Cytomegalovirus reactivation in patients with inflammatory bowel disease

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CYTOMEGALOVIRUS

- Herpesviridae family
- Primary infection: mononucleosis-like syndrome
- Latent infection: viral DNA in many cells (monocytes, endothelial cells, hematopoietic progenitor cells)
- Reactivated during dysregulation of immune system
- 40-90 % of population CMV-seropositive
CMV and inflammatory bowel disease (IBD)

- Patients with IBD are at special risk, particularly those with ulcerative colitis with poor response to corticosteroids

- **Our results**: immunohistochemistry on 100 consecutive patients with IBD
  - Low incidence in IBD (5%), higher in UC (9%), highest in UC with poor response to steroids (30%)
Clinical significance of CMV in patients with inflammatory bowel disease

- Self limited disease which does not require antiviral treatment?
- Serious complications such as perforation and haemorrhage are possible.
- Antiviral therapy would be beneficial in these patients.
- Which patients must be treated with antiviral therapy?
Endoscopic/macroscopical features

- Nonspecific
- Erythema, edema, erosions, ulcers, haemorrhage
- Perforation!
- Similar features in IBD
- IBD with and without CMV cannot be distinguished endoscopically (macroscopically).
Microscopical features of CMV colitis

- Nuclear and cytoplasmic inclusions
- Owl’s eye appearance
- Rare in colon
- Smaller, without halo - atypical inclusions

Microscopical features of CMV colitis

- 9 CMV+ patients with IBD: typical inclusions in 3, atypical in 3, no inclusions in 3 patients
- Use of immunohistochemistry: greater than fivefold increase in CMV detection rate
- Always use immunohistochemistry when CMV colitis is suspected

Diagnosis of CMV colitis

• several methods, varying sensitivity and specificity
• on blood, peripheral leukocytes, body fluids → limited value in IBD
• biopsy + immunohistochemistry - golden standard
• European Crohn’s and Colitis Organisation (ECCO) recommends the use of PCR, no consensus on how to use it
• specificity of PCR: does it prove an active disease or just latent infection?
Comparison of IHC and qPCR for diagnosing CMV in IBD

• **12 patients with bowel resection:**
  - 5 patients CMV pos.
  - 5 patients CMV neg.
  - 2 patients CMV pos. in biopsy, but CMV neg. in resected specimen

• **3 samples:** ulcer base and edge, and uninvolved mucosa
Results of immunohistochemistry and qPCR for CMV in the resected bowel from patients with inflammatory bowel disease with CMV-reactivation.

<table>
<thead>
<tr>
<th>Patient No</th>
<th>Immunohistochemistry (pos. cells per mm²)</th>
<th>qPCR (viral copies per mg)</th>
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<tbody>
<tr>
<td></td>
<td>Ulcer base</td>
<td>Ulcer edge</td>
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<tr>
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Results of immunohistochemistry and qPCR for CMV in the resected bowel from patients with inflammatory bowel disease without CMV-reactivation.

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Comparison of IHC and qPCR for CMV in resected bowel

1. IHC: low density of pos. cells, highest density in samples from edge of ulcers
2. PCR: high copy numbers in samples from edge or base of ulcers
3. Normal mucosa: neg. IHC, neg. or low viral copies on PCR
CONCLUSIONS

- Incidence of CMV reactivation in patients with IBD is low (5%), but it is higher in ulcerative colitis (9%), particularly steroid-resistant (30%).
- Immunohistochemistry and qPCR can be used for diagnosing CMV in patients with IBD.
- qPCR can be used on paraffin-embedded tissue.
- The base and the edge of ulcers is optimal site for endoscopic biopsy.
CONCLUSIONS

- The number of samples is more important than the choice of diagnostic method.
- qPCR should be used as an adjunct to IHC in biopsies in which IHC is neg. or equivocal, but a strong clinical suspicion for CMV exists.
