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Oral Presentation of Haematological Disease: Part II – Iron Deficiency Anaemia

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ABSTRACT

Introduction

Iron deficiency anaemia may be responsible for diverse oral mucosa changes due to the reduced oxygen-carrying capacity of red blood cells, but also due to changes in the oral mucosal structure and defence mechanisms.

Aims and objectives

This study aims to report on three patients with iron deficiency anaemia who presented with distinct oral mucosal clinical features.

Design/Methods

The oral mucosal features of three patients who presented at the University of Pretoria Oral Health Centre with iron deficiency anaemia, of variable causes, were recorded. Special investigations were performed and reflected their degree of iron deficiency. The patients were managed collaboratively with their respective physicians to address the underlying cause of anaemia.

Results

These cases demonstrate that dentists should explore the presence of anaemia to explain oral mucosal changes. Anaemia may present with wide-ranging clinical features, from recurrent to persistent oral ulcers, mucosal pallor, and *Candida* infection. Collaboration with attending physicians may help establish the cause of anaemia as a nutritional deficiency, gastric ulceration, or infective and inflammatory disease.

Conclusions

Dentists are pivotal in diagnosing haematological diseases such as iron deficiency anaemia. The oral features of ulceration, glossitis, *Candida* infection and mucosal pallor are important diagnostic indicators of iron deficiency anaemia.

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Keywords

anaemia, iron deficiency, candida, recurrent aphthous ulceration, gastrointestinal, nutrition, oral presentation, Helicobacter pylori

ABBREVIATIONS

CD:	Coeliac disease
CRP:	C-reactive protein
DMT-1:	divalent metal transporter
EPO:	erythropoietin
FBC:	full blood count
GIT:	gastrointestinal tract
Hb:	haemoglobin
HCP1:	haem carrier protein
HPI:	*Helicobacter pylori* infection
HP:	*Helicobacter pylori*
IBD:	inflammatory bowel disease
ID:	iron deficiency
IDA:	iron deficiency anaemia
IRT:	iron replacement therapy
LF:	lactoferrin
MCH:	mean cell/corpuscular haemoglobin
MCHC:	mean cell/corpuscular haemoglobin concentration
MCV:	mean cell/corpuscular volume
OMC:	oral medicine clinic
PPI:	proton-pump inhibitor
RAU:	recurrent aphthous ulceration
RBC:	red blood cell
RCC:	red cell count
RDW:	red cell distribution width
RES:	reticuloendothelial system
SAT:	stool antigen test
SF:	serum ferritin
TfR:	transferrin receptor
UBT:	urea breath test
WCC:	white cell count
WHO:	World Health Organisation

INTRODUCTION

Anaemia, characterized by either reduced numbers of circulating red blood cells (RBC) or reduced haemoglobin (Hb) concentration, results in an impaired means of carrying oxygen.[1] Anaemia affects one-quarter of the world's population, with iron deficiency (ID) being the predominant cause.[1, 2] Anaemia implies ID until proven otherwise.[1] Africa shoulders the highest anaemia burden, with women and preschool children at greatest risk, regardless of geography or socioeconomic status.[1]

The average person contains 3 grams of iron, 2 grams in erythrocyte Hb, and the remainder in storage (ferritin and hemosiderin) and enzymes.[3-5] The bone marrow uses most circulating iron to produce Hb for RBC, while muscle fibres use the remainder to produce myoglobin.[4, 6] Daily iron requirements are met by iron bound to tissue ferritin, predominantly found in the liver, spleen and bone marrow.[4]

Because of continuous losses that occurs, mostly from the gastrointestinal tract (GIT) (1-2 mg/day),[5] and despite significant recycling processes by the reticuloendothelial

www.sada.co.za / SADJ Vol. 79 No.6
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macrophages which break old RBC down (20 mg/day), 10mg of iron has to be obtained daily from the diet.[3-7]

Regulation of iron levels

A fine balance of iron levels is required because excess iron is toxic, generates damaging reactive oxygen species, and supports the growth of pathogens.[4] Accordingly, iron is not efficiently absorbed, transported by transferrin in the plasma, and stored by ferritin in the liver, so that the body is protected from free iron.[4]

Our diets contain approximately 5–15mg of elemental iron and 1–5mg of haem iron, yet only 1-2mg is absorbed daily, mostly from the duodenum and the proximal jejunum.[4, 8] Haem iron, found in animal products, is the most bioavailable form. While the absorption of non-haem iron from plant sources is limited because it is present as insoluble ferric iron.[4, 5, 9] Reducing agents, like ascorbic acid, and gastric acid, reduce ferric iron to ferrous iron, making it soluble and easier to absorb.[4, 5, 10] Ascorbic acid also facilitates other pathways of iron release, binding and intestinal barrier function, making it the most effective enhancer of dietary iron absorption.[4] On the other hand, dietary phytate, found in cereals, bran, legumes, nuts and seeds, reduces iron absorption by binding tightly to iron.[4, 5, 11] And polyphenols found in tea, fruits and vegetables reduce non-haem iron absorption by forming insoluble iron-tannate complexes.[12, 13] Mineral supplementation also decreases iron absorption because zinc and manganese bind competitively with the DMT-1 transporter, and calcium alters the function of the transporter.[4]

Haem and non-haem iron also follow different absorption paths from the lumen of the gut into the enterocyte. Haem iron is absorbed directly through a haem carrier protein (HCP1) while, non-haem iron has to be reduced from ferric iron to ferrous iron by the duodenal cytochrome B enzyme[7] before passing into the enterocyte through a divalent metal transporter (DMT-1).[4] Iron is then either stored in the enterocyte as ferritin[4] or leaves the basolateral membrane of the enterocyte through the ferroportin export protein or the FLVCR1 receptor[14] to be immediately bound by transferrin in the plasma and carried in the circulation to cells with transferrin receptors.[4-6, 15] Transferrin usually carries 0.1% of total body iron in plasma.[5]

Hepcidin tightly regulates iron absorption because excess iron cannot be excreted.[5, 16] When sufficient iron is present, hepatocytes produce hepcidin to sequester iron intracellularly by blocking and destroying the iron-loaded ferroportin molecule[4, 5, 17] so that iron cannot be released into the circulation from enterocytes, macrophages and hepatocytes.[5] The intracellular accumulation of iron further reduces the expression of the DMT-1 transporter so that less dietary iron is absorbed.[4]

Inflammation and infection also upregulate hepcidin production to sequester iron intracellularly, to keep this nutrient away from pathogens, resulting in a 'relative' or 'functional' IDA.[17]

When iron demand increases, DMT-1 expression is upregulated to absorb more iron in the gut, and hepcidin production is reduced to release more iron from the enterocytes and macrophages.[4, 5]

Role of iron

Iron is an essential nutrient, it cannot be substituted, nor self-generated.[9]

Because iron readily donates and accepts electrons, it participates in complex biological redox reactions, such as the functioning of haemoproteins for oxygen transport and cytochrome enzymes for energy production.[4] Iron-containing metalloproteins are involved in DNA synthesis, gene regulation, cell proliferation and differentiation, drug metabolism, steroid hormone synthesis and neutrophil phagocytosis.[4]

In ID, erythropoiesis is prioritized at the expense of other functions, such as the functioning of the central nervous system and the immune system.[4] Therefore, depression, reduced endurance and work performance, and impaired cognitive functions may become evident before the classic features of IDA appear.[4]

Permission was obtained from the University of Pretoria, Faculty of Health Sciences, Research Ethics Committee clearance number 20/2024, following informed consent from the participants.

CASE 1

Clinical case presentation

A 79-year-old woman presented to the Oral Medicine Clinic (OMC) of the University of Pretoria Oral Health Centre (UPOHC), complaining of a burning sensation in her mouth, aggravated by spicy foods and toothpaste. The patient suffers from hypertension, hypercholesterolemia, irritable bowel syndrome, osteoporosis, multiple sclerosis, and anaemia. She uses enalapril and hydrochlorothiazide for hypertension and paracetamol and tramadol for headaches. Due to financial constraints, she consumes limited quantities of red meat.

The patient is partially edentulous and wears an acrylic denture to replace her missing teeth. The physical examination revealed a tongue that is smooth, pale and fissured, and red crusting of the corners of her mouth, suspicious of angular cheilitis (Figure 1).

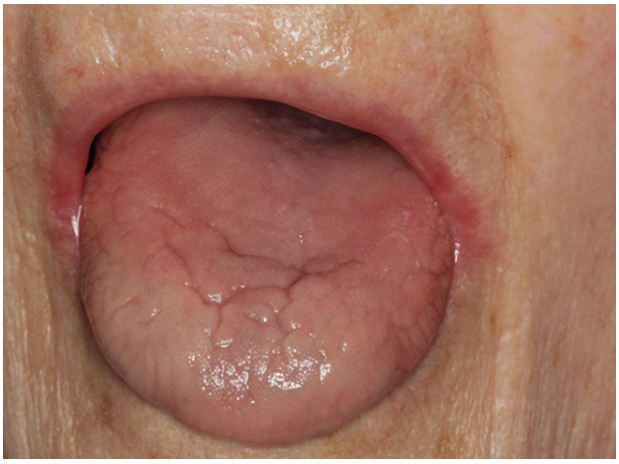

Figure 1: Smooth, pale tongue with fissuring and red crusting of the corners of the mouth.

Special investigations

Her full blood count (FBC) displayed hypochromic microcytic anaemia as evidenced by a low red cell count (RCC) (3.88

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x 10^{12}/L), Hb (6.6 g/dL), mean corpuscular volume (MCV) (63.7fL), and mean corpuscular haemoglobin concentration (MCHC) (26.7 g/dL). (See Table I). Serum iron studies confirmed the diagnosis of IDA (low serum iron (2.8 µmol/L), transferrin saturation (3%) and ferritin levels (4µg/L), and increased transferrin levels (4.08g/L)). (See Table II). The patient provided no history of gastrointestinal or vaginal bleeding.

Table I: Red blood cell indices

Test	Result	Unit	Reference
Red cell count	3.88	X 10^{12}/L	3.93 – 5.40
Haemoglobin	6.6	g/dL	11.6 – 16.4
Haematocrit	0.247	L/L	0.340 – 0.480
MCV	63.7	fL	78.9 – 98.5
MCH	17.0	pg	26.1 – 33.5
MCHC	26.7	g/dL	32.7 – 34.9
Red cell distribution width	20.7	%	12.4 – 17.3

Table II: Haematinics

Test	Result	Unit	Reference
Iron	2.8	µmol/L	9.0 – 30.4
Transferrin	4.08	g/L	1.73 – 3.60
% Saturation	3	%	15 – 50
Ferritin	4	µg/L	5 - 204
Vitamin B12	329	pmol/L	138 - 652
Serum folate	41.8	Nmol/L	7.0 – 46.4

Management

The patient was managed with topical antifungals (miconazole oral gel), which she applied to the corners of her mouth and dorsum of the tongue, 3-4 times a day for 14 days. She was also instructed on denture and oral hygiene. The patient was referred to internal medicine, where the diagnosis of IDA due to malnutrition was confirmed and corrected through iron supplementation.

Outcome

Effective management of the *Candida* infection and the underlying nutritional deficiency resolved the patient's symptoms.

CASE 2

Clinical case presentation

A 55-year-old man presented to the OMC of the UPOHC with a complaint of oral ulcers that started seven months earlier but had recently become unbearable. The ulcers developed soon after undergoing multiple dental extractions, during which the patient self-medicated with aspirin. The patient continues to take high doses of aspirin to manage pain from the oral ulcers. The patient suffers from high blood pressure, anaemia and a gastric ulcer, for which he uses sucralfate suspension but does not know which other medications he is taking. Two years earlier, he had received surgery for a bleeding gastric ulcer. The patient has a 60-pack-year history of cigarette smoking and used to consume ten units of alcohol per day. Upon extra-oral examination, the patient appeared very pale. Intra-oral examination revealed ulcers of the dorsum of the tongue: centrally, a deep ulcer with irregular margins covered by a grey, necrotic slough, and, more anteriorly, a superficial ulcer (Figure 2). The lower labial mucosal was covered by an ulcer to the depth of the vestibule. (see Figure 3). Given the chronic history of the ulcers, deep fungal infection, EBV-associated mucocutaneous ulcer, or CMV-induced ulceration, was considered as differential diagnoses.

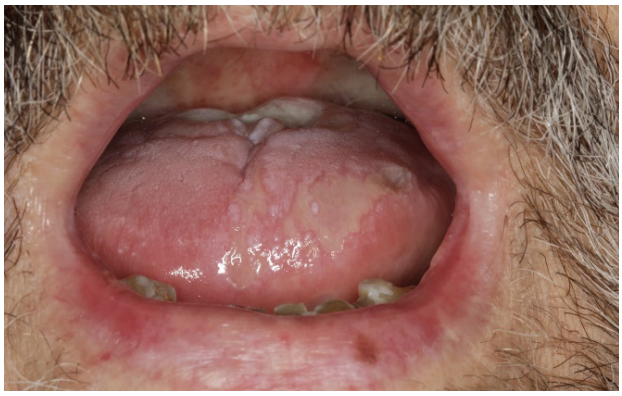

Figure 2: Ulcers of the tongue dorsum

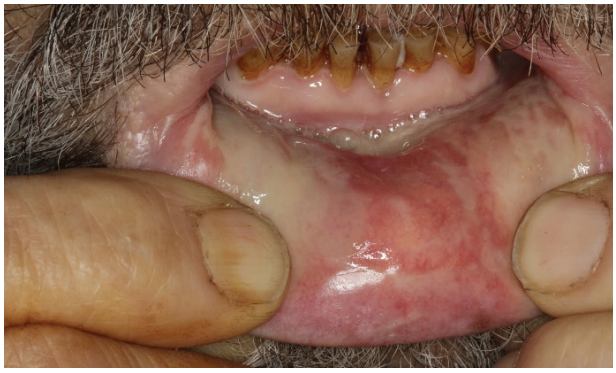

Figure 3: Ulcers of the lower labial mucosa

Special investigations

The patient was instructed to discontinue aspirin use before an incisional biopsy was performed at the edge of the central ulcer of the tongue and labial mucosa. The histopathological examination revealed a non-specific ulceration devoid of any infective aetiology. A FBC and differential white cell count (WCC) was obtained (see Table III and Table IV), which revealed a low RCC (3.51 x 10^{12}/L), Hb (6.0g/dL), haematocrit (0.240 L/L), MCV (68.4 fL), MCH (17.1 pg), and MCHC (25.0 g/dL). The red cell distribution width (RDW) was elevated (26.5%). The WCC was elevated, mostly due to an increase in neutrophils (10.01 x 10^{9}/L,) likely due to the oral ulcers.

Table III: Full blood count

Test	Result	Unit	Reference range
Red cell count	3.51	X 10^{12}/L	4.19 – 5.85
Haemoglobin	6.01	g/dL	13.4 – 17.5
Haematocrit	0.240	L/L	0.390 – 0.510
MCV	68.4	fL	83.1 – 101.6
MCH	17.1	pg	27.8 – 34.8
MCHC	25.0	g/dL	33.0 – 35.0
Red cell distribution width	26.5	%	12.1 – 16.3
Platelet count	683	X 10^{9}/L	171 - 388

The RBCs were stacked in aggregations (Rouleaux formation).

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Table IV: Differential white cell count

Test	Result	Unit	Reference range
White cell count	13.44	x 10^9/L	3.92 – 10.40
Neutrophils	10.01 (74.50 %)	x 10^9/L	1.60 – 6.98
Lymphocytes	1.90 (14.10 %)	x 10^9/L	1.40 – 4.20
Monocytes	0.91 (6.80 %)	x 10^9/L	0.30 – 0.80

The results demonstrated a hypochromic microcytic anaemia, indicative of ID.

Management

A 5-day course of prednisone (30mg/day) and a course of topical glucocorticoids was prescribed to manage the oral ulcers, but gastric discomfort necessitated the discontinuation of prednisone. The patient subsequently admitted that he was not being treated for anaemia. He was given Ferrimed (folic acid with iron poly-maltose) and referred back to the gastro-enterology department for assessment of his gastric ulcer.

Outcome

Two weeks later, the ulcer of the lower labial mucosa had healed completely, and the remaining ulcer appeared more superficial and continued to heal completely.

CASE 3

Clinical case presentation

A 60-year-old woman was referred to the OMC of the UPOHC, complaining of multiple recurrent oral ulcers, which started 12 months earlier and left her unable to eat solid foods. Previous treatment attempts included prednisolone oral rinse, antifungal therapy (fluconazole and nystatin), antibiotics (amoxicillin) and a topical anaesthetic (tetracaine hydrochloride).

The patient suffered from rheumatic fever as a child and retained a cardiac lesion. She also suffers from hypertension, diabetes mellitus, hypothyroidism, and chronic pain following a motor vehicle accident. She was taking sufentanil, lamotrigine, donepezil, carvedilol, levothyroxine, sertraline, calciferol, vildagliptin and sitagliptin with metformin.

Upon extra-oral examination, it was noted that her lower lip and cheeks were swollen. Tender submandibular lymph nodes were palpable on the right. The intra-oral examination was limited due to pain. Still, multiple discrete oral ulcers could be seen on the labial and buccal mucosa. Some ulcers were confluent, covered by a yellow fibrinopurulent membrane, and appeared on a bed of erythema (Figure 4, and Figure 5).

Given the recurrent nature of the ulcers and the location on non-keratinized mucosa, a differential diagnosis of recurrent aphthous ulceration (RAU) was made.

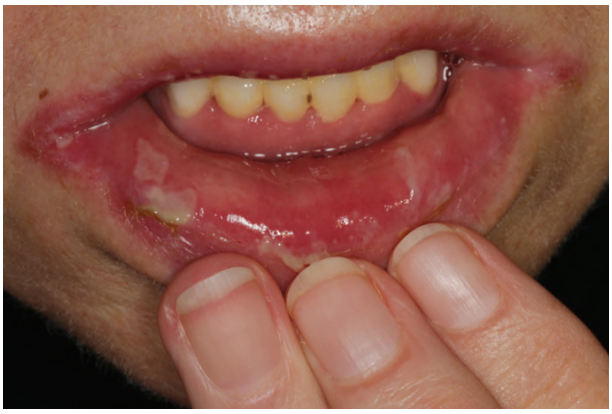

Figure 4: Multiple ulcers of the labial mucosa.

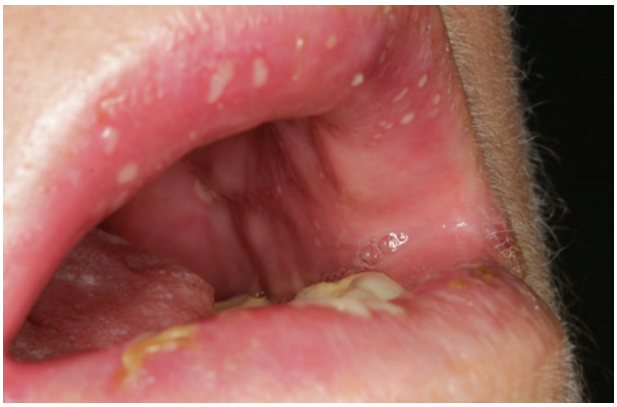

Figure 5: Multiple ulcers of the buccal and labial mucosa

Special investigations

The complex presentation of RAU required an assessment of the underlying cause.

The FBC demonstrated an elevated WCC (15.09 x 10^9/L), mostly attributed to an increase in neutrophils (12.38 x 10^9/L) (see Table V). Although the RCC and haematocrit were normal, the Hb (11.6 g/dL), MCH (25.3 pg) and MCHC (30.9 g/dL) were low. The erythrocyte sedimentation rate (ESR) (33 mm/hr) and C-reactive protein (CRP) (73 mg/L) values were elevated.

Table V: Full blood count

Test	Result	Unit	Reference range
White cell count	15.09	X 10^9/L	3.92 – 9.88
Neutrophils Abs	12.38 (82%)	X 10^9/L	2.00 – 7.50
Red cell count	4.59	X 10^{12}/L	4.13 – 5.67
Haemoglobin	11.6	g/dL	12.1 – 16.3
Haematocrit	37.5	%	37.0 – 49.0
MCV	81.7	fL	79.9 - 8.91
MCH	25.3	pg	27.8 – 32.0
MCHC	30.9	g/dL	31.0 – 37.0
Red cell distribution width	14.5	%	10.0 – 17.3
Platelet count	412	X 10^9/L	150 - 450
ESR	33	0 - 20	mm/hr
C-reactive protein	73	< 5	mg/L

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Table VI: Haematinics

Test	Results according to date				Unit	Reference range
	12/08/15	19/01/21	20/01/21	21/04/19		
Iron	13.6	11.7	7.7	4.1	µmol/L	9.0 – 30.4
Transferrin	3.5	3.6	3.6	4.2	g/L	2.5 – 3.8
% Saturation	16	13	9	4	%	15 – 50
Ferritin	13	51	16	31	ng/mL	10 - 120
Vitamin B12				329	pmol/L	107 - 443
Serum folate				41.8	nmol/L	10.0 – 45.1

A cumulative report on the patient's iron values revealed a progressive decline in iron levels (4.1 µmol/L) and saturation percentage (4%) (see Table VI), while her transferrin was elevated (4.2 g/L), and ferritin stores were normal (31ng/L). Previous ANA and ENA screening tests were negative.

This was interpreted as depleted iron stores in the presence of an acute phase response/non-specific tissue damage.

Management

The oral ulcers were diagnosed as complex aphthosis or aphthous-like lesions due to relative iron deficiency and treated with topical and systemic glucocorticosteroids (Betamethasone mouth rinse, Clobetasol ointment, and prednisone 50mg/day for five days).

Outcome

The patient was referred to her physician to determine the cause of her relative iron deficiency. Bone marrow aspirate and colonoscopy revealed no abnormalities, but gastroscopy and endoscopic biopsy identified *H pylori* infection (HPI). Treatment of the infection resulted in the resolution of the oral ulcers.

DISCUSSION

Definition of IDA

According to the World Health Organization (WHO), anaemia is defined as a haemoglobin (Hb) concentration of less than 13 g/dl in males and less than 12 g/dl in females,[18] which qualifies all three presented patients with anaemia (6.6, 6.01 and 11.6 g/dL for patients 1, 2 and 3 respectively). In addition, a Hb concentration of less than 8 g/dL, regardless of gender, is considered severe anaemia, which would be consistent with the first two patients.[18]

Pathophysiology of IDA

Absolute ID reflects a negative iron balance due to excessive blood loss (patient 2), inadequate dietary iron intake (patient 1), or absorption that fails to meet physiological requirements.[5] A relative, or functional, ID occurs during inflammation when iron is sequestered from the plasma, resulting in iron-deficient erythropoiesis and anaemia despite adequate body iron stores (patient 3).[5]

A comprehensive history should search for clues as to the cause of IDA, such as patient 1's acknowledgment of inadequate dietary intake, and patient 2's history of a gastric ulceration,[2, 4] but the identification of any of these factors should not preclude further assessment of the GIT.[2]

Blood loss

One milligram of iron is usually lost daily due to the sloughing of epithelial cells and their iron-containing cytochromes. Still, GIT micro-erosions and other forms of occult blood loss may add another 1-2 mg to daily iron losses, while acute loss of 2 L of blood can deplete iron stores.[6] Gastrointestinal blood loss is the most important and common cause of ID in men and postmenopausal women[5, 6, 19] while menstruation is often to blame among premenopausal women.[2] Common upper GIT causes of bleeding include erosions or ulcers related to aspirin and non-steroidal anti-inflammatory drugs (NSAIDs) use and peptic ulcer disease.[5] The second patient had both a history of gastric ulceration, and aspirin use. A thorough assessment of the GIT is essential in all adults with a new diagnosis of IDA without an obvious explanation.[2, 6, 19, 20] Initial investigations should include urinalysis or urine microscopy, screening for Coeliac disease (CD) through serology or biopsy, and endoscopic examination of the upper and lower GIT to rule out neoplastic disease (colonic adenocarcinoma), inflammatory (peptic ulceration), and infective (parasitic/hookworm) causes of chronic blood loss.[2] Inflammatory bowel diseases (IBD) are common culprits in ID because they may be associated with chronic bleeding, iron-deficient dietary patterns, poor absorption,[6, 20] bowel resection, and be further complicated by a relative IDA as well.[4, 6] Chronic blood loss may also occur from the genito-urinary and respiratory tract.[2]

Inadequate dietary intake

Pre-adolescents and younger children have high iron requirements due to the growth spurt, which is often compounded with poor dietary quality, and a reluctance to comply with oral iron therapy.[21]

An iron-deficient diet (less than 1-2 mg of dietary iron/day), which may be seen in strict vegans, can deplete iron stores within three years.[3]

The different types of iron found in the diet, and dietary and other influences on absorption, have already been discussed.

Malabsorption

Hypochlorhydria, caused by atrophic glossitis, HPI, gastrectomy or gastric bypass, and long-term proton-pump inhibitor (PPI) use,[22, 23] reduces iron absorption.[2] The risk of IDA progressively worsens following Roux-en-Y gastric bypass (RYGB) surgery because it also bypasses the duodenum, the primary site for iron absorption.[6, 24]

The chelation of iron by tea, coffee, calcium, flavonoids, oxalates, phytates and antacids reduce iron uptake.[2] Iron absorption is also impaired in Coeliac and Crohn's disease, NSAID enteropathy, and genetic disorders, such as iron-refractory IDA, and Divalent metal transporter one mutation.[2]

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Helicobacter pylori infection (HPI)

IDA, unexplained and unresponsive to oral iron therapy, may be associated with HPI,[19, 21, 25, 26] and therefore, in patients with normal gastroscopy and colonoscopy results, HPI should be sought and eradicated.[19] Eradication of HPI, with or without iron replacement, improves IDA.[4, 25-29]

HPI causes persistent gastric inflammation, which is rarely associated with gastrointestinal symptoms.[21, 25, 26] The IDA in HPI seems unrelated to intestinal blood loss, diet, malabsorption or diversion in the reticuloendothelial system (RES).[25, 30] Instead, iron is likely diverted to an extramedullary focus, such as the HP-infected antrum.[25]

Low tissue iron levels are usually maintained to prevent bacterial infection, but in the presence of infection, the liver produces more ferritin, and neutrophils release lactoferrin (LF) (which captures iron from transferrin) to reduce extracellular iron further.[25] Macrophages capture the LF-iron complex and are eliminated from the circulation by the RES.[25] However, HP uses LF as an iron source and sequesters iron by producing a ferritin molecule that stores iron in the bacterial cytoplasm.[25] As the bacterium rapidly multiplies, the dead bacteria and accompanying iron stores are quickly lost in the stools.[25]

HPI is normally diagnosed through endoscopic biopsy and histopathological examination using conventional histochemical staining[31] but should be supplemented with immunohistochemistry if histochemical staining is negative in a patient with chronic gastritis.[32]

Non-invasive tests, such as urea breath tests (UBT), stool antigen tests (SAT) and serology, can be used in patients without a history of PPI or antibiotic use and in young patients with dyspepsia only.[31, 32] But, when IDA is present, or there is a high risk of gastric cancer, an endoscopic examination is required.[32]

HPI should be managed despite the relative absence of symptoms.[32] Treatment relies on clarithromycin-based strategies, which are supplemented with bismuth quadruple or non-bismuth quadruple therapies, with the addition of a PPI, amoxicillin, and a nitroimidazole, according to the resistance profile of the individual and population.[32, 33]

Oral and systemic findings of IDA

ID, with or without anaemia, may result in symptoms of fatigue, lethargy, reduced concentration, dizziness, tinnitus, pallor, or headache and physical signs such as alopecia, dry hair and skin, koilonychia (spoon-shaped nails), blue sclera, atrophic glossitis, and angular cheilitis.[3, 5, 15] Pica, the appetite for ice, clay, soil or paper, may also be seen.[3] In the most severe presentation of IDA, known as Plummer-Vinson syndrome, oesophageal webs result in dysphagia.[3, 34]

The dental practitioner should recognise that the oral mucosal changes may be the first manifestation and serve as a sensitive indicator of ID and IDA, which may even precede fatigue.[35, 36] Oral mucosal pallor is particularly common, may be seen in 30 to 97% of patients with IDA,[35-37] and correlates with Hb and ferritin levels in some,[38] but not all studies.[39] The Hb and ferritin levels also correlate with the experience of a sore mouth,[38] which is the most common complaint of patients.[35, 40] This burning sensation is largely attributed to *Candida* infection, which is prevalent among 85% of patients, presenting as angular cheilitis (63%), atrophic glossitis (59%) and pseudomembranous candidiasis (44%).[35] *Candida* infection is more severe in the presence of IDA.[41] Rarely, angular cheilitis may appear independently of infectious aetiologies in ID.[37]

Atrophic glossitis, which presents with loss of filiform papillae, redness and tenderness of the tongue, is another common finding[36, 37, 39] and may involve the entire tongue dorsum or occur in patches.[36] This is likely another clinical presentation of *Candida* infection.[34, 42] Antifungal treatment successfully improves the burning sensation of the tongue, and is followed by regeneration of the tongue papillae.[35] Correction of the ID may resolve the *Candida* infection on its own,[35] while relapses are likely if the IDA is not corrected.[41] Therefore, patients with persistent or recurrent *Candida* infection should be screened for IDA.[41]

Recurrent aphthous ulceration is also seen in patients with IDA[35, 40] and occurs in 6-15% of IDA patients.[35-37, 39] Some authors found that RAU correlates with the duration of IDA but not with the severity of IDA[37, 43], and it may even be seen in ID only.[44]

Other hematinic deficiencies may also be seen in patients with RAU,[45] but iron deficiency is the most prevalent.[44-48] Because hematinic deficiencies are more common than anaemia per se, and correction of these deficiencies reduces ulcer experience,[41, 46, 48, 49] patients should routinely be screened for iron, folic acid, and vitamin B12 deficiency.[35, 45, 49]

Explanation of the oral manifestations of IDA

IDA results in immunologic dysfunction and structural changes to the oral mucosa, which may predispose patients to *Candida* infection and RAU, as seen in the patients presented here.

Iron is essential for proper cell differentiation and growth and is a critical component of peroxide- and nitrous oxide–generating enzymes that ensure the proper enzymatic functioning of immune cells.[15, 41] Cell-mediated immunity is impaired in ID because iron regulates cytokine production and function; the number of T-lymphocytes, their protein kinase C activity, and IL-2 production are all reduced in ID.[15, 41] The innate immune system is also impaired because macrophages and neutrophils are unable to produce adequate amounts of the bactericidal, iron-containing enzyme, myeloperoxidase.[15, 41]

ID also affects various structural, histochemical, and clinical features of the oral mucosal epithelium, which may occur before significant alterations in red cell morphology or Hb levels are noted.[41] The epithelium is characterized by atrophy due to a reduced cytoplasmic diameter of cells in the middle cell layers, increased basal cell replication, hyperkeratinization and a pronounced lymphocytic infiltrate.[41] The structural changes correlate with the duration of IDA and low ferritin levels, independent of anaemia, and can be reversed by iron therapy Rennie 1984.[41] In addition, decreased levels of the iron-containing enzyme, cytochrome C, have been found in the buccal mucosa from anaemic patients.[41] Experimentally, these changes may increase the risk of squamous cell carcinomas.[41]

Evaluation of IDA

The assessment of IDA may be fairly complex. A normal Hb value does not exclude ID since Hb levels only decline

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after a significant amount of iron has been lost,[4, 50] because Hb production is maintained at the expense of other iron needs.[4] In the presence of normal Hb, the diagnosis of IDA requires a ferritin level below 15ug/L.[9, 20]

Table VII Discriminatory characteristics of IDA and anaemia of chronic disease (51)

	IDA	Anaemia of chronic disease
Serum ferritin (SF)	↓	N or ↑
Serum iron	↓	↓
Transferrin	↑	↓ or N
Transferrin saturation	↓	↓
Mean corpuscular volume (MCV)	↓	↓ or N
Iron-binding capacity	↑	↓
Serum transferrin receptor (TfR)	↑	N
Serum transferrin receptor index	High (>2)	Low (<1)
C-reactive protein (CRP)	N	↑
Erythropoietin (EPO)	↑	N or slightly ↑
Cytokine levels	N	↑

N: normal

Standard investigations of IDA include an FBC with film to demonstrate a reduced number of RBC (anaemia), which are small (microcytic) and pale (hypochromic) but with an increased RDW (anisocytosis), and elongated (pencil-shaped) cells.[5, 9, 20, 50] However, an increase in RDW indicates other nutritional deficiencies, such as vitamin B12 and folate, and is not specific to iron deficiency.[4]

The decreased availability of transferrin-bound iron delivered to erythroid precursors results in reduced Hb production, seen as a reduced RBC count and, subsequently, a reduced MCV once the Hb levels reach 10 g/dL.[3] Therefore, pale RBC (with reduced MCH) precedes small RBC (with reduced MCV) and is an important first sign of ID,[2, 9, 20, 50] and may even be seen in the presence of a normal Hb.[50]

Serum ferritin (SF) is the most specific test for ID. Still, because SF is also an acute phase protein, specific thresholds should be justified relative to the evidence of concurrent inflammation.[2, 4-6] As an acute phase protein, ferritin levels appear normal in the presence of inflammation. Therefore, simultaneous measures of inflammation (C-reactive protein) are necessary.[4] (See Table 7) Similarly, obesity, malignancy, liver disease and chronic alcohol consumption are marked by inflammation and subsequently increase hepcidin secretion.[4] Without inflammation, SF of < 15 µg/L indicates absent iron stores, and < 30 ug/L suggests low body iron stores, but anything < 45 µg/L is a good trade-off between sensitivity and specificity in clinical practice.[2] Yet, in the presence of inflammation, this cut-off may be extended to 150 µg/L.[2] Therefore, the 3rd patient, with apparent normal SF (31 ng/mL) should still be considered to have IDA, because of the concurrent evidence of inflammation (CRP 73 mg/L).

Transferrin transports iron from tissue stores, but when iron stores are depleted, transferrin saturation drops and insufficient iron is delivered to essential body iron proteins.[5, 15] Serum transferrin levels are usually elevated in ID, but because it is a negative acute-phase protein, it may be normal or even reduced in inflammation.[20] In addition, both serum iron concentration and transferrin saturation (< 20%) are reduced in ID and inflammation.[2, 4, 5, 20] An increase in serum transferrin receptor (TfR), which reflects an increase in iron demand, may be a better marker of ID because it increases with ID even before IDA becomes evident and is not subject to the influence of inflammation.[4, 52]

However, if there is still any uncertainty in interpreting the results of iron studies, a good response to iron therapy (a Hb rise ≥ 10 g/L within two weeks) will confirm absolute ID.[2]

Other serum markers used in the assessment of ID include raised total iron-binding capacity, raised red cell zinc protoporphyrin, and low reticulocyte Hb (Retic-Hb).[2, 20]

Treatment of IDA

The treatment of IDA should first and foremost address the cause of ID before iron replacement therapy (IRT) , or rarely, red blood cell transfusion is initiated.[2, 9]

Therapy aims to replenish iron stores and normalize Hb levels.[9] Dietary interventions are rarely sufficient, yet advice should be given to favour iron-rich foods.[3] Vitamin C-rich foods should be taken concurrently, while tea should be avoided for at least 1-2 hours.[3]

Oral ferrous salts (such as ferrous sulphate, ferrous gluconate and ferrous fumarate) are preferred as first-line therapy because of their safety, bioavailability, cost, and efficacy.[2, 53] The preparations are equally efficacious and have the same side-effect profile, although they differ in elemental iron content.[2, 5] The bioavailability of iron salts is significantly (75%) reduced if taken with food and should therefore be taken between meals.[2] The ferrous salts may cause severe GIT symptoms,[5] such as constipation, nausea, and diarrhoea,[2] which may limit compliance.[2, 5]

The current recommendation by the British Society of Gastroenterology is to administer a single daily dose of 50 – 100 mg of elemental iron, which, if not well tolerated, may be given on alternate days,[5, 9] or replaced by ferric maltol.[2, 9] In elderly patients, an elemental iron dose of 15 mg daily may be sufficient and well-tolerated.[2] Alternate-day therapy and lower dosages reap the same benefits because of reduced hepcidin activation.[2, 5, 9]

The response to IRT should be monitored to identify non-responders due to non-compliance, malabsorption, continued bleeding or other comorbidities.[2] An Hb increase of at least 10 g/L should be seen after two weeks of daily oral IRT or four weeks of alternate-day therapy.[2] If treatment failure occurs on daily dosing, the patient should be switched to alternate-day therapy, ferric maltol, or parenteral iron.[2] Monitoring should continue at monthly intervals until the Hb levels have normalized, and IRT should continue for 2-3 months thereafter to ensure the repletion of iron stores.[2]

www.sada.co.za / SADJ Vol. 79 No.6
https://doi.org/10.17159/sadj.v79i06.18081

However, because of the risk of recurrent IDA and the prevalence of persistent anaemia, long term monitoring is advised. Serum ferritin is normally not routinely monitored.[2]

Parenteral iron should be considered in patients with moderate or severe anaemia, severe clinical symptoms, poor response, malabsorption, significant ongoing bleeding, intolerable adverse effects, or non-compliance because of better Hb improvement and quicker replenishment of body iron stores.[2, 5, 9, 20] Parental iron is particularly preferred among patients with IBD or malabsorption syndromes because it bypasses the GIT, where oral preparations may further aggravate the symptoms of IBD.[2, 20, 24]

The choice of parenteral preparations is determined by cost, preference and availability.[54] Ferric derisolmatose, ferric carboxymaltose, and iron sucrose have different infusion times, number of required infusions, and restoration time of Hb levels.[2, 9]The carbohydrate shell of these iron preparations allows for the slow release of iron.[5] Low molecular weight dextran preparations have a reduced risk of anaphylactoid reactions compared to the older preparations but are still greater than newer, non-dextran preparations.[54] Parenteral iron therapy may rarely be associated with infusion or hypersensitivity reactions, hypophosphataemia or the extravasation of iron, which results in a tattoo-like skin discolouring.[2, 9]

RBC transfusion should be a last resort for patients with severe anaemia who are haemodynamically unstable or have comorbidities and should be further supplemented to ensure success.[9] However, transfusion is seldom warranted because parenteral therapy gives a clinically meaningful Hb improvement in only one week.[2]

CONCLUSION

These three clinical cases demonstrate that it is critical for dentists to recognize oral mucosal disease, such as oral ulceration and *Candida* infection, as a feature of IDA. Only the successful treatment of IDA and its associated cause will successfully manage oral mucosal disease. Recognition of the oral features of IDA and its appropriate investigation allows for the successful multidisciplinary management of the patient with IDA.

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