Acute myeloid leukaemia: an update for dentists

Précis

This report highlights the oral manifestations of leukaemia. It illustrates the classification, the signs and symptoms, and the differential diagnoses of leukaemia that are relevant for a dental practitioner. There is also an example of a case report, which highlights some of the intra-oral presentations of acute myeloid leukaemia (AML).

Abstract

Many systemic diseases exhibit oral involvement. These intra- and extra-oral signs can have diagnostic weighting. Acute myeloid leukaemia (AML) is just one of a number of conditions that can present in the mouth. AML is a haematological malignancy, seen generally in the older population. Cervical lymphadenopathy and gingival enlargement, attributed to AML are the two most common signs that may present in a dental setting.

The case report also demonstrates that the treatment of systemic diseases can resolve the oral complications of the particular disease. In this case report, the treatment of the AML resulted in a resolution of the gingival hyperplasia.

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Introduction

Leukaemia is defined as a malignant, haematological proliferation of white blood cell precursors.[1] Lymphocytes are a subgroup of white blood cells, which originate from lymphoid progenitor cells. Red blood cells and platelets in comparison are derived from myeloid progenitor cells.

The myeloid progenitor cells also produce a subgroup of white blood cells called granulocytes, namely monocytes, neutrophils, basophils and eosinophils. The lymphoid and myeloid progenitors originate from self-renewing stem cells in the bone marrow.[2] Lymphoid cells mature into lymphocytes and regulate the adaptive immune response. They also regulate the production and life cycle of immunoglobulins.[3,4]

In a patient with leukaemia, the balanced ratio of white blood cells, red blood cells and platelets is disproportionate (**Figure 1**). The levels of white blood cells may be unusually high or low and the complete blood count values for red blood cells and platelets are also outside their normal remit. A bone marrow biopsy is a confirmative test for leukaemia. Cytological screening of the defective cells can provide additional information about the malignant cells and their nature.[1,4]

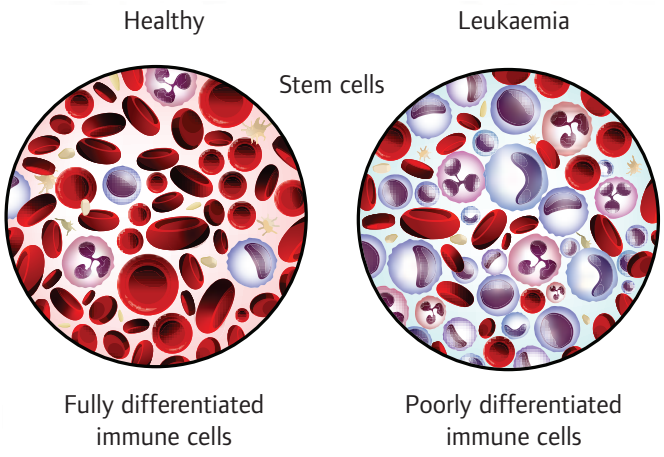

FIGURE 1: A schematic diagram depicting stem cell differentiation in normal and pathological processes.

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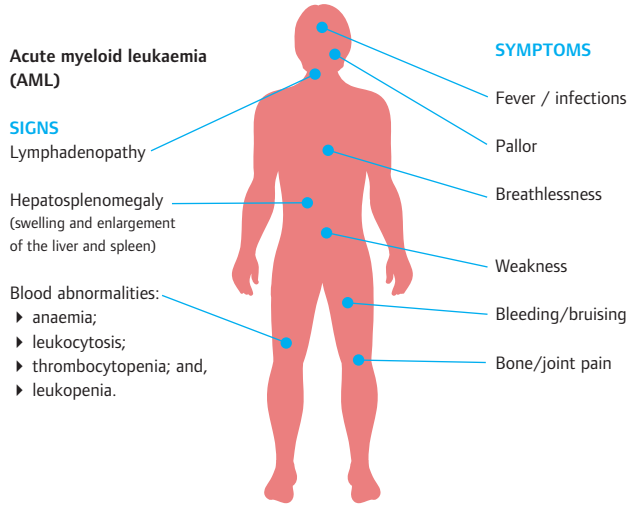

FIGURE 2: Systemic signs and symptoms of leukaemia.

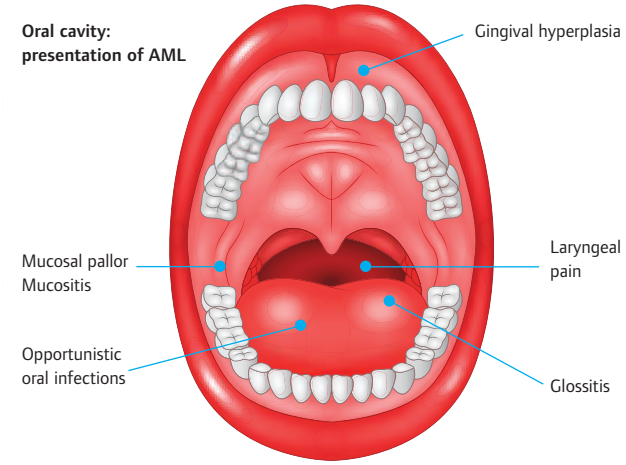

FIGURE 3: Oral signs and symptoms of acute myeloid leukaemia.[4]

A classification of leukaemia has been devised, which divides leukaemia into the nature of the disease, namely acute or chronic and the haemopoietic origin of the cells involved; either lymphoid or myeloid.[5] The four classes of leukaemia are as follows:

- acute lymphocytic leukaemia (ALL);
- acute myeloid leukaemia (AML – **Figure 2**);
- chronic lymphocytic leukaemia (CLL); and,
- chronic myeloid leukaemia (CML).[6]

Alternative classifications of leukaemia have been proposed, such as the French-American-British (FAB) classification and the World Health Organisation (WHO) classification, which are commonly used worldwide. In 2016, the WHO revised its classification of leukaemia, which incorporates both haematopoietic and lymphoid tumours. This classification addresses the clinical picture, the morphology, the immune-phenotypes, the cytogenetics, and molecular genetics of the defective cells.[7]

AML is more commonly seen in the older population, with peak incidence noted in the seventh decade. In comparison, ALL is more prevalent in the younger population, constituting 80% of childhood leukaemia. There is no known definitive aetiology for leukaemia. However, there are primary risk factors for both ALL and AML, which include genetic abnormalities, Down syndrome, Fanconi anaemia and chromosomal fragility.[2]

There are a number of secondary risk factors for leukaemia; these include high-dose radiation, therapeutic radiation and exposure to toxic hydrocarbons such as benzene. AML has a number of additional risk factors including smoking and haematological conditions such as: myelodysplasia; myeloproliferative disorders; myelofibrosis; aplastic anosmia; and, polycythaemia rubra vera.[2]

Chronic, long-standing leukaemia can take multiple years to reach a definitive diagnosis, whereas acute leukaemia can be fatal within a matter of weeks.[2]

Leukaemia can present with intra-oral findings (**Figure 3**) of the malignancy.[8] These signs may be of primary origin, which is a direct result of migration of the defective cells into the oral tissues. They may be of secondary presentation, which is a consequential complication of leukaemia. Tertiary presentation results in the direct effect of antineoplastic therapy.[4]

Oral signs and symptoms of AML

Additional signs and symptoms of AML may include lymphadenopathy, petechiae and the presentation of opportunistic bacterial, fungal and viral infections.[5]

CASE REPORT

A 53-year-old male presented to the Oral Surgery Department at the Cork University Dental Hospital with regard to gingival enlargement (**Figure 4**). He was referred by his haematologist, who was managing his myelodysplastic syndrome.

The medical history included insomnia, myelodysplastic syndrome, and hypertension. His medications included zopiclone and amlodipine. He denied smoking cigarettes or drinking alcohol.

On presentation, there were generalised gingival enlargement and gingival petechiae. The gingivae were erythematous, inflamed, and lobulated with a distinct lack of stippling. There were signs of oral mucositis, an area of ulceration on the dorsum of the tongue and a diffuse, soft red patch on the hard palate. Lymphadenopathy was not detected on presentation.

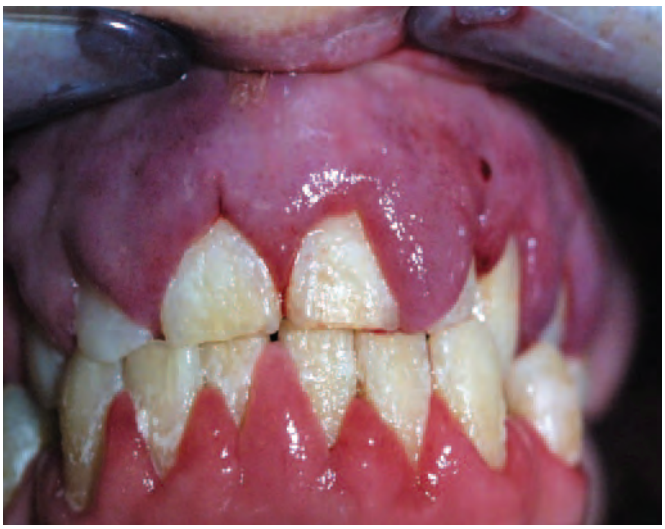

FIGURE 4: Gingivae on presentation to the Cork Dental University Hospital, depicting the leukemic infiltrate in the gingival tissues. Poor oral hygiene was also noted.

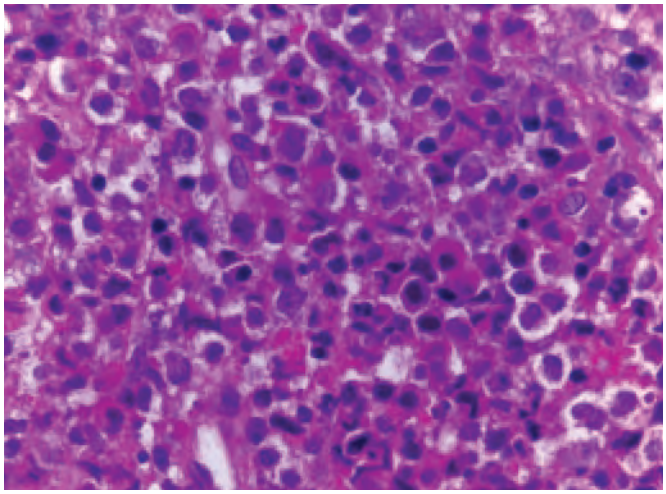

FIGURE 5: Microscopic view of the incisional biopsy from the gingivae.

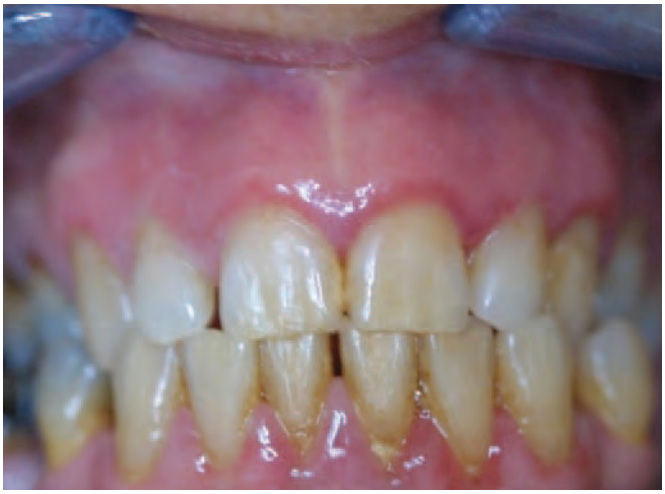

FIGURE 6: Gingival tissues following the first phase of chemotherapy.

Investigations

The following special tests were performed: a microbial culture swab of the dorsum of the tongue; an incisional biopsy of the hard palate; and, an incisional biopsy of the swollen, attached gingivae. A platelet infusion was arranged prior to the surgical procedures.

Differential diagnoses

Medication-induced gingival enlargement (calcium channel blockers), which the patient was taking and secondary metastatic deposits, were eliminated due to the histological appearance of AML.

Histology

The histopathology report of the erythematous patch on hard palate revealed an acute and chronic inflammatory response with fungal hyphae. There was no evidence of dysplasia. These results were indicative of oral candidiasis.

The second biopsy of the upper left attached, swollen gingival tissues revealed the presence of atypical cells with irregular cytoplasmic granules. This histopathological report is indicative of AML.

Normal gingival architecture does not have the presence of dense cytoplasmic granules, which are highlighted by the dark purple stain in **Figure 5**.

Treatment

The patient was prescribed amphotericin B and voriconazole for oral candidiasis. BMX mouth wash and analgesics were prescribed for the oral mucositis. BMX is a compounded medication, which contains nystatin, hydrocortisone and diphenhydramine.

There was a consultation with the haematologist and in conjunction with a bone marrow biopsy, the AML was treated with a chemotherapeutic regime. The chemotherapy regime included cytarabine and daunorubicin.

Outcome

After the first phase of chemotherapy there was a complete resolution of the gingival enlargement and oral mucositis. Frontal photographic view of the gingival tissues after the chemotherapy regime indicates smooth, pink, healthy gingivae (**Figure 6**). Note the presence of plaque-induced gingivitis. This highlights the dual effect of both inflammation and a systemic disease on the gingival architecture. Maintenance periodontal treatment and regular dental check-ups were performed by the general dental practitioner.

Discussion

AML is a malignancy of unknown aetiology. However, it can develop from a precursor of leukaemia such as myelodysplastic syndrome. AML can be diagnosed in any age group of the population but most notably in the older population.

AML can present initially in the oral cavity.[6-8] There are a number of oral findings that are commonly detected in the leukemic patient. Both direct and indirect physiological effects of leukaemia will render many patients neutropenic, anaemic, thrombocytopenic and myeloid-suppressed.[3,4] Consequentially, the prevalence of opportunistic bacterial, fungal and viral infections is abundant.[2,4,9-11] The most common opportunistic infection seen in patients with leukaemia is the herpes simplex virus 1 (HSV-1), which can be confirmed in conjunction with the clinical scenario using cytology and immunofluorescent antibody to HSV-1 and a viral culture. HSV can present as vesicles and areas of ulceration predominantly in the oral cavity, but can also present in the pharynx, eyes, face and lips. Herpetic gingiva-stomatitis is also common amongst this cohort.

Another oral complication of AML is the sequelae of thrombocytopenia. The signs and symptoms may be attributed to number of causes, namely myelosuppression, and the reduction of platelets and clotting capacity of the blood cells. Thrombocytopenia can be haematologically defined as a platelet count of 20,000/cu.mm or below.[12] Spontaneous intra-oral bleeding, mucosal petechiae and prolonged post-extraction bleeding times are prevalent amongst these patients.[4]

A retrospective study conducted by Hou *et al.* reported a variation in the oral presentation of leukaemia, depending on the form of the malignancy.[12] AML and ALL exhibited similar prevalence of oral and extra-oral involvement, notably lymph node enlargement (45%), gingival bleeding (43.2%) and laryngeal pain (37.3%). The most prevalent systemic symptom in all leukemic patients was fever (92.2%). As a result of the high prevalence of cervical lymphadenopathy, a full examination of these chains is recommended.

Lymphadenopathy that persists for more than six weeks, a lymph node that is 2cm or greater in size, widespread lymphadenopathy, or night sweats with associated splenomegaly, are significant according to the National Institute for Health and Care Excellence (NICE) referral guidelines for a suspected cancer (2005).

Hou *et al*. correlated a platelet count and consequential prevalence of gingival bleeding in patients, which was noted as their first sign of thrombocytopenia.[8] A total of 83% of patients with a platelet count less than 25,000mm^{-3} had gingival bleeding compared to 15% of patients with a platelet count of 100,000mm^{-3} or greater.[12]

Conclusion

The early detection of AML can be noted by the dental practitioner. This can directly influence both the morbidity and mortality of the malignancy, especially in the acute cases.[7] These cases may present to a dental setting with findings such as loss of appetite, loss of weight, persistent lymphadenopathy, and unexplained petechiae, laryngeal pain and gingival hyperplasia. If there is suspicion surrounding these findings, this should prompt a medical enquiry. The NICE guidelines 2017 for the referral of suspect cancer state that a referral process must be arranged for the patient to attain the appropriate medical appointment and seen within a two-week timeframe. AML may present in the dental setting and it is imperative to identify these clinical indictors.

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CPD questions

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CPD

1. Certain medication can induced gingival hyperplasia. Which of the following medication is a well-known cardiac medication that may cause gingival enlargement?

- ○ A: Amlodipine
- ○ B: Losartan
- ○ C: Furosemide
- ○ D: Valsartan

2. Oral candidiasis and petechiae may be an oral sign of leukaemia. They are classified as a:

- ○ A: Primary presentation
- ○ B: Secondary presentation of leukaemia.
- ○ C: Tertiary presentation
- ○ D: None of the above

3. There is no definitive aetiology for leukaemia; however, the following are associated as risk factors for the haematological condition except:

- ○ A: Fanconi anaemia
- ○ B: Myelodysplastic syndrome
- ○ C: Fanconi syndrome
- ○ D: Myeloproliferative disorders.