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Case Report

Oncology Section

Hypoxaemia without Respiratory Distress in a Patient with Oral Cancer: A Case Report

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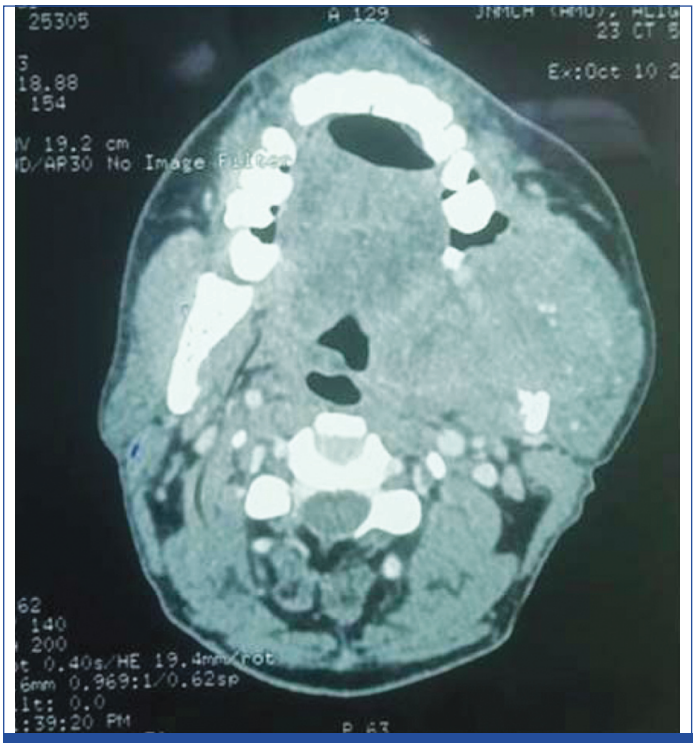
ABSTRACT

Methaemoglobinaemia is a rare disorder caused by oxidisation of divalent ferrous-iron (Fe^{2+}) of Haemoglobin (Hb) to ferric-iron (Fe^{3+}) of Methaemoglobin (MetHb), and it has a life-threatening potential. Here, we present a case of oral cancer with methaemoglobinaemia. A 40-year-old male patient reported to us with a swelling on the left-side of the face since six months. He was diagnosed with resectable oral cancer and hence planned for surgery. He had a very peculiar finding with low SpO_2 without any respiratory distress. After obtaining pre-anaesthetic-clearance, he was operated under general anaesthesia. Brown ring test was positive, which was suggestive of methaemoglobinaemia. Serum methyloglobin was found to be present in a concentration of 9.7% when the blood sample was sent for testing. Patient was administered 5 mL of Methylene Blue (MB) intravenously in 100 mL Normal Saline (NS) at 3-4 drops per minute within 1/2-1 hour daily. Improvement in SpO_2 on the pulse-oximeter was observed, from about 20% to about 66% in five days after administration of MB. Thus, it was concluded that methaemoglobinaemia is not always a life threatening condition, and knowledge about previous history of exposure to the substance that might lead to methaemoglobinaemia is important, so that such substances can be avoided in the future to prevent further worsening of the condition.

Keywords: Hypoxaemia, Methaemoglobinaemia, Oral cancer

CASE REPORT

The patient presented to the department of surgical oncology with a swelling on the left-side of the face since six months. Twenty years back, he had a habit of tobacco chewing for six months, and he had resumed the habit just few months back when he reported to us. Preoperative biopsy report confirmed Oral Squamous Cell Carcinoma (OSCC) of the left buccal mucosa. Contrast-Enhanced Computed Tomography (CECT) of the face revealed a large, heterogeneously enhancing soft-tissue mass lesion measuring 68×78×70 mm (AP×TR×CC), epicentered in the left submandibular region with likely infiltration of buccal and sublingual space, with possible involvement of mylohyoid and hyoglossus muscles on the ipsilateral side [Table/Fig-1].



[Table/Fig-1]: Axial view of the CECT demonstrating the extent of cancer.

Patient had a low SpO_2 of 51% on pulse-oximeter, on account of which ABG was done and showed SpO_2 as 82% with the pH of 7.388. There was no respiratory distress, and hence preoperative anaesthetic clearance was obtained after getting all necessary investigations done. The patient was operated under general anaesthesia. Intraoperatively, he developed cyanosis on his tongue and hands with SpO_2 of 81% in ABG and pH of 7.427. Blood sample was sent for confirmation of methaemoglobinaemia. Brown ring test was performed by putting some drops of blood on the blotting paper, which was found to be positive, suggestive of methaemoglobinaemia [Table/Fig-2]. Postoperatively on the same day of surgery, he was put on 8 L of oxygen therapy but the SpO_2 in ABG was found to almost the same (increased only by 2%). The pH had increased to 7.444, while Hb had reduced from 12.3 g/dL

[Table/Fig-2]: Positive brown ring test suggestive of methaemoglobinaemia.

preoperatively to 10.9 g/dL, which was due to surgical blood loss. However, when ABG was repeated on the first postoperative day at room air, the SpO_2 got reduced to 73.6% and Hb to 4.6 g/dL, while pH became 7.436. On the pulse-oximeter, SpO_2 was found to be as low as 9-20%, with generalised body weakness and headache. General Blood Picture (GBP) revealed normocytic normochromic anaemia with mild thrombocytopenia, and the presence of tear drop cells.

Patient was given moist oxygen inhalation via T piece at 2-4 litres per minute. Tablet Acetylcysteine 600 mg was given TDS with a glass of water through Ryle's tube and 5 mL of injection vitamin C was given with intravenous infusion of 500 mL of Dextrose Normal Saline (DNS) at 30 mL/hour. Presence of serum Methaemoglobin (MetHb) was confirmed, with a concentration of 9.7%. Hence, 5 mL of MB was added and administered intravenously in 100 mL NS at 3-4 drops per minute within 1/2-1 hour daily. It was advised to stop the infusion and injection Hydrocortisone Sodium Succinate 100 mg and Pheniramine Maleate 1 ampule were administered through intravenous route immediately, in case the patient developed hypersensitivity to MB. SpO_2 on the pulse-oximeter improved from 20% to about 66% in five days after administration of MB, and body weakness and headache as well as cyanosis also subsided. Cough with sputum developed during the course of this therapy, but that too subsided with time. Postoperative infection developed but it was managed. Bilateral air entry in the lungs was present and only mild basal crepts could be heard. Surgical site took a lot of time to heal, leading to a delay in the adjuvant treatment, and SpO_2 level in ABG varied from 20-80% even after two months of operation, without any respiratory distress. However, the condition of the operated site improved as time passed, due to regular dressings and proper care.

DISCUSSION

Methaemoglobinaemia is a rare disorder associated with oxidisation of divalent ferrous-iron (Fe^{2+}) of Haemoglobin (Hb) to ferric-iron (Fe^{3+}) of MetHb, and it can be inherited or acquired. Acquired forms are most common, mainly due to the exposure to substances that cause oxidation of the Hb both directly or indirectly. Inherited forms are either due to autosomal recessive variants in the CYB5R3 gene or to autosomal dominant variants in the globin genes, collectively known as HbM disease [1]. Infants are particularly susceptible to methaemoglobinaemia. Early weaning of infants before 4 months of age can also be the cause as this exposes them to nitrate-contamination [2]. However, it can also occur in adults. Here, we present a case of methaemoglobinaemia in a 40-year-old male patient, who was operated under general anaesthesia for carcinoma of the left buccal mucosa.

Signs and symptoms of methaemoglobinaemia depend on the patient's percentage of serum MetHb, the rate at which MetHb is accumulated, the individual's ability to intrinsically clear it, the underlying health status of the patient as well as duration and magnitude of exposure to an oxidising agent. Signs and symptoms of methaemoglobinaemia based on the percentage of MetHb are presented in [Table/Fig-3] [3]. MetHb's percentage is calculated by dividing the concentration of MetHb by that of total Hb. It is likely a better indicator of illness severity than overall concentration, as underlying medical conditions play an important role. Anaemia, congestive heart failure, Chronic Obstructive Pulmonary Disease (COPD), and any pathology that impairs the ability to deliver oxygen may worsen the symptoms of methaemoglobinaemia. Increased levels of MetHb results in functional anaemia [3]. In our case, MetHb level of 9.7% was sufficient to reduce Hb to 4.6 g/dL. Dacrocytes (teardrop cells) in a peripheral blood smear correlate with several diseases such as iron deficiency anaemia, haemolytic anaemia, megaloblastic anaemia and metastatic carcinoma due to bone marrow infiltration and myelofibrosis [4]. In our case, the tear drop cells were associated with haemolytic anaemia that was found in association with methaemoglobinaemia. The agents producing methaemoglobinaemia may also produce oxidant induced haemolysis, leading to a combination of methaemoglobinaemia and haemolytic anaemia [5].

Amount of methaemoglobin	Symptoms
<15%	Patients are generally asymptomatic
15-30%	Presence of cyanosis, anxiety, light headedness, fatigue, headache
30-50%	Tachypnoea, confusion, syncope
50-70%	Seizures, arrhythmias, metabolic acidosis, coma
>70%	Death

[Table/Fig-3]: Signs and symptoms based on the level of methaemoglobin [3].

Some of the published cases have features similar and contrasting to our case. Veltri KT and Rudnick E described case of a female with benzocaine-induced methaemoglobinaemia, who was found to be cyanotic and "blue" and also felt shortness of breath, dizziness, and fatigue. She was immediately placed on 2 L of oxygen via nasal cannula, but she desaturated to 83% and thereafter placed on 100% fraction of inspired oxygen (Fi02). An ABG was ordered stat and showed a MetHb level of 38.8%. MB therapy was started and the patient became less cyanotic, and her oxygenation improved [6]. Mun SH et al., described two cases of fatal methaemoglobinaemia caused by self-poisoning with sodium nitrite. One was a male who had a cardiac arrest after taking sodium nitrate in a suicidal attempt, and he soon became unconscious and died despite providing standard advanced cardiac life support. The methaemoglobin concentration was 90.3%. Other was a female who also ingested sodium nitrite to attempt suicide. She vomited repeatedly, and had an initial reading on pulse-oximeter as 86%. Although, she was alert, she was having dyspnoea and cyanosis. Initial methaemoglobin level was 54.6%, but after MB therapy it reduced to 1.2% in three hours, and her symptoms rapidly improved within an hour [7]. Malik MJ et al., described the case of a female who had taken Adderall and cocaine in addition to drinking alcohol during a party, as a result of which she developed blue-grey skin discolouration and appeared lethargic but responsive, with no focal neurological deficits noted on physical examination. Pulmonary examination was clear to auscultation but she was short of breath with conversation and any exertion. SpO_2 in ABG remained 85-88% even while on the non rebreather mask, and serum methaemoglobin level was 30%. SpO_2 improved after MB therapy [8]. Similar to these cases, our patient also developed cyanosis intraoperatively. However, he did not have any respiratory symptoms or any chest discomfort although the SpO_2 was lower as compared to that of patients described in these published case reports. The serum methaemoglobin level was also much lower. When MB therapy was given postoperatively, his SpO_2 level took few days to improve and cyanosis also subsided, but even after months of treatment, SpO_2 level varied from 20-80%, and thus the condition was suspected as refractory haemoglobinaemia. However, the patient still did have any respiratory distress.

Oxidising agents accelerate the oxidation of Hb 100 to a 1,000 times, and eventually overwhelm the capacity of reducing endogenous systems. They include drugs such as local anaesthetics (benzocaine, lidocaine, and prilocaine), dapsone, phenacetin derivatives, and anti-malarials. Intoxication with pesticides, herbicides, and fertilisers, automobile exhaust fumes and industrial chemicals, as well as aniline and rasburicase are other causes [2,3,9]. Disparity between pulse-oximeter as well as ABG readings of SpO_2 is suggestive of methaemoglobinaemia [5]. Brown ring test is a standard procedure to detect the presence of nitrates in aqueous solution [10]. Since, it was positive in our patient, we suspected nitrate-induced methaemoglobinaemia, which was possibly caused due to his habit of tobacco chewing, as ammonia is in the list of harmful and potentially harmful FDA approved constituents in tobacco products

and tobacco smoke [11]. Nitrates may also be present in contaminated water or in certain green and rooted vegetables [2]. Benzene, which is another causative agent of methaemoglobinaemia, is also a constituent of tobacco [11]. Other possibilities could be some local anaesthetic or contrast agent. Prolonged anaesthesia during surgery or inevitable exposure to drugs is likely to worsen methaemoglobinaemia [1]. To find out if there was some congenital aetiology, the patient was also advised to undergo gene testing for CB5R [2], but refused for the same as it was expensive.

Treatment like airway maintenance, supplemental oxygen, haemodynamic support, neurological assessment, activated charchoal and discontinuation of triggering agents are considered [5,12]. MB, a thiazine dye with antiseptic and dose-dependent redox properties, is an antidote for methaemoglobinaemia. It is used carefully in patients with renal failure and in pregnant women [1,2]. Certain cases refractory to MB therapy include sulfhaemoglobinaemia, inadequate gastrointestinal decontamination with ongoing toxin absorption, G6PD deficiency, congenital NADPH, MetHb reductase deficiency or a rare toxin. Unresponsive methaemoglobinaemia may require hyperbaric oxygen or exchange transfusion [13]. Our patient was also suspected to have unresponsive methaemoglobinaemia and hence advised for exchange transfusion to further improve SpO_2 but refused.

CONCLUSION(S)

Methaemoglobinaemia is a rare entity. It is not always a life threatening condition, thus enabling us to carry out the necessary surgical intervention under general anaesthesia for a disease that can worsen if not treated on time. However, knowledge about previous history of exposure to the substance that might lead to methaemoglobinaemia is important, so that such substances can be avoided in the future and no further worsening of the condition occurs.

Compliance with Ethical Standards

Ethical approval: All activities involving human participants followed the ethical guidelines established by the Ethical Committee of Rohilkhand Medical College and Hospital, Bareilly, Uttar Pradesh, India. The procedures also adhered to the principles of the 1964 Helsinki Declaration and its later revisions, or equivalent ethical standards.

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