Oral Crohn Disease

Clinical Characteristics and Long-term Follow-up of 9 Cases

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Background: Oral localization of Crohn disease is uncommon and must be differentiated from nonspecific lesions. Its natural course and its long-term prognosis are unknown.

Observations: We studied 9 patients (8 male, 1 female; age range, 7-52 years; median age, 16 years) with Crohn disease and specific oral lesions, including deep linear ulcers, pseudopolyps, and/or labial or buccal swelling and induration. The prevalence of such lesions was 0.5%. The median follow-up was 11 years. Oral localization developed before (n = 2), at the same time as (n = 2), or after (n = 5) the onset of the digestive disease. Notable associated localizations were observed in the ano-perineum (n = 8) and the esophagus (n = 3). The median duration of the oral lesions was 4 years (range, 1-13 years), without necessary parallelism with the digestive localization. Five patients had complete healing after a median delay of 2 years.

Conclusions: Oral localization of Crohn disease is characterized by a marked male predominance, a young age at onset of Crohn disease, and a very protracted course. The high prevalence of associated anal and esophageal involvement suggests that Crohn lesions have a particular trophicity for squamous cell epithelium.

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Crohn disease (CD) may involve any segment of the gastrointestinal tract, from the mouth to the anus. In the mouth, nonspecific lesions, including aphthous ulcers, lesions related to poor nutrition, and adverse effects of medication, are common. Specific oral lesions, defined by macroscopic and microscopic changes similar to those observed in the gastrointestinal tract of patients with CD, are uncommon. However, in many studies, no distinction was made between specific and nonspecific oral lesions. Thus, the characteristics of oral CD, especially in relation to digestive disease, vary from one study to another. Moreover, the evolution of their long-term course has not been described. We report 9 cases involving specific oral localization of CD and describe the clinical characteristics of specific oral CD lesions, their relationship with the gastrointestinal disease, and their long-term prognosis.

REPORT OF CASES

CASE 1

A 19-year-old man presented with a 6-month history of chronic indurated swelling of his left cheek and lower lip associated with recurrent buccal ulcerations. Oral examination revealed bilateral, painful, angular cheilitis (Figure 1) and mucosal pseudopolyps on the infiltrated cheek. The buccal mucosa and lower lip were swollen and indurated. There were deep linear ulcerations of the buccal mucosa. The patient denied any digestive symptoms. However, the anal examination disclosed 2 deep fissures and a skin tag. Endoscopic investigation revealed ulcerations of the terminal ileum. The esophagus, stomach, duodenum, and colon were normal. Histologic examination disclosed epithelioid granuloma in the lip, duodenum, and terminal ileum. Prednisolone (1 mg/kg daily) was administered systematically, resulting in complete healing. However, adhesions developed that limited the patient’s ability to open his mouth.

CASE 2

A 49-year-old man presented with a 1-year history of chronic swelling of his lower lip and right cheek associated with angular cheilitis. Incomplete remissions followed exacerbations. There was no evidence of facial palsy or digestive symptoms. A lip biopsy specimen demonstrated epithelioid granulomas. Melkersson-Rosenthal syndrome was diagnosed. One year later, the patient was referred because of mucosal discharges. Examination disclosed erythema and induration of the perianal skin, associated with a tight anal.
stenosis, and a large supra-anal diverticulum. A linear indolent ulceration of the buccal mucosa was also found. The findings of colonoscopy were normal. The oral lesions responded to intralesional treatment with triamcinolone acetonide (40 mg once a month for 3 months). Then, typical Crohn colitis developed. Despite successive therapy with sulfasalazine (3 g/d), prednisolone (1 mg/kg per day), clofazimine, and azathioprine and a diverting colostomy, the buccal lesions persisted, the perianal disease worsened, multiple fistulae developed, and a proctectomy was performed. Subsequently, the intestinal disease remained inactive, but mild induration of the upper lip persisted, with some recurrent buccal ulcerations.

CASE 3

Diarrhea and massive weight loss led to a diagnosis of diffuse jejunoileal CD in a 16-year-old boy. Five years later, small-bowel stenosis and enterocutaneous fistulas developed, leading to an extensive small-bowel resection. The patient regained 15 kg. One year later, he presented with painful edema and major induration of the lips associated with angular fissurated cheilitis, resulting in limitation of the buccal aperture. Speaking and eating were severely impaired. On examination, the whole oral cavity was involved with hyperplastic folds, cobblestoning, and multiple linear ulcerations of the buccal mucosa (Figure 2). Crohn disease of the mouth was diagnosed. As there was no concomitant intestinal involvement, topical treatment with 0.05% betamethasone dipropionate cream (applied twice a day) was initiated, without effect, but an improvement was observed with topical 5-aminosalicylate. After 1 month, the induration persisted, but the ulcerations were healed and the patient could speak and eat normally. Mild oral induration persisted unchanged for 3 years, when episodes of dysphagia developed. Endoscopy disclosed Crohn ulcerative esophagitis and a voluminous esophageal pseudopolyp. Topical 5-aminosalicylate therapy was beneficial, and the dysphagia gradually resolved. During the subsequent 13 years, the patient remained paucisymptomatic, with occasional bouts of diarrhea and abdominal pain. No buccal sequelae were observed.

RESULTS

The prevalence of oral CD in our study was 0.5%; oral CD was diagnosed in 7 of 1405 patients with CD. The characteristics of the 9 patients are summarized in the Table. Eight patients were male and 1 was female. The median age when the first symptoms developed was 15 years (range, 7-52 years). The cumulative localization of the digestive disease included the intestine (small bowel, n = 3; colon, n = 3; and both, n = 3), the anoperineum (n = 8), and the esophagus (n = 3). In the latter 3 patients, esophageal involvement was revealed by dysphagia. Oral localization of CD developed either before (n = 2), at the same time as (n = 2), or after (n = 5) the onset of symptomatic digestive CD. Linear ulcerations and thickening and edema of the buccal mucosa were the most frequent signs observed in the oral cavity (Figure 3).

PATIENTS AND METHODS

Macroscopic features of specific oral CD include indurated taglike lesions; deep linear ulcers with hyperplastic margins; and labial, buccal, or gingival swelling and induration, with a cobblestone or hyperplastic appearance of the buccal mucosa. Microscopic features include epithelioid granulomas in up to 77% of cases reported. Oral CD was diagnosed when such macroscopic features were found in patients with a previous or subsequent definite diagnosis of intestinal CD according to the criteria of Lennard-Jones. Oral lesions were considered mild when oral functional symptoms were lacking or discrete, moderate when lesions were painful but without severe impairment, and severe when eating and/or speaking was impaired. During the years 1980 to 1997, specific oral CD was diagnosed in 9 patients. Seven patients were recruited from a file of 1405 patients with CD who attended the Department of Gastroenterology at Rothschild Hospital, Paris, France, and 2 patients were seen first at the Department of Dermatology at Henri-Mondor Hospital, Creteil, France. The medical records, clinical presentation, tobacco status, and treatment of these 9 patients were reviewed retrospectively. All the patients were regularly followed up until the end of 1997.
Ulceration was lacking in only 1 patient (patient 5), who presented with a gingival localization of short duration. Adhesions occurred in 2 patients after several years of severe oral lesions, resulting in a mild limitation of the buccal opening. Histologic examination of the oral lesions disclosed epithelioid granulomas in 7 of the 8 patients who underwent a biopsy. Three patients were current smokers; 6 patients never smoked. None chewed tobacco. No parallelism could be made between the smoking status and the severity of the oral or intestinal CD.

The oral CD varied in severity, but it often showed a chronic protracted course, with occurrence of oral and/or digestive flares through years. No necessary parallelism was observed between oral and digestive CD. The evolution of intestinal CD was benign in 4 patients and severe in the other 5, requiring excisional surgery either alone (n = 1) or in association with immunosuppressive drug therapy (n = 4). Improvement of oral CD was achieved with 0.05% clobetasol propionate cream (applied twice a day) in one patient and with topical 5-aminosalicylate in another patient. Two patients improved dramatically with systemic prednisolone therapy, while 2 others were corticosteroid resistant. The latter 2 patients received azathioprine, with remission in 1. At last assessment, after an 11-year median follow-up (range, 2-24 years), oral CD lesions were persistent in 4 patients after a median 4-year duration (range, 1-13 years). Five patients were healed after a median delay of 2 years (range, 1-4 years).

**Table: Characteristics of Patients with Oral Crohn Disease (CD)**

<table>
<thead>
<tr>
<th>Patient No./Sex/Age, y*</th>
<th>Extraintestinal Locations of CD†</th>
<th>Interval Between Intestinal and Oral CD, y‡</th>
<th>Characteristics of Oral Lesions‡</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Esophagus</td>
<td>Anoperineum</td>
<td>Linear Ulcers</td>
</tr>
<tr>
<td>1/M/19</td>
<td>–</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>2/M/52</td>
<td>–2</td>
<td>NI</td>
<td>+</td>
</tr>
<tr>
<td>3/M/16</td>
<td>+6</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>4/M/15</td>
<td>–2</td>
<td>NI</td>
<td>+</td>
</tr>
<tr>
<td>5/M/40</td>
<td>+2</td>
<td>–</td>
<td>+</td>
</tr>
<tr>
<td>6/M/7</td>
<td>+8</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>7/F/11</td>
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</tr>
<tr>
<td>9/M/30</td>
<td>+4</td>
<td>–</td>
<td>+</td>
</tr>
</tbody>
</table>

*Age at development of first intestinal symptoms.
†The zeros indicate that oral and intestinal lesions developed at the same time; the numbers with a minus sign indicate the number of years that oral lesions developed after intestinal lesions; and the numbers with a plus sign indicate the number of years that oral lesions developed before intestinal lesions.
‡Minus sign indicates absent; plus sign, present; and NI, not investigated.

**Figure 3.** Patient 4. Indolent swelling of the lower lip.

**Figure 4.** Patient 9. Cobblestone appearance of the buccal mucosa.

In our series, oral CD was characterized by a very low prevalence, a marked male predominance, a young age at onset of CD, and a high prevalence of associated esophageal and anal localizations. The oral lesions had a very protracted course. As reported in other series, the oral lesions of CD were similar to those observed endoscopically in the intestine, with linear ulcerations and edema with induration, associated with a cobblestone architecture and pseudopolyps. Adhesions as sequelae that resulted in a limitation of the buccal aperture were an additional finding in 2 of our patients. Such a finding has rarely been reported in the mouth. The prevalence of oral CD is difficult to assess. Its prevalence varies from 0% to 9% in patients with CD, depending on inclusion criteria and probably on the
results of selection bias studies. Only 7 of our cases were found through a screening of a computerized registry of 1405 patients who attended a gastroenterology department in a referral center, leading to a prevalence of 0.5%. Such a prevalence can be underestimated because minor changes may have been undetected. Male predominance in patients with oral CD is well established and was confirmed in the present series. This male predominance is in contrast with the higher incidence of CD in women. Oral lesions can occur at any time during the course of the intestinal disease. They may precede the intestinal symptoms by several years. Therefore, the diagnosis of isolated oral lesions with granulomatous changes may be difficult.

Miescher cheilitis and Melkersson-Rosenthal syndrome are the principal differential diagnoses when digestive symptoms are lacking. Both entities have associated edema, induration, angular cheilitis, chronic protracted evolution, and granulomatous histologic features. Precedence on 1 cheek and facial palsy are additional characteristics of Melkersson-Rosenthal syndrome. The term orofacial granulomatosis has been proposed to include these conditions. If digestive symptoms are lacking, in our opinion the presence of recurrent, linear, deep ulcers, as opposed to common aphthous ulcerations or superficial erosions, which are occasionally encountered in Melkersson-Rosenthal syndrome, should raise a high index of suspicion for the diagnosis of CD. Moreover, pseudopolyps are not a feature of Melkersson-Rosenthal syndrome. Similarly, anal localizations whose presentation can be indolent fissures must systematically be looked for in patients with apparent isolated macrocheilitis or Melkersson-Rosenthal syndrome. However, endoscopic and radiological investigations are necessary for the diagnosis of CD. These investigations are cost-effective and are not devoid of morbidity. So the decision to perform such investigations, and their appropriate timing, must be balanced with the expected benefits for the patient. It depends mostly on the presence of clinical digestive symptoms and/or biological inflammatory signs.

Oral CD was associated with a high prevalence of anal involvement. Only one third of the patients with CD develop anal lesions. Although bipolar (exclusively oral and anal) cases of CD have been previously reported, such an association does not emerge from a review of the literature; however, information on anal involvement is lacking in many reports. The high frequency of esophageal involvement must be emphasized. Actually, symptomatic esophageal involvement is very uncommon, with a prevalence of less than 2% in CD. The high prevalence of anal and esophageal involvement associated with oral CD suggests a particular tropicity of CD lesions for squamous cell epithelium.

The pathogenesis of CD is unknown, and the role of genetic, infectious, immune, and environmental factors continues to be debated. Oral localization of CD raises more acutely the question of the role of environmental factors. Toothpaste has been proposed as a causal factor of CD, but this hypothesis was not confirmed. Smoking clearly increases the risk for CD, and worsens its course, but this hypothesis was not confirmed. Tobacco was not the cause of the oral localization.

In our series, the long-term follow-up demonstrates that the course of oral CD is very protracted, with a risk of exacerbations over the years. Nevertheless, healing was observed in 5 of our patients but with adhesions in 2 of them. Because of the spontaneous relapsing and remitting course of the disease, efficacy of therapy is difficult to assess. Indeed, oral CD shows a variable and unpredictable response to topical and systemic therapy. Two of our patients did experience some symptomatic improvement with topical therapy, either with 5-aminosalicylate or with class I corticosteroids. Similar results have been reported by others using intralesional steroid injections or topical less-potent corticosteroids. Treatment that is strictly topical may yield complete remission in up to 50% of patients. Topical treatment should be used as first-line therapy in patients with asymptomatic intestinal disease. Systemic treatment (steroids and/or azathioprine) should be considered when topical treatment fails to control symptoms.

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Reprints not available from the authors.

REFERENCES