Case Report

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Successful management of Methemoglobinemia and G6PD deficiency in a patient posted for surgical excision of branchial cyst

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Abstract:

A 27-year-old female patient who came for branchial cyst excision was found to have cyanosis and a saturation gap during preanesthetic check-up and hence she was referred to haematology for further workup. She had a Hb of 9 gm% with all other baseline tests as normal. Blood samples were sent for methaemoglobin estimation and related work up to the National Institute of Immunohematology (NIIH) Mumbai. She was diagnosed as a case of Methemoglobinemia with a methaemoglobin level of 68.7% with NADH cytochrome B5 reductase activity of 10.82 IU/g Hb. The drug of choice for treatment is Methylene blue and hence G6PD deficiency had to be ruled out prior to initiating therapy. She was found to have a concurrent existence of G6PD deficiency. The blood sample was further sent to NIIH for genetic confirmation. We avoided methylene blue and other precipitating factors that could trigger a haemolysis. She was further consulted by the Patient blood management team to optimize her erythropoiesis and avoid unnecessary transfusions. Anaesthetic consultation and planning were done to avoid drugs that could induce haemolysis. She was started on Vitamin C, Niacin, hematinic and advised to follow up after a month. She was symptomatically better. Cyanosis had reduced, and Hb improved to 12 gm%. She was taken up for surgery with all precautions. The surgery and the post-operative period were uneventful. She was discharged on postoperative day 4 with an advice to continue Vitamin C & Niacin and to follow-up in Haematology OPD after a month.

Keywords:

Glucose-6-phosphate dehydrogenase, methemoglobinemia, novel mutation

Introduction

Methemoglobin is the reduced form of hemoglobin which is normally found in blood in levels <1%.[1] Methemoglobinemia is a disorder which is characterized by methemoglobin levels >1% in blood. Heme iron configuration is in ferric (Fe3+) form.[2] It can be congenital or acquired methemoglobinemia. The incidence of congenital methemoglobinemia is not exactly known with some studies showing as low as 0.067%.[3] Three congenital causes for hereditary methemoglobinemia have been described (i) HB M disease, (ii) cytochrome B5R deficiency, (iii) cytochrome B5 deficiency and to distinguish between these, we need pedigree analysis and biochemical analysis.

Treatment includes methylene blue, ascorbic acid, riboflavin, and avoiding precipitating agents (local anesthetics, nitrates/nitrites, and certain drugs).

Glucose-6-phosphate dehydrogenase (G6PD) deficiency is the most common enzymatic deficiency which is an inherited disorder due

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to a defect in red blood cell (RBC) enzyme G6PD affecting around 400 million people worldwide.[4] G6PD deficiency is an X-linked recessive genetic disease, caused by deficiency of an enzyme in the hexose-mono-phosphate shunt pathway of carbohydrate metabolism, and results in decreased production of nicotinamide adenine dinucleotide phosphate hydrogenase (NADPH). NADPH protects cells from oxidative stress, thus, defective RBC is more susceptible to hemolysis by oxidative stress.[5] Predisposing factors include sulfonamide powder, infection, liver conjugation defect, fava beans, and oxidant drugs such as Chinese herbs or naphthalene balls. Management includes avoidance of exposure to oxidant drugs, transfusion support in acute hemolytic crisis, intravenous fluids, and antioxidants.

Case Report

A 27-year-old female patient was referred to the hematology outpatient department (OPD) from the anesthesia department for fitness of surgery. The patient was planned for a right cervical exploration and a suspected branchial cyst. She had a history of swelling on the right side of the neck for 2 years and was planned for surgery from an outside hospital but was postponed due to failure to receive anesthesia fitness from the same hospital. She had recurrent infections of the cyst which made her approach our hospital for surgery.

Her history includes treatment for a cold abscess in 2018, following which antitubercular treatment was initiated and completed. She was born of a nonconsanguineous marriage and had no history of similar illness reported in the family. She is married and has a 7-year-old son. She was not on any medication when she presented to our surgery OPD.

Following surgery consultation in our hospital, she underwent ultrasonography and fine-needle aspiration cytology. The findings were consistent with branchial cyst. Preanesthetic workup picked up a saturation gap (SPO2 was 84% in room air with ABG showing PO2 of 98.5 mmHg) for which a hematology consultation was done.

A detailed evaluation was done at the hematology department which revealed a history of dark brown-colored blood on cuts in the past. A history of giddiness and easy fatigability was present. On examination, she had cyanosis in oral cavity and tongue. There is no history of exposure to any chemicals, antimalarial, fava beans, drug allergy. Considering all the positive finding including saturation gap, a decision was taken to evaluate for methemoglobinemia.

A complete workup including a complete blood count, reticulocyte count, peripheral blood smear, liver function test, renal function tests was done. Cardiology and pulmonology evaluation to rule out secondary causes of cyanosis was also done. Special tests to investigate for methemoglobinemia were also advised done. Her blood investigation is as shown in Table 1.

Genetic analysis revealed a novel mutation (R192C) in CYBR3 gene which is associated with an autosomal recessive congenital methemoglobinemia type 1. NADH-cytochrome b5 reductase (cytb5r) enzyme activities were measured by standard methods, and molecular analysis was performed by polymerase chain reaction followed by DNA sequencing. The interpretation of mutation effect and the molecular modeling were performed by using specific software and PyMOL molecular graphics program. Spectroscopic analysis of the hemolysate showed normal peaks suggesting the absence of Hb-M. Molecular characterization showed a novel homozygous mutation p. Arg192Cys in CYB5R3 gene is an evolutionarily conserved position located in exon 7. This mutation has been elucidated as a possibility of high prevalence of heterozygous in Indian population causing type I restrictive cardiomyopathy.[6] The patient was started on Vitamin C and niacin. Samples were sent for G6PD levels before initiating methylene blue for surgery. Unfortunately, her G6PD levels came back as deficient: 5.9 units/g of Hb (6.97–20.5). She was advised to continue Vitamin C and niacin and to review after 1 month. It was also decided to do a G6PD genetic workup too for the patient.

Her G6PD genetic study was suggestive of G6PD Kerala Kalyan pathogenic heterozygous variant.[7] In India, around 13 variants have been characterized biochemically and as per the mutation studies, the most common variants are G6PD Mediterranean (563 C-->T; 60.4%) followed by G6PD Kerala Kalyan (949 G-->A; 24.5%) and G6PD Orissa (131 C-->G; 13.3%). G6PD Chatham (1003 G-->A) with undetected red cell enzyme activity and G6PD Insuli (989 G-->A) with normal G6PD activity were very rare in the Indian population.[8]

Table 1: Haematological and biochemical Investigations

Parameters	Patient & Reference Value
Hb	12.2 g/dl (12.0-14.0)
HCT	36.4% (36-47)
RBC count	4.5 million/cumm (4-5)
TC	10500 cells/cumm (4000-11,000)
Blood urea	19 mg/dl (10-45)
Creatinine	0.8 mg/dl (052-1.1)
Total bilirubin	0.4 mg/dl (0.3-12)
LDH	155 u/l (120-246)
Methemoglobin level	68.47% (<2%) @ NIIH Mumbai
NADH cytochrome B5 reductase	10.82 (30-40 IU/g Hb) @ NIIH Mumbai

Hb=Hemoglobin, RBC=Red blood cell, LDH=Lactate dehydrogenase, HCT=Haematocrit, TC=Total count, NADH=Nicotinamide Adenine Dinucleotide Hydrogen

G6PD Kalyan, a mildly deficient variant first described in the Koli, a tribal group inhabiting the Kalyan district of Bombay. G6PD Kerala reported in Indians living in the Pacific North West of America, originating from Kerala state. Both were independently identified and later clubbed together to become Kerala Kalyan pathogenic heterozygous variant G6PD. A single base change was found, namely a G—A transition at nucleotide position 949 in exon 9, resulting in the substitution of lysine for glutamic acid at amino acid position 317. Being a mild variant, she was taken up for surgery with adequate precautions. She reviewed after 1 month with a preoperative saturation of 90% in room air. After detailed discussion with anesthesia department, a patient-specific protocol was formulated to ensure safe surgery. Our plan was to avoid methylene blue and dehydration along with monitoring for acidosis, hypoxia, sensorium, and renal function. Plan for hyperbaric oxygen therapy and exchange transfusion if the need arises was also discussed. Propofol and atracurium were used for induction and muscle relaxation, respectively. Maintenance of anesthesia was achieved using oxygen, air, and sevoflurane. Throughout the surgery, her saturation was maintained at 93%. The surgery and postoperative period were uneventful. She was discharged on postoperative day 4. It was also decided to the send the blood samples of family members for Methemoglobinemia and G6PD genetic screening as it is a rare phenomenon.

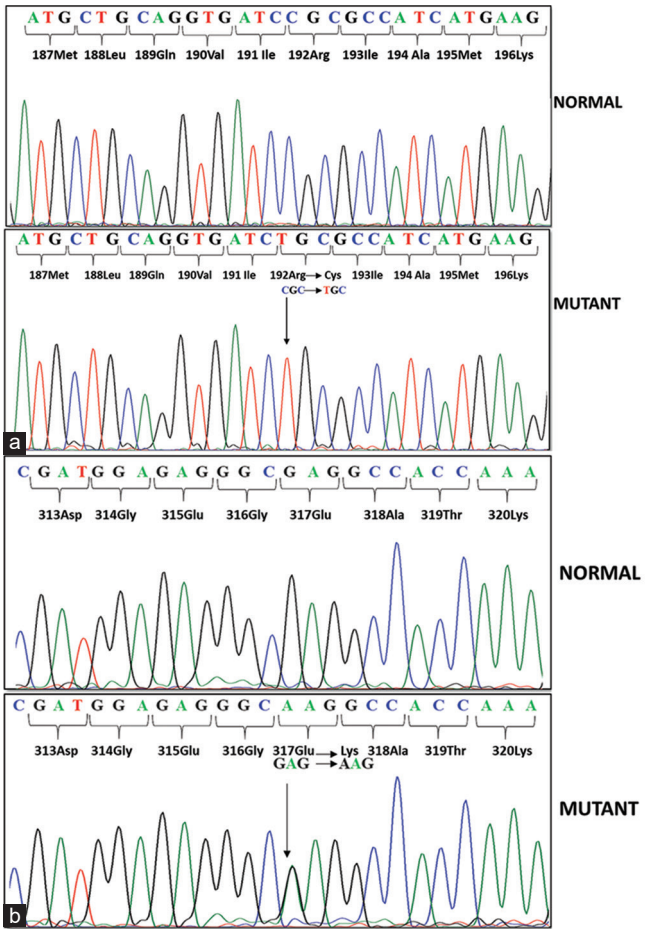

Figure 1: (a) Electropherogram showing the normal and RCM I Pathogenic homozygous variant at nt. 574C>T (192Arg/Cys) mutation in exon 7. (b) Electropherogram showing the normal and G6PD Kerala Kalyan heterozygous variant at nt. 949G>A (317 Glu - Lys) mutation in exon 9

Discussion

This patient had a rare combination of methemoglobinemia and G6PD which posed a conundrum for the anesthesia care in a major surgery. Methylene blue, even though preferred as medication to treat methemoglobinemia before surgery, in this patient, due to G6PD deficiency, it is contraindicated. Methylene blue can cause hemolysis in a patient with G6PD deficiency. Hence, we opted for treatment with Vitamin C and niacin. Even high concentrations of Vitamin C>1000 mg are known to cause hemolysis in such patients.

Anesthetic management should focus on avoiding any drugs that are implicated in hemolysis and continued monitoring of hemolysis, if and when it occurs. The mechanism of hemolysis is due to membrane damage by oxidized hemoglobin.

Both Recessive congenital methemoglobinemia type 1(CYB5R 3 variant c.574C>T p. Arg192Cys) , G6PD (Kerala Kalyan pathogenic heterozygous variant) is highly uncommon in a population and the combination of both of them in same patient is considered extremely rare. Arg192Cys and G6PD Kerala Kalyan pathogenic heterozygous variant are considered in itself extremely rare, let alone a combination of both in a same patient. Any illness which can be managed conservatively should be managed as such and invasive procedures requiring anesthesia should be the last resort.

Due to the extensive preoperative evaluation, every precaution was taken to avoid hemolytic stress in the patient. All drugs precipitating methemoglobinemia and G6PD hemolysis were avoided. Detailed counseling of the patient was done to educate the nature of the disease and therapeutic outlines and possible complications. Even though a rare occurrence, it is advisable to check G6PD deficiency before administration of methylene blue.

Conclusion

Even though combined deficiency of congenital methemoglobinemia and G6PD deficiency is rare, care should be taken to evaluate for G6PD deficiency as it may lead to life-threatening hemolysis in a patient with congenital methemoglobinemia. It is preferable to evaluate

for G6PD deficiency as soon as the patient is diagnosed with congenital methemoglobinemia. An earlier discussion with the surgical and anesthesia team would facilitate better patient management and a successful outcome.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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