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Histopathological features of gastrointestinal mucosal biopsy specimens in children with epidermolysis bullosa

Epidermolysis bullosa (EB) is a term used to represent a group of conditions characterized by cutaneous blistering due to abnormalities of ultrastructural components anchoring epithelial cells to either each other or to the basement membrane. There are a range of subtypes, which were traditionally classified on the basis of the level of the epidermal separation, more recently delineated on the basis of the underlying genetic defect. The vast majority of the clinical literature in these conditions is based around the cutaneous complications. There is a reported association between some subtypes of epidermolysis bullosa and pyloric stenosis, but there are no previous reports of mucosal histopathological features, despite these patients sometimes exhibiting significant gastrointestinal symptoms.

We report the gastrointestinal mucosal histopathological features in a series of patients with epidermolysis bullosa who underwent endoscopic evaluation for gastrointestinal symptoms at a single specialist centre.

Methods
Since 2003 it has been our policy to investigate all children seen in the epidermolysis bullosa clinic with significant abdominal symptoms by upper and lower gastrointestinal endoscopic examination with mucosal biopsies. During this three-year period, all cases that underwent endoscopic examination with this indication were identified. The findings at the time of endoscopy were reviewed in addition to other clinical details such as basic demographic information, symptomatology, and the specific type of EB. The histopathological specimens were reviewed by a consultant paediatric pathologist who was blinded to the endoscopic findings and clinical details regarding the type of EB. Histological features of significance were recorded and compared to the clinical information. The study was approved by the local research ethics committee.

Results
During the study period there were nine patients identified in whom endoscopic examination had been carried out and mucosal biopsies performed. Table 1 presents demographic information, clinical details and a summary of the histopathological gastrointestinal findings. The mucosal biopsy specimens showed features ranging from no histological abnormalities to moderately severe inflammatory changes, such as an increase in lamina propria inflammatory cell density, including predominant eosinophils, and focal active inflammation with neutrophils present in surface epithelium. In addition, a striking finding, noted in four of the nine cases, was an abundance of karyorrhectic cellular debris located within the lamina propria beneath the surface epithelium of the colonic biopsy specimens. All these changes were exhibited in biopsy specimens from children with recessive dystrophic EB subtype. Furthermore, in three cases, patchy granular brown pigment-containing macrophages were also identified within the lamina propria, which stained positively with Perl’s stain, indicating haemosiderin pigment deposition. In no case was morphologically apparent epidermal separation or clefting identified, and no morphological features indicating vasculitis could be seen.

Discussion
The findings of this study have documented, for the first time, the specific histological abnormalities identifiable on routine gastrointestinal mucosal biopsies in children with EB who experience gastrointestinal symptoms. The predominant pathological finding in the abnormal cases was varying degrees of inflammatory change. The mechanism of this inflammatory process in this clinical setting is uncertain, but it is possible that the abnormal epithelial cell adhesion, both to other mucosal epithelial cells and to the underlying basement membrane, may facilitate passage of antigenic molecules across the mucosal surface to stimulate an inflammatory process. Alternatively, the underlying mechanism may be an autoimmune-type process, with base membrand membrane splitting resulting in exposure of normally “hidden” antigenic components and induction of autoimmunity. Furthermore, although only present in a proportion of the cases, where identified, a most striking finding was a florid increase in the amount of colonic subepithelial lamina propria karyorrhectic debris, with or without associated haemosiderin deposition. Such a feature may occasionally be seen in other clinical settings in otherwise unremarkable colonic mucosal biopsy specimens or those with inflammatory changes, but not to the extent encountered in this scenario. It is likely that this material represents cellular debris, presumably related to increased cell turnover at the epithelial–basement membrane junctional zone; such a feature may be

Table 1: Epidermolysis bullosa (EB) subtype, clinical gastrointestinal symptoms and summarised endoscopic and positive histopathological findings in a gastrointestinal mucosal biopsy series from nine children with EB

<table>
<thead>
<tr>
<th>Case (age, sex)</th>
<th>EB type</th>
<th>Symptoms</th>
<th>Endoscopic findings</th>
<th>Histopathological findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 (14, M)</td>
<td>JEB</td>
<td>Diarrhoea, GOR, FTT</td>
<td>No villous structures seen</td>
<td>Duodenum: partial villous atrophy</td>
</tr>
<tr>
<td>2 (7, F)</td>
<td>EBS</td>
<td>FTT</td>
<td>Mild colitis</td>
<td>Colon: neutrophil polymorphs in epithelium and lamina propria. Mixed inflammatory infiltrate including eosinophils</td>
</tr>
<tr>
<td>3 (6, F)</td>
<td>RD</td>
<td>Diarrhoea/constipation, GOR</td>
<td>Gastritis</td>
<td>Colon: lamina propria debris ++</td>
</tr>
<tr>
<td>4 (7, F)</td>
<td>RD</td>
<td>Diarrhoea, GOR, FTT</td>
<td>Mild colitis</td>
<td>Colon: lamina propria debris ++</td>
</tr>
<tr>
<td>5 (7, F)</td>
<td>RD</td>
<td>Diarrhoea, GOR, FTT</td>
<td>Gastritis</td>
<td>Colon: lamina propria debris ++</td>
</tr>
<tr>
<td>6 (6, F)</td>
<td>RD</td>
<td>Diarrhoea, GOR</td>
<td>Mild pancolitis</td>
<td>Colon: increased eosinophils. Prominent lymphoid aggregates. Haemosiderin-laden macrophages</td>
</tr>
<tr>
<td>7 (6, F)</td>
<td>RD</td>
<td>Diarrhoea, abdominal pain</td>
<td>Mild pancolitis</td>
<td>Colon: chronic inactive gastritis</td>
</tr>
<tr>
<td>8 (4, F)</td>
<td>Kindlers</td>
<td>Diarrhoea</td>
<td>Mild distal colitis</td>
<td>Colon: increased eosinophils</td>
</tr>
<tr>
<td>9 (7, F)</td>
<td>RD</td>
<td>Diarrhoea, abdominal pain</td>
<td>Mild colitis</td>
<td>Colon: increased eosinophils, haemosiderin-laden macrophages</td>
</tr>
</tbody>
</table>

EBS, EB Simplex; M, male; F, female; RD, recessive dystrophic; JEB, junctional; FTT, failure to thrive; GOR, gastro-oesophageal reflux.

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References
suggesstive of the diagnosis if confirmed in larger series.

Significant gastrointestinal problems are common in EB, with most studies showing up to 50% or more of the patients being affected.1 Constipation is the most common complaint, affecting about one third of patients; this frequent clinical problem is often due to the combination of recurrent anal fissuring together with a low fibre diet and poor fluid intake. Treatment in this group largely centres on polyethylene glycol products, such as low dose Movicol (1–2 sachets a day). Gastro-oesophageal reflux is common in patients with dystrophic EB types and is the second most common gastrointestinal problem, being present in up to a third of all children with EB. Dysphagia, partly due to structuring, leads to great deal of morbidity in these children; recurrent dilatation, usually of the proximal oesophagus, is required, with most such cases of oesophageal strictures treated by balloon dilatation of the oesophagus under general anaesthesia.2

Those cases with colonic lamina propria karyorrhectic debris and inflammatory changes in their gastrointestinal biopsy specimens appear to represent a sub-group of children primarily with recessive dystrophic EB. Diarrhoea is the most prominent lower gastrointestinal problem affecting 10% of these children, causing significant morbidity. Following demonstration of histological evidence of the presence of inflammation, as provided in this series, both anti-inflammatory and immunosuppressive therapies, including sulphasalazine and slow weaning courses of prednisolone, have been used with significant subjective clinical improvement in symptoms.

We have reported the gastrointestinal mucosal biopsy findings in patients with EB, and shown that they may exhibit inflammatory changes, iron-laden macrophages and a florid increase in colonic mucosal lamina propria karyorrhectic debris, predominantly in cases of recessive dystrophic EB. The mechanism underlying these changes remains to be elucidated but we hypothesise that the defective cell adhesion in this condition results in both altered epithelial cell turnover and abnormal mucosal permeability.

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References

Urinary bladder xanthoma: a report of 2 rare cases highlighted with anti-CD68 antibody

Xanthomata are non-neoplastic, reactive tumour like processes, usually arising in response to lipid profile disturbances. They represent a localised collection of tissue histiocytes containing lipid (foamy macrophages). A Xanthomata occur more frequently in the skin, tendon, subcutaneous tissue and gastrointestinal tract, but, unlike them, urinary bladder xanthoma (UBX) appears to be a rare condition, with only 12 cases (including our two cases) reported in the Japanese and English literature.3,4 It is believed that xanthomata are reactive proliferations of histiocytes secondary to alterations in the lipid serum. Because xanthoma is one of the presentations of hyperlipidaemia, all patients, irrespective of the site, should be investigated for an underlying lipid disorder.5 However, only 50% of patients with UBX have hyperlipidaemia. Xanthoma may occur in either primary hyperlipidaemia, or secondary hyperlipidaemia, such as in diabetes mellitus. Occasionally, xanthomata occur in normolipidaemic states. Interestingly, xanthomata can occur as part of many tumour or inflammatory processes, and be related to trauma or surgery, as has been hypothesised for stomatogastric xanthoma.6 The latter was probably due to disturbances in lipid metabolism in the mucosa which might explain their development. In contrast, it has been suggested that stromal, histiocytic, endothelial or even epithelial cells may have transformed into xanthoma cells. It is interesting to note that 6 of the 12 cases (50%) were reported in the Japanese literature.

Case reports

Case 1: A 74-year-old woman was referred to the urology department with urinary frequency and incidental finding of microscopic haematuria. There were no other significant lower urinary tract symptoms. Physical examination was unremarkable and vaginal examination showed atrophic vaginitis. Urinary cytology showed no malignant cells and culture failed to grow any organisms. Ultrasound scan of the kidneys was normal. Flexible cystoscopic examination revealed a yellow patch on the dome of the bladder.

Case 2: A 53-year-old man presented with microscopic haematuria. Physical examination was unremarkable with no lymphadenopathy or organomegaly. A transurethral resection of the prostate scan and biopsies were negative.