Oral manifestations of Crohn's disease

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SUMMARY  In a systematic study of 100 patients with Crohn's disease, 100 with ulcerative colitis, and of 100 normal subjects matched for age, sex, and denture status, nine patients with Crohn's disease, two with ulcerative colitis, and one normal control were found to have oral lesions. In Crohn's disease, the macroscopic and histological appearances resembled those encountered elsewhere in the gastrointestinal tract and their incidence was related to the activity of the disorder. The lesions in the other two groups were different macroscopically and histologically.

Production of salivary IgA was found to be reduced in Crohn's patients with active bowel disease. It is suggested that the occurrence of oral lesions in patients with Crohn's disease might represent a local immunological reaction to oral antigens.

There have been a number of reports of 'apparently specific' oral lesions in Crohn's disease (Dudenev and Todd, 1969; Issa, 1971; Schiller, Golding, Peebles, and Whitehead, 1971; Bishop, Brewster, and Antonioli, 1972; Ellis and Truelove, 1972; Stankler, Ewen, and Kerr, 1972), which macroscopically and histologically resemble those found in the gastrointestinal tract. A retrospective analysis by Croft and Wilkinson (1972) of 332 Crohn's patients also showed that 6% of such patients had given a history of oropharyngeal ulceration. However, patients without Crohn's disease commonly suffer from recurrent 'aphthous type' ulceration, which was found by Sircus, Church, and Kelleher (1957) to have an incidence rate of 19.3% in a sample of 1783 patients attending hospital outpatient and general practitioner clinics.

Oral lesions in general are often associated with low serum iron and folate levels (Jacobs and Cavill, 1968; Dolby, 1972), findings which are common in patients with Crohn's disease (Swan, 1969; Dyer, Child, Mollin, and Dawson, 1972). It has also been suggested that immunological mechanisms could be relevant to the aetiology of mouth ulcers (Lehner, 1972). Consequently, the finding of alterations in humoral and cellular reactivity in many such patients (Kraft and Kirsner, 1971) may be relevant.

The present study was carried out to compare the incidence of oral lesions in patients with Crohn's disease with that in controls and to study their macroscopic and histological features; secondly, to study the interrelationship of mouth lesions with other manifestations of Crohn's disease; and lastly to correlate them with haematological and biochemical values and the results of salivary IgA estimations with a view to establishing their possible aetiology and pathogenesis.

Materials and Methods

One hundred patients with Crohn's disease (38 men and 62 women) were examined for the presence of oral lesions and their incidence was compared with that in two further groups, one consisting of 100 normal control subjects attending the Conservation Department of the Dental Hospital, matched for age, sex, and denture status, and the other consisting of 100 patients with ulcerative colitis (42 men and 58 women). Based on the macroscopic appearances corresponding with the previous descriptions of oral Crohn's lesions, four lesions were considered —cobblestone, ulcerative, tags, and erythema migrans. Recurrent aphthous type ulcers were not included.

A biopsy of each oral lesion was carried out under local anaesthesia. Step serial 8 μ-thick sections were prepared from paraffin-embedded specimens and stained with haematoxylin and eosin for routine histological examination, with Gram's iodine with fast green counterstain for microorganisms, with PAS to disclose Candida albicans, with Weigert's...
stain for internal elastic lamina of the blood vessels, and with the silver cyanate reaction for peripheral nerves (Rowles and Brain, 1960).

In Crohn's patients the overall incidence of oral lesions was correlated with age, sex, primary site of the disease, and the presence of perianal and skin lesions, and also with the serum levels of folate, B12, iron, albumin, and seromucoids.

Finally, in 20 patients with Crohn's disease and 20 age- and sex-matched volunteers (hospital staff and laboratory personnel), a timed sample of saliva was collected in an ice-cooled test tube from the right parotid duct under acid drop stimulation and its volume measured. The saliva was immediately centrifuged at 8000 g for 10 minutes at 4°C and a drop of 1 in 100 merthiolate in distilled water added to the supernatant before being stored at -20°C. The level of total IgA was estimated within one month by a modified Mancini single radial diffusion technique (Fahey and McKelvey, 1965) using a monospecific IgA antiserum raised in rabbits and a normal control reference serum as standard. The parotid IgA secretion rate was then calculated.

Fig 1  Cobblestone lesion on the labial gingiva above central and lateral incisor teeth of Crohn's patient.

Fig 2  Ulcerative lesion on lateral margin of the tongue of a Crohn's patient, showing linear shape, hyperplastic margins, and depth.

Fig 3  Ulcerative lesion on palate of a patient with ulcerative colitis. Compare shape, size, and margin of the ulcer with figure 2.

Fig 4  Tags on the inner side of the cheek of Crohn's patient. Tongue at lower right corner.
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Results

CLINICAL FINDINGS
An increased incidence ($p < 0.05$) of mouth lesions was found in Crohn's disease (9/100) compared with that in patients with ulcerative colitis (2/100) and controls (1/100). The ages of the nine patients with Crohn's disease ranged from 21 to 72 years and six were female. Involvement of both the small and large intestine was present in eight patients, whilst one had Crohn's colitis only: perianal disease was found in six, and one had an eczematous skin lesion.

MACROSCOPIC APPEARANCES
Four patients with Crohn's disease had areas of overt hyperplasia of the oral mucous membrane with an inflamed and deeply fissured surface, producing a cobblestone appearance (fig 1). The oral ulcers seen in three patients with Crohn's disease were deep, linear in shape, and with a nodular hyperplastic margin and clean base (fig 2). In contrast, the ulcers seen in two patients with ulcerative colitis were irregular in shape, with rolled margins, and were covered by a greyish-white slough (fig 3). The oral tags seen in one patient with Crohn's disease were fleshy and inflamed (fig 4) and quite distinct to that seen in the normal control, having the typical appearance of leukoedema. The appearance of erythema migrans in one Crohn's patient was characteristic of that condition.

HISTOLOGY
Of the nine oral lesions in Crohn's disease only one showed epithelioid cell follicles in the lamina propria and submucosa (fig 5), some with giant cells. Although lymphoid follicles were found in one other biopsy only (fig 6), the lamina propria and submucosa in all biopsies showed abnormal focal collections of lymphocytes and perivascular infiltrates of mononuclear cells. Other non-specific signs of chronic inflammation, such as neuronal hyperplasia, lymphangiectasia, and oedema of the

Fig 5  Epithelioid cell follicle in submucosa of oral mucous membrane. Cobblestone lesion from Crohn's patient ($\times 200$, H & E).

Fig 6  Secondary lymphoid follicle with germinal centre in submucosa of another cobblestone lesion from Crohn's patient ($\times 200$ H & E).
Table  Incidence of abnormal serum levels in Crohn's disease with and without oral lesions

<table>
<thead>
<tr>
<th>Oral Lesions</th>
<th>Serum Folate</th>
<th>Vitamin B₁₂</th>
<th>Iron</th>
<th>Seromucoid</th>
<th>Albumin</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>Percentage</td>
<td>Mean</td>
<td>Percentage</td>
<td>Mean</td>
</tr>
<tr>
<td>With</td>
<td>12.68 ± 1.33</td>
<td>22</td>
<td>479.55 ± 36.65</td>
<td>11</td>
<td>71.08 ± 3.58</td>
</tr>
<tr>
<td>Without</td>
<td>15.69 ± 5.78</td>
<td>16</td>
<td>413.34 ± 17.14</td>
<td>5</td>
<td>71.86 ± 13.85</td>
</tr>
</tbody>
</table>

Table Incidence of abnormal serum levels in Crohn's disease with and without oral lesions

lamina propria and submucosa, were found regularly. In addition, of particular interest was the presence of focal collections of lymphocytes within the stromal connective tissue (fig 7) and signs of acinar atrophy and duct hyperplasia in the minor salivary glands included in the biopsies.

In ulcerative colitis, the biopsies were quite distinct with the lamina propria and submucosa containing a polymorphonuclear infiltrate and a large number of eosinophils with evidence of perivascular deposition of fibrin. That from the control individual showed parakeratosis and acanthosis of the surface epithelium with slight inflammation of the superficial layers of the lamina propria typical of leukoedema (Shafer, Hine, and Levy, 1974). Finally bacteria and Candida were not seen in the histological specimens.

HAEMATOLOGY AND BIOCHEMISTRY

No significant differences were found in the mean values or in the incidence of low levels for serum folate, B₁₂, or serum iron between Crohn's patients with and without oral lesions (see table). In contrast, an increased number of patients with oral lesions had raised serum seromucoid levels and low serum albumin levels compared with the incidence in patients without oral lesions (p < 0.05) (table I).

SALIVARY IgA LEVEL

The parotid secretion rates for healthy controls and for Crohn's patients showed no significant difference. However, Crohn's patients with raised serum seromucoid and low serum albumin levels had significantly lower (p < 0.05) IgA secretion rates than patients with low serum seromucoid and high

Fig 7  Minor salivary gland from Crohn's patient. Focal lymphocytic infiltration of stromal connective tissue with acinar atrophy and duct dilatation (× 200, H & E).

Fig 8  Regression of parotid IgA secretion rate on serum seromucoid and serum albumin in Crohn's patients.
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serum albumin levels when compared with healthy controls. The parotid IgA secretion rate of patients with Crohn's disease also showed a significant regression ($p < 0.05$) when plotted against their serum seromucoid and serum albumin levels (fig 8).

Discussion

In this study, oral lesions occurred more commonly in patients with Crohn's disease compared with the situation in normal controls and patients with ulcerative colitis. The age range, sex distribution, and site of disease in Crohn's patients with oral lesions were similar to those reported in the literature (Dudeney and Todd, 1969; Issa, 1971; Schiller et al, 1971; Bishop et al, 1972; Bottomley, Giorgini, and Julienne, 1972; Stankler et al, 1972; Varley, 1972; Eisenbud, Katzka, and Platt, 1972) and to those in the total sample of Crohn's patients examined, suggesting that these factors were unimportant in influencing the incidence of mouth lesions.

In several respects the oral lesions macroscopically and histologically resembled those seen in the gastrointestinal tract in Crohn's disease suggesting that they were due to the same disease process. However, typical granulomatous-like granulomas were not seen. Such granulomas are thought to be the most useful histological sign of Crohn's disease, occurring in 60% of resected bowel specimens (Williams, 1964; Morson, 1971; Cook, 1972). The failure to find them in the biopsies of the mouth lesions may be related to the small size of the biopsy. Also the incidence of granulomas varies from tissue to tissue with only 19% occurring in rectal biopsies from patients with Crohn's disease (Dyer, Stansfeld, and Dawson, 1970).

In the absence of sarcoideal granuloma, an aggregated pattern of lymphocytic infiltration of the lamina propria and the submucosa, some lymphocytes with germinal centres, perivascular infiltration of lymphohistiocytic cells, and neuronal hyperplasia was found in the oral lesions; these features have been considered as good indicators of Crohn's disease (Morson and Dawson, 1972; Cook and Dixon, 1973). On this basis the histological features of the mouth lesions in our patients were consistent with a Crohn's lesion. Of additional interest were the findings in minor salivary glands. These were similar to changes described in autoimmunity such as Sjögren's disease, rheumatoid arthritis, and lupus erythematosus (Whaley, Williamson, Chisholm, Webb, Mason, and Buchanan, 1973), and, as far as we can ascertain, they have not been reported previously in Crohn's disease.

To explain the extraintestinal lesions of Crohn's disease, various mechanisms have been proposed. Crohn and Yarnis (1958) suggested that perianal lesions may be brought about by faecal contamination and/or by the effects of gravitation. A retrograde flow in the lymphatic channels connecting the aggregations of lymphoid tissue of the ileum and the perianal region has also been suggested (Fielding, 1972). However, such mechanisms cannot be responsible for the development of either the metstatic lesions of the skin (McCallum and Kinmont, 1968; Mountain, 1970) or of the oral lesions. In Crohn's disease low serum albumin and high serum seromucoid levels are considered good indices of disease activity (Cooke, Fowler, Cox, Gaddie, and Meynell, 1958). Hence the present finding of a significant correlation between the presence of oral lesions in Crohn's patients and low serum albumin and high serum seromucoid levels suggests that they are related to active Crohn's disease. In contrast, the lesions were not related to a deficiency of folate, B₁₂, or iron, as reflected in serum levels of these substances.

Finally, reduced secretion rates of parotid salivary IgA have been found with increasing activity of the bowel disease. This can be explained if it is postulated that in active disease a transient transepithelial block to IgA develops in the parotid glands, similar to that which has recently been demonstrated in diseased epithelium of resected bowel specimens (Green and Fox, 1973). Alternatively in active disease part of the parotid IgA could exist as polymers which would result in falsely low IgA estimates with the technique used. Finally, it could also be postulated that in patients with active disease IgA plasma cells destined for the parotid gland are diverted to the site of maximum antigenic stimulation in the bowel. As IgA is thought to be important in the defence of mucosal surfaces (Tomasi and Bienenstock, 1968), then the relative lack of IgA in the mouth of patients with active bowel disease may allow invasion of the oral mucous membrane by the food or bacterial antigens in the mouth (Ivanyi and Lehner, 1970), so producing an oral lesion.

References


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