CASE REPORT

Colonic involvement in Stevens-Johnson syndrome

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Severe gastrointestinal tract involvement is a rare manifestation of Stevens-Johnson syndrome (SJS). The case is described of a 17 year old man who developed SJS secondary to phenytoin. In addition to the cutaneous, ocular, and oral mucosal lesions typical of SJS, he also developed persistent, bloody diarrhoea associated with life threatening malnutrition. Serial colonoscopy showed severe and progressive colitis. He was treated with a combination of long term nutritional support, probiotic therapy, and supportive measures. He was eventually discharged from hospital six months after admission when the diarrhoea improved and he began to gain weight.

Stevens-Johnson syndrome (SJS) comprises a widespread, cutaneous eruption with features resembling erythema multiforme in combination with constitutional symptoms and mucosal lesions classically affecting the eyes, mouth, and genitalia.¹ In a review of 150 cases of SJS, at least two mucosal surfaces were involved in more than 80% of patients. Fever ($>38.5^{\circ}\text{C}$) was also present in more than half of patients. The most common precipitants for SJS were drugs, in particular sulphonamide antibiotics and anticonvulsants. Less common causes included infections with mycoplasma or herpes virus.²

Other than the oral mucosa, clinically manifest gastrointestinal tract involvement in SJS is rare. Oesophageal and hepatic involvement have been reported previously.³⁻⁷ Detailed case reports describing SJS involving the small intestine and colon have only been recorded on two occasions. In both instances the patients followed an aggressive clinical course culminating in a fatal outcome.^{5, 8}

CASE REPORT

A 17 year old Afro-Caribbean man presented to our hospital with a widespread desquamating maculopapular rash (arms, legs, and trunk), periorbital swelling, oral ulceration, constitutional symptoms, and watery diarrhoea. Seven weeks previously he was admitted to another hospital after an assault, sustaining a right orbital fracture complicated by orbital cellulitis and a localised soft tissue collection infected with *Streptococcus milleri*. Subsequently he had two grand mal seizures and was given phenytoin. He was discharged with a continuing prescription of phenytoin 200 mg once daily. Four weeks after starting phenytoin therapy he consulted his GP with a widespread rash, conjunctivitis, and oral ulceration. The GP suspected sensitivity to phenytoin, which was withdrawn and replaced with sodium valproate 200 mg once daily.

Two weeks later he presented to our hospital. On admission he was dehydrated, feverish (39.5°C), with a sinus tachycardia. A widespread maculopapular eruption was noted with areas of desquamation over the hands and arms with several blisters and bullae over the trunk. There was generalised facial swelling, conjunctivitis, and oral ulceration. He was noted to be tender in the epigastrium. Blood tests

showed a leucocytosis ($12 \times 10^9/\text{l}$) and eosinophilia ($0.83 \times 10^9/\text{l}$). Serum sodium was 122 mmol/l but urea, creatinine, and other electrolytes were normal. Bilirubin ($59 \mu\text{mol/l}$), alanine transaminase (122 U/l), alkaline phosphatase (483 U/l) and γ -glutamyltransferase (1655 U/l) were all raised. No specific pathogens were isolated from multiple blood and sputum cultures. Thirteen stool cultures (including *Clostridium difficile* toxin assays, *Cryptosporidium* oocysts and other ova, cysts, and parasite testing) were all negative. Mycoplasma, herpes simplex virus, hepatitis virus (A, B, C, and E), and HIV serology were all negative. Computed tomography (CT) of the head showed only mucosal thickening in the ethmoid sinus and a resolving right periorbital soft tissue swelling. CT of the chest, abdomen, and pelvis were normal.

All pre-admission drugs were stopped and empirical broad spectrum antibiotics were started by the admitting team. Three days after admission his condition remained unchanged with persistent high fever, tachycardia, and continuing watery diarrhoea. He was transferred to the high dependency unit and given intravenous hydrocortisone 100 mg four times daily and gentamicin 80 mg twice daily. Skin lesions were treated with topical emollients and twice weekly dressings. A punch biopsy was taken from the eruption on the right forearm. Histological examination showed hyperkeratosis and upper dermal perivascular and lichenoid accumulation of mononuclear cells, consistent with erythema multiforme (fig 1).

Re-epithelialisation of the skin lesions was noted at two weeks after admission but the diarrhoeal illness persisted with the passage of up to 10 loose stools daily with blood and mucus. Colonoscopy showed pale and congested mucosa throughout. Microscopically there was ulceration with non-specific inflammatory changes. Over the following month he remained in the high dependency unit with persistent fevers,

Figure 1 Skin biopsy showed hyperkeratosis and upper dermal perivascular and lichenoid accumulation of mononuclear cells. Haematoxylin and eosin stain (original magnification $\times 80$).

Figure 2 Colonoscopy showed an erythematous, friable mucosa with ulceration and mucopurulent exudates throughout the colon.

tachycardia, and systemic upset. His appetite was poor with minimal oral intake. Oesophagogastrroduodenoscopy was macroscopically normal, although some non-specific inflammatory changes were seen on duodenal biopsy. Despite nasogastric feeding he continued to lose weight (nadir 39.5 kg) and albumin fell to 14 g/l. Subsequently, total parenteral nutrition was started. Later a percutaneous endoscopic guided gastrostomy (PEG) feeding tube was sited and elemental feeding started. The patient refused prednisolone enemas.

Over the following months his skin lesions healed completely with scarring and some areas of depigmentation. The diarrhoea continued, however, with passage of up to 20 loose stools each day with blood and mucus. Colonoscopy was repeated, showing confluent, mucopurulent exudates with widespread ulceration affecting the entire colon (fig 2) and also involving the terminal ileum. Microscopic changes included severe ulceration with inflamed granulation tissue. There were no granulomata.

Over the next six months he experienced recurrent episodes of systemic sepsis with a variety of organisms including methicillin resistant *Staphylococcus aureus* and *Escherichia coli*, treated appropriately with antibiotics. In addition to PEG feeding we started a twice daily probiotic supplement (Culture Care, Lifeplan, UK). Each two gram sachet contained 1.25 billion colony forming units of *Lactobacillus casei*, *Lactococcus lactis*, *Lactobacillus acidophilus*, and *Bifido bacterium bifidus*.

Gradually the volume and frequency of diarrhoea started to reduce. His oral intake improved and he began to gain weight. He was discharged from hospital with oral nutritional supplements, overnight PEG feeding, and continuing probiotic supplementation. At outpatient review three months after discharge his bowel habit had considerably improved (two to three loose stools each day with no blood or mucus) and his weight increased to 58.7 kg. Overnight PEG feed and probiotic therapy was stopped.

DISCUSSION

We have reported the case of a 17 year old man patient with SJS secondary to phenytoin therapy. In addition to the typical

skin, ocular, and oral mucosal lesions he also experienced severe gastrointestinal symptoms associated with a progressive, inflammatory pancolitis. The histological changes were non-specific resembling the microscopic changes seen in the skin lesions. Despite resolution of the skin lesions the colonic involvement persisted and was associated with profound, life threatening malnutrition. The diarrhoea eventually improved and he started gaining weight after prolonged nutritional support and introduction of probiotic therapy.

There are too few detailed descriptions in the literature of colonic involvement in SJS to make meaningful comparison. Two detailed reports of intestinal involvement in SJS have been published since 1979.^{3,8} Both cases occurred in middle aged women and were probably precipitated by antibiotic therapy. On both occasions significant macroscopic abnormalities of the small and large bowel were apparent. Like our patient, diarrhoea was a prominent symptom, however, in both previously reported cases rapid clinical deterioration ensued and death occurred within two weeks of initial presentation. Interestingly, in both instances, small bowel and stomach involvement was noted with sparing of the oesophagus. In our patient the small bowel was involved (although the jejunum was not visualised, there were macroscopic changes in the terminal ileum and microscopic changes in the duodenum), but both the stomach and oesophagus were unaffected.

The persistent and progressive colonic changes seen in our patient are a novel description. The first colonoscopy showed a pale and congested mucosa typical of a mild colitis. The second colonoscopy performed six weeks later showed a much more severe, ulcerated mucosa with mucopurulent discharge. These macroscopic appearances mirrored the clinical manifestations of worsening bloody diarrhoea. We did consider the possibility that repeated courses of antibiotics may have contributed to, or exacerbated the colonic symptoms. However, the progressive macroscopic deterioration of the colonic mucosa seen in this case is not a feature of antibiotic associated diarrhoea. Furthermore, the appearances were not typical of pseudomembranous colitis and multiple *Clostridium difficile* toxin assays and cultures were negative rendering antibiotic associated *Clostridium difficile* infection an unlikely cause for the persistent symptoms. The patient also experienced extended periods without antibiotic therapy but without any abatement in his symptoms.

The management of SJS is largely supportive. There are no randomised, controlled trials evaluating systemic corticosteroids or other immunosuppressants. Small case series have reported favourable outcomes in patients treated with systemic corticosteroids and intravenous immunoglobulins.⁹⁻¹¹ On account of its rarity, there is no consensus opinion on the treatment of gastrointestinal involvement in SJS.

The use of probiotics in colonic disease is currently the subject of considerable interest. It has been proposed that colonic luminal bacteria develop an intimate relation with the host immune system. In some instances commensal bacteria may stimulate the host mucosal immune system resulting in an exaggerated inflammatory response. Other bacteria are proposed to favour an immunomodulatory response from the host immune system leading to reduced mucosal inflammation. In a randomised, double blind, placebo controlled trial, probiotic therapy was associated with reduced expression of pro-inflammatory cytokines and improved histological appearance of the colonic mucosa in patients with active ulcerative colitis, suggesting a possible immunomodulatory action of probiotic bacteria.¹²

The pathogenesis of SJS is probably an immune mediated process. Activated T lymphocytes are believed to stimulate apoptosis of keratinocytes through a combination of direct

cell-cell interactions (via CD95 and Fas ligand mediated signalling) and secretion of soluble factors such as perforins and pro-inflammatory cytokines such as tumour necrosis factor α (TNF α).^{11–13} It is not clear why some patients with the characteristic skin and oral mucosal lesions typical of SJS might also experience colonic inflammation. Interestingly, the colonic mucosa constitutively expresses CD95.¹⁴ Furthermore, TNF α has been implicated as a key mediator in the colonic mucosal damage seen in inflammatory bowel disease.¹⁵

One possible hypothesis for the events seen in our patient is that an immune mediated reaction analogous to the skin lesions seen in SJS also occurred within the colonic mucosa. These inflammatory changes led to damage and loss of integrity of the colonic mucosal barrier, which in turn led to increased exposure of the host immune system to luminal bacterial antigens. Furthermore, the additional damage sustained by the colonic mucosa as a consequence of the exaggerated host response may have galvanised a self perpetuating cycle of yet further antigenic exposure, increased pro-inflammatory stimulus, and further mucosal damage. Such a process would be consistent with the clinical pattern of persistent and deteriorating colonic inflammation seen in our patient when all other lesions were healing. It is tempting to speculate that the probiotic bacteria given to our patient may have repopulated the colon and instigated an immunomodulatory action on the mucosal immune response facilitating a resolution in the inflammatory cycle. Of course in isolated case reports it is impossible to be certain that particular therapeutic interventions are responsible for observed clinical responses, or whether the intervention merely coincides with the resolution of symptoms that would have occurred as part of the natural history of the disease. Further research on the use of therapeutic probiotic bacteria in colonic inflammation is warranted.

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REFERENCES

- 1 **Warrell DA**, Cox TM, Firth JD. *Oxford textbook of medicine*. Oxford: Oxford University Press, 2003:870–1.
- 2 **Auquier-Dunant A**, Mockenhaupt M, Naldi L, *et al*. Correlations between clinical patterns and causes of erythema multiforme majus, Stevens-Johnson syndrome, and toxic epidermal necrolysis: results of an international prospective study. *Arch Dermatol* 2002;**138**:1019–24.
- 3 **Lamireau T**, Leaute-Labreze C, Le Bail B, *et al*. Esophageal involvement in Stevens-Johnson syndrome. *Endoscopy* 2001;**33**:550–3.
- 4 **Heer M**, Altorfer J, Burger HR, *et al*. Bullous esophageal lesions due to cotrimoxazole: an immune-mediated process? *Gastroenterology* 1985;**88**:1954–7.
- 5 **Zweiban B**, Cohen H, Chandrasoma P. Gastrointestinal involvement complicating Stevens-Johnson syndrome. *Gastroenterology* 1986;**91**:469–74.
- 6 **Morelli MS**, O'Brien FX. Stevens-Johnson syndrome and cholestatic hepatitis. *Dig Dis Sci* 2001;**46**:2385–8.
- 7 **Srivastava M**, Perez-Atayde A, Jonas MM. Drug-associated acute-onset vanishing bile duct and Stevens-Johnson syndromes in a child. *Gastroenterology* 1998;**115**:743–6.
- 8 **Beck MH**, Portnoy B. Severe erythema multiforme complicated by fatal gastrointestinal involvement following co-trimoxazole therapy. *Clin Exp Dermatol* 1979;**4**:201–4.
- 9 **Tripathi A**, Ditto AM, Grammer LC, *et al*. Corticosteroid therapy in an additional 13 cases of Stevens-Johnson syndrome: a total series of 67 cases. *Allergy Asthma Proc* 2000;**21**:101–5.
- 10 **Metry DW**, Jung P, Levy ML. Use of intravenous immunoglobulin in children with Stevens-Johnson syndrome and toxic epidermal necrolysis: seven cases and review of the literature. *Pediatrics* 2003;**112**:1430–6.
- 11 **Viard I**, Wehli P, Bullani R, *et al*. Inhibition of toxic epidermal necrolysis by blockade of CD95 with human intravenous immunoglobulin. *Science* 1998;**282**:490–3.
- 12 **Furrie E**, Macfarlane S, Kennedy A, *et al*. Synbiotic therapy (Bifidobacterium longum/Synergy 1) initiates resolution of inflammation in patients with active ulcerative colitis: a randomised controlled pilot trial. *Gut* 2005;**54**:242–9.
- 13 **Bachot N**, Roujeau JC. Physiopathology and treatment of severe drug reactions. *Current Opinion in Allergy and Clinical Immunology* 2001;**1**:293–8.
- 14 **Moller P**, Koretz K, Leithauser F. Expression of APO-1 (CD95), a member of the NGF/TNF receptor superfamily, in normal and neoplastic colon epithelium. *Int J Cancer* 1994;**57**:371–7.
- 15 **Wang J**, Fu YX. Tumour necrosis factor family members and inflammatory bowel disease. *Immunol Rev* 2005;**204**:144–55.