Periodontal and Implant Research (2024) 8:2
https://doi.org/10.1007/s41894-024-00129-4

CASE REPORT

Gingival enlargement as a periodontal manifestation of acute myeloid leukemia

David Kiramira[1] · Matthias M. Gaida[2,3] · Pablo Cores Ziskoven[1]

Received: 12 March 2024 / Accepted: 18 April 2024 / Published online: 7 May 2024

Abstract

Non-plaque-induced gingival diseases represent a heterogeneous group of systemic conditions that affect the gingival tissues. According to the current classification, they include genetic/developmental disorders, specific infections, inflammatory and immunological diseases and lesions, reactive processes, neoplasms, endocrine, nutritional and metabolic diseases, traumatic lesions and gingival pigmentation (Holmstrup et al. in J Periodontol 89:S28–s45, 2018). They can be challenging for the dentist, as they are often the first symptoms of a serious disease and are often difficult to distinguish from typical diseases of the oral mucosa. An early and correct diagnosis can be crucial for the patient's survival. A 57-year-old woman presented at the Department of Periodontology and Operative Dentistry at Johannes Gutenberg University Mainz. She complained that her gums had been swollen for a week and stated that she had difficulty with oral hygiene as the gums were painful and bled at the slightest touch. She had previously taken amoxicillin 1000 mg (1-1-1) for a week, but this did not lead to any improvement. A blood sample and a biopsy of the gingival enlargement led to the diagnosis of acute myeloid leukemia. The gingival enlargement regressed during the subsequent chemotherapy. After oncological rehabilitation, dental treatment was carried out.

Keywords Gingival enlargement · Gingival hyperplasia · Acute myeloid leukemia · Non-plaque-induced gingival diseases · Neoplasms · Leukemic cell infiltration

✉ David Kiramira
david.kiramira@unimedizin-mainz.de

[1] Department of Periodontology and Operative Dentistry, Johannes Gutenberg-University, Mainz, Germany

[2] Institute of Pathology, University Medical Center Mainz, Johannes Gutenberg University, Mainz, Germany

[3] Research Center for Immunotherapy, University Medical Center Mainz, Mainz, Germany

Case presentation

A 57-year-old patient was referred by her general practitioner to the Department of Periodontology and Operative Dentistry at Johannes Gutenberg University Mainz. He had diagnosed her with "extensive gingivitis of unclear etiology". A small blood count showed a slight increase in CRP to 7 mg/l (norm < 5 mg/l) and was otherwise unremarkable. The general dentist prescribed her amoxicillin 1000 mg (1-1-1) for one week, but this did not lead to an improvement. At her initial presentation, her general condition was good. The patient's medical history included high blood pressure, hypothyroidism and reflux. In 2017, she had a tumor in her lower abdomen, which was surgically removed, and a hernia operation in the same year. The medications included candesartan (antihypertensive), L-thyroxine (thyroid hormone) and pantoprazole (proton pump inhibitor). She was also a smoker (40 pack years). She complained that her gums had been swollen for a week and stated that she had difficulty with oral hygiene at home because her gums were painful and bled even when lightly touched (Fig. 1). General symptoms that could indicate a malignant disease, such as B symptoms (symptom triad of fever, night sweats and weight loss), were absent [2]. A digital panoramic radiograph was requested from the referring dentist (Fig. 2). The clinical findings revealed dentition with prosthetic and conservative restorations and poor oral hygiene (plaque and calculus). The gingival enlargement on all teeth with bleeding on probing was conspicuous. The maxillary sinus, temporomandibular joints, carotid and parotid regions were, as far as could be assessed, without pathological findings. The panoramic radiograph taken by the referring

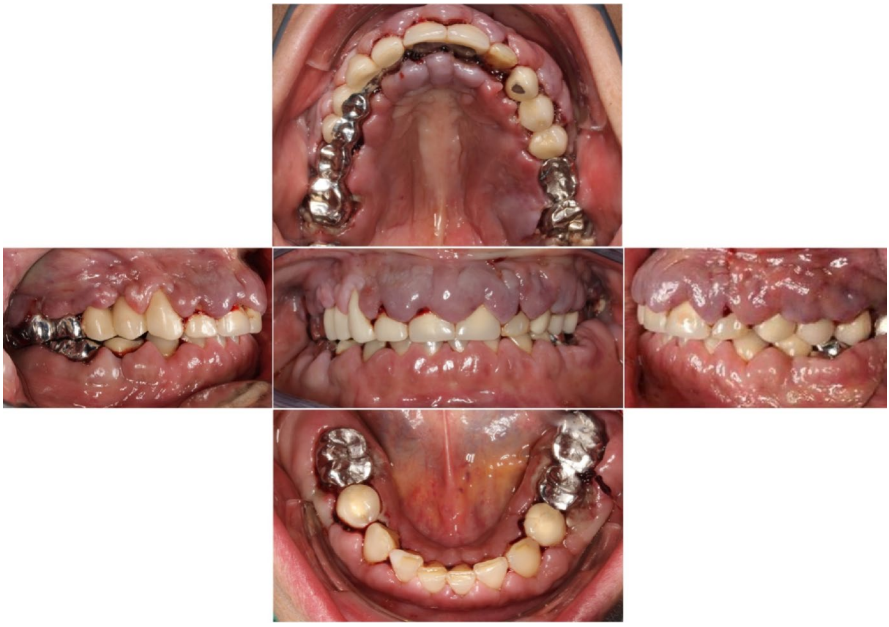


Fig. 1 Initial situation

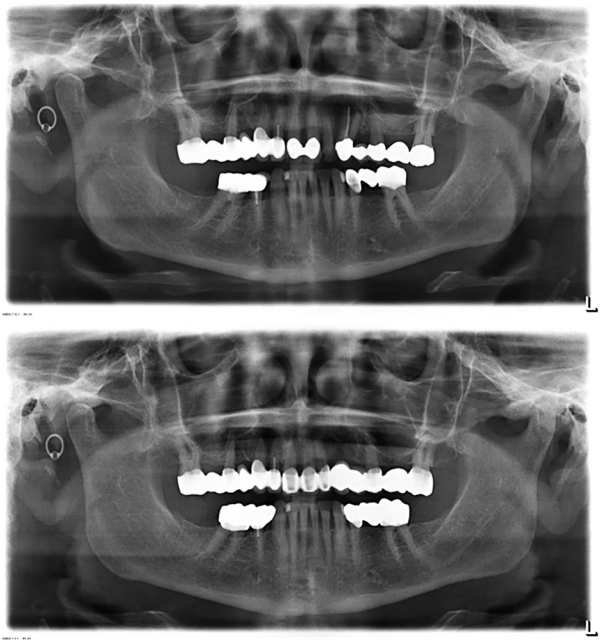


Fig. 2 X-rays (1: Baseline X-ray; 2: X-ray after chemotherapy, removal of 23 and prosthodontics)

dentist showed a restoratively and prosthetically treated dentition. A generalized horizontal alveolar bone loss with a vertical bone defect mesial to tooth 46 was noted. The longitudinal fractured tooth 23 (fracture visible on the X-ray) was excluded as the cause of the generalized gingival enlargement. Medication could also be ruled out as an etiological factor. Due to the significant microbial plaque accumulation and the patient's age, the initial suspected diagnosis was "Plaque-induced gingivitis with reactive enlargement of the gingiva", with menopause as systemic risk factor. After informing the patient, the detailed periodontal status was recorded. The first step of our treatment plan was the removal of plaque and calculus under local anesthesia using manual and ultrasonic instruments and Airflow cleaning to reduce the bacterial load. This was accompanied by irrigation of the pesudopockets with 3% hydrogen peroxide (H_2O_2). The ongoing antibiotic treatment was not interrupted but modified to Amoxicillin 500 mg and Metronidazole 400 mg 3/d. Oral hygiene at home was supplemented with a mouth rinse containing Chlorhexidine gluconate (Chlorhexamed Forte 0.2% without alcohol), which was to be used twice daily (rinse with 10 ml for one minute). She was given a gel containing lidocaine (XYLOCAIN GEL 2%) to reduce localized pain. A recall was carried out every second day. At the next visit, the patient stated that she was suffering less pain, but the clinical appearance of the gums remained unchanged. The papillae appeared detached. Ulcerations were now visible at the edge of the gingiva in the palatal aspect of the upper molars and in the lingual and vestibular aspect of the lower molars. Despite adequate biofilm control and concomitant antibiotic therapy, the gingival hyperplasia persisted over a period of one week. As no clear odontogenic focus could be identified, the

tentative diagnosis was dismissed consecutively and replaced by the diagnosis: "gingival hyperplasia linked to a hematologic systemic disease". To confirm the diagnosis, a blood sample was taken for a complete blood count (complete blood count plus differential blood count of leucocytes) and a local excisional biopsy was performed to rule out hematological disease. The results of the complete blood count were available after four hours on the same day. An increase in CRP to 78 mg/l (norm < 5 mg/l) despite ongoing antibiotics and previous anti-infective therapy as well as thrombocytopenia with 34 thrombocytes per nanoliter (norm: 150–360/nl) were conspicuous. The leukocytosis suggested a malignant hematological disease: the number of leukocytes was 117 per nanoliter (norm leukocytes 3.5–10/nl). The result of a blood smear was forwarded to the Department of Hematology, Oncology, and Pneumology at the University Medical Center of the Johannes Gutenberg-University of Mainz. The patient had to present to the emergency department immediately afterwards and was admitted as an inpatient. Table 1 shows the course of some characteristic blood values during inpatient stay. 4 days after excisional biopsy, we received the findings from the Institute of Pathology, University Medical Center Mainz: keratinized, stratified squamous epithelia with subepithelial round body infiltrates were visible under the light microscope (Fig. 3). These infiltrates were then examined using immunohistochemical methods and were identified as myeloid blasts, which are typical of acute myeloid leukemia. Based on the molecular and cytogenetic methods, the patient's prognosis was classified as favorable [3]. In order to achieve remission, the haemato-oncologist began induction therapy with high-dose cytostatic drugs. The oncological treatment proved to be difficult: after the first chemotherapeutic cycle, the patient suffered a septic shock, accompanied by atrial fibrillation, which required cardioversion. She also had to be treated in intensive care due to kidney failure and acute respiratory insufficiency. 3 months after these adverse events, the cytostatic treatment could be continued. The patient underwent four cycles of chemotherapy within five months. The gingival enlargement disappeared completely during chemotherapy without any dental intervention (Fig. 4). A stem cell transplant was not indicated.

7 months after diagnosis, the patient's general condition had stabilized with normal blood values, which is a sign of remission. She continues to receive outpatient long-term follow-up for hematological oncology.

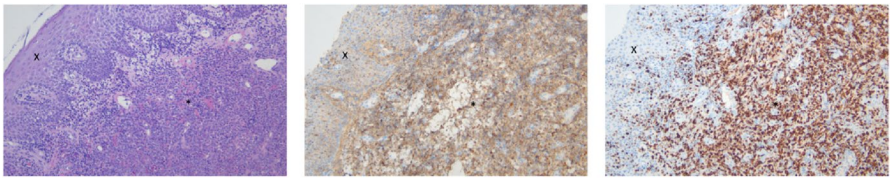
The oncologists agreed to continued dental treatment: The fractured tooth 23 was removed under local anesthesia and with antibiotic prophylaxis. The wound was treated using a Rehrmann buccal flap. The wound healing was timely (Fig. 5). Further prosthetic care was carried out by the referring dentist (Fig. 6). The patient is satisfied with the treatment results and is characterized by high adherence. Oral hygiene has improved.

Discussion

Leukemia refers to neoplasms of different precursor cells of hematopoiesis. Depending on whether precursors of the myeloid cell line or the lymphatic cell line are affected, the disease is categorized as myeloid or lymphatic leukemia. Patients may show acute

Table 1 Course of blood values during the inpatient stay

	Initial visit	24th day	25th day	27th day	29th day	63th day	66th day	Unit	References
Clinical chemistry (lithium-heparin plasma)									
Lactate dehydrogenase (LDH)	922						221	U/I	< 245
C-reactive protein (CRP)	78	98	69	45	52	18	14	mg/l	< 5
Haematology (EDTA blood)									
Leucocytes	117	9.1	9.75	10.4	11.5	13.9	12.2	/nl	3.5–10
Thrombocytes	34	211	268	325	388	376	354	/nl	150–360
Haemoglobin concentration (Hb value)	9.6	9.2	8.9	8.8	9.7	10.6	10.7	g/dl	12–16
Haematocrit	28,5	27.9	27.5	26.6	29.0	31.9	33.4	%	34–44



3.1 = **HE staining (haematoxylin-eosin staining)**: Dense monotonous tumour cell infiltrate
3.2 = **Myeloperoxidase staining**: The marker myeloperoxidase used detects the myeloid origin of the tumour cells
3.3 = **Immunohistochemical** staining of the growth fraction of the tumour with antibodies against Ki-67
(The proliferation marker Ki-67 indicates a very high proliferation rate [approx. 90%])

X = oral mucosa
* = tumour cells

Fig. 3 Histological staining and immunohistochemical antibody staining of the biopsy

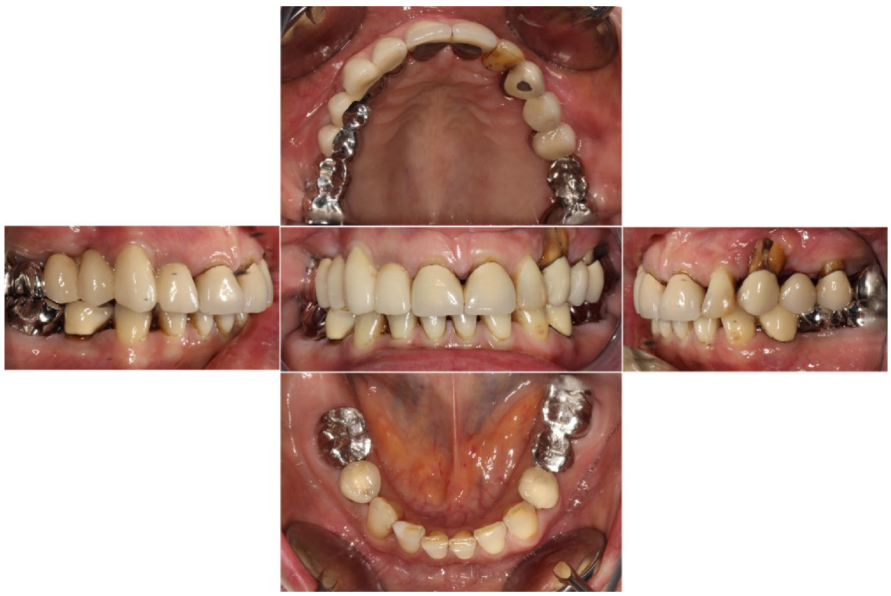


Fig. 4 Clinical picture during chemotherapy (4 months after initial presentation)

symptoms or more insidious manifestations, which explains the basic classification into acute and chronic leukemia. In contrast to solid tumors, there is no TNM classification (classification by staging and grading), but instead disease-specific stages are distinguished. The classification is supplemented by cytological, cytochemical, immunological and molecular genetic characteristics. The FAB classification (FAB: French-American-British Cooperative-Group) differentiates the subtypes of AML according to cytomorphological criteria [4], while the WHO classification of 2022 is based on molecular genetic, cytogenetic and immunological criteria [5]. This malignant disease of the hematopoietic system is characterized by the development of immature or non-functional precursors of hematopoiesis in the bone marrow and blood, which displace the original blood cells (erythrocytes, thrombocytes, granulocytes; the blood count

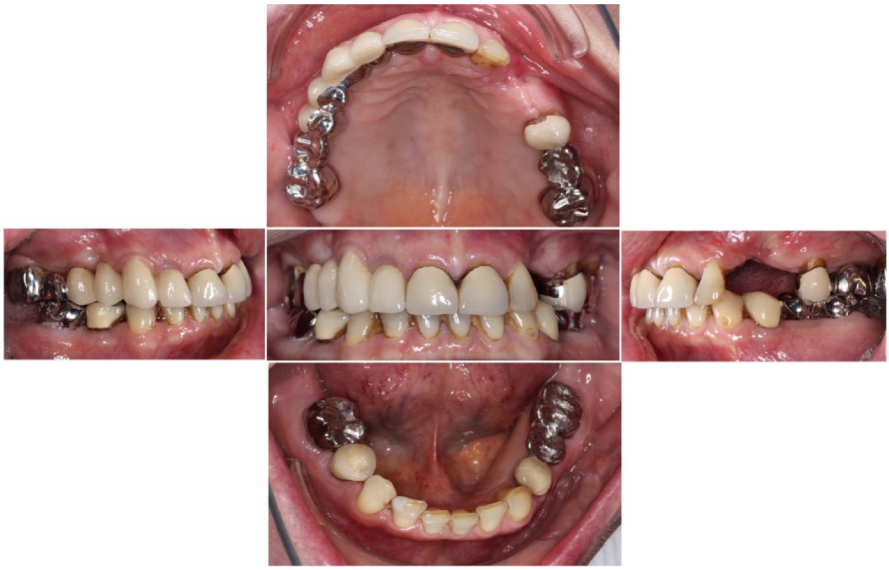


Fig. 5 Clinical picture after chemotherapy and removal of 23 (7 months after initial visit)

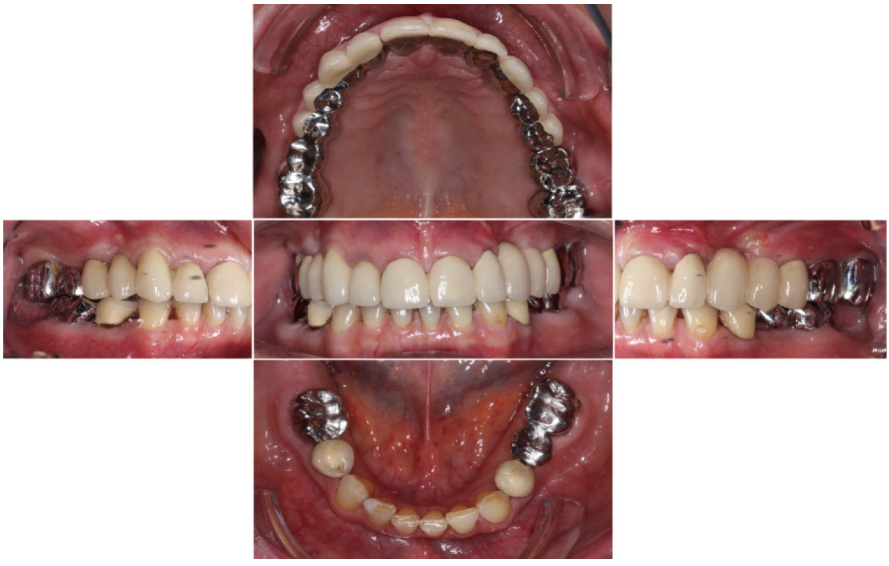


Fig. 6 Clinical pictures after chemotherapy and prosthetic restoration (9 months after initial visit)

shows anemia, thrombocytopenia and lymphopenia). Leukemic cells proliferate in the bone marrow and blood and can infiltrate other organs. The blood count may show a leukocytosis (with a leukocyte count > 100/nl), but the leukocytes can no longer fulfil the actual function of blood cells. As these functionless cells divide uncontrollably and have

an extended half-life, the normal blood cells (and thus the physiological hematopoiesis) are displaced. In the present case, the reduced platelet count, erythrocyte count and granulocyte count as well as the significantly increased leucocyte count can therefore be explained by the defect in the myeloid progenitor cell. Possible clinical symptoms include B-symptoms, increasing coagulation disorders, increased vulnerability to infection, pallor, dizziness and, in advanced stages, dyspnea. There may also be symptoms of leukemic organ infiltration, such as the infiltration of the oral mucosa in the present case.

In the present case, the gingival enlargement is not a hyperplasia, which is defined by an increase in tissue size due to an increasing number of cells. In leukemia-induced gingival proliferation, there is no proliferation of gingival fibroblasts and the extracellular matrix or inhibition of collagenases, as is the case with Drug-Induced Gingival Overgrowth [6]. Gingival proliferation is primarily caused by leukemic infiltrates. It is an uncontrolled immigration and proliferation of myeloid or lymphatic progenitor cells [7].

The relationship between the occurrence of gingival enlargement and poor oral hygiene status as a risk factor in AML patients has not been clearly established. However, it has been shown that such oral manifestations of systemic diseases do not occur in the edentulous jaw and are significantly less common in children [8]. It is not possible to predict in which cases gingival overgrowth will occur. However, chronically inflamed periodontal tissue with loose connective tissue may be more vulnerable [9].

In view of the poor oral hygiene, relatively good general condition and almost normal blood values (only CRP of 7 mg/l), the initial suspected diagnosis of plaque-induced gingival enlargement seems reasonable at first. However, in the case of persistent symptoms, despite adequate elimination of possible etiological factors, we had to question the suspected diagnosis immediately. The erosive areas and the livid color of the oral mucosa also spoke against the erosive areas and the livid color of the oral mucosa also spoke against induction by dental biofilm. A systemic cause had to be considered immediately and further diagnostic measures initiated. This case impressively demonstrates that non-plaque-induced gingival diseases are often the first symptoms of a serious disease and are often difficult to distinguish from typical diseases of the oral mucosa. An early and correct diagnosis can be crucial for the patient's survival.

Conclusion

In cases of gingival enlargement local factors (such as oral biofilms, orthodontic appliances, insufficient restorations, poor fitting dentures, mouth breathing) or drug-related causes (e.g. antihypertensives, anticonvulsants and immunosuppressants) appear to be obvious. However, possible systemic causes (e.g. leukemia, hormonal factors, Wegener's granulomatosis, scurvy) should also be considered. The patient's external appearance and general condition do not necessarily indicate a systemic disease. If possible odontogenic or local foci can be detected, their immediate elimination and close follow-up are recommended. The general practitioner should be involved immediately (e.g. for a general medical examination and blood test). In the event of persistence, further diagnostics (possibly by specialists) are recommended. In this case, a referral to a

haematooncologist in a special center would be necessary, as immediate medical treatment can be crucial for the patient's survival.

Author contributions David Kiramira and Pablo Cores wrote the main manuscript text. David Kiramira prepared Figs. 1, 2, 4, 5 and 6. Matthias Gaida prepared Fig. 3. David Kiramira prepared Table 1.

Funding Open Access funding enabled and organized by Projekt DEAL.

Data availability No datasets were generated or analysed during the current study.

Declarations

Conflict of interest The authors declare no competing interests.

References

1. Holmstrup P, Plemons J, Meyle J (2018) Non-plaque-induced gingival diseases. J Periodontol 89(Suppl 1):S28-s45. https://doi.org/10.1002/jper.17-0163
2. Carbone PP, Kaplan HS, Musshoff K, Smithers DW, Tubiana M (1971) Report of the committee on Hodgkin's disease staging classification. Cancer Res 31(11):1860–1861
3. Döhner H, Wei AH, Appelbaum FR, Craddock C, DiNardo CD, Dombret H et al (2022) Diagnosis and management of AML in adults: 2022 recommendations from an international expert panel on behalf of the ELN. Blood 140(12):1345–1377. https://doi.org/10.1182/blood.2022016867
4. Bennett JM, Catovsky D, Daniel MT, Flandrin G, Galton DA, Gralnick HR et al (1976) Proposals for the classification of the acute leukaemias: French-American-British (FAB) co-operative group. Br J Haematol 33(4):451–458. https://doi.org/10.1111/j.1365-2141.1976.tb03563.x
5. Arber DA, Orazi A, Hasserjian RP, Borowitz MJ, Calvo KR, Kvasnicka HM et al (2022) International consensus classification of myeloid neoplasms and acute leukemias: integrating morphologic, clinical, and genomic data. Blood 140(11):1200–1228. https://doi.org/10.1182/blood.2022015850
6. Brunet L, Miranda J, Farré M, Berini L, Mendieta C (1996) Gingival enlargement induced by drugs. Drug Saf 15(3):219–231. https://doi.org/10.2165/00002018-199615030-00007
7. Hasan S, Khan NI, Reddy LB (2015) Leukemic gingival enlargement: Report of a rare case with review of literature. Int J Appl Basic Med Res 5(1):65–67. https://doi.org/10.4103/2229-516x.149251
8. Cooper CL, Loewen R, Shore T (2000) Gingival hyperplasia complicating acute myelomonocytic leukemia. J Can Dent Assoc 66(2):78–79
9. Dreizen S, McCredie KB, Keating MJ, Luna MA (1983) Malignant gingival and skin "infiltrates" in adult leukemia. Oral Surg Oral Med Oral Pathol 55(6):572–579. https://doi.org/10.1016/0030-4220(83)90373-0