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Oral manifestations as an early clinical sign of acute myeloid leukaemia: a case report

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ABSTRACT

Leukaemia is the most common malignancy in children and one of the most common malignancies in young adults. Acute myeloid leukaemia is often associated with early oral manifestations. The purpose of this study is to report the case of a 49-year-old male with spontaneous gingival bleeding for over two years with undiagnosed leukaemia. Haematological investigation was instigated and on referral to the Haematology Department at Dunedin Public Hospital, the diagnosis of an acute myeloid leukaemia was confirmed. Since oral lesions can be one of the early events of acute myeloid leukaemia, they may be considered as an important diagnostic indicator for oral health practitioners, and their roles in diagnosing and treating such patients.

Keywords: Acute myeloid leukaemia, leukaemia, oral manifestations, spontaneous bleeding.

Abbreviations and acronyms: AML = acute myeloid leukaemia; CBC = complete blood count.

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INTRODUCTION

Oral manifestations are often potential indicators of systemic diseases, so recognizing them can lead the way to a prompt diagnosis and management. The oral cavity can act as a mirror that reflects many internal problems. Oral health practitioners should be familiar with the oral manifestations of systemic diseases as some are disease-specific. Leukaemia is a malignancy of haematopoietic cells characterized by the proliferation of malignant leucocytes and destruction of the bone marrow. General manifestation of leukaemia may include fatigue, anaemia, lymphadenopathy, recurrent infection, bone and abdominal pain, bleeding and purpura.[1] Oral manifestations of leukaemia may include petechial haemorrhages of the tongue, lips, posterior hard and soft palate, gingival hyperplasia and spontaneous gingival bleeding.[1,2] Oral ulcerations are common. They may be due to either neutropenia or direct infiltration by the leukaemic cells.[3] Patient may also suffer from severe viral, bacterial and fungal infections as a consequence of pancytopenia.[4] The relationship between leukaemia and a wide variety of oral lesions has been well documented in many studies.[1,5–8] It has been suggested that oral manifestations of leukaemia could be considered as diagnostic indicators of the disease.[9]

CASE REPORT

In September 2013, a 49-year-old male was referred by the Urgent Care Unit to the Dental House Surgeon Clinic (Dental School, Dunedin, New Zealand) for evaluation and treatment of persistent bleeding gingivae palatal to his maxillary central incisors that the patient had first noticed two years previously. He had not been concerned until the previous evening when the bleeding would not stop. In addition to the bleeding gingivae, he had a history of exertional breathlessness, which had worsened over several weeks. The gingivae were painless and showed no abnormal swelling during this period. He had no history of facial trauma. Medically, he had chronic muscular skeletal back and neck pain, congenital glaucoma with bilateral goniotomies and right buphthalmos. He was taking clindamycin due to tonsillitis. He had no regular medications and supplements. He was allergic to penicillin. He had no family history of any bleeding disorders. He worked as an information technology consultant and was married with two young children. He did not smoke and rarely drank alcohol.

On extraoral examination, no regional lymphadenopathy or salivary gland swelling was observed. However, the patient appeared very fatigued, weak and pale. Spoon-shaped fingernails (koilonychia) were

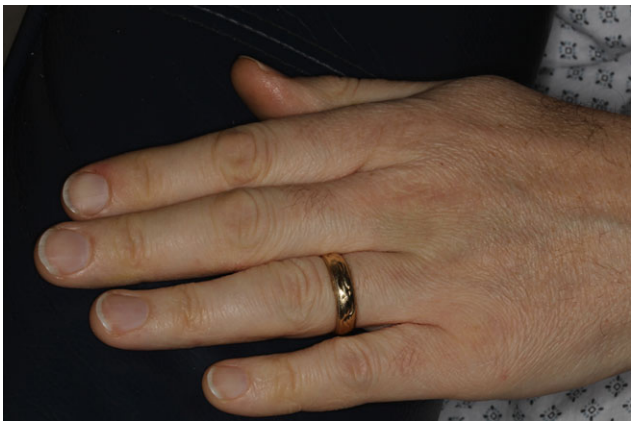

Fig. 1 Spoon-shaped fingernails (koilonychia).

noted (Fig. 1). Intraoral examination revealed buccal mucosal pallor (Fig. 2) and severe gingival haemorrhage around tooth 11 and 21 palatal gingival margin. The gingivae bled spontaneously without any touching or probing. Both Tooth 11 and 21 were positive to sensibility testing. Periodontal pocket depths were less than 3 mm. No dental plaque or calculus deposits were detected clinically. Panoramic and periapical radiographs showed no abnormal dental or osseous finding. Haematological tests, including complete blood count (CBC), liver function test, kidney function test, clotting profile, C-reactive protein, rheumatoid factors and anti-nuclear antibodies were ordered. He was given tranexamic acid 5% mouthwash to arrest the bleeding. The patient's CBC revealed a marked decrease in haemoglobin (63 g/L), haematocrit (0.19), platelet count ($23*10^9$/L) and leucocytes ($0.5*10^9$/L) (Table 1). Neutrophils are the body's main defence against bacterial and fungal infection. When neutrophil counts fall to <500/μL, normal inflammatory response may be muted and endogenous microbial flora can cause infection. Acute, severe neutropenia (<500/μL) can lead to rapidly fatal infections. The CBC also showed pancytopenia with

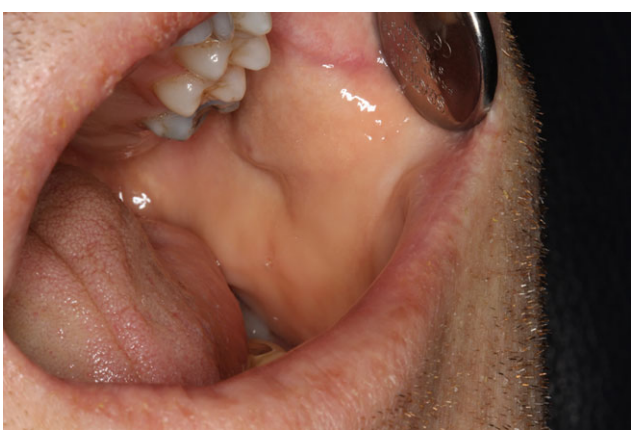

Fig. 2 Mucosal pallor.

rare circulating blast cells. Other haematologic and laboratory exams are shown in Tables 2 and 3. He was admitted to the Department of Haematology (Dunedin Public Hospital, New Zealand) immediately due to pancytopenia. A bone marrow biopsy confirmed hypoplastic acute myeloid leukaemia (AML) without maturation. Cytogenetics studies showed deletion of chromosome 7q and an additional copy of one chromosome 8 in cell cultures. He received standard dose daunorubicin/cytarabine induction chemotherapy, achieving complete morphologic and cytogenetic remission. As this patient's leukaemia had been determined high risk by the AML 17 risk score, he had been given consolidation therapy with a more intensive chemotherapy regimen known as FLAG/Idarubicin. As his AML was unlikely to be cured with chemotherapy alone, an allogeneic stem cell transplant was planned.

DISCUSSION

AML is an aggressive myeloid neoplasm that results from clonal transformation of haematopoietic precursors through the acquisition of chromosomal rearrangements and multiple gene mutations.[10]

In New Zealand, the Ministry of Health reported leukaemia was the seventh most commonly registered cancer and 591 patients were diagnosed with leukaemia in 2010.[11] Under the age of 24, leukaemia was the most common cancer for both males (44 registration) and females (22 registrations).[11] Although the incidence of acute leukaemia accounts for less than 3% of all cancers, it is still the leading cause of death due to cancer in children.[12] AML is a relatively uncommon disease, accounting for approximately 25% of all leukaemias in adults in the western world.[13] It comprises 1.2% of cancer deaths in the United States.[14] In New Zealand of the 591 patients diagnosed with leukaemia, 185 patients were diagnosed with AML in 2010.[11] In addition, some of the risk factors for developing AML have been identified, as summarized in Table 4. However, these recognized risk factors account for only a small number of observed cases.[15]

AML is an aggressive disease that predominantly occurs in older adults, with a median age at diagnosis of over 65 years.[16,17] AML is rarely diagnosed before the age of 40 years and thereafter the incidence increases in parallel with age.

The incidence of AML varies with gender and ethnicity. AML in adults has a slight male predominance in most countries. For example, in New Zealand the male registration rate was more common than the female (1.5:1), and the male mortality rate was nearly twice as high as the female in 2010.[11] The population of New Zealand is approximately four million. New

Table 1. Complete blood count 18–24 September 2013

	18th	20th	21st	22nd	23rd	24th	Normal value range
Haemoglobin	63	90	81	74	98	85	130–175 g/L
HCT	0.19	0.27	0.24	0.22	0.29	0.25	0.4–0.52
MCV	103	96	97	96	94	93	80–99 fL
MCH	34.8	32.6	32.5	33	31.3	32.1	27–33 pg
Platelets	23	21	53	35	31	21	150–400 $*10^9$ /L
WBC	0.5	0.5	0.7	0.3	0.4	0.2	4–11 $*10^9$ /L
Neutrophils	0.0	0.0	0.0	0.0	0.1	0.0	1.9–7.5 $*10^9$ /L
Lymphocytes	0.4	0.4	0.6	0.2	0.3	0.2	1–4 $*10^9$ /L
Monocytes	0.1	0.1	0.1	0.0	0.0	0.0	0.2–1.0 $*10^9$ /L
Eosinophils	0.0	0.0	0.0	0.0	0.0	0.0	<0.6 $*10^9$ /L
Basophils	0.0	0.0	0.0	0.0	0.0	0.0	<0.3 $*10^9$ /L

Markedly decreased circulating haemoglobin level, and increased MCV and MCH suggests macrocytic hyperchromic anaemia. Neutrophils count was zero from 18th to 22nd September. This patient with neutrophil counts (<500/μL) is at greatest risk of rapidly fatal infection. Abnormal low platelets count (thrombocytopenia) results in spontaneous bleeding or causes delay in the normal process of clotting.

Table 2. Biochemistry, liver function tests, C-reactive protein, urea and creatinine 18–24 September 2013

	18th	20th	21st	22nd	23rd	24th	Normal value range
Na	141	140	138	138	133	131	135–145 mmol
K	4.9	4	4	3.9	4.3	4.1	3.5–5.2 mmol
Urea	6.5	4.0	3.5	3.6	4.7	4.6	3.2–7.7 mmol
Creatinine	74	64	60	60	62	60	50–110 μmol
Albumin	38	35				29	35–50 g/L
Total protein	74	65				60	64–83 g/L
Total bilirubin	13	7				9	2–20 μmol/L
Alk phosphatase	86	85				71	30–150 U/L
ALT	19	15				10	0–40 U/L
GGT	13	12				19	10–50 U/L
CRP	95	94	97	131	143	162	<5 mg/L

Elevated level of CRP indicates inflammation.

Table 3. Blood clotting test 18–24 September 2013

	18th	20th	21st	22nd	23rd	24th	Normal value range
Prothrombin time	13.8	13.3				14.4	9.0–14.0 seconds
INR	1.2	1.1				1.3	0.8–1.2 seconds
APTT	35	31				34	22–34 seconds
Fibrinogen	6.7	6.3				6.0	1.8–4.0 g/L

Elevated fibrinogen level may suggest inflammation as it is an acute-phase protein.

Zealand has four main ethnic groups: Caucasians, Maori, Pacific Islanders and Asians. New Zealand Asians had the lowest rate for AML.[18] Maori and Pacific Islanders had a higher incidence compared to Caucasians during 1993 to 2002.[18]

Clinical presentation

AML has a variable presentation and results from leukaemic infiltration in vital organs causing splenomegaly, hepatomegaly and lymphadenopathy. Replacement of normal bone marrow haematopoietic stem cells results in neutropenia, thrombocytopenia and anaemia. Most of these clinical signs and symptoms are related to the reduction of leucocytes and erythrocytes. Therefore, AML patients commonly present with signs and symptoms of pancytopenia, such as fever, fatigue, pallor, bleeding and purpura, bone and abdominal pain and recurrent infections.[12]

Oral manifestations

Oral manifestations may occur in any of the leukaemias, but they are more common in AML.[19] Oral examination may show mucosal pallor due to anaemia, spontaneous bleeding and petechial haemorrhages of gingivae, palate, tongue or lip as a result of thrombocytopenia, and gingival hyperplasia due to leukaemic infiltration. Oral ulcerations are common and may result from either neutropenia or direct infiltration by the leu-

Table 4. Risk factors associated with AML

Genetics	Down syndrome
	Klinefelter syndrome
	Bloom syndrome
	Patau syndrome
	Ataxia telangiectasia
	Diamond-Blackfan syndrome
	Shwachman syndrome
	Kostman syndrome
	Neurofibromatosis I
	Fanconi anaemia
	Li-Fraumeni syndrome
Chemical exposure	Benzene
	Drugs such as pipobroman
	Pesticides
	Cigarette smoking
	Embalming fluids
	Herbicides
Radiation	Radiation exposure (Non-therapeutic or therapeutic radiation)
Chemotherapy	Alkylating agents
	Topoisomerase-II inhibitors
	Anthracyclines
	Taxanes
Preleukaemia	Myelodysplastic syndrome
	Myeloproliferative disease

kaemic cells. Patients may also have severe recurrent viral, bacterial and fungal oral infection as a result of immunosuppression.[7,8,19] Oral signs and symptoms of laryngeal pain, gingival bleeding, oral ulceration and gingival hyperplasia were the most prevalent complaints.[7,19] Fever was the most common reported symptom at the initial physical examination. It may be associated with neutropenia and bone marrow aplasia.[20,21] Laryngeal pain and oral ulceration were the second common complaints.[19] Therefore, all oral health practitioners should be aware of the significance of these oral manifestations in relation to AML.

There are many situations in which a patient presents with gingival bleeding, including poor oral hygiene, malpositional teeth, trauma to the gingivae, Vitamin K, Vitamin C deficiency, hormonal changes in female, bleeding disorders, medications, liver disease and cancers. The most common gingival bleeding is caused by a chronic inflammatory process produced by dental plaque in gingivitis and is not spontaneous. In this case, gingivitis by dental plaque was ruled out because of the severity of spontaneous gingival bleeding related to relatively good dental hygiene. Oral signs of thrombocytopenia are the most common patient complaint and are often found at the initial clinical examination.[7] It has been suggested that thrombocytopenia is due to infiltration of the leukaemic cells in the bone marrow.[22] In addition, as a result of inadequate synthesis, excessive consumption, or excessive destruction of coagulation factors, high levels of fibrinolytic activity and hypofibrinogenemia may contribute to increased gingival bleeding.[23,24]

Gingival swelling is commonly observed in patients with AML. The enlargement of the gingival swelling may be due to infiltration of gingival tissue by leukaemic cells particularly since it develops in patients with the highest leucocyte count.[19,25,26]

Gingival infiltration of leukaemic cells as one of the oral manifestations of AML has been reported in several studies.[27–30] Gingival hyperplasia is characterized by progressive proliferation of fibrous connective tissue causing enlargement of the interdental papillae, the marginal and attached gingiva, slowly covering the crowns of the teeth.[6] Pre-existing periodontal disease can exaggerate the leukaemic infiltration and worsen the gingival enlargement.[31] Biopsy and fine needle aspiration cytology can be used to confirm leukaemic cells infiltration.[32,33] Another oral sign, such as mucosal pallor is difficult to evaluate objectively. Diffused chronic mucocutaneous candidiasis, recurrent herpetic gingivostomatitis and bacterial infection suggest immunosuppression.[1]

Leukaemic patients often fall sick and deteriorate fast. Neutropenia is usually asymptomatic until infection develops. The main concerns in the orofacial region are infection and bleeding. Oral health practitioners should always take non-specific spontaneous bleeding seriously, and simple haematologic laboratory tests such as CBC, liver function tests and clotting profile should be ordered. In addition, infection of the orofacial region may be associated with neutropenia or caused by dental treatment. Because the inflammatory response is limited, neutropenic patients are particularly predisposed to viral, bacterial and fungal infections. Therefore, oral health practitioners should be alert to septicaemia. Antibiotic prophylaxis must be given for invasive operative procedures during the neutropenic period.[34]

CONCLUSIONS

Systemic diseases may present with abnormalities in the oral cavity. Oral lesions are one of the initial manifestations of acute myeloid leukaemia. This case emphasizes that oral health practitioners should be familiar with the systemic manifestations and oral complications of blood diseases and leukaemia in particular, since they are frequently consulted by the leukaemia patient because of accompanying oral complications, thereby providing an opportunity for timely diagnosis and early referral to physicians.

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