

Original Article

A clinical and fine needle aspiration cytology study of gingiva in acute leukemia

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ABSTRACT

Background: Oral manifestations are frequently the initial signs of acute leukemia, prompting the patient to consult the dentist first. The gingival tissue is one site commonly involved either by leukemic infiltration or by inflammatory reactive hyperplasia, causing gingival enlargement. The gingival infiltration may also be present without gingival enlargement. Early recognition of clinical findings in the oral cavity leads to its timely diagnosis and management. Since biopsy is highly contraindicated, gingival fine needle aspiration cytology was performed to assess its diagnostic value in detecting gingival infiltration in acute leukemia patients.

Materials and Methods: Fifty patients of acute leukemia received clinical and gingival cytological examination. The cases were diagnosed based on bone marrow aspiration findings and classified according to the French–American–British criteria. The absence or presence of intraoral findings was recorded. Site for gingival fine needle aspiration cytology was selected.

Results: Leukemic gingival infiltration was found to be more common in acute lymphoblastic leukemia, while the characteristic oral findings were seen more commonly in acute myeloblastic leukemia. All the eight cases of acute lymphoblastic leukemia that were positive for leukemic gingival infiltration showed no clinical evidence of gingival enlargement. In terms of leukemic gingival infiltration, L2 subtype was the only subtype involved, while M5 was more commonly involved than M4 subtype. Two cases of L2 subtype showed gingival enlargement due to local factors like plaque/calculus rather than due to leukemic infiltration.

Conclusion: The technique was found to be safe and of definitive diagnostic value in detecting gingival infiltration in acute leukemia patients.

Key Words: Acute leukemia, fine needle aspiration cytology, gingiva

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INTRODUCTION

The leukemic cell population in acute lymphoblastic leukemia (ALL) and acute myeloblastic leukemia (AML) results from clonal proliferation by successive divisions from a single abnormal stem or progenitor

cell. The accumulation of these cells results in the replacement of the normal hematopoietic precursor cells of the bone marrow, ultimately leading to bone marrow failure.^[1]

The great majority of cases of both ALL and AML appear to arise sporadically, and no precipitating factors can be identified. However, epidemiological studies have identified a number of congenital syndromes and environmental factors which appear to predispose toward the development of acute leukemia (AL).^[2]

It is now proposed that AML occurs as a result of acquisition within hematopoietic stem/progenitor cells of mutations in two distinct classes.^[3,4] Class I

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mutations result in an abnormal proliferative signal and typically occur as mutations of genes in receptor tyrosine kinases such as FLT3 or the RAS oncogene. Class II mutations result in a block in differentiation of leukemic progenitors and are typically caused by non-random chromosomal translocations that result in the generation of mutated transcription factors and the inhibition of hematopoietic gene expression.^[2]

Oral manifestations are frequently the initial signs of leukemia, particularly in the acute forms, prompting the patient to consult the dentist first.^[5] The oral cavity, and especially the gingival tissue, is one site commonly involved either by leukemic infiltration or by inflammatory reactive hyperplasia causing gingival enlargement.^[6] The frequency of mucosal lesions differs significantly between ALL and AML.^[7] The gingival infiltration may also be present without gingival enlargement.^[8]

It is therefore imperative that the dentist recognize these leukemic lesions as early as possible because of the danger, in some instances, of oral surgical interference and also the necessity of medical attention.^[5] For the diagnosis of leukemic infiltration, a biopsy is required. Since patients with AL are likely to develop bleeding and infection due to pancytopenia, surgical biopsies should be carried out with extreme caution. As an alternative procedure, fine needle aspiration cytology (FNAC) has been advocated for the diagnosis of such lesions in AL patients in different body organs such as testes, skin, lymph nodes and breast. It has been proved to be an effective, safe and simple technique.^[9-12]

Early recognition of clinical findings in the oral cavity by an astute clinician and investigation into potential systemic causes may uncover an underlying systemic disease and lead to its timely diagnosis and management.^[13] Therefore, gingival FNAC was performed as a diagnostic procedure with an aim to assess its diagnostic value in detecting leukemic gingival infiltration in AL patients presenting with or without gingival enlargement.

MATERIALS AND METHODS

Fifty AL patients (32 males and 18 females; age range 11–55 years) received a clinical and cytological examination of gingiva by the use of FNAC. Before the procedure, informed consent from each subject was taken. The AL cases confirmed by bone marrow aspiration findings were included in the study.

The absence or presence of intraoral findings was recorded. Then, the site for FNAC was selected in the gingiva. For patients with generalized or localized enlargement, the site with maximum enlargement was selected. In patients with no gingival enlargement, the sites were selected without restriction.

Gingival aspiration technique

Prior to aspiration, 10% xylocaine spray was applied to anesthetize the surface and the selected area was rubbed with a piece of cotton to remove tissue debris. A 5 ml syringe with 24 gauge needle was used. Two cubic centimeter of air was left before the aspiration procedure, to be used later to express the aspirated materials. The selected site was quickly punctured by needle tip, with its bevel directed away from the mucosal side. The plunger was retracted slowly to create a negative pressure inside the syringe barrel. While the needle was introduced inside the gingiva with the negative pressure maintained, a slight rotation of the needle was done for proper tissue aspiration.

When the material was aspirated, the plunger was released to the starting mark (2 cm³), the needle was quickly withdrawn from the tissue, and the material was expressed on the slide, smeared and stained with Leishman's stain. A peripheral blood film was prepared for each patient at the time of the aspiration procedure.

To exclude the possibility of contamination of the aspirated material by blood, each aspirated sample was compared with the peripheral blood and the following points were used for comparison: a) differences in the degree of gingival infiltration and the WBC in the peripheral blood and b) the difference between the type of cells in the aspirate and that in the peripheral blood.

RESULTS

In the present study, 50 patients of AL received clinical and cytological examination of gingiva by the use of FNAC. All the cases were diagnosed based on bone marrow aspiration findings and classified according to the French–American–British (FAB) criteria.

The age group included in this study ranged from 11 to 55 years. The maximum number of patients (54%) was in the age group of 11–20 years. The number of patients gradually declined toward higher age group. Regarding the sex distribution, male patients (64%) outnumbered female patients (36%).

Table 1 indicates the distribution of the cases of AL according to FAB classification. When comparing the distribution of ALL and AML among the selected 50 cases, it was observed that 28 patients (56%) were of ALL and 22 patients (44%) were of AML. Among the 28 cases of ALL, 26 were of L2 subtype, and L1 and L3 subtypes had 1 patient each. Among the 22 cases of AML, 11 cases were of M2 subtype, 7 were of M5 and 4 were of M4 subtype.

In the 50 cases studied, 14 were positive for gingival infiltration by leukemic cells: 8 (28.57%) of ALL and 6 (27.27%) of AML. In terms of leukemic gingival infiltration, among AML subtypes, M4 (2 cases) subtype [Figure 1a] was less commonly involved than M5 (4 cases) subtype [Figure 1b]. Among ALL subtypes, L2 subtype (8 cases) [Figure 2] was the only type to be involved [Table 1]. The type of cells in AML and ALL cases showing positive gingival infiltration was compared with that of their respective peripheral blood film picture.

Among the 28 cases of ALL, gingival bleeding was seen in 2 cases (7.14%), while gingival enlargement with prominent deposits of plaque/calculus was seen in 2 cases (7.14%). Twenty-four cases (85.71%) lacked characteristic oral findings. Among the 22 cases of AML, gingival bleeding as the only oral manifestation was seen in 4 cases (18.18%), while gingival bleeding with gingival enlargement was seen in 6 cases (27.27%). Twelve cases (54.55%) lacked characteristic oral findings [Table 2]. In the present study, characteristic oral findings were seen more in AML than in ALL cases.

Among the patients with positive leukemic infiltration in gingiva (8 in ALL and 6 in AML), all the 6 patients (100%) of AML manifested gingival bleeding with gingival enlargement as oral findings [Figures 3a and 3b], whereas all the 8 cases of ALL that were positive for leukemic gingival infiltration showed no clinical evidence of gingival enlargement [Table 3].

Two cases of L2 subtype showed gingival enlargement due to local factors like plaque/calculus rather than due to leukemic infiltration and the aspirate showed sheets of epithelial cells.

DISCUSSION

Leukemia is characterized by an abnormal proliferation of immature leukocytes and their precursors in bone marrow. The leukemic cell population also has the

Table 1: Distribution of cases showing gingival leukemic infiltration according to French–American–British (FAB) classification

Type of leukemia	No. of cases	Total cases	Leukemic infiltration	Percentage
M0 Minimally differentiated leukemia	0		-	
M1 Myeloblastic leukemia without maturation	0		-	
M2 Myeloblastic leukemia with maturation	11	22	-	
M3 Promyelocytic leukemia	0		-	
M4 Myelomonocytic leukemia	4		2	27.27
M5 Monocytic leukemia	7		4	
M5a: Undifferentiated monoblasts				
M5b: Differentiated monocytes				
M6 Erythroleukemia	0		-	
M7 Megakaryoblastic leukemia	0		-	
L1 Acute lymphoid leukemia; childhood variant	1	28	-	
L2 Acute lymphoid leukemia; adult variant	26		8	28.57
L3 Burkitt-like lymphoid leukemia	1		-	

Table 2: Findings in the oral cavity in ALL and AML cases

Type of acute leukemia	ALL (28 cases)		AML (22 cases)	
	No. of cases	Percentage	No. of cases	Percentage
Gingival bleeding only	2	7.14	4	18.18
Gingival enlargement only	-	-	-	-
Both gingival bleeding and enlargement	-	-	6	27.27
Plaque/calculus with gingival enlargement	2	7.14	-	-
No characteristic findings	24	85.71	12	54.55

ALL: Acute lymphoblastic leukemia, AML: Acute myeloblastic leukemia

Table 3: Gingival findings in acute leukemic patients with gingival infiltration

Type of acute leukemia	Total no. of cases showing gingival infiltration	No. of cases showing gingival findings			Percentage
		Gingival bleeding	Gingival enlargement	Both gingival bleeding and enlargement	
ALL	8	-	-	-	-
AML	6	-	-	6	100

ALL: Acute lymphoblastic leukemia, AML: Acute myeloblastic leukemia

propensity to invade extramedullary tissues and its presence as leukemic infiltrates has been reported in the kidneys, lungs, bowels, breasts, testes, eyes, meninges, lymph nodes, liver, prostate, skin, and

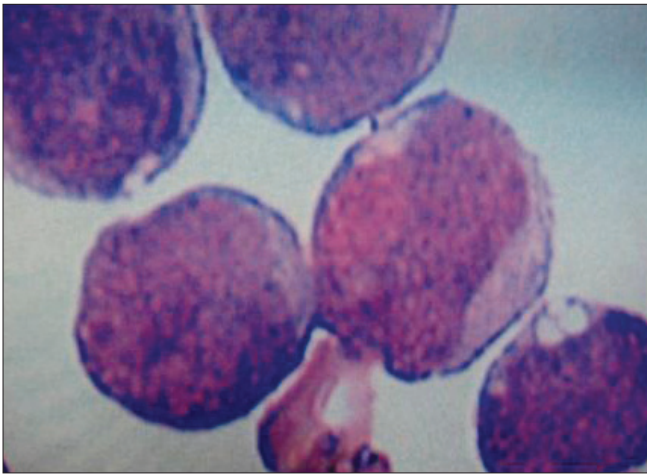


Figure 1a: Gingival aspirate from AML (M4 subtype) showing infiltration by blast cells (Leishman's stain, ×1000)



Figure 3a: Leukemic gingival enlargement in patient with M4 subtype (AML)

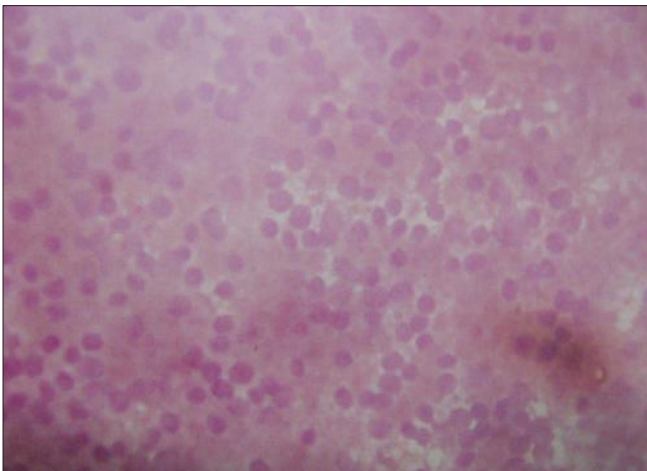


Figure 1b: Gingival aspirate from AML (M5 subtype) showing infiltration by monoblasts (Leishman's stain, ×400)



Figure 3b: Leukemic gingival enlargement in patient with M5 subtype (AML)

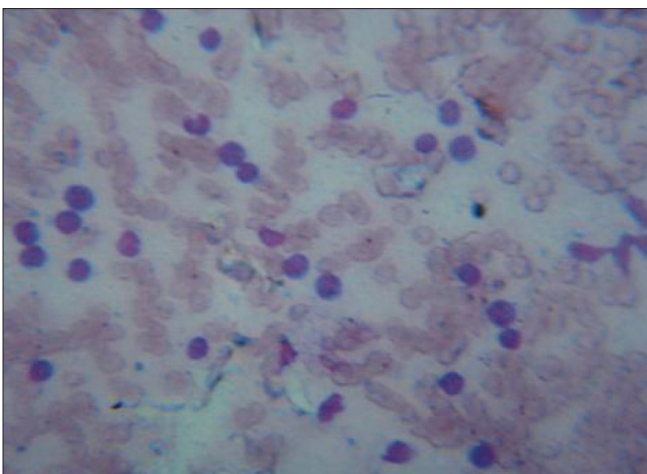


Figure 2: Gingival aspirate from ALL (L2 subtype) showing infiltration by lymphoblasts (Leishman's stain, ×400)

oral cavity.^[14] Gingival tissues are considered more susceptible to leukemic cell infiltration because of

their microanatomy and expression of endothelial adhesion molecules which enhance infiltration of leukocytes.^[15]

Oral lesions may be the presenting feature of ALs, and are therefore important diagnostic indicators of the disease. The most common oral findings include gingival enlargement, local abnormal color or gingival hemorrhage, petechiae, ecchymosis, mucosal ulceration and oral infections.^[16] In rare cases, atypical features like chin numbness and tooth pain have been reported.^[17]

Gingival overgrowth has several causes, including poor oral hygiene, drugs, systemic illnesses and neoplastic conditions. The presenting characteristics of gingival enlargement vary according to its etiology. The gingiva shows slow growth rate and appears pink with a firm consistency and minimal inflammatory component when it is genetically induced. In case

of blood dyscrasias, the gingiva appears soft and edematous with tenderness and bleeding tendency.^[18]

Bleeding diathesis, gingival hyperplasia and extramedullary leukemic infiltration are more frequently seen in the context of acute rather than chronic leukemia.^[19,20] In AL, monocytic (M5), myelomonocytic (M4), and myelocytic (M1, M2) subtypes have been reported with gingival hyperplasia in 66.7%, 18.5%, and 3.75% of cases, respectively. Despite its frequency, the occurrence of gingival infiltration is unpredictable in leukemic patients.^[6,21]

The present study was carried out with an objective to assess if FNAC is of diagnostic value in detecting gingival leukemic infiltration in patients with AL.

In the present study, the maximum number of patients (54%) was in the age group of 11–20 years, as the study included only AL cases that are commoner in younger age group. Male patients outnumbered female patients and this predominance of AL in males is in agreement with the reports of Abdullah *et al.*,^[1] and Sinrod.^[5] The predominance of ALL over AML cases is in agreement with one of the previous studies conducted by Advani *et al.*^[22]

Gingival infiltration by leukemic cells was found to be more common in ALL. Such findings are in contrast with those of Abdullah *et al.*,^[1] and Appel *et al.*^[23] which showed gingival infiltration to be more common in AML than ALL.

Characteristic oral findings were seen more commonly in AML than in ALL cases. Such findings are in agreement with a study done by Forkner,^[24] who stated that the oral manifestation of marked swelling, particularly in gingiva, can usually be regarded a characteristic typical of acute monocytic leukemia and is usually absent in AL of the myelogenous or lymphatic varieties, while Shepard^[25] reported that the monocytic type produces the most severe oral complications, followed by myeloblastic and lymphoblastic leukemia in the descending order of severity. Barrett^[6] stated that oral bruising and/or frank bleeding were observed more commonly in AML than in ALL. Further, several case reports have stressed the role of oral cavity as a diagnostic indicator in leukemia. Gingival enlargement together with gingival bleeding as an initial manifestation of AML cases has been reported in the dental literature.^[15,16,18,26-28]

In the present study, all the eight cases of ALL that were positive for leukemic gingival infiltration

showed no clinical evidence of gingival enlargement. This is in agreement with the finding of White^[8] who reported leukemic infiltration in autopsy material of gingival tissue in a child with ALL with no gingival enlargement. Similarly, in the study done by Abdullah *et al.*,^[1] of the cases with no clinical evidence of gingival enlargement seen, cytological examination showed four cases with definitive gingival infiltration.

Concerning the AML subtypes, M5 was more commonly involved than M4 subtype in terms of leukemic gingival infiltration. Among the ALL subtypes, L2 was the one involved in leukemic gingival infiltration. This is in agreement with the findings of Abdullah *et al.*,^[1] who concluded that M5 and M4 subtypes are considered the most common subtypes of AL, causing gingival infiltration.

CONCLUSION

FNAC was shown to be simple, safe and effective diagnostic procedure in studying gingival changes in patients with AL. Thus, in a patient reporting with gingival bleeding and/or gingival enlargement without commensurate presence of deposits and relevant history, AL could be suspected and the patient should be referred for hematological opinion as the importance of this disease to the dentist cannot be overemphasized, since he is in an ideal position to detect it relatively early in its course.

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