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Occurrence of Corrugated White Patch Lesions on Lateral Border of Tongue in Lymphoma Patients during Cytostatic Treatment

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The question of whether or not there was an association between immunosuppression and occurrence of corrugated white patch lesions on the lateral border of the tongue was studied in 79 patients being treated for non-Hodgkin lymphoma or Hodgkin's disease. The mouths of 55 patients (mean age 47.8 years, 34 males, 21 females) were examined during periods of chemotherapy. All patients were HIV-seronegative. White non-removable lesions on the lateral margins of the tongue were noted in 27 patients (42.8%) 74 days after commencement of chemotherapy and 10 days after termination of medication. In 12 cases (44.4%) the lesions were bilateral. Epstein–Barr virus (EBV) DNA was found by gene amplification using polymerase chain reaction (PCR) in one of the two biopsy samples taken. No white lesion on the lateral border of tongue had been seen in any patient before treatment, nor were any evident 1 year after treatment. Leucocyte counts were significantly ($P=0.001$) lower when the lesion was present than when it was not detected. Before chemotherapy, 70.4% of patients with lesions and 47.6% of patients without lesions had positive salivary yeast cultures. Yeasts could be cultued from the saliva of 80.5% of patients when the lesions were present. In 2 patients clinical oral candidiasis was diagnosed at the time of the lesion. The study revealed a correlation between the occurrence of corrugated white, non-removable lesions of the lateral borders of the tongue, high salivary yeast counts and leucocytopenia. Clinical diagnosis of the lesion was consistent with oral hairy leukoplakia (OHL) or pseudo oral hairy leukoplakia (pseudo OHL), but histological studies are needed to confirm the diagnosis of the lesion. However, the lesion may be an early clinical sign of immunosuppression.

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INTRODUCTION

ORAL HAIRY LEUKOPLAKIA (OHL) was originally noted in cases of human immunodeficiency virus (HIV) infection [1–3]. OHL has also been observed in non-HIV-infected, immunocompromised transplant recipients [4–8] and furthermore, the lesion has been described in relation to tongues that appear normal [9]. Recently, OHL has been regarded as a sign of general immunosuppression rather than immunosuppression associated with HIV infection. Patients with malignancies receiving chemotherapy suffer immunosuppression caused by the tumour and therapy.

OHL has well-defined morphological features. Demonstration of the presence of the Epstein–Barr virus (EBV) by an *in situ* hybridisation technique has been regarded essential for the diagnosis of OHL [9–11]. Pseudo OHL resembles clinically and histologically OHL but no EBV DNA can be demonstrated in the epithelial cells [9, 12, 13]. The similar clinical appearance of other white lesions in the mouth, such as frictional keratosis, leukoplakia associated with smoking, mucosal alterations seen in hyperplastic candidiasis or in oral graft vs. host disease (GVHD), complicate accurate diagnosis [5, 8]. The prevalences of OHL and pseudo OHL in patients suffering from iatrogenic immunosuppression has not yet been systematically studied.

Candida infection is present in about 50% of OHL cases [8, 10]. Oral candidiasis is also common in immunocompromised patients who have been given broad spectrum antibiotics. The occurrence of candidiasis reflects immunodeficiency and increased risk of infection during chemotherapy [14, 15].

This study reports the prevalence of corrugated white patch lesions on the lateral border of the tongue in patients suffering from Hodgkin's disease or non-Hodgkin lymphoma and who were receiving cytostatic drugs. The patients were examined before, during and after immunosuppressive treatment.

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MATERIALS AND METHODS

Patients

63 consecutive patients with non-Hodgkin lymphoma and 16 consecutive patients with Hodgkin's disease admitted to the Department of Radiotherapy and Oncology of Helsinki University Central Hospital, Finland, between 1987 and 1989 were enrolled into the study. Each patient was followed-up for 1 year. Combination chemotherapy was given with curative intent. The life expectancy of each patient was at least 1 year. The patients received no medication other than chemotherapy for their malignancy. While receiving cytostatic medication, 1 patient died, 3 became too ill to participate in the study, 4 moved away, 13 refused to participate, and 3 received radiotherapy and were therefore excluded. Table 1 shows the characteristics of the remaining 55 patients. Table 2 gives the details of the 63 patients with non-Hodgkin lymphoma.

The principles of the Declaration of Helsinki in its revised form were observed throughout the study [16]. The consent form had been approved by the Ethical Committee of the department.

Cancer chemotherapy

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

Clinical observations

The orodental status of each patient was recorded by the author in a normally equipped dental surgery at the hospital. Status before chemotherapy was recorded (baseline status). Each patient was examined 2, 4 and 6 weeks, and 2, 4, 6 and 12 months after the study began. During the initial visit the oral mucosa was photographed. During subsequent visits any mucosal changes were photographed.

Diagnosis of oral mucosal lesions took place in accordance with generally accepted criteria [17–19]. All participants were questioned about their smoking habits and alcohol consumption.

Salivary yeast counts

Salivary yeasts were studied by incubating samples of saliva on modified Nickerson agar (Oricult-NTM, Orion Diagnostica) at 37°C for 2 days. Growth of yeasts was graded using the Budtz-Jörgensen classification (0 = no growth; 1 = 1–20 colonies, 2 = 21–50 colonies and 3 = > 50 colonies [20]).

Biopsies

For ethical reasons, only two biopsy specimens could be taken from the lesions observed on the lateral border of the tongue. Biopsy specimens were stained with haematoxylin and eosin and examined by routine light microscopy. To detect the presence of the EBV, *in situ* hybridisation [21] and polymerase chain reaction (PCR) [22] techniques were used.

Other laboratory tests

Blood samples were taken for blood cell counting in accordance with the treatment protocol. Samples were tested using enzyme-linked immunosorbent assay (ELISA) for the presence of HIV antibodies. IgG and IgM antibodies against

Table 1. Patients' characteristics

	Patients followed-up (55)	Drop-outs (24)
Mean age (years)	47.8	51.9
Range (years)	(22.5–81.7)	(19.1–69.0)
Sex (M/F)	34/21	6/18
Hodgkin's disease	13	3
Non-Hodgkin lymphoma	42	21
History of smoking (%)	29.1	34.8

Table 2. B/T cell grouping of 63 patients with non-Hodgkin lymphoma enrolled into the study

Subgroups of non-Hodgkin lymphoma	Patients with non-Hodgkin lymphoma (63)			Patients with non-Hodgkin lymphoma who exhibited a lesion during chemotherapy (22)		
	M	F	T	M	F	T
B-cell lymphoma	27	27	54	7	11	18
T-cell lymphoma	1	4	5	1	2	3
B/T cell lymphoma		2	2			
Non B/T cell lymphoma	1		1	1		1
Undiagnosed		1	1			
Totals	29	34	63	9	13	22

the VC antigen of EBV were measured using an immunofluoresence technique (Gull Laboratories, Salt Lake City, U.S.A.).

Statistical analyses

Two-tailed Student's *t*-tests and Mann-Whitney nonparametric U-tests for unpaired samples were used to evaluate the significance of differences. The significance of differences between the sexes were assessed by means of the χ^2 tests. Differences were considered statistically significant if P was <0.05.

RESULTS

Chemotherapy lasted for 4.8 months, on average (range 1.3–7.1 months). Asymptomatic white plaques on the side of the tongue were observed in 27 of the 55 patients. In 12 cases (44.4%) there were lesions on both sides of the tongue. 22 of the 27 patients concerned were suffering from non-Hodgkin lymphoma, 5 from Hodgkin's disease. No differences in the appearance of the lesions between the two groups were observed. The lesion was significantly more common in women than in men ($P=0.025$). In 17 patients the lesion was observed during only one examination. 2 patients had the lesion with subsequent regression twice. In 8 patients, the lesion persisted for 1.8 months on average (range 0.7–4.7 months). No lesions were noted before treatment, or during the 1-year follow-up examination.

Lesions were found in 51.4% and 60.0% of patients who received M-BACOD and M-BECOD therapies, respectively. During MOPP–ABV-hybrid chemotherapy, 50.0% exhibited the lesion. The condition was seen in only 1 patient on ABVD therapy. Lesions lasted on average for 9.7 days ($\pm$13.8 days) after chemotherapy ceased and for 74.2$\pm$57.0 days after initiation of chemotherapy.

Yeasts were cultured from 70.4% of the salivary samples taken during the initial visit from patients who developed the lesion and from 47.6% of the salivary samples taken from patients who exhibited no lesion during chemotherapy. When the lesion was present, yeasts were cultured from 80.5% of the salivary samples of the patients. In 56.1% of patients, the mean yeast colony count was higher when the lesion was present than when it was not. Clinically oral candidiasis was found in 7 patients (25.9%) who had the lesion. A candida infection on the buccal mucosa and one on the dorsal surface of the tongue was obtained concomitantly with the lesion. Ketoconazole was given to 2 patients. 1 patient was treated topically with amphotericin B. No lesion on the sides of the tongue was diagnosed after antifungal treatment. 2 patients had angular cheilitis when the lesion was present.

The sera of patients were negative for HIV. EBV IgG antibodies were found in all serum samples taken during the initial visit. There were no IgM antibodies against EBV.

At the time of the lesion 85.4% of patients were leucocytopenic. The lowest leucocyte counts (mean 2.48, S.D.$\pm$1.37 E9/l) when the lesion was present were statistically significantly different ($P=0.001$) from baseline counts and counts at the end of follow-up (Fig. 1). Platelet counts were below normal ($<$140 E9/l) in 1 patient when the lesion was present. Despite the leucocytopenia, only 4 patients (14.8%) were suffering from an infection when the lesion was diagnosed. 3 other patients had a slight fever ($t_{ax}<38.5$°C).

A biopsy specimen from one lesion of a patient with bilateral lesions diagnosed at 4.7 months exhibited histological characteristics of HL but no infection (Fig. 2a–c). *In situ* hybridisation did not reveal EBV DNA. However, EBV DNA was detected using the PCR technique. The histology of a biopsy specimen taken from another patient was normal except for hyperkeratosis.

DISCUSSION

In the study reported here, the prevalence of corrugated white patch lesions on the lateral border of the tongue was investigated in immunocompromised patients with lymphoma. Clinically, the lesions were similar to OHL or pseudo OHL. Because only two biopsy specimens were obtained, histological studies were limited, and evidence of the presence of EBV DNA is also minimal. 2 linqua geographica cases and 1 lichen-like lesion were the other white lesions found on tongues.

The lesions on the lateral sides of the tongue were commoner in women than in men, possibly because more of the women (53%) than the men (33%) who had the lesion were smokers. On the other hand, women (4 cigarettes per day) smoked less than men (12 cigarettes per day) during chemotherapy and no tobacco-related oral leukoplakia was found at the initial visit. *Candida albicans* has been considered as a predisposing factor for mucosal membrane keratosis [23] and Bastiaan and Reade [24] reported the prevalence of *C. albicans* to be greater in women than in men. 96% of salivary yeast cutures of women and 61% of cutures of men were positive, when the lesion was found. This agrees with the report of Bastiaan and Reade [24] and may partly explain the higher prevalence of the lesion in women than in men and may indicate an association of the white patch lesion to hyperplastic candidiasis.

Infection is the main cause of death in patients whose immune defences have been impaired by chemotherapy [25, 26]. A wide-spectrum antibiotic combination was given to 12 of the 27 patients with the lesion. In spite of high salivary yeast counts, whitish yellow, creamy candida colonies were found

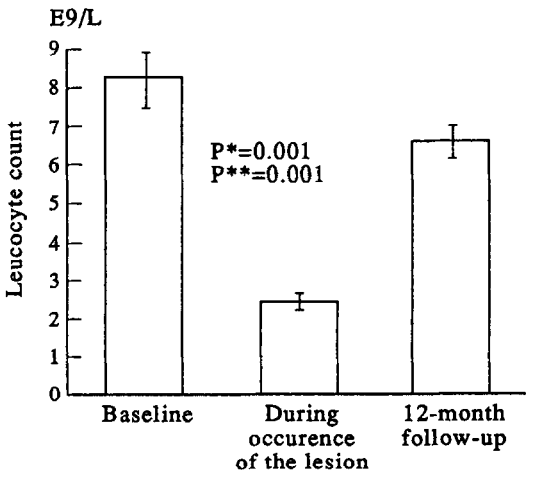

Fig. 1. Mean blood leucocyte counts in patients at baseline, when white, non-removable lesions were present on the lateral border of the tongue and at the end of the 12-month follow-up period. The differences between the mean counts at baseline and during the presence of the lesions (P^*), and during the presence of the lesions and at the end of the 12-month follow-up period (P^{**}) are significant ($P=0.001$).

only twice in other sites of mouth simultaneously with the lesion. No erythematous ulcers were detected on the lesion areas. Hyperplastic candidal variant can be distinguished from OHL histologically [27], but, as said, the patients of this study were able to be followed only clinically. Regardless of a superficial candida infection HL responds only slightly or not at all to antifungal treatment [9]. 3 patients of the present study were given antifungal treatment when the lesion was detected. No lesions were then observed during subsequent examinations. The response to antifungal therapy supports the diagnosis of candida infection in these patients, but the disappearance of the corrugated white lesion can also be related to periodic immunosuppression during chemotherapy. The short, cyclic periods of immunosuppression can be the reason, too, since only 44% of the lesions were found bilaterally, while 90% of OHLs have been reported to be present on both sides of the tongue [9, 10].

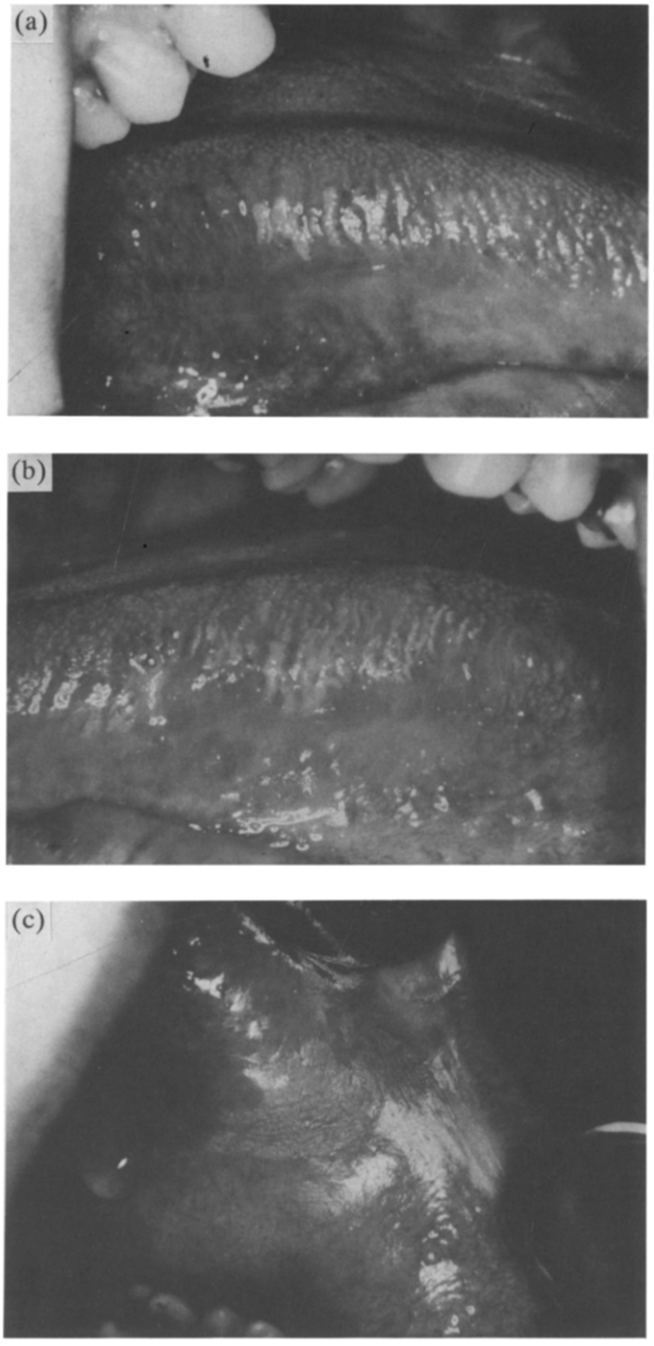

Fig. 2. Right (a) and left (b) sides of the tongue of a patient with vertical corrugated, white non-removable lesions lasted for 4.7 months. There were similar lesions on the buccal mucosa bilaterally at the level of the side of the tongue (c).

A defect in the Langerhans cells has been suggested as a reason for EBV infection of the border of tongue in immunocompromised patients [9]. Cell-mediated immunity is impaired in patients with lymphoid malignancies and is further compromised by chemotherapy [28, 29]. Von Bültzingslöwen [30] reported administration of 5-fluorouracil to reduce the proliferation of T-cells in oral soft tissue. However, even though the effect of various antineoplastic agents on immune defence of oral soft tissues is not completely understood, the reduction in local immunity of epithelial cells during chemotherapy could lead to epithelial infection. In the present study EBV IgG antibody was found before treatment in all serum samples from patients. The existence of the malignancy or the immunosuppression caused by chemotherapy could therefore have led to EBV activation, or to a new EBV infection on the border of the tongue. To confirm this hypothesis, however, further studies will be needed, because for ethical reasons and the risk of infection caused by incision biopsy in immunocompromised patients, it was impossible to obtain more than two biopsy samples during this study. If a study of oral cytological smears is possible, scraping of lateral borders of tongue with a blunt spatula has been proved to be a valuable and non-invasive technique to confirm the presence of EBV in cells of lesions [31–33].

HL responds well to acyclovir [9]. Organ transplant recipients are often given acyclovir or an analogue prophylactically. This might be why HL is uncommon in such patients [34]. No patient in the present study was given acyclovir before the lesion was diagnosed, or while it was present. 3 patients were given acyclovir later. This may be another explanation why 42.8% of the present patients experienced the lesion.

In the study reported here, an association was noted between the prevalence of a corrugated white patch lesion on the lateral border of the tongue and leukocytopenia. High numbers of positive salivary yeast cultivations concomitantly with the lesion may possibly indicate a hyperplastic candidiasis. Impairment of the local immune defence in oral soft tissues during antineoplastic therapy may open the way to (EBV) epithelial infection which also raises the question about diagnosis of OHL or pseudo OHL. However, more biopsy samples must be studied to understand the factors behind the white patch lesion on margins of the tongue associated with cytostatic treatment, but the presence or absence of EBV in lesion cells can be studied by taking cytological smears of the mucosa of the tongue.

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