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Lesions of the Oral Mucosa in Lymphoma Patients Receiving Cytostatic Drugs

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The 1-year incidence of oral mucosal lesions during cytostatic therapy was investigated in 67 patients [34 men and 33 women (mean age 49 years)] out of 79 original patients, being treated for non-Hodgkin lymphoma or Hodgkin's disease. The incidence of lesions during examinations was 43.4%. Recurrent lesions were observed in 19.4% of cases. Mean leukocyte counts were statistically significantly lower ($P < 0.01$) during lesion periods than before cytostatic therapy in all lesion groups. Leukocytopenia was found in 85.4% of patients with hairy leukoplakia-like lesions (HLL), and in 81.8% of the patients with angular cheilitis. 5 out of 14 patients with oral ulcers (35.7%) had episodes of septicaemia. Mean thrombocyte counts of patients in various lesion groups were normal (<140 × 10/l). However, low thrombocyte counts were more statistically significant ($P < 0.05$), when haemorrhages or HLL were present. Clinical candidiasis was diagnosed in 28.4% of patients during the treatment. However, cultivation revealed that 62.3% of salivary yeast cultures were positive. The study reported here shows a correlation between mucosal ulcers and septicemia, and between leukocytopenia, angular cheilitis and HLL. The disparity between clinically diagnosed candidiasis and the occurrence of salivary yeast counts suggests that antifungal drugs might be of prophylactic value during cytostatic therapy.
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INTRODUCTION

AN ASSOCIATION between ulcerative oral mucosal lesions and cytostatic therapy in patients with malignancies is well established [1–5]. Cytostatic drugs can cause atrophy of oral mucosa, which is sensitive to trauma [3, 5]. Injury to oral mucosa allows invasion by micro-organisms [6, 7]. Infection is the main cause of death during chemotherapy [1, 8, 9]. Broad-spectrum antibiotic treatment and immunosuppression can lead to fungal infections [10, 11]. In immunosuppression, oral mucosal lesions are similar, whether caused by chemotherapy or by a virus, such as HIV. There are differences in side-effects between cytostatic drugs as far as the oral mucosa is concerned but there is no drug-related site of lesion predilection. Recurrence of lesions in association with anticancer therapy cannot be predicted.

Leukocytopenia and thrombocytopenia are characteristic side-effects of cytostatic drugs [12]. Blood-cell counts reflect the immune status of patients. A correlation between thrombocytopenia and haemorrhages has been described [3, 13]. Risk of infection is high if there is leukocytopenia.

This paper describes a study of oral mucosal changes in lymphoma patients during cytostatic therapy. Oral mucosal lesions were related to patients' leukocyte and thrombocyte values, and to occurrence of candidiasis.

PATIENTS AND METHODS

Patients and inclusion criteria

79 consecutive patients [40 men and 39 women (mean age 47 years, range 19–81)], treated in the Department of Radiotherapy and Oncology of Helsinki University Central Hospital, Finland, between 1987 and 1989, were enrolled in a 1-year study. 63 patients had non-Hodgkin lymphoma and 16 patients had Hodgkin's disease.

Combination chemotherapy was given with curative intent. Patient life-expectancy was at least 1 year. Karnofsky performance status was 60 or more [14]. The patients were given no medication other than chemotherapy for their malignancy. Table 1 shows the characteristics of the 79 patients. Numbers of patients during consecutive examinations are shown in Fig. 1. 67 patients were examined during cytostatic treatment. 51 of the patients completed the 1-year study. 8 of the original

Table 1. Patients' characteristics

	Patients examined and followed-up ($n = 67$)	Drop-outs ($n = 12$)
Mean age (years)	49.3	50.6
Range (years)	81.0–22.5	19.9–63.2
Sex (M/F)	34/33	6/6
Non-Hodgkin lymphoma (n)	53	10
Hodgkin's disease (n)	14	2
History of smoking (%)	21.5	13.3

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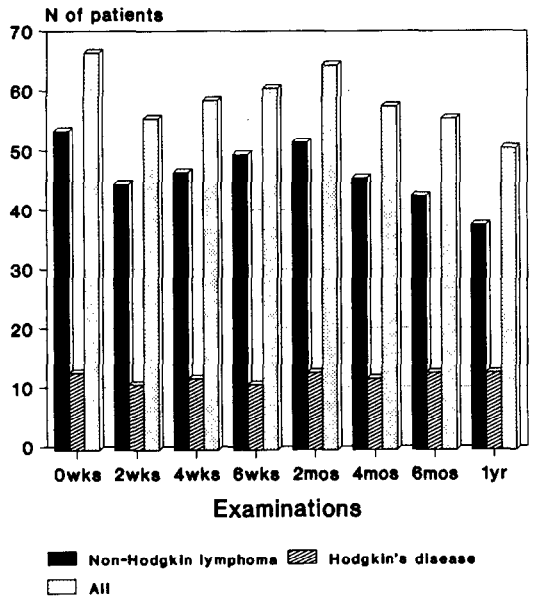

Fig. 1. Times of examinations and numbers of 67 patients during examinations before and during cytostatic therapy and at the 1-year follow-up.

79 patients refused to take part and 4 others moved away. 3 patients dropped out after radiotherapy of the head.

During the initial appointment each patient was informed in detail about the study. The Declaration of Helsinki in its revised form was followed throughout the study [15]. The consent form had been approved by the Ethical Committee of the Hospital.

Cancer chemotherapy

The patients received combinations of doxorubicin–bleomycin–velbedacarbazine (ABVD) or mustine–oncovine–procarbazine–prednisone (MOPP)–ABV hybrid chemotherapy for Hodgkin's disease. For non-Hodgkin lymphoma, combinations of methotrexate–bleomycin–doxorubicin–epiadriamycin–cyclophosphamide–oncovin–dexamethasone (M-BACOD or M-BECOD) were given. MOPPABV was given at intervals of 1 month for 6 months, ABVD at intervals of 2 weeks for 6 months and M-BACOD or M-BECOD for 3-week intervals for 7 months.

Clinical observations

Patients' orodental status was recorded by the same oral surgeon (P.L.) in a normally equipped dental surgery at the hospital. Baseline status was recorded before chemotherapy. Figure 1 shows the sequence of follow-up examinations. During the first visit a panoramic tomograph was taken and the oral mucosa was photographed. During subsequent examinations, any mucosal changes detected were photographed. Oral mucosal lesions such as ulcers, vesicles, haemorrhages, candidiasis, angular cheilitis and hairy leukoplakia-like lesions (HLL) were diagnosed on the basis of generally accepted criteria [16–18]. Bleeding of the gingiva was recorded by means of the Gingival Bleeding Index (GBI) [19]. Periodontal records have been described in another publication [20].

Patients' diary

Patients were asked to keep diaries on their oral health and symptoms.

Salivary sampling and yeast counts

Paraffin-stimulated whole saliva was collected for salivary flow rate measurements. 0.5 ml of saliva were applied on agar dipslides and salivary yeasts were cultivated by incubating saliva on modified Nicherson-agar (Oricult-N™, Orion Diagnostica) at 37°C for 2 days. Growth of yeasts on the agar was graded using the Budtz-Jörgensen classification: 0 = no growth; 1 = 1–20 colonies. 2 = 21–50 colonies and 3 = >50 colonies [21].

Other laboratory tests

Blood samples were taken for blood cell counting in accordance with the treatment protocol by the Department of Radiotherapy and Oncology. Samples were also tested for the presence of HIV antibodies by enzyme-linked immunosorbent assay (ELISA).

Statistical methods

To determine the significances of differences, two-tailed Student's *t*-tests and Mann–Whitney non-parametric U-tests for unpaired samples were used. Differences between disease groups and the sexes were tested using the χ^2-test. Differences were considered statistically significant if P was <0.05.

RESULTS

All patients were HIV-seronegative. 4 patients (6.0%) exhibited no mucosal alterations during cytostatic therapy. Oral mucosal changes were found during 152 of 362 examinations (43.4%) during cytostatic treatment. Recurrent changes were observed in 19.4% of examinations. 26 out of 63 patients (41.3%) had only one lesion, 22 patients (34.9%) had two lesions, and 13 patients (20.6%) had three lesions. 2 patients had four mucosal lesions. Figure 2 shows the existence of the lesions before, during and after cytostatic therapy. The locations of lesions in the oral cavity are shown in Fig. 3. There were a total of 48 haemorrhages, 18 (37.5%) of which were present at the border of the soft and hard palates. Haemorrhages were found in 8 patients (11.9%) before cytostatic therapy and in 2 patients (3.9%) after the therapy.

Other mucosal changes found were leukoedema of the buccal mucosa (3 cases), lingua geographica (2 cases) and a

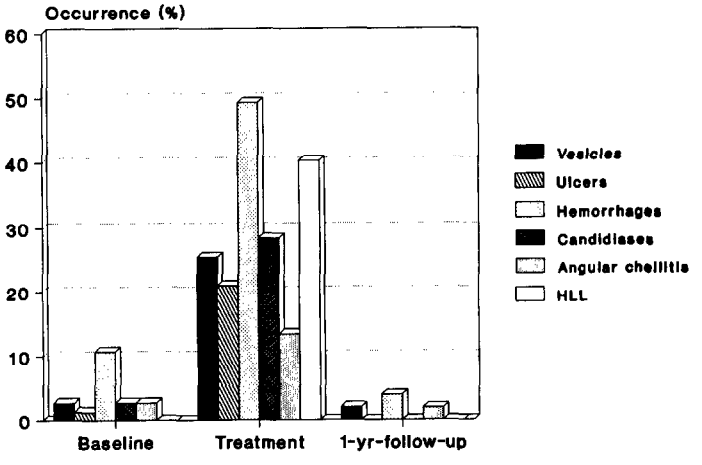

Fig. 2. Incidence of oral mucosal lesions in lymphoma patients before and during chemotherapy and 1 year after treatment had started. The incidence of lesions was markedly higher during the initial visit than during the 1-year follow-up visit.

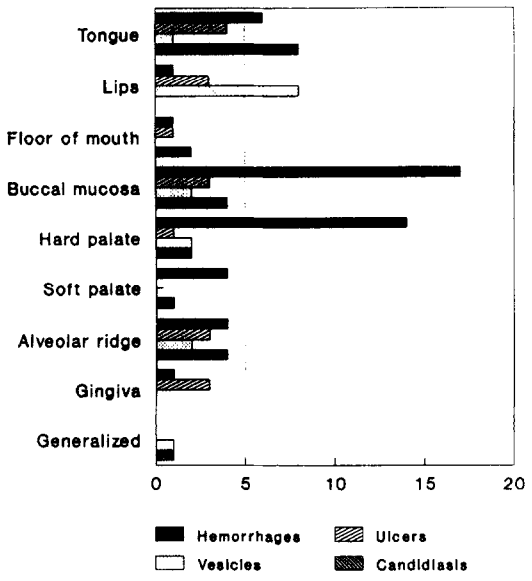

Fig. 3. Numbers of cases with haemorrhages, vesicles, ulcers and clinically detected candidiasis at different sites of the oral cavity in lymphoma patients during chemotherapy.

lichen-like lesion (1 case). Pigmentation of the gingiva was seen once, 6 weeks after initiation of cytostatic therapy. Acute pericoronal infections of partially erupted third mandibular molars were recorded twice.

Table 2 summarises the characteristics of the oral lesions seen in the patients during cytostatic therapy. Leukocyte counts were statistically significantly lower ($P<0.05$) when mucosal lesions were present than before treatment. During the occurrence of lesions, in most cases (95.0%) thrombocyte counts exceeded the normal value (140×10^9/l). Thrombocytopenia was seen only once, when candidiasis, HLL or angular cheilitis was present. When haemorrhages and vesicles were present, 3 and 2 patients, respectively, were thrombocytopenic. All patients with ulcers had thrombocyte counts over 140×10^9/l. In patients with HLL ($P=0.04$) or haemorrhages ($P=0.03$) statistically significantly lower thrombocyte values were found than before cytostatic therapy.

A clear association between oral ulcers and episodes of septicaemia was detected (Table 2). 5 patients (35.7%) had a superinfection concomitantly with ulcers. It was found that 47.4% of patients with ulcers were leukocytopenic. The incidence of fever varied between 5.9% and 14.8% when mucosal lesions other than ulcers were present.

In 3 patients, candidiasis was seen for 2 weeks and in 1 patient for 2 months. In 1 patient it was found 2 weeks and 6 months after cytostatic therapy began. Ketoconazole was given to 2 patients. 6 patients were treated topically, with amphotericin B. Salivary yeast counts were positive in 49.3% of cultures before and in 62.3% of cultures during cytostatic therapy. More than 20 colonies were observed in 35.8% of the cultures.

Neither chemotherapy nor the appearance of oral mucosal lesions had any effect on salivary flow rate (Table 2).

According to the patients' diaries, the commonest symptom was vesicles on the lips, 6 cases (9.0%). When cytostatics were started, smarting pains in the gingiva and on the tongue were reported in 4 cases (6.0%) Ulcers were also reported in 6.0% of cases. Only 1 patient mentioned hypersensitivity of the teeth.

DISCUSSION

An association between thrombocytopenia, haemorrhages and chemotherapy has previously been demonstrated by Dreizen *et al.* [12], and by Wahlin and Mattson [3]. Hypofibrinogenemia, circulating anticoagulants, fibrinolytic activity, disseminated intravascular coagulation and vitamin K deficiency have been suggested to be the additional reasons for haemorrhages [3, 13]. In the study reported here, most patients had thrombocyte counts over 140×10^9/l when oral

Table 2. Characteristics of oral mucosal lesions in lymphoma patients during chemotherapy

Oral mucosal lesions	Patients (*n*)			Diseases (*n*)		Smokers	Salivary flow rate	Periods of lesion (*n*)			Recurrent lesions
	T	M	F	nH	H	%	(ml/min)	T	M	F	(%)
Haemorrhages	33	18	15	25	8	21.2	1.7±0.9	48	29	19	45.5
Ulcers	14	10	4	12	2	20.0	1.3±0.6	18	13	5	28.6
Vesicles	16	10	6	14	2	16.7	1.5±0.8	16	10	6	0
Candidiasis	19	7	12	16	3	27.8	1.4±0.7	22	7	15	27.8
HLL	27	12	15	22	5	25.9	1.3±0.7	41	21	20	37.0
Cheilitis	9	5	4	7	2	36.4	1.5±0.6	12	6	6	22.2

Oral mucosal lesions	Occurrence of fever (%)*	Time elapse (days)†	Leukocytopenia (%)	Leukocyte count (mean±S.D.) (10^9/l)	Thrombocyte count (mean±S.D.) (10^9/l)
Haemorrhages	12.1	16±21	64.3	4.1±3.1	272±89
Ulcers	35.7	10±10	47.4	4.7±2.7	283±118
Vesicles	5.9	14±29	68.8	3.5±3.3	296±130
Candidiasis	9.1	16±29	63.6	4.6±3.4	297±81
HLL	14.8	10±14	85.4	2.5±1.4	271±106
Cheilitis	11.1	12±16	81.8	2.7±1.4	294±107

T = total; M = male; F = female; H = Hodgkin's disease; nH = non-Hodgkin lymphoma; HLL = hairy leukoplakia like-lesion;
* Indicates frequency of septicaemia periods during occurence of oral lesions; † Time elapse since last cytostatic treatment.

lesions were present. In only 3 cases were low values associated with haemorrhages. On the other hand, individual thrombocyte values were statistically significantly lower during the occurrence of haemorrhages than before chemotherapy. In our study, haemorrhages were found in 49.3% of patients. Haemorrhages have previously been reported in 12–87% of leukaemic patients [3]. We found the incidence of haemorrhages in patients with Hodgkin's disease to be greater than that in patients with non-Hodgkin lymphoma ($P<0.05$). The results of our study support the hypothesis that factors other than thrombocytopenia may be involved in haemorrhages. The low incidence of thrombocytopenia when haemorrhages were present in our patients may reflect the significance of the malignancies themselves and of treatment methods as causes of bleeding.

Haemorrhages were most often found at the border of the hard and soft palates. Heat caused by smoking or trauma can damage atrophic mucosa of the palate resulting from administration of cytostatics. Smokers accounted for 27.8% of those experiencing candidiasis and 36.4% of those suffering angular cheilitis in our study (Table 2). However, only 2 out of 14 patients with haemorrhages on their hard palates smoked during chemotherapy. On the other hand, Kaposi's sarcoma in AIDS patients has been shown to overlay the blood vessels in the posterior hard and anterior soft palates [22]. The same characteristic palatal site for haemorrhages and Kaposi's sarcoma in two different immunocompromised patient groups draws attention to the role of major palatal vessels in lesions. It also casts doubt on correctness of diagnoses of Kaposi's sarcoma when these are not based on biopsy findings.

Leukocytopenia is well known in immunocompromised patients during chemotherapy. Oral mucosal lesions have been regarded as possible routes of infection leading to septicaemia. Ulcers were found in 20.9% of patients in this study during cytostatic therapy. The mean leukocyte count was highest when ulcers were observed. Leukocyte counts in patients with ulcers were, however, statistically significantly lower than leukocyte counts before chemotherapy. The oral ulcers in such patients might have been caused by cytomegalo virus infection, as recently shown in HIV-infected patients [23]. Our findings thus emphasise the patients' capacity to respond to superinfection, although the administration of cytotoxic drugs compromised bone marrow function. The high incidence of leukocytopenia and the lower incidence of infection in patients with angular cheilitis or HLL than in those with ulcers emphasise the role damaged mucosa can play, as a port of entry for infection. Our finding also shows that the correlation between oral lesions, leukocyte counts and infection in patients during cytostatic therapy is complex.

Fungal infection is common and serious in immunocompromised patients. The mortality caused by candidaemia has been reported to be 52% [11]. The pathogenicity of *Candida albicans* and other yeast species is low. Infection needs local or systemic predisposing factors [9]. The high number of positive salivary yeast cultures (61.2%) in our patients during chemotherapy raises the question of whether antifungal medication should not be used prophylactically. However, the mere presence of the organism in the oral cavity is not enough to allow diagnosis of a candida infection. In 54% of candidaemia cases no port of entry of infection has been found [10]. The high number of salivary yeasts in the absence of clinical symptoms in the oral cavity demonstrates the difficulty of finding reasons for superinfection in patients on cytostatic therapy.

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