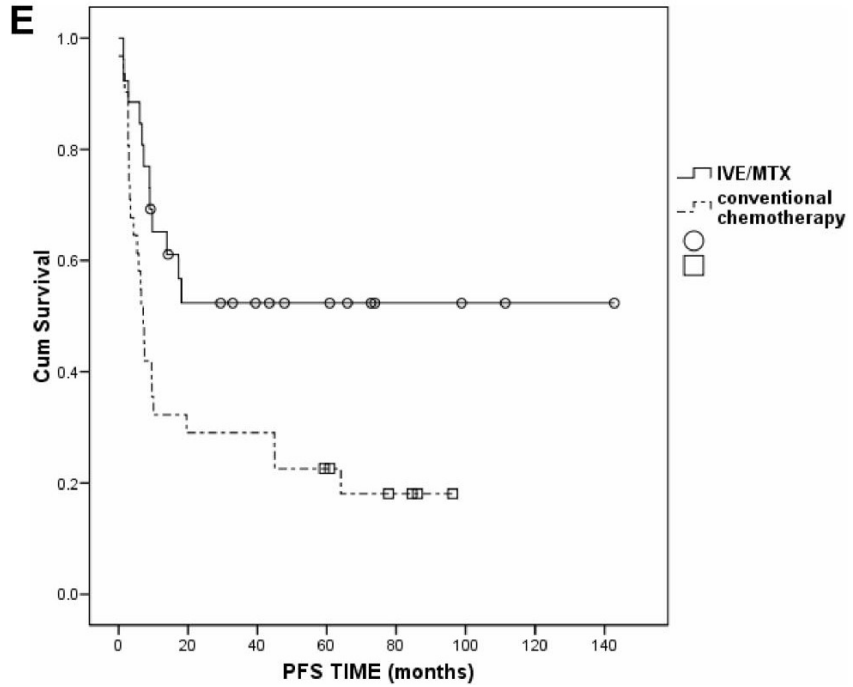
5-year survival in chemotherapy alone <20%

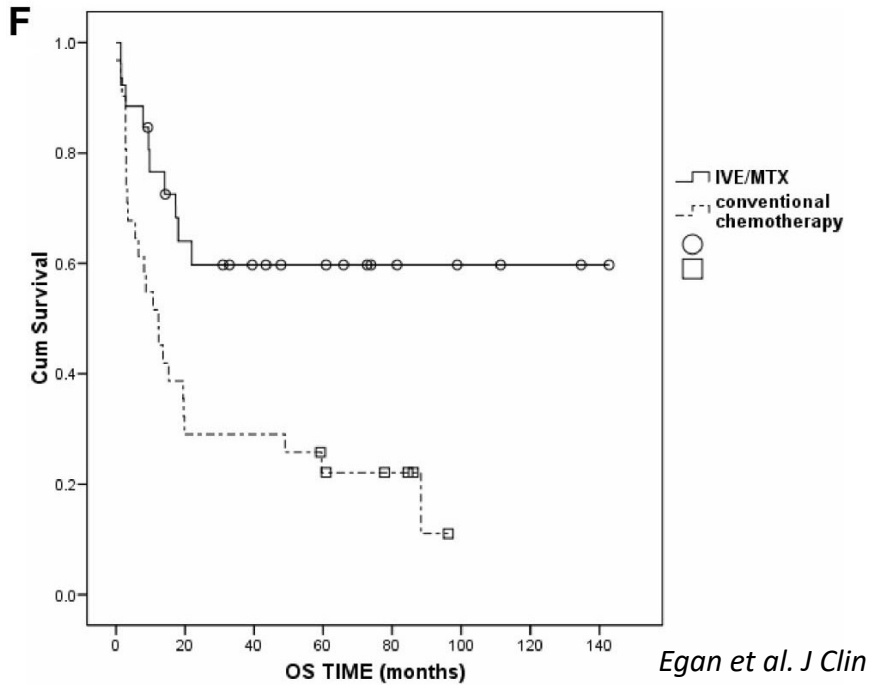
Gluten-free diet
Nutritional support
Infection prevention

Conventional:
antracycline-based

VS

New regimen:
ifosfamide, vincristine,
etoposide/methotrexate
+ ASCT after 4-6 weeks





Egan et al. J Clin Gastroenterol 1995
Gale et al. J Clin Oncol 2000
Sieniawski et al. Blood 2010

Conclusions

- EATL rare but often fatal complication of CD
- Poor evidence
- No routine screening recommended in CD
- Compliance to gluten-free diet in CD
- Multidisciplinar management in referral centers