Envoi SPECIALIST PATHOLOGISTS *inside insights*

Update No.9 - 2016 *Dr Ian Brown*

Refractory coeliac disease (RCD)

Definition of refractory coeliac disease (RCD): Proven coeliac disease in which either one of the following circumstances apply:

- No improvement despite 12 months (some use 6 months) of a strict gluten free diet
- Requirement for further intervention because of severe or deteriorating clinical symptoms

Histology: Persisting villous blunting, lamina propria inflammation and intraepithelial lymphocytosis (IEL) typical of usual coeliac disease (see Fig. 1.). Sometimes the crypts may become shortened and subepithelial collagen deposition may be seen.

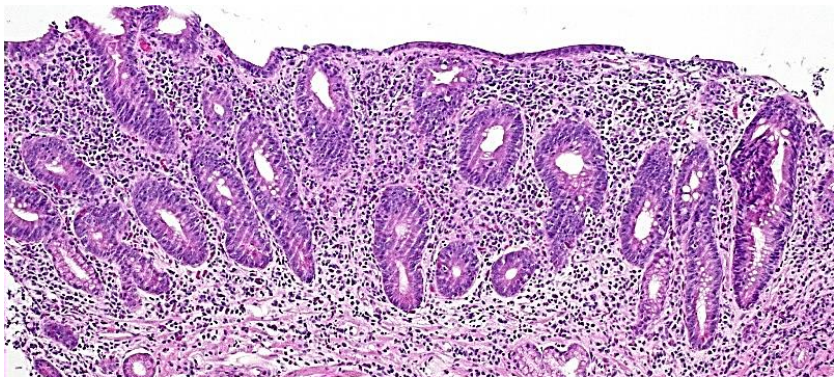


Fig. 1. RCD showing histology identical to usual type coeliac disease.

Classification: RCD is sub-divided on the basis of the immunophenotype of the intraepithelial lymphocytes. Distinction relies on a combination of immunohistochemical profiling of the intraepithelial T cells using CD3 and CD8, flow cytometric analysis of unfixed biopsy tissue and PCR T cell receptor (TCR) clonality studies. PCR studies are the most likely to produce inconclusive results, so flow cytometry is the favoured diagnostic investigation.

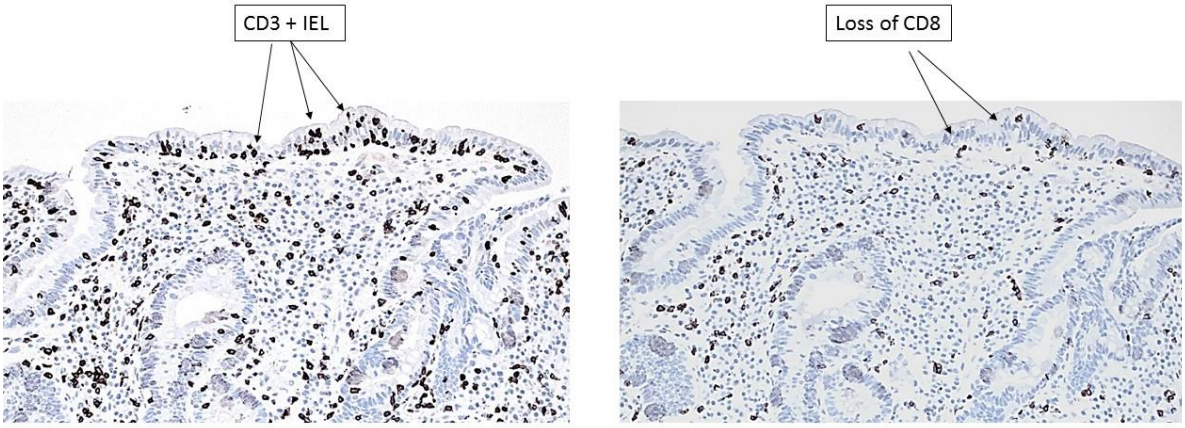
- **Type 1 RCD – IEL phenotype identical to usual coeliac disease**
- **Type 2 RCD - aberrant IEL phenotype**

In ***Type 1 RCD*** the IEL phenotype is identical to usual coeliac disease with immunohistochemical expression of CD8 in the majority of CD3 positive IELs. Flow cytometry shows surface CD3, CD7, CD8, CD103 and TCRβ. TCR gene rearrangement should be polyclonal, although, a dominant clone can occasionally produce a false monoclonal result. There is no increased risk of enteropathy type T cell lymphoma (ETTL), beyond usual coeliac disease. Importantly, immunosuppression can be used for treatment.

Type 2 RCD is characterised by immunophenotypic abnormality in the IEL population. Immunohistochemistry shows cytoplasmic CD3 with loss of surface CD8 in >50% of IEL (see Fig.2.). Flow cytometry shows loss of multiple surface T cell markers including CD3, CD7 and CD8 in >20% of IEL. Monoclonal TCR is consistently identified but this is less helpful as a clonal T cell population can be found in RCD1. Type 2 RCD is at risk for development of overt enteropathy type T cell lymphoma (ETTL) which has a 5 year survival of only 40-50%.

	CD3/CD8 IHC	**Flow cytometry (requires fresh tissue)**	**TCR rearrangement**	**Risk of ETTL**
Coeliac disease	CD3 = CD8	No loss of surface T cell markers	Polyclonal	None
RCD1	CD3 = CD8	No loss of surface T cell markers	Oligo/polyclonal	None
RCD 2	CD8 lost in > 50% of CD3 positive IEL	Loss of surface CD3, CD7 and CD8 in > 20% of IEL	Oligo/monoclonal	Increased

Fig.2. Loss of >50% CD 8 staining in CD3 positive intraepithelial lymphocytes in Type 2 refractory coeliac disease.



Differential diagnosis: If compliance with a strict gluten free diet is confirmed then other conditions to consider include the following:

- collagenous sprue
- autoimmune enteropathy
- tropical sprue
- immunodeficiency disorders e.g. CVID
- medications e.g. olmesartan
- Crohn's disease

Further reading:

Ho-Yen C, Chang F, van der Walt J, Mitchell T, Ciclitira P. Recent advances in refractory coeliac disease: a review. Histopathology. 2009; 54: 783.

Rubio-Tapia A, Murray JA. Classification and management of refractory coeliac disease. Gut. 2010; 59(4):547-57.

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