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Salivary Immunoglobulins in Cancer Patients With Chemotherapy-related Oral Mucosa Damage

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In 40 patients with neoplastic disorders treated with chemotherapy containing anthracyclines or 5-fluorouracil, objective changes of the oral mucosa were registered in 22 patients (55%). Serum IgG and IgA levels and the mean serum IgG/IgA ratio were normal. On the contrary, the mean IgG/IgA salivary ratio was 1.27 (normally below 1.0) due to an increased salivary concentration of IgG (mean 0.095 g/l), but also due to a decreased IgA concentration (mean 0.075 g/l); the IgG/IgA ratio in saliva was higher in patients with objective changes of the oral mucosa (1.53). Values of the periodontal indices were compatible with the diagnosis of a manifest periodontal disease, which tended to be more severe than in control groups. A positive correlation between the gingival index and concentration of IgG in saliva, a non-linear correlation between the gingival index and salivary IgA and a positive linear correlation between serum IgA concentration and intensity of periodontal attachment level recession, indicate local and systemic immune responses to periodontal tissue alterations and dental plaque components. The IgA related local humoral immune response is, however, operating at a lower concentration level than in healthy individuals.

Keywords: saliva, immunoglobulins, chemotherapy, oral mucosa damage, periodontal tissue alterations

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INTRODUCTION

FACTORS implicated in oral cavity protection are intact oral mucosa and preserved function of salivary protein components. Anticancer drugs induce with different frequency oral mucosa damage, bone marrow depression and additional immunodeficiency in patients with neoplastic disorders. Immune dysfunction in those patients is supposed to be an additional factor for the damage involving the oral mucosa and periodontal tissue. Anticancer drugs most often associated with oral mucosa damage and stomatitis are 5-fluorouracil and the anthracyclines, doxorubicin and epirubicin.

Stomatitis has been reported as a rather uncommon but characteristic and troublesome toxicity manifestation for these three drugs and the severity seems more related to individual reaction to single dose level per cycle than to cumulative drug dosage levels. The occurrence of stomatitis of any grade, assessed by WHO criteria [1], has been reported to be 10/189 for high dose 5-fluorouracil (400 mg/m^2 per cycle) in head and neck cancer [2], 7/111 for epirubicin 120 mg/m^2 in small cell bronchogenic carcinoma [3] and 2/35 for epirubicin 180 mg/m^2 in advanced soft tissue sarcoma [4]. High dose doxorubicin 75 mg/m^2 in non-Hodgkin lymphoma was associated with a similar incidence of overt stomatitis, but oral mucosa damage became a major toxicity problem when the dose was escalated further to 120 mg/m^2 per cycle [5], which is now not a generally accepted dosage. It is, however, possible that without a proper stomatological anamnesis and examination, a number of cases of mild (WHO grade I) drug-related stomatitis could be missed, and, therefore, not reported in large studies; so, the true occurrence of drug-related oral mucosa damage might have been underestimated.

Oral mucosa is covered by a mucin layer whose function includes preservation of tissue integrity [6]. Preservation of oral mucosa integrity is also contributed by the mechanical cleansing of the oral cavity, performed by the action of buccal, labial and lingual muscles, with significant help from the saliva which facilitates actions during speech, mastication and swallowing. Saliva is a composite secretion originating from three pairs of large, and a number of smaller, salivary glands. Secretory IgA is the quantitatively most important salivary immunoglobulin whose function is to protect the oral mucosa both from noxious activity of microorganisms and from antigen penetration by interfering with antigen resorption through the intact oral mucosa. IgA is more resistant than other immunoglobulins to proteolytic degradation [7]. Gingival fluid is responsible for the presence of IgG and IgM in saliva. The IgG/IgA ratio in the saliva is normally in favour

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of IgA (i.e. below 1.0), the opposite of the serum ratio which is in favour of IgG [8].

The aim of the present investigation is: to present a preliminary overview reassessment of the frequency of oral mucosa and periodontal tissue changes registered in patients with advanced neoplastic disease treated with anthracyclines or 5-fluorouracil-containing chemotherapy regimens; to determine the immunoglobulin (IgA and IgG) content of the unstimulated saliva and its relation to oral mucosa and periodontal tissue damage caused by chemotherapy in these patients; to assess the integrity of local and systemic IgA and IgG related humoral immune response to periodontal changes and dental plaque components in patients already pretreated with anthracyclines or 5-fluorouracil chemotherapy. This last point, as a model for mucosa damage associated humoral immune response, might bring further insight into the pathogenesis of overt stomatitis which might follow therapeutic applications of these drugs (especially of the role of eventual treatment-induced immunodeficiency aggravating drug-induced oral mucosa damage), and into the possibility of chemotherapy-related induction of appearance or aggravation of the pre-existing periodontal disease.

MATERIALS AND METHODS

The investigations were performed on 40 patients with different metastatic neoplastic disorders. The age of the patients was 28–73 years. All patients were pretreated with several cycles of chemotherapy regimens containing anthracyclines (doxorubicin or epirubicin) or 5-fluorouracil, and still receiving chemotherapy. Median interval following start of chemotherapy and the assessments in the present study is 6 months (range 5–9 months). The patients, according to these drug dosages applied could be classified into 5 groups:

(i) patients on low dose 5-fluorouracil: breast cancer patients;
(ii) patients on high dose 5-fluorouracil: patients with head and neck cancer (patients with cancer of the oral cavity were not included in the study);
(iii) patients on high dose doxorubicin: non-Hodgkin lymphoma patients;
(iv) patients on intermediate dose epirubicin: patients with small cell bronchogenic carcinoma;
(v) patients on high dose epirubicin: soft tissue sarcoma patients.

Other cytotoxic drugs used in conjunction in the chemotherapy regimens were those not usually recorded, in the dosages and schedules applied, to be associated with induction of oral mucosa damage. None of the patients received any prior radiotherapy involving head and neck regions. These data are presented in Table 1.

Serum and saliva IgA and IgG levels were determined by radial immunodiffusion [9] on M and LC partigen plates (Behringwercke). Serum IgA and IgG were determined in fresh serum originating from blood from the cubital vein. Salivary immunoglobulins were determined in unstimulated saliva taken from the patients before determination of the clinical parameters, with EACA and transexamic acid added to prevent *in vitro* immunoglobulin proteolytic degradation. Reference values for our laboratory obtained from analysis of 30 healthy subjects were 10.9–17.0 g/l for serum IgG, 1.55–3.33 g/l for serum IgA; the mean normal level in

Table 1. Basic data concerning patients and chemotherapy regimens

Neoplastic disease	No. of patients	Dosage of the drug per cycle in the regimen possibly related to development of stomatitis	Other drugs included in the chemotherapy regimens	Median number of cycles applied	Range of the numbers of cycles applied
Breast cancer	8	5-Fluorouracil 500 mg/m^2 × 4 days (2000 mg/m^2 per cycle)	Cyclophosphamide 300 mg/m^2 × 4 Methotrexate 30 mg/m^2 × 2	6	5–8
Head and neck cancer	8	5-Fluorouracil 1000 mg/m^2 × 4 days (4000 mg/m^2 per cycle)	Cisplatin 30 mg/m^2 × 4	4	4–6
Non-Hodgkin lymphoma	9	Doxorubicin 75 mg/m^2 × 1 day	Cyclophosphamide 1.5 g/m^2 × 1 Vincristine 1.4 mg/m^2 days 1 and 7 Bleomycin 10 mg/24 h days 1 and 7	5	4–6
Small cell bronchogenic carcinoma	8	Epirubicin 120 mg/m^2 × 1 day	Cisplatin 30 mg/m^2 × 4	5	4–6
Soft tissue sarcoma	7	Epirubicin 60 mg/m^2 × 3 days (180 mg/m^2 per cycle)	Cisplatin 30 mg/m^2 × 4	4	4–6

unstimulated saliva in 30 healthy subjects with no disorder affecting oral mucosa and periodontal tissue for salivary IgA was 0.194 g/l and for salivary IgG 0.014 g/l.

Stomatological examinations included stomatological anamnesis and registration of both subjective complaints and objective changes involving oral mucosa and periodontal tissue.

Subjective complaints which have been looked for included a dryness sensation, burning sensation and pain. The subjective assessment by the patients, through the study, was recorded as absent or present—being either slight to moderate or severe [10]. Objective changes registered during stomatological examination included: enanthema, atrophy of the lingual papillae, xerostomia, oral erosions, oral ulcerations and angular cheilitis. Local assessment of the oral mucosa of the patients included a "semiquantitative" assessment of objective changes: area of changes (mm^2), depth of ulcer (1—epithelium; 2—connective tissue; 3—muscular/fatty tissue), granulation or epithelisation (1—very good; 2—good; 3—moderate, 4—none).

The status of the periodontal tissue was assessed with the following indices: plaque index, (Silnes and Löe), calculus surface index (Green), gingival index (Silnes and Löe), papillary bleeding index (Cowell) and tooth mobility index according to staging of the Clinic for Oral Medicine in Belgrade [10]. The criteria were as follows.

Plaque index

0: gingival area of tooth free of plaque; 1: no plaque observed *in situ* by the unaided eye, but plaque is made visible on the point of a probe after the probe has been moved over the tooth surface at the entrance of the gingival crevice; 2: gingival area covered by a thin to moderately thick layer of plaque visible to the naked eye; 3: heavy accumulation of soft matter, the thickness of which fills the crevice produced by the gingival margin and the tooth surface.

Calculus surface index

0: no calculus; 1: calculus not exceeding 0.5 mm in width and/or thickness; 2: calculus not exceeding 1.0 mm in width and/or thickness; 3: calculus exceeding 1.0 mm in width and/or thickness.

Gingival index

0: absence of inflammation; 1: mild inflammation; 2: moderate inflammation; 3: severe inflammation.

Papillary bleeding index

0: no bleeding; 1: bleeding some seconds after probing; 2: bleeding immediately after probing; 3: bleeding on probing spreading towards the marginal gingiva.

Tooth mobility index

0: normal mobility; 1: 0.2 mm; 2: 0.2–1.0 mm; 3: 1.0–2.0 mm; 4: over 2.0 mm; 5: severe mobility facio-lingually and/or mesio-distally combined with vertical displacement.

Measurement of recession of periodontal attachment and the depth of periodontal pockets were expressed in millimetres.

Values of the plaque index, gingival index and measurement of recession of periodontal attachment were also determined in two control groups:

(i) a control group consisting of 20 age and sex matched healthy persons;
(ii) a control group consisting of a disease distribution, age and sex matched population of 30 patients with metastatic neoplastic disorders prior to any chemotherapy.

Statistical analysis included determination of linear and non-linear correlations and Spearman's rank correlation.

RESULTS

Out of 40 patients, 13 were symptomless, while 27 had subjective complaints related to the oral cavity. Objective changes of the oral mucosa were registered in 22 patients (55%) and were manifested by different combinations of erythema, atrophy of the lingual papillae, xerostomia, angular cheilitis and oral ulcerations. All patients with objective changes of the oral mucosa belonged to the group also presenting subjective complaints.

Values of periodontal indices were found to indicate that the patients had a manifest periodontal disease. The mean level of the plaque index was 2.18 with the range from 1 to 3. The mean calculus surface index was 1.23. The gingival index was usually found to be consistent with gingival inflammation and its mean value was 1.60. The mean value of the papillary bleeding index was 1.432. The periodontal attachment was found to migrate for a mean of 3.45 mm while the mean depth of the periodontal pocket was 2.43 mm. The consequence of the aforementioned changes was increased tooth mobility, the mean index being 1.49. The periodontal disease appeared to have a tendency to be more severe in patients under the present study, as compared to both healthy controls and the matched group of patients with metastatic neoplastic disease before any chemotherapy (Table 2); the highest mean values for the gingival index, plaque index and recession of the periodontal attachment level were recorded in patients undergoing chemotherapy.

The serum IgG level in our patients ranged from 9.0 to 39.3 g/l with a mean of 16.72 g/l. The mean value for serum IgA was 3.17 g/l with a range from 1.0 to 6.7 g/l. The mean serum IgG/IgA ratio in the patients was 5.27.

IgG salivary levels were in the range 0.02–0.24 g/l with a mean concentration of 0.095 g/l. IgA salivary levels were in the range 0.03–0.12 g/l with a mean of 0.075 g/l. The mean IgG/IgA ratio in the unstimulated saliva was 1.27. Thus, mean levels of serum IgA and IgG tended to be slightly higher than in normal controls, and with a wider range of extreme values. In contrast, levels of IgA in unstimulated saliva were lower than in normal controls, and those of IgG higher.

In patients with subjective complaints related to the oral cavity the IgG/IgA ratio in saliva was 1.50; patients without subjective complaints had a mean IgG/IgA ratio of 1.12. The IgG/IgA ratio in saliva of patients displaying objective changes of the oral mucosa was 1.53 while it was 1.24 in patients with an apparently intact oral mucosa.

In our study, different diagnoses of metastatic malignant disorders also corresponded to different therapeutic groups

Table 2. Values of the periodontal indices in the group of patients under the present study and control groups

Parameter	Healthy controls*	Patients with neoplastic disease prior to chemotherapy	Patients under the present study
n	20	30	40
Gingival index ($x \pm$ S.D.)	1.21 ± 0.60	1.32 ± 0.73	1.60 ± 0.46
Plaque index ($x \pm$ S.D.)	1.39 ± 0.65	1.57 ± 0.90	2.18 ± 0.51
Recession of the periodontal attachment in mm ($x \pm$ S.D.)	2.37 ± 0.32	2.38 ± 0.42	3.45 ± 1.92

*Population of healthy persons, not necessarily free from stomatological problems usually present in the population, some of them related to hygienic attitudes concerning oral cavity and tooth cleaning in the local population.

Table 3. Immunoglobulin levels in unstimulated saliva, IgG/IgA ratio and gingival index in patients with metastatic neoplastic disease treated with anthracyclines and 5-fluorouracil-containing regimens

	Patients on 5-fluorouracil		Patients on high dose doxorubicin	Patients on epirubicin	
Parameter	Low dose breast cancer $n=8$	High dose head/neck cancer $n=8$	Non-Hodgkin's lymphoma $n=9$	Intermediate dose small cell lung cancer $n=8$	High dose sarcoma $n=7$
Number of patients with chemotherapy-related oral mucosa damage	3/8	6/8	4/9	4/8	5/7
Salivary IgA (g/l)					
$x \pm$ S.D.	0.071 ± 0.017	0.078 ± 0.023	0.080 ± 0.010	0.073 ± 0.018	0.063 ± 0.017
Median	0.08	0.08	0.08	0.075	0.07
Range	0.03–0.08	0.05–0.12	0.07–0.10	0.05–0.10	0.03–0.09
Salivary IgG (g/l)					
$x \pm$ S.D.	0.086 ± 0.032	0.101 ± 0.059	0.074 ± 0.013	0.122 ± 0.061	0.098 ± 0.039
Median	0.07	0.085	0.08	0.11	0.08
Range	0.04–0.15	0.08–0.24	0.07–0.10	0.05–0.24	0.07–0.16
Mean IgG/IgA ratio	1.21	1.28	0.92	1.67	1.55
Gingival index					
$x \pm$ S.D.	1.386 ± 0.470	1.778 ± 0.187	1.546 ± 0.481	1.363 ± 0.416	2.851 ± 0.340
Median	1.305	1.75	1.68	1.40	2.00
Range	0.7–2.26	1.5–2.0	0.66–2.0	0.7–2.0	1.3–2.33

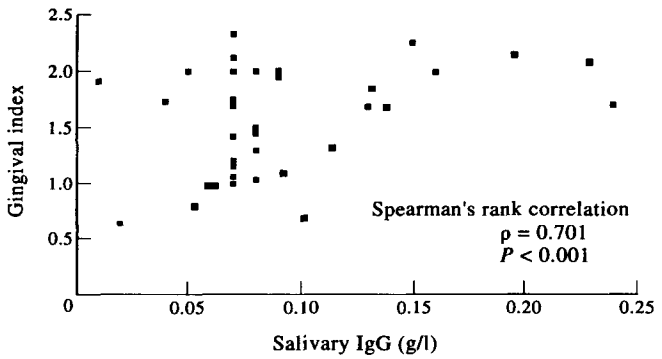

Fig. 1. Correlation between gingival index and concentration of IgG in the saliva.

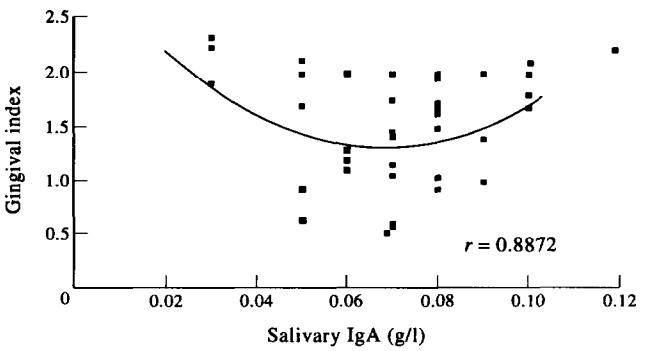

Fig. 2. Non-linear correlation between gingival index and concentration of IgA in the saliva.

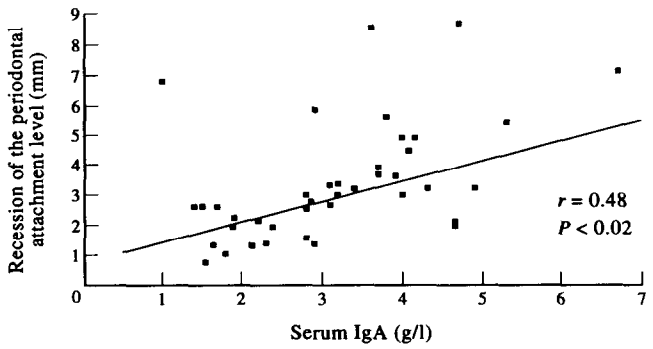

Fig. 3. Linear correlation between intensity of the recession of the periodontal attachment level and serum IgA concentration.

and it is difficult to differentiate treatment induced IgG/IgA alterations from eventual disease induced ones. Nevertheless, the comparative results of salivary IgA and IgG levels, IgG/IgA ratio, gingival index and recession of periodontal attachment level are presented in Table 3. IgA salivary levels were apparently equally distributed in all five groups. Patients on either intermediate or high dose epirubicin presented the highest mean salivary IgG levels, resulting in the highest salivary IgG/IgA ratios. Patients on both high dose epirubicin and high dose 5-fluorouracil (sarcoma and head and neck cancer patients) had the highest mean gingival indices.

The statistical analysis of the values of periodontal parameters and immunoglobulin levels in serum and saliva in the whole group of 40 patients revealed a positive correlation between the gingival index and IgG salivary level, Spearman's rank correlation $\rho = 0.701$, $P < 0.001$ (Fig. 1). The correlation between gingival index and salivary IgA was a nonlinear one; high gingival indices were observed both in a subpopulation of patients with very low salivary IgA and in a subpopulation with the highest recorded salivary IgA levels in the group (Fig. 2). There was a positive linear correlation between serum IgA level and intensity of periodontal attachment level alterations, $r = 0.48$, $P < 0.02$ (Fig. 3). A slight positive correlation was present between the plaque index and salivary IgG level ($\rho = 0.32$; $P < 0.05$).

DISCUSSION

Immunoglobulins and other proteins in whole saliva originate from three principal sources: large salivary glands, small mucosal salivary glands and gingival fluid. A population of immunoglobulin molecules enters the oral cavity by direct transit through the epithelium, especially if inflamed [11]. Whole saliva in the oral cavity is a mixture of unstimulated saliva, gingival fluid and saliva excreted upon stimulation. Sixty-five percent of unstimulated saliva originates from the submandibular gland, 25% from the parotid gland, 4% from the sublingual gland and 8% from other salivary glands. During maximal stimulation, achieved during mastication, the contribution of parotid gland saliva rises to 50% of the total salivary volume. Therefore, measurement of salivary immunoglobulins, especially for those originating from the gingival fluid was, in the authors' opinion, better performed in unstimulated saliva, as the parotid gland contribution to the total volume tends to decrease their concentrations to lower limits of measurability levels.

There are few literature data concerning the topic of salivary immunoglobulin alterations induced either by chemotherapy or by widespread or local neoplastic disease. Salivary IgA concentration in patients with oesophageal cancer was found to be identical to that in healthy people [7]. Patients with carcinoma of the oral cavity have been found to have either higher [12] or lower levels [13] of salivary IgA as compared to healthy individuals. An increase of salivary IgA level was found to be present in patients with acute myeloid leukaemia, returning to normal values following remission [14]. Chemotherapy did not appear to depress the salivary immunoglobulin levels [15] and increased values of salivary IgA were found in children with active neoplastic disease [16]. However, determination of salivary flow rates would be of importance for assessment of daily IgA output into the oral cavity. Reduction in salivary volumes might lead to a reduction in total IgA output in spite of an increase in concentration.

Our results seem to demonstrate that, if signs of oral mucosa damage in patients treated with anthracyclines (doxorubicin and epirubicin) and 5-fluorouracil are specifically looked for, they are present in a significantly larger number of patients than usually reported, and the percentage of such patients rises to about 50%. Whether the repeated noxious effects, during subsequent chemotherapy cycles, tend to induce or aggravate the pre-existing periodontal disease remains a matter of speculation, but should be taken seriously into account, especially as there is a tendency for high doses of both anthracyclines and 5-fluorouracil to be used in adjuvant settings and in chemotherapy sensitive neoplasia with curative intent. Thus, it would be of interest to make a prospective study, starting from chemotherapy naive patients, and to continue to follow them during subsequent chemotherapy cycles, assessing the effect of chemotherapy on both salivary imunoglobulin levels and mucosal and periodontal alterations.

The serum immunoglobulin levels in our patients were not depressed, notwithstanding treatment with cytotoxic drugs. However, IgG concentration in the saliva tended to be higher and the IgA concentration lower than reported in healthy individuals [11]. The IgG/IgA ratio in secreta is usually lower than 1.0 while this ratio in serum is 4.0–5.0 [8, 17]. In patients included in this study the IgG/IgA ratio in the serum was 5.27 which could be considered not to be different from normal values. The same ratio in the saliva was 1.27 and is higher than reported in normal individuals, reaching 1.53 in patients with overt stomatitis. Our results seem to be comparable with similar results previously reported [18]. In inflammatory changes of the oral mucosa following chemotherapy, because of increased capillary leakage and serum protein transudation, the local immunoglobulin concentration originating directly from serum could induce changes in the IgG/IgA ratio in the saliva. The increased IgG/IgA ratio in our group of patients, however, was not only caused by an increased IgG level in unstimulated saliva, but also to a decreased IgA level. The measurement of antibody concentrations in saliva is complicated by several factors which should be taken into account when comparing such levels in disease. Whole saliva is often contaminated by materials which modify the level of detectable immunoglobulins (bacterial enzyme contamination reduce the level, whereas transudation of immunoglobulins via the gingival crevice increases the levels). We have not determined the salivary flow rates in our patients and thus the daily IgA output into the oral cavity, but there are no data that would bring us to speculate that the daily salivary volume in our patients was increased more than 2-fold, which would

bring the predicted IgA daily output into normal levels (provided the IgA concentration in saliva secreted upon stimulation is the same as in unstimulated saliva). Thus, the statement that in our group of patients the salivary IgA level was depressed appears to be a sound one.

This would also account for the finding that the IgG/IgA ratio was higher than normal even in patients with no signs and symptoms of stomatitis, although lower than in patients displaying this adverse treatment effect. In this subgroup it seems that the altered IgG/IgA ratio was more or less the consequence of a decreased salivary IgA level than increased salivary IgG level.

Braudtzaeg has reported a significant increase of salivary IgA concentration in patients with periodontal disease [7]. In our patients we have found a positive correlation between the gingival index and IgG levels in saliva, a non-linear correlation between gingival index and IgA levels in saliva and a positive correlation between periodontal attachment level recession and serum IgA concentration. The positive correlation between gingival index and IgG salivary level could indicate an attempt of systemic and local immune response to dental plaque components. The non-linear correlation between the gingival index and salivary IgA levels was due to a "bimodal" distribution of the salivary IgA level in relation to gingival indices. In fact, high gingival indices were associated both with the lowest and highest salivary IgA levels recorded in our study. This would mean that the IgA-related local immune response in a subpopulation of patients under chemotherapy is lacking. There might also be a difference in the relationship between the impact of mucosal and periodontal changes and the potential for transudation of IgG between patients on anthracycline (especially epirubicin) and 5-fluorouracil treatment.

Thus, the altered IgG/IgA ratio in the saliva of our patients was due to both the presence of an increased level of salivary IgG and a depressed IgA level. The principal salivary immunoglobulin is IgA and the principal immunoglobulin of the gingival fluid is IgG [17]. The concentration of IgG in saliva is in direct connection with the intensity of gingival inflammation, as IgG from serum reaches the saliva via the gingival fluid during inflammatory phenomena in periodontal disease. Longitudinal investigations in compromised patients have shown that their degree of destruction of periodontal tissue is not significantly different from the degree of destruction of periodontal tissue in healthy people [19].

The positive correlation between periodontal attachment level alterations and serum IgA and the correlation between gingival index and both salivary IgA and IgG seems to indicate that both systemic and local humoral immune responses are operating in patients receiving chemotherapy, (although it must be stated that the IgA-related local humoral immune response is operating on a lower concentration level than expected, and that it is apparently lacking in a subpopulation of patients). Thus, stomatological treatment of patients with chemotherapy-induced changes in the oral cavity should be performed according to usual criteria and standards [20]. The subpopulation of patients with depressed IgA-related local immune response should be more precisely defined and the true clinical impact of this local IgA-related immune deficiency assessed.

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