IBD and EBV associated LPD in GIT

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Lymphoproliferations in immunodeficiency

- Primary immunodeficiencies
  - Large variation in conditions and lesions
- Acquired immunodeficiencies
  - HIV: changes related to therapy
- Iatrogenic immunodeficiencies
  - PTLD: prototype, but not what it used to be
  - Methotrexate
  - Others, including those in treated autoimmune disease, IBD

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Inflammatory bowel disease and cancer

- Well known association with adenocarcinoma
- **ECCO Guideline Statement 3A:**
  IBD patients show a trend toward higher risks of developing haematological malignancies. Compared with the general population, UC patients are significantly more likely to develop leukaemia, whereas those with CD are at higher risk for lymphoma, especially non-Hodgkin lymphoma [EL1]

Annese et al. European Evidence-based Consensus: Inflammatory Bowel Disease and Malignancies. J Crohns Colitis. 2015;9:945-65

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Increased risk for lymphoma in IBD

- Not in all studies
- Early disease onset, male gender and age > 65 are risk factors
- Mainly in Crohn's disease: in 9462 immunosuppression-naïve CD-patients risk of lymphoma twice as high (all sites!)
- Patients with hematological malignancy and IBD:
  - increased mortality rate
- *Problem smaller than recent literature suggests?*

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Case 1

- Male, 38 years of age
- Crohn's disease for 14 years
- Long term thiopurine use
- Anti-TNF-alfa since 6 months
- Increasing complaints

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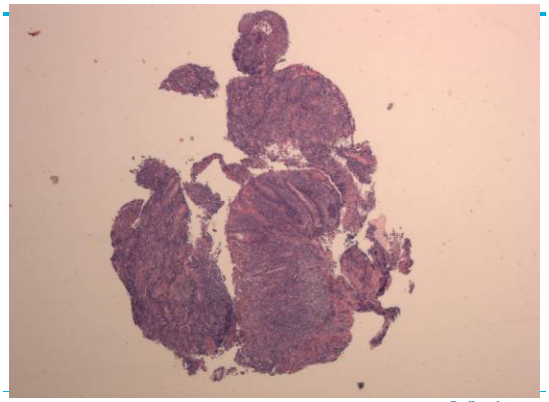

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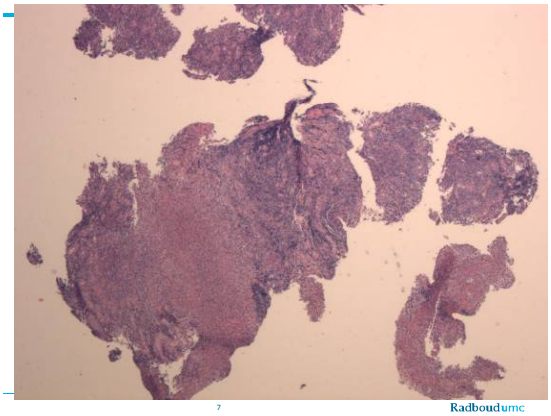

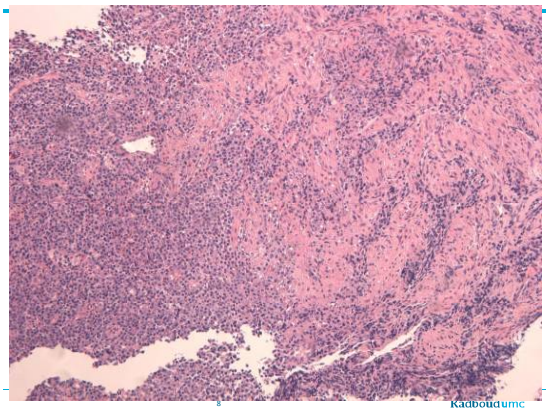

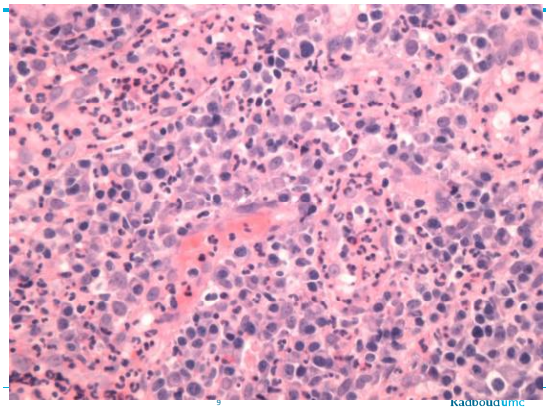

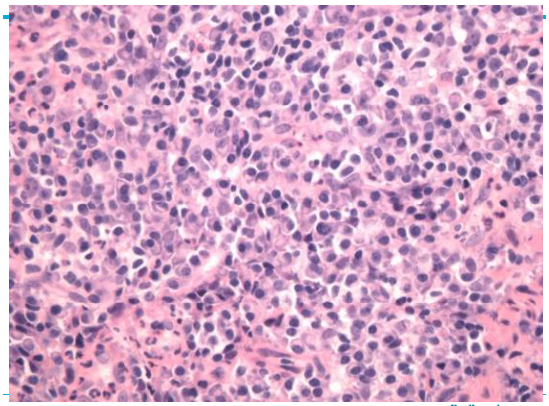

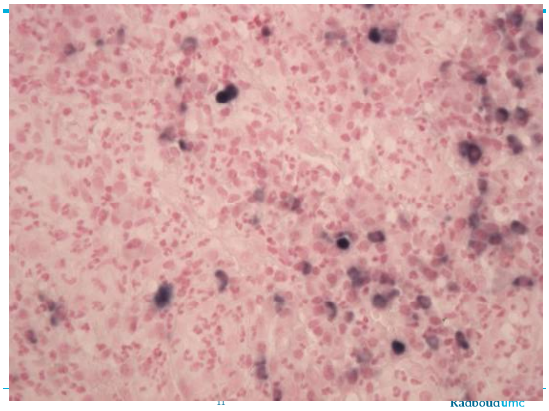

Crohn's disease and EBV

- Association with immunesupression: azthioprine aand 6-mercaptopurine
- Case reports with infliximab (anti TNF-alfa)
- Pathology:
  - Atypical infiltrate
  - B-lymphocytes some with large nucleï
  - EBER-ISH positive
  - Subclassification clinically not very relevant

IBD and EBV

- After thiopurine therapy most patients EBV-positive
- Recent studies indicate association with IBD and EBV-related lymphoproliferation
- Current immunesurpressive therapy increases the risk to 4 times

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- **ECCO Statement 5D**
  Given the risk of post-mononucleosis lymphoma, alternatives to thiopurine therapy should be considered in young male IBD patients who are EBV-seronegative [EL5]
- **ECCO Statement 5B:**
  In IBD patients treated with thiopurines, there is an excess risk of lymphoma [EL1], which can be reversed by drug withdrawal [EL3]. There is no evidence of an overall excess risk of lymphoma in IBD patients treated with anti-TNF agents alone [EL4]
- **ECCO Statement 5C:**
  Post transplant-like lymphomas caused by the reactivation of chronic latent EBV infection cannot be prevented in adult IBD patients treated with thiopurines [EL 5]

Annese et al. European Evidence-based Consensus: Inflammatory Bowel Disease and Malignancies. J Crohns Colitis. 2015;9:945-65

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EBV in IBD: The Spectrum of Intestinal LPD (Nissen et al J Crohn's Colitis, 2015:398)

- Retrospective analysis of all 58 IBD patients with EBV testing (2004-2013)
- 28 EBV positive, 30 negative
- An atypical infiltrate more frequently in EBV-positive samples
- High EBV load more often in EBV-positive patients undergoing colectomy
- Monomorphic lymphoproliferative disorders, including two overt lymphomas (both presented with perforation, one after primo-infection, the other reactivation), were present in 10 patients.

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EBV in IBD: The Spectrum of Intestinal LPD (Nissen et al J Crohn's Colitis, 2015:398)

- The two lymphoma patients (EBV-positive DLBCL) were treated according to standard protocol and are well without disease
- Reduction of immunosuppression resulted in histological normalization and loss of EBV expression in seven of eight non-lymphoma patients.

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Conclusions

- The presence of atypical infiltrate in the intestinal mucosa of IBD patients warrants EBV testing
- Reduction of immunosuppression is an effective strategy to achieve morphological normalization and loss of EBV.
- Lymphoproliferation related to IBD appears to have less aggressive clinical behaviour than PTLDs.

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Caveats

- Tertiary centre
- Biopsy in case of therapy non-responsiveness
- No routine viral testing
- No standard treatment

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EBV testing in IBD

- Morphology is a good guidance:
  - Atypical infiltrate
  - Large cells
- Low numbers of EBV-positive (small) cells irrelevant (present in >60% of IBD patients)
- Distinction between desctructive and non-destructive (like in PTLD) not feasible due to underlying disease

Other EBV-positive lesions in IBD

- 1: Juan A, Lobatón T, Tapia G, Mañosa M, Cabré E, Domènech E. Epstein-Barr virus-positive mucocutaneous ulcer in Crohn's disease. A condition to consider in immunosuppressed IBD patients. Dig Liver Dis. 2017 Mar 28. pii: S1590-8658(17)30791-0. doi: 10.1016/j.dld.2017.03.011. [Epub ahead of print] PubMed PMID: 28454852.
- 2: Xiao HJ, Li J, Song HM, Li ZH, Dong M, Zhou XG. Epstein-Barr Virus-Positive T/NK-Cell Lymphoproliferative Disorders Manifested as Gastrointestinal Perforations and Skin Lesions: A Case Report. Medicine (Baltimore). 2016 Feb;95(5):e2676. doi: 10.1097/MD.0000000000002676. Erratum in: Medicine (Baltimore). 2016 Apr;95(15):e7342. PubMed PMID: 26844502; PubMed Central PMCID: PMC4748919.

Clonality and EBV-positive LPD

- Retrospective analysis 86 patients (2000-2012)
- Divided between PTLD (n=62) and other iatrogenic (n=24)
- Treatment indvidualized
- Morphology according to original PTLD classification
  - Polymorphic/reactive
  - Monomorphic
  - Overt lymphoma classified as such
- Clonality testing according Biomed 2 standards

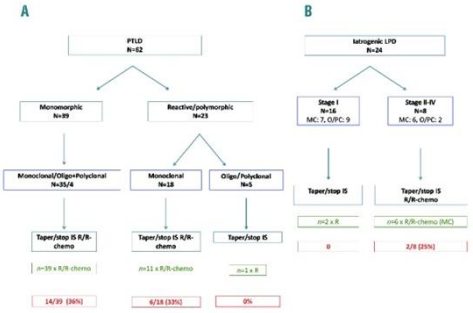
- *Identification of IG-clonality status as a pre-treatment predictor for mortality in patients with immunodeficiency-associated Epstein-Barr virus-related lymphoproliferative disorders. Van de Velde et al, Hematologica 2015;100:152-154*

Risk for mortality in EBV-positive LPD

Risk factor	EBV-LPD mortality	OR univariable (95%CI)	P univariable	OR multivariable (95%CI)	P multivariable
Age					
≥ 50 years	13/36 (36%)	2.6 (1.0-6.9)	0.08	3.6 (1.2-11)[1]	0.03
< 50 years	9/50 (18%)				
Sex					
Male	17/55 (31%)	2.3 (0.8-7.1)	0.2	–	–
Female	5/31 (16%)				
Diagnosis					
PTLD	20/62 (32%)	5.2 (1.1-24.5)	0.03	1.5 (0.3-8.7)[1]	0.6
Iatrogenic EBV-LPD	2/24 (8%)				
Stage					
II-IV	21/59 (36%)	14.4 (1.8-113.5)	0.001	13.8 (1.6-117.2)[1]	0.02
I	1/27 (4%)				
Extranodal disease					
Yes	12/46 (26%)	1.1 (0.4-2.8)	1.0	–	–
No	10/40 (25%)				
Morphology					
Monomorphic	15/45 (33%)	2.5 (0.9-6.8)	0.14	–	–
Reactive/polymorphic	7/41 (17%)				
IG clonality[2]					
Monoclonal	21/66 (32%)	8.9 (1.1-70.7)	0.02	6.6 (0.8-59.1)[1]	0.09
Oligo/polyclonal	1/20 (5%)				
EBV load at diagnosis[3]					
≥ log 3	17/45 (38%)	1.5 (0.5-4.3)	0.5		
< log 3	3/12 (25%)				

P <= 0.05 was considered statistically significant. OR: odds ratio. [1]Model with four covariates. [2]Model with three covariates. [3]Data on EBV load only present in 57 patients.

Treatment plan EBV-associated LPD



Conclusion

- Clonality predicts poor outcome better than morphology
- Oligoclonal/polyclonal processes have good outcome
- Other iatrogenic LPD have much better outcome compared to PTLD

Case 2

- Male, 36 year of age
- Long term ulcerative colitis
- Remaining complaints under prednisone en mesasoline

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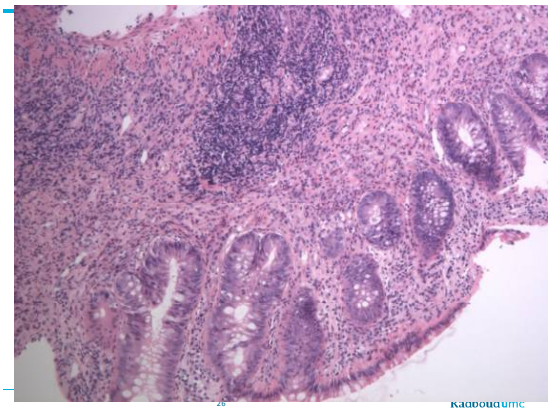

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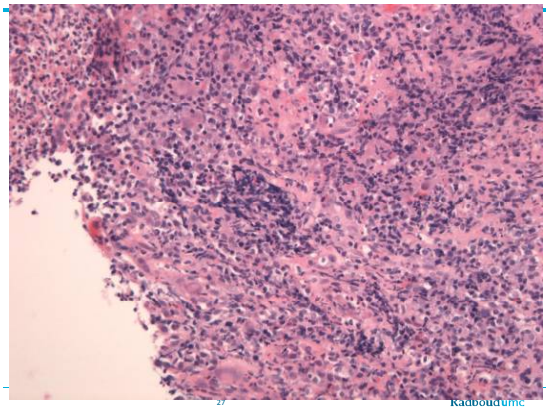

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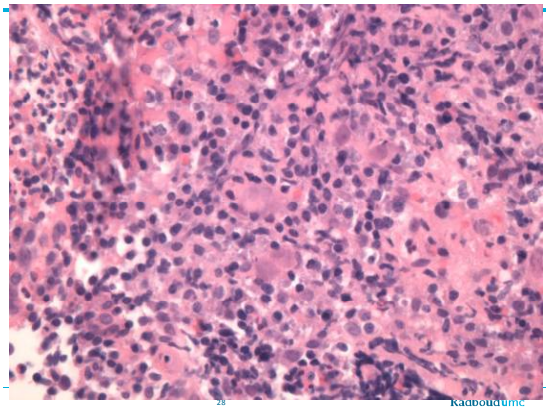

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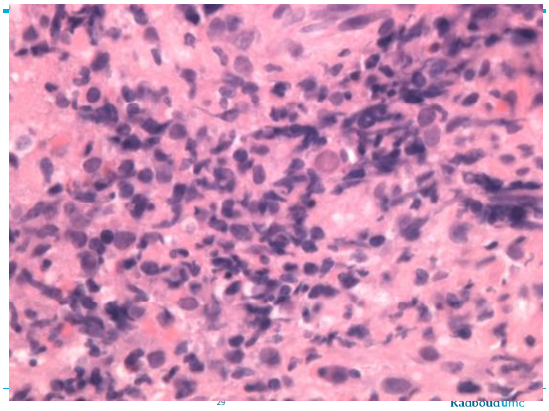

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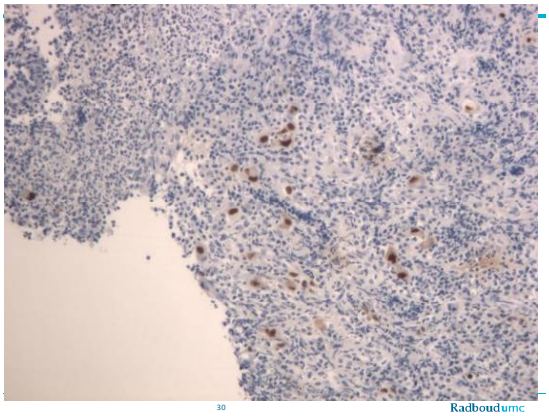

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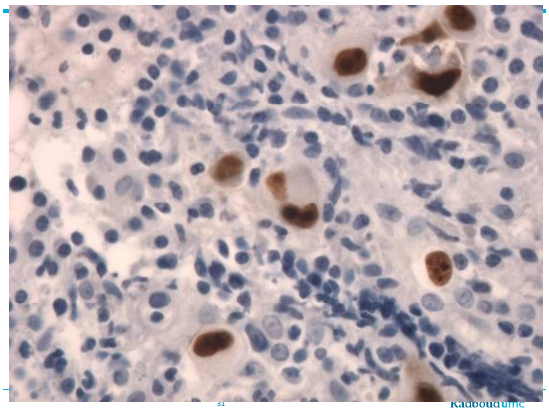

CMV and IBD

- PCR often positive but overt disease not very common
- More often in ulcerative colitis
- No association with EBV

Discussion: role of the pathologist

- How to identify viral colitis in IBD?
  - Increased risk, even in untreated patients
  - Cause or consequence?
  - Biopsies are not taken randamly, but at exacerbation that may be viral colitis
  - No reliable criteria
- When to test for viruses?
  - Based on morphology
    - Large B-cells: EBER
    - Viral incusions: CMV
- What to report?
  - Careful with analogy with PTLD
  - Descriptive rather than lymphoma
  - Indicate the possibilty of viral colitis as cause of symptoms