Case Report

Leukemic gingival enlargement- A case report and review

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ABSTRACT

Oral signs are an early indicator for a variety of systemic diseases. Gingival enlargement can be due to local factors, certain medications, hormonal changes, and malignant diseases. Leukemia is a malignancy characterized by the proliferation of abnormal white blood cells within the bone marrow; oral changes may be the first and only presenting feature in these patients, making it imperative for dental surgeons to make accurate diagnosis and timely referral to prevent a fatal situation. This article aims to discuss a case of acute myeloid leukemia (AML) that came with the chief complaint of swollen gums for 2-month duration. The case was provisionally diagnosed as a leukemic gingival enlargement on the basis of oral manifestation and lymph node examination. Accurate diagnosis and early initiation of chemotherapy for leukemic gingival enlargement can improve the prognosis of the patient and also helps in avoiding complications. Around 50–80% of patients with AML achieve complete remission, more often in children and patients under the age of 60. This paper aims at emphasizing the importance of thorough oral examination and careful investigations to identify the underlying life-threatening condition.

Key words: Gingival enlargement, Leukemia, Lymph node examination, Oral signs

Gingival enlargement, otherwise called gingival overgrowth is an increase in the size of the gingiva. Gingival enlargement can be localized, generalized, marginal, papillary, diffuse, and discrete. It can be broadly classified based on their etiologic factors and pathologic changes as inflammatory enlargement, drug-induced enlargement, enlargements associated with systemic diseases or conditions, idiopathic gingival enlargement, neoplastic enlargement, and false enlargement [1]. Systemic diseases that cause gingival enlargement are leukemia, granulomatous diseases such as Wegener's granulomatosis which presents as strawberry gingivitis formed by reddish -purple exophytic gingival swelling with petechial haemorrhages [2] and sarcoidosis which is a multiorgan disorder, commonly presenting with other features such as pulmonary infiltration, hilar lymphadenopathy, dermal, ocular lesions and raised eosinophil count [3], Crohn's disease which appears pink and firm gingival enlargement with a characteristic pebbled surface and associated with bowel disorders, fever and ulcer [4]. Tuberculosis manifesting solely as gingival enlargement is extremely rare and can be diagnosed based on a history of fever, weakness, loss of appetite, and weight loss [5]. Other systemic diseases which can cause gingival enlargement are hypothyroidism and lysosomal storage diseases, though not frequently seen, must be considered in the differential diagnosis of generalized gingival enlargement [6]. Many life-threatening diseases may present with oral lesions as the initial or only manifestation. Literature reveals about 68% of leukemia patients presented oral mucosa lesions [7], thus familiarization with various causes of gingival enlargement is necessary to identify the underlying life-threatening condition.

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CASE REPORT

A 12-year-old female patient came to the Department of Oral Medicine and Radiology, Tamil Nadu Government Dental College and Hospital with the chief complaint of swollen gums and difficulty in chewing food for the past 2 months. The patient was apparently normal 2 months back, after which she noticed swelling of gums which progressed slowly for the first 1 month and remained the same in size for the next month. The patient also gave a history of cough for the past 2 months. The patient underwent consultation and routine blood investigations in a private dental hospital which showed that the parameters were within normal range except for hemoglobin (7.9 g%) and was prescribed anti-inflammatory and antibiotic medications at the private dental hospital which she was taking on and off for the

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past 2 months and noticed not much response.

On general examination, the patient was calm, conscious, and cooperative with normal stature. The patient was moderately built and moderately nourished with a normal gait. The pallor of the palpebral conjunctiva was present. The pulse rate was 80 beats/min, the respiratory rate was 18 cycles/min, the blood pressure was 120/80 mmHg, the temperature was 97.6 F, and the height and weight of the patient were 156 cm and 37 kg, respectively. Extraoral examination revealed that the patient had a symmetrical face with a convex profile. Lymph node examination revealed palpable bilateral submandibular lymph nodes measuring approximately 3×2 cm and was firm and non-tender on palpation (Fig. 1). Intraoral examination revealed generalized gingival enlargement on both the facial and lingual aspects of marginal and attached gingiva extending to more than two-thirds of the crowns of the maxillary and mandibular teeth sparing the incisal and occlusal surfaces. Gingiva was pale pink in color, firm, and edematous in consistency, with a loss of normal contour and loss of stippling. Bleeding on probing was present. Periodontal pocket and pus discharge were absent (Fig. 2). Based on the history and clinical examination, a provisional diagnosis of leukemic gingival enlargement was made. Differential diagnoses of idiopathic gingival enlargement, hormone-induced gingival enlargement - puberty gingivitis, sarcoidosis, and tuberculous gingivitis were considered.

On radiographic evaluation, a dental panoramic radiograph revealed generalized mild interdental bone loss. Erupting 17 and 27, tooth buds of 38 and 48 were seen (Fig. 3).

Her previous routine blood investigations showed that the parameters were within the normal range except for hemoglobin (7.9 g%) (Table 1). The patient was referred to repeat the blood investigations along with the peripheral blood smear examination. The repeated complete blood count revealed that the total white blood cell (WBC) count was abnormally increased (55,000 cells/Cu.mm) and decreased red blood cells (RBC) count (1.97 million/Cu.mm) (Table 1). The peripheral blood smear revealed RBC series showing moderate anisopoiklocytosis with predominantly oval and round macrocytes, polychromatophils, and occasional nucleated RBC, markedly increased total number of WBC series with the presence of blast cells (>80%) and decreased platelets, suggestive of acute leukemia with severe macrocytic anemia and thrombocytopenia. Chest X-ray revealed a normal chest shape with no visible deformities (Fig. 4). Based on the history, clinical examination, and investigations, a final diagnosis of leukemic gingival enlargement was made.

The patient was immediately referred to the department of hematology, where the patient was admitted and further flow cytometry, cytogenetics, and fluorescence *in situ* hybridization (FISH) were performed. Flow cytometry was positive for a few myeloid and monocytic markers (CD33, CD117, MPO, and CD45) suggestive of acute myeloid leukemia (AML), AML-M2/M3v. Chromosomal analysis revealed a normal female karyotype. FISH was negative. FTL3 mutation assay revealed that mutations in FTL3 gene were not detected in leukocytes. Serial complete blood count and serial electrolytes have been advised for the patient till the end of treatment. Transfusions of Packed RBC and platelets have been started.

The patient has been started on injection cytarabine 100 mg/m^2 – IV over 3 h BD for 7 days (14 doses)-12-h interval between each dose, injection daunorubicin 60 mg/m^2 IV OD for 3 days, tablet. Sulfamethoxazole + Trimethoprim (5 mg/kg – in 2 divided doses on alternate days) from day 1 till the end of treatment, tablet fluconazole 150 mg–4 mg/kg/day has been advised to start after chemotherapy.

DISCUSSION

Leukemia is defined as a malignancy affecting the WBCs of the bone marrow which results in a drastic increase in immature or abnormal WBC in the circulation. It was first recognized by Virchow and Bennet in 1845 [8]. The etiology of leukemia is poorly defined, certain factors such as chemical injuries, chromosomal abnormalities, radiation exposure, and viral infections are implicated [9]. The incidence of leukemia is 3.7/100,000 persons and mortality of 2.7 to almost 18/100,000 persons, accounting for about 4% of all deaths from malignancies [10].

Leukemia is mainly classified according to its clinical course as acute and chronic and according to its histogenicity as lymphocytic and myelocytic. Acute lymphocytic leukemia is more common in children accounting for 50% of all neoplasms and 80%

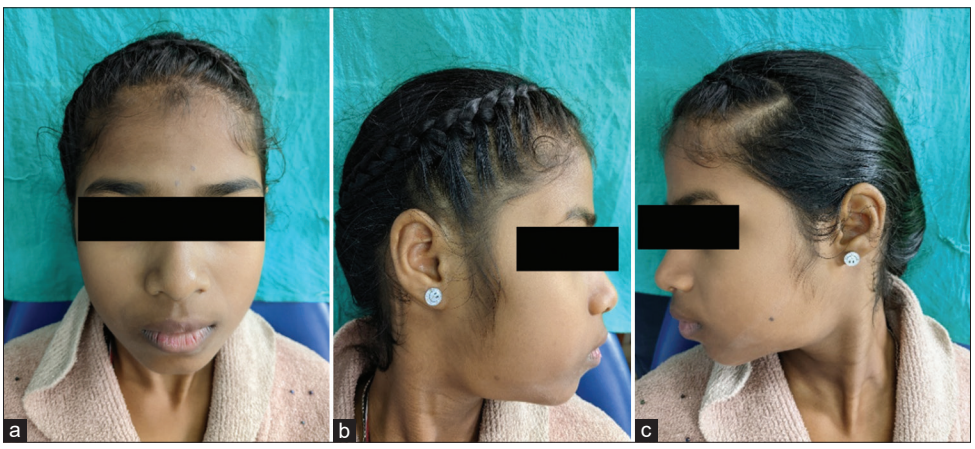

Figure 1: Extraoral images revealing symmetrical face and convex profile

of all leukemia's in children [11]. The incidence of AML increases with age, especially among people older than 65 years of age [12]. French - American - British classification further subdivided AML based on the degree of differentiation along cell lines and the extent of cell maturation as 8 subtypes (M0 to M7) [13].

The symptoms of leukemia are associated with the influence of neoplastic cells on the hematopoietic cells causing myelosuppression. A decrease in the production of erythroblasts causes anemia, pallor, weakness, and constant fatigue. A decrease in granulocyte production causes fever and infections. Decreased platelet production which results in spontaneous bleeding, petechiae, ecchymoses, and bruising. Our patient did not complain of spontaneous gingival bleeding which could be due to the platelet count (1,58,000 lakhs/Cu.mm) still remaining within the normal range. The potential complication of leukemia relating to gingival enlargement is secondary infection decreased granulocytes and massive hemorrhage on invasive dental procedures done without evaluating the blood parameters. It occurs due to decreased platelets. Leukemic cells get infiltrated into the body tissues such as in skin, spleen, gingiva, lymph nodes, and central nervous system [14]. The leukemic cell infiltration of the gingival tissue associated with gingival enlargement can be the first manifestation in acute leukemia as it was in our case. Gingival enlargement occurs in both acute and chronic leukemia, especially the myeloid type.

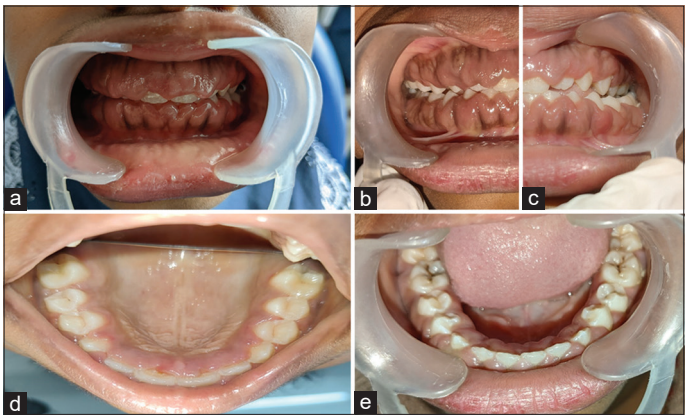

Figure 2: (a-e) Intra oral images revealing generalized gingival enlargement on the labial, buccal, palatal and lingual aspect of marginal and attached gingiva extending to more than two-thirds of the crowns of the maxillary and mandibular teeth

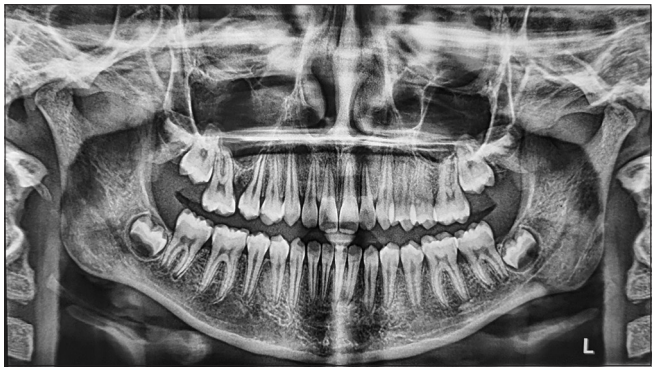

Figure 3: Orthopantomogram revealing mild interdental bone loss

Diagnosis of leukemia is made by physical examination and investigations such as complete blood count and peripheral blood smear. Following which, a bone marrow biopsy is done to evaluate the presence of leukemic cells in the bone marrow. Other specific tests to determine the prognosis and type of leukemia include chromosome abnormalities (cytogenetics) and flow cytometry. In this patient, the flow cytometry was positive for a few myeloid and monocytic markers (moderate expression of CD33, dim expression of CD117, dim-to-moderate expression of MPO and cluster in CD45 dim region) suggestive of AML, AML-M2/M3v. Chromosomal analysis revealed a normal female karyotype. FISH was negative for PML/RARA translocation, AML1/ETO (RUNX1/RUNX1T1) translocation, inversion of chromosome 16, and CBFB gene rearrangement. FTL3 mutation assay revealed that mutations in the FTL3 gene were not detected in leukocytes. The national comprehensive cancer network 2019 guidelines [15] recommends the following investigations as a part of AML workup: complete blood count with manual differential and routine chemistry profile, coagulation profile, bone marrow aspiration including cytogenetics, immunophenotyping, molecular testing for mutations, and HLA typing of patient

Table 1: Comparison of the complete blood count taken 1 month before the patient reported to our institute and repeated after some times

Investigations	Normal range	1 month before	Repeat investigations
Haemoglobin	Female- 12–15 g% Male- 13–17 g%	7.9 g%	5.7 g%
Total WBC count	4000–10,000 cells/cumm	11,000 cells/Cu.mm	55,000 cells/Cu.mm
Differential count			
Neutrophil	50–70%	54%	22%
Lymphocytes	20–40%	40%	70%
Eosinophil	1–10%	6%	6%
Monocytes	2–10%	0%	2%
Basophil	0–1%	0%	0%
RBC count	4.0–5.0 million/cumm	2.6 million/Cu.mm	1.97 million/Cu.mm
MCV	80–99 fL	68 fL	93.4 fL
MCH	26–32 pg	28 pg	29.8 pg
MCHC	32–36 %	30 %	30.9 %
Platelet count	1.5–4.0 lakhs/Cu.mm	1,90,000 lakhs/Cu.mm	1,58,000 lakhs/Cu.mm
ESR	5–20 mm/h	17 mm/h	35 mm/h

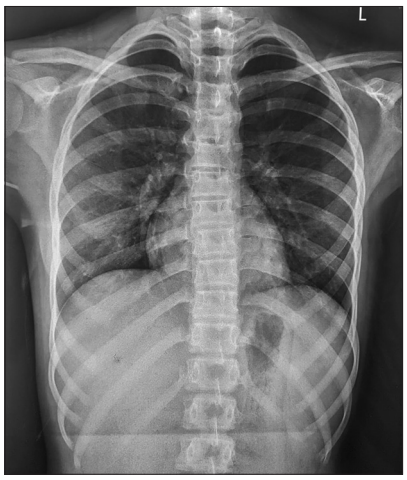

Figure 4: Chest X-ray revealing normal chest shape with no visible deformities

and family. After the cytogenetics and molecular testing, risk stratification should be performed which will guide the treatment decisions and prognosis of the patient.

The standard of care for AML is induction therapy, which is highly toxic to bone marrow causing pancytopenia and bleeding complications. It consists of the "7+3" regimen that includes a continuous infusion of cytarabine for 7 days along with anthracycline on days 1–3. Individuals who achieve a complete remission with a blast count of <5% in the bone marrow after induction therapy tend to have increased survival. After this, consolidation therapy is initiated with high-dose cytarabine and hematopoietic cell transplantation. It is initiated to prevent any risk of relapse by eliminating the residual disease [16]. Most initial treatment decisions for AML are based on age, history of prior myelodysplasia or cytotoxic therapy, and performance status. Karyotypes and molecular markers are powerful predictors of outcomes. The risk stratification based on cytogenetics and molecular abnormalities can be classified as favorable risk (t(8;21), t(15;17), inversion of chromosome 16 or t(16;16), or normal cytogenetics with NPM1 gene mutation in the absence of FTL3-ITD, biallelic CEBPA mutation), intermediate risk (t(9;11), normal cytogenetics +8 or t(8;21), inversion of chromosome 16, t(16;16) with c-Kit mutation), and poor/adverse risk (complex (>3 clonal chromosomal abnormalities or normal cytogenetics with FTL3-IDT mutation) [17]. Risk stratification is the most important for predicting the remission rate, relapse risks, and overall survival outcome of the patient. The results are suboptimal even in favorable patients with age >65 years. The recommendations for induction therapy for favorable, intermediate, and adverse-risk patients vary based on a higher or lower risk of treatment-related mortality. According to the literature, the overall life expectancy with recent treatments has increased slightly, but most patients have a shortened lifespan [17].

CONCLUSION

In this case, the patient was provisionally diagnosed with leukemic gingival enlargement solely on the basis of oral manifestation and lymph node examination. Although the initial blood investigations done elsewhere did not show any abnormality, upon repeating the blood investigations along with the peripheral smear study the diagnosis was confirmed. Local periodontal therapy without proper diagnosis is unwarranted in such cases and may lead to life-threatening complications. Thus, it is imperative for dental surgeons and specialists in oral Medicine, to be aware of the systemic causes of gingival enlargement and elicit proper history and perform thorough general examination and oral examination, followed by a thorough investigations to arrive at an accurate diagnosis and timely referral to prevent life-threatening complications.

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