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Symptoms of Acute Leukemias in the Oral Cavity

Gebri E[1], Kiss A[2], Hegedűs C[3] and Baksa B[4]*

[1]Department of Periodontology, University of Debrecen Clinical Centre, Hungary

[2]Department of Medicine, University of Debrecen Clinical Centre, Hungary

[3]Department of Biomaterials and Prosthetic Dentistry, University of Debrecen Clinical Centre, Hungary

[4]Department of Pediatric Dentistry, University of Debrecen Clinical Centre, Hungary

Abstract

Background: The clinical symptoms and mortality of acute leukemias are primarily associated with bone marrow failure as well as other organic infiltrations. These syndromes have many manifestations in the oral cavity which help early diagnosis and more efficient treatment.

The purpose of this study was to show the first symptoms in the oral cavity in AML (Acute Myeloid Leukemia) and ALL (Acute Lymphoid Leukemia) and the most common side effects of the treatments used.

Methods: Final reports of patients with AML and ALL were processed. 30 patients undergoing chemotherapy and 30 patients not suffering from malignant haematological diseases were also included. We examined the nature and frequency of the most common symptoms in the oral cavity resulting from an underlying malignant haematological disease and the changes occurring as a result of treatment.

Results: Following chemotherapy, mycosis was the most common change in both AML and ALL, followed by mucositis and herpes infection. Changes were more common in AML. Chemotherapy was accompanied by pain, dry mouth and loss of taste.

Conclusion: Close cooperation between the two fields' specialists is indispensable in order to prevent complications during therapies (removal of focal dental infections) and to reduce severity of already existing changes (treatment of the lesion of the mucosa).

Keywords: AML; ALL; Symptoms in the oral cavity; Chemotherapy; Mucositis

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Correspondence:
Enikő Gebri, Department of Periodontology, University of Debrecen Clinical Centre, Debrecen, Nagyerdei krt.98, 4012, Hungary, Tel: 06/70-367-1629;
E-mail: gebri.eniko@dental.unideb.hu

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Introduction

The clinical symptoms and mortality of acute leukemias are primarily associated with anaemia, thrombocytopenia and neutropenia associated with bone marrow failure as well as other organic infiltrations [1-5]. These syndromes have many manifestations in the oral cavity which, either by themselves or combined with other general accompanying symptoms, help early diagnosis and more efficient treatment (Table 1; Figure 1A and B).

At the same time patients with acute leukemias receive intensive cytostatic treatment. Relapses are common. In chemotherapy resistant cases allogeneic or autologous peripheral stem cell or bone marrow transplantations are used. In the absence of an appropriate donor, autologous peripheral stem cell or bone marrow transplantation can be performed. All these treatments are accompanied by severe immunosuppression, which has numerous side effects with complicated manifestations in the oral cavity [6-8]. One of these, oral mucositis, is rather common, and contributes to the severity of the particular disease. The mechanism of its development is not yet fully known, but, since it is a syndrome of multifactorial etiopathogenesis, its prevention and treatment are also multifactorial [9,10] (Figure 2). Thus, in the course of the treatment of acute leukaemias we can achieve allogeneic transplantation, in which we need to consider the possibility of the development of graft-versus-host disease, which may also have numerous oral manifestations (such as lichenoid mucositis, xerostomia, erythema, mucosal atrophy, scleroderma, and pyogenic granuloma) [11-13]. The development of these manifestations indicate poor prognosis and their timely detection is of paramount importance (Figure 3).

Last, in acute leukemia different infections are among the most common causes of death [14]. Due to the high mortality rate caused by these infections it is especially important to pay attention

Table 1: Symptoms of acute leukaemias in the oral cavity (resulting from the underlying disease) and the changes observed in the maxillofacial region during routine extra- and intraoral stomatological examinations.

Symptoms of bone marrow failure	
Anaemia	pale, bloodless mucosa
Thrombocytopenia	bleeding of the purpura type
	petechia
	ecchymosis
	haematoma
	gingival bleeding during tooth brushing/ spontaneous gingival bleeding
	often persistent bleeding as an extraction complication
Leukopenia/neutropenia	ulceration of the oral mucosa
	chronic recurring oral ulceration
	deep gangraenosus ulcers
	Acute necrotizing ulcerative gingivitis/parodontitis/stomatitis
	aphta, aphthoid ulceration
	mycosis
	angulus infectiosus oris
	laryngeal hyperaemia
	slow wound healing as extraction complications
	abscesses
Symptoms of organ infiltration	
Lymphadenomegalia	potentially causing difficulty swallowing
Swelling of the salivary glands	
Gingiva	gum pain, gingival enlargement (acute myeloid leukaemia M4, M5)-infiltration of immature blasts
	reactive hyperplasia
	teeth are painful on percussion
	extrusion, increased mobility
Symptoms in the nervous system	negligible or negative reaction to an electric vitality test primarily in the premolar and the molar teeth of the mandible
	anterior open bite
	Radiograph: disappearance of the mandibular canal
	widening of the pariapical space
	thinning and disappearance of the lamina dura
	alveolar bone loss
	paraesthesia of the lower lip
	tenderness of the mental foramen
	Bell's palsy
	hypoglossal nerve paresis
	Zoster, Hunt zoster

to the proper reduction of the oral microflora and the possible retention of the integrity of the protective mucosal barrier. The oral cavity is full of microbes which can (and often do) potentially turn into pathogens in an immunosuppressed state (Fusobacterium nucleatum, Streptococcus viridans, Neisseria speciesek, Candida and aspergillus species are the most frequent ones) [15-23]. With this in mind, we need to be aware that, in full possession of appropriate knowledge of internal medicine, the observed changes should arouse the dentist's suspicion of a potentially malignant haematological disease, securing timely diagnosis and successful treatment. Also, dental "first aid" is necessary before the use of chemotherapies. In the course of the induction chemotherapy of acute leukemias fast and efficient dental treatment is necessary during complete remission (this is not necessary at the beginning of the disease). Fast and efficient dental treatment is indispensable before autologous and allogeneic peripheral stem cell transplantations, too.

Close cooperation between the specialists of the two fields is indispensable in order to prevent complications during therapies (removal of focal dental infections) and to reduce the severity of the already existing changes (treatment of the lesion of the mucosa).

Materials and Methods

In 2012, a total of 56 patients with acute leukaemia were treated in the Division of Haematology of the Institute of Internal Disease of the University of Debrecen Clinical Centre.

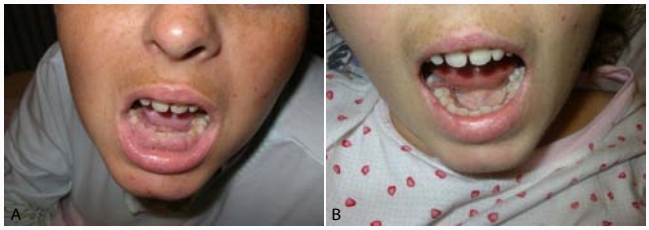

Figure 1A: 23 –year-old woman in 26th week of pregnancy with pronounced gingival hyperplasia (leukaemic infiltration) (AML-M4).
Figure 1B: Disappearance ofgingival hyperplasia in complete remission following induction therapy.

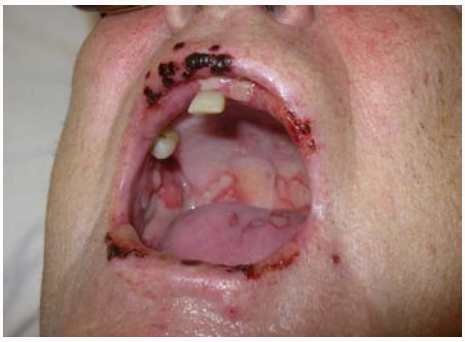

Figure 2: 66-year-old male patient following autologous peripheral stem cell transplantation. There are bleeding sloughs on the lips and in the nostrils. We can see serious oral mucositis (Grade IV.) on the tongue, both side of the bucca, and the hard and soft palate in the oral cavity.

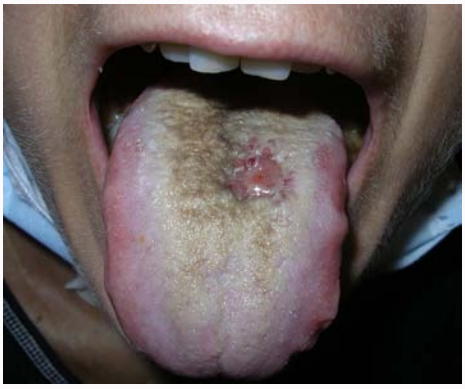

Figure 3: 38-year-old female patient 2 months after her second autologous peripheral haemopoietic stem cell transplantation. Lingua pilosa nigra. Ulcer 2cm in diameter and 0.5 cm deep on the back of the tongue. In her therapy amphotericin and iv. immunglobulin proved to be efficient.

Of the 42 patients with AML 22 were males and 20 females. The frequency of the disease among men and women was almost identical, with a mean age of 60, 8 years. Of the 14 patients with ALL 5 were females and 9 males, with a mean age of 39, 2 years.

- We processed the final reports of these patients based on the following major aspects:What changes are found (and with what frequency) in the oral cavity on admission?

- Similarly, what changes occur (and with what frequency) during chemotherapy?

- The individual changes and their frequencies were compared in AML and ALL and the relationship they showed with lab tests was examined.

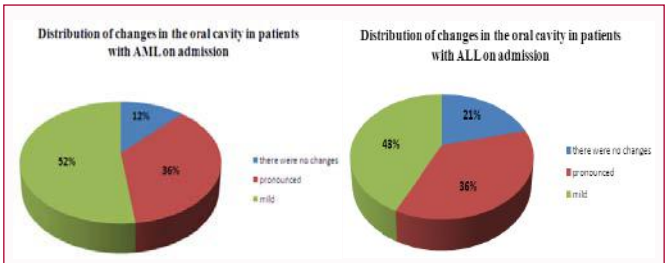

Figure 4: Distribution of changes in the oral cavity in patients with AML and ALLon admission.

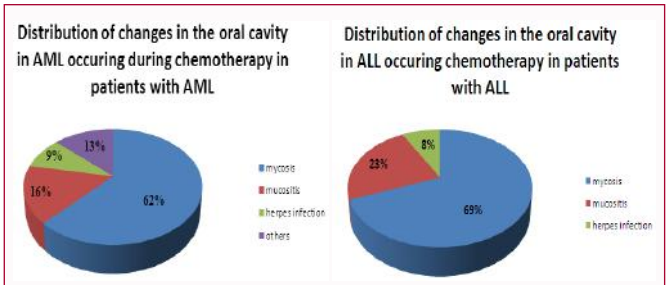

Figure 5: Distribution of changes in the oral cavity in AML and ALL occurring during chemotherapyin patients with AML and ALL.

In the course of processing the questionnaires we compared 30 patients with acute leukemia receiving chemotherapy with 30 individuals not suffering from malignant haematological diseases, who at the time were waiting for primary care at the Faculty of Dentistry. Mean age was 50, 4 years both in the patient population and in the control population. The answers to these questions provided us with an insight into the patients' habits of visiting a dentist and a rough idea of oral hygiene status, too. We examined to what extent the oral cavity milieu changes in the patient population compared with the control population as a result of the underlying haematological disease and its treatment. We also examined what the most frequent side effects of chemotherapy were. Finally, we made digital photos of the major changes in the oral cavities of patients in the Division of Haematology and Haemopoetic Transplantation Centre.

Results

- On admission, there was only a small portion of cases with no changes in the oral cavity suggestive of an underlying haematological disease both in AML (in 5 out of 42 cases, 12%) and in ALL (in 3 out of 14 cases, 21%).

- Manifestation of the syndrome in the oral cavity was more common in patients with AML than in patients with ALL, although the percentages of the more severe changes were the same in both. Of these the gingiva and the lymphoid nodes were the most often affected in both cases (Figure 4, Table 2 and 3).

- Following chemotherapy, mycosis (62%; 69%) was the most common change both in patients with AML and in patients with ALL, followed bymucositis (16%; 23%) and herpes infection(13; 8%). Thus, the above changes showed almost identical frequencies but the frequency of the occurrence of changes was greater in patients with AML (Figure 5).

- Based on the questionnaires, we can conclude that dry mouth, pain, loss of taste and difficulty eating were all accompanying features (side effects) of chemotherapy. Moreover, these often occur not alone but rather concomitantly during the therapy, making it

Table 2: Changes in the oral cavity and in the maxillo-facial region in patients with AML on admission.

	Frequency	Nature	AML type	Sex	Labs
1.gingiva	4	1.persistent bleeding following extraction	M6	M	THR:22G/L
		2.spontaneous gingival bleeding	M0	M	THR:6G/L
		3.medium-grade gingival hyperplasia	M5	F	WBC:1,17G/L
		4.painful gingiva	M2	F	WBC:74,09G/L
2.changes in the oral cavity involving bleeding	4	1.spontaneous bleeding of the mucosa	M6	M	THR:8G/L
		2.purpura on the bucca and the hard palate	M6	M	THR:18G/L
		3.purpura on the front of the tongue	M6	M	THR:68,5G/L
		4.haematoma of a 10HUF coin size on the left bucca	M5	M	THR:20G/L
3.lymphadenomegaly	4	1.left submandibular lymph nodes, peanut size, not tender	M0	F	WBC:0,2 G/L
		2.lymph nodes conglomerate in the cervical region causing difficulty swallowing	M0/M2	F	WBC:17,7 G/L
		3.lymphadenomegaly in the sub-, retromandibular and cervical region	M0	F	WBC:7,1G/L
		4.enlargement of the right submandibular lymph nodes	IRSA-AML	F	WBC: 54,6 G/L
4.extraction complication	3	1.slow wound healing	M6	M	WBC: 1,35 G/L
		2.alveolitis	M5	M	WBC: 2,67 G/L
		3.bleeding	M5	M	THR: 35 G/L
5.laryngeal hyperaemia	3	1.sore throat	MDS-AML	M	MCHC: 70,33g/L
		2.fever, weakness	AML-M4	F	MCHC: 85,3 g/L
		3.cough, arthralgia	M0/M2	F	MCHC: 74,5 g/L
6.white coating	3	1.on the soft palate and the bucca	M4	F	WBC: 1,56 G/L
		2.tongue-throat	M4	F	WBC: 3,24 G/L
		3.tonsils	M0/M2	F	WBC: 2,45 G/L
7.tooth ache	2	1.does not subside even on narcotic pain killer administering	M0/M1	M	WBC: 23,5 G/L
		2.trepanation was needed	M4	M	WBC: 1,74 G/L
8.changes on the tounge	2	1.white coating	MDS-AML	M	WBC: 3,24 G/L
		2.purpura	M4	F	THR: 54 G/L

Abbreviations: FAB: French-American-British Classification of AML (Acute Myeloid Leukemia); M0: Acute Myeloblastic Leukemia, Minimally Differentiated; M1: Acute Myeloblastic Leukemia, without Maturation; M2: Acute Myeloblastic Leukeima, with Granulocytic Maturation; M3: Acute Promyelocytic Leukemia; M4: Acute Myelomonocytic Leukemia; M5: Acute Monoblastic/Monocytic Leukemia; M6: Acute Erythroid Leukemia; M7: Acute Megakaryoblastic Leukemia; MDS: Myelodysplastic Syndrome; IRSA: Idiopathic Refractory Sideroacrestic Anemia; M: Male; F: Female; WBC: White Blood Cell; THR: Thrombocytes; MCHC: Mean Corpuscular Hemoglobin Concentration

Table 3: Changes in the oral cavity and maxillofacial region in patients with ALL on admission.

	Frequency	Nature	ALL type	Sex	Labs
1. lymph node	3	1.enlargement of the left supraclavicular lymph nodes	L2	M	WBC:3,7 G/L
		2.cervically not sensitive, mobile lymph nodes	L2	F	WBC:1,83G/L
		3.garland-like, bean-size enlargement lymph nodes on both sides of the neck	L2	F	WBC:5,1G/L
2. gingiva	2	1-2. gingivostomatitis herpetica	L1,L1	M,M	WBC:5,1G/L; 2,84G/L
					NEUT%:49,8%; 26%
					LYMP%:37,9%; 69,3%
3. tongue	1	white coating	L2	F	WBC:2,35 G/L
4. laryngeal hyperaemia	1	sore throat	L1	M	RBC:3,82 T/L
5. bleeding in the oral cavity	1	petechia, suffusion	L3	F	THR:14G/L

Abbreviations: FAB: French-American-British classification of ALL (Acute Lymphoid Leukemia); L1: Small Uniform Cells; L2: Large Varied Cells; L3: Large Varied Cells with vacuoles (bubble-like features); M: Male; F: Female; WBC: White Blood Cell; NEUT: Neutrophils; LYMP: Lymphocytes; RBC: Red Blood Cell; THR: Thrombocytes

Table 4: Type, intensity and frequency of symptoms in the oral cavity observed during chemotherapy in percentages based on the questionnaires.

Type of symptom	Intensity of symptom	Frequency
Pain in the oral cavity	not present during treatment	23,30%
	mild	10%
	medium	50%
	strong	10%
	observed as almost unbearable during treatment	6,70%
		76,70%
Dry mouth	not present	10%
	mild	16,70%
	medium	53,30%
	strong	20%
	observed as almost unbearable during treatment	0%
		90%
Difficulty eating	not at all	30%
	slightly	10%
	medium	23,30%
	very	20%
	to the extent necessitating parenteral feeding	16,70%
	feeding was on the whole obstructed	***in 70%***
Taste	same sensation as before	16,60%
	decreased sensation	36,70%
	hardly any sensation	16,70%
	no sensation at all	30%
	observed as a symptom during treatment	***83,40%***

even more difficult for patients to tolerate it (Table 4).

- We also gained an insight into our patients' habits of visiting a dentist. The results are rather saddening as 63, 3 % of those asked saw a dentist only when they had acute complaints.

Discussion

Acute leukaemia is one of the most common malignant haematological diseases these days with numerous symptoms in the oral cavity. Often it is these signs that appear first. Symptoms in the oral cavity result partly from the underlying disease, partly from the intensive cytostatic treatment used. This seems to be supported by our retrospective results, too.

We observed initial symptoms resulting from bone marrow failure and organ infiltration both in AML and in ALL, but, in accordance with literature data, they were more common in AML than in ALL [24]. Although this source suggests a frequency of 40% in AML and of 20-25% in ALL, these figures were much higher in our investigations if the mild and pronounced symptoms are all taken together (88,1% in AML and 78,6% in ALL). At the same time, the ratios of pronounced changes were observed to be the same (35,7%).

In relation to the changes observed in AML on admission we can conclude the following:

In accordance with literature data [1,2], we found leukemic gingival enlargement in our own material in AML-M4 and AML-M5 in our patient population, too (e.g. a 23-year-old pregnant woman and a 61-year-old female patient). This seems to support the fact that in these types of monocytic leukemia gingival hyperplasia is of diagnostic value. We found no such changes in ALL in our study.

We observed symptoms of pancytopenia caused by bone marrow failure and organ infiltration in our patient population, too - in great agreement with literature data. In four patients we found changes involving bleeding in the oral cavity in accordance with a decreased thrombocyte count while in a further four patients we saw enlarged lymph nodes in the maxillofacial region [24].

Three patients showed extraction complications, pharyngeal hyperaemia and a white deposit in the oral cavity accompanying the existing neutropenia [24].

Two patients reported toothache. In one of the two cases the pain did not subside even after a narcotic painkiller was administered. All this seems to support the view that acute leukemias produce symptoms in the nervous system, too [4].

Based on our investigations in patients with ALL and compared with literature data, we concluded the following:

We observed enlargement of the lymph node, the most common symptom in the maxillofacial region, in 21,4%. This finding was in agreement with literature data that in myeloid leukemia it is the internal organs (e.g. gingiva) that are most affected (swollen) [24].

Further, two patients produced complaints of stomatitis affecting the gingiva and vesicule formation, too, but no gingival hyperplasia was detected. In addition, in a couple of patients there was a whitish coating on the tongue, pharyngeal hyperaemia and changes involving bleeding, respectively, in the oral cavity. There were no extraction

complications in the medical history in patients with ALL since nobody reported tooth ache. This finding seems to support the fact that symptoms in the oral cavity are less frequent in patients with ALL [24], while it contradicts the fact that the manifestation of the syndrome in the nervous system is more frequent in patients with ALL [4].

The intensive cytostatic therapy used in the treatment of acute leukemias may also cause diverse changes in the oral cavity. The changes that occurred in the patient population investigated were also more common in AML (79, 3%), (with 61, 5% in ALL) [24]. However, the changes which occurred (mycosis, mucositis, and herpes infection) in the two cases showed almost identical incidence.

- Mycosis in AML: 62%, in ALL: 69% [17]
- Mucositis in AML: 16%, in ALL: 23% [6,7,22]
- Herpes infection in AML: 9%, in ALL: 8% [18]

Average white blood cell count considerably lagged behind the lower limit of the normal range in both AML and ALL.

These findings show a correlation and agreement with literature data. Thus, we can conclude that treatment induced cytopenia frequently predisposes patients to the formation of potentially life-threatening changes [14]. No literature data were available to us about whether mycosis has such a dominant role among the occurring changes in every case and whether herpes infection is less frequent than oral mucositis.

Based on the results of our questionnaires, dry mouth, pain, loss of taste and the consequent difficulty eating were further common side effects of chemotherapy, which, according to literature data, can be attributed to xerostomia, oral mucositis and other oropharyngeal infections that occur as a result of the cytostatic treatment [6-8].

It is common knowledge that the dental and oral health status of the overwhelming majority of the Hungarian population is disastrously neglected and bad. (This is borne out by the fact that 63, 3% of the subjects we asked saw a dentist only if they had complaints).

Furthermore, we also need to consider, primarily in men, the high frequency of smoking, and, unfortunately, of alcohol consumption. In the sixth and seventh life decades metabolic disorders (diabetes mellitus, kidney related diseases, etc.) occur in men. In women, obesity, hormonal changes and related problems are more frequent.

Conclusion

The results of our investigations show that dentists have a prominent role in the early diagnosis of acute leukemia and, in order to prevent severe oral complications that occur as a result of treatments, in the comprehensive exploration and removal of focal infections and prevention. We should not disregard the importance of close observation and regular dental check-ups after the treatment used, either. Suffice it to mention the possible manifestations in the oral cavity of the "graft- versus -host disease" following an allogeneic tissue transplant, which, unfortunately, indicate poor outcome.

Understandably, patients' dental medical history and status are not sufficiently precise in the clinical picture in internal medicine. It is therefore recommended to give every single haematoligical patient a dental examination and advice.

There are numerous open questions waiting to be answered in connection with this issue. The answers to these questions might reduce the morbidity of this threatening disease. Thus it would be important for internists-haematologists and dentists to work closely together in future, to continue research and to highlight the importance of the issue of oral medicine both in the general and in the dental medical curricula.

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