Blue after splenectomy

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ABSTRACT

Introduction: We present a 51 year old, African American, female who presented with persistent hypoxemia. She had been taking dapsone for many years for prophylaxis against Pneumocystis jiroveci with no symptoms but eventually developed methemoglobinemia only after a splenectomy. From our literature review there are no documented cases that have demonstrated this relationship between dapsone, splenic function and methemoglobin and we hope to share our perplexing case and shed light on the interaction.

Description: Our patient has type 1 diabetes and underwent multiple pancreas transplants and an initial kidney transplant during her disease course. One year prior to her presentation she underwent a distal pancreatectomy and an incidental splenectomy during the same procedure. She had been taking dapsone for approximately 17 years due to her allergy to sulfamethoxazole/trimethoprim and her immunosuppressive regimen included tacrolimus, sirolimus, and low dose prednisone. She had presented for a routine, post-surgery follow up visit when she was diagnosed with hypoxemia. After an extensive but unsuccessful work up for persistent hypoxemia, she presented to our clinic for a second opinion. Repeat testing of the arterial blood gas in clinic showed a significant methemoglobin (MHb) level of 16.6 mg/dl.

Discussion: Although methemoglobinemia is a well-known risk of dapsone exposure, we report a case that suggests that splenectomy can interact with dapsone to further increase the risk of methemoglobinemia. We believe that our patient did not develop methemoglobinemia initially, despite being on dapsone for many years because her spleen was able to remove older more susceptible erythrocytes from the circulation leaving the more robust younger erythrocytes. With the splenectomy, the number of older erythrocytes in the peripheral circulation increased and resulted in an accumulation of MHb leading to the low oxygen saturations. Her dapsone was immediately stopped and she was started on vitamin C with a 3 day follow up revealing resolution of her methemoglobinemia and normal oxygen saturation on room air.

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1. Introduction

Methemoglobin (MHb) is an abnormal form of hemoglobin (Hb) and is created in the body when deoxygenated Hb is transformed by oxidation so that the iron present in the heme moiety is converted from the usual ferrous state to the ferric state [1]. Dapsone is a well-recognized cause of methemoglobinemia. As many as 13% of stem cell recipients exposed to dapsone will develop MHb [2]. We present a patient who was taking dapsone for many years without any symptoms but developed methemoglobinemia only after a splenectomy. From our literature review there are no documented cases that have demonstrated this relationship between dapsone, splenic function and MHb and we hope to share our perplexing case and shed light on the interaction.

2. Case history

We introduce a 51 year old, African American, female who was referred to the pulmonologist’s office because of persistent hypoxemia. Her past medical history is significant for type 1 diabetes for which she received a pancreas transplant along with a kidney transplant, 17 years prior. She subsequently required 2 more pancreas transplants, 10 and 11 years after the initial transplant. One year prior to presenting to our office she underwent a distal pancreatectomy for an intra-ductal mucinous neoplasm and an...
incidental splenectomy during the same procedure. She had been taking dapsone for approximately 17 years due to her allergy to sulfamethoxazole/trimethoprim. Her immunosuppressive regimen included tacrolimus, sirolimus, and low dose prednisone.

Her hypoxemia was first noted on a routine check-up 6 months after her splenectomy. Her oxygen saturations were noted to be persistently between 80 and 85%. With two liters per minute of oxygen her saturations increased to 92%. Her initial work up consisted of a chest x-ray revealing an incidental nodule in her left upper lobe. A ventilation/perfusion scan and a duplex ultrasonography of her lower extremities revealed no signs of thromboembolic events. Echocardiography with bubble study revealed normal cardiac function and with estimated pulmonary artery pressure of 27 mmHg and no signs of right to left shunting. She also has a right heart catheterization which was normal. Pulmonary function testing (PFTs) showed a restrictive disease pattern with a moderately decreased diffusion capacity of carbon monoxide. 8 months after she was initially found to be have low oxygen saturations she sought a second opinion. A room air arterial blood gas was checked which showed pH: 7.41; pCO2: 35; pO2: 295.5; HCO3: 21.8. Her oxygen saturation was 85.2 with an A-a gradient of 8.9. Her Hgb was 12.3mg/dl and her MHB level was found to be 16.6 mg/dl.

3. Discussion

Heme is a tetramer molecule. Under conditions of oxidative stress, partial oxidation of the heme subunits occurs, causing the remaining non-oxidized portions of the heme molecule to have a very high affinity for oxygen. Because of this they do not easily release oxygen to the tissues, thus shifting the oxygen dissociation curve to the left [3]. Because erythrocytes are continuously exposed to oxygen, a physiologic amount of MHB is produced [4]. It is maintained at low levels; usually less than 1% by compensatory mechanisms.

Nicotinamide adenine dinucleotide (NADH) dependent cytochrome b5 reductase is the major enzyme responsible for reducing MHB. Nicotinamide adenine dinucleotide phosphate (NADPH) also participates in the reduction of MHB. Two non-enzymatic antioxidants include ascorbic acid and glutathione [5].

Erythrocytes are uniquely susceptible to oxidative stress. Red blood cells are equipped with NADH and NADPH but are unable to respond to increased oxidative stress by increasing enzyme production because of a lack of cellular organelles. As erythrocytes age, the amount of enzyme they contain degrades over time making the older cells more prone to oxidative stress than the younger cells [6].

Methemoglobinemia occurs when the MHB is being produced at a rate that is faster than the rate at which it can be reduced back to Hb by the regulatory mechanisms of the body. It can be hereditary or acquired. Acquired Methemoglobinemia is induced by exposure to chemicals or drugs. The most common agents seen in the medical field are nitrates, nitrites, naphthalene, phenazopyridine, dapsone, benzocaine and aniline dyes [7].

Dapsone (diaminodiphenylsulfone) is an antibiotic that decreases folate synthesis by inhibiting the enzyme dihydropteroate synthetase and is used to treat leprosy, malaria, and dermatitis herpetiformis and provide prophylaxis of Pneumocystis jiroveci infections. It undergoes reversible acetylation by N-acetyltransferase (NAT2) to monoacetyl dapsone and via the cytochrome P450 mediated N-hydroxylation to dapsone hydroxylamine in the liver. Dapsone monohydroxylamine is rapidly taken up by erythrocytes and is primarily responsible for the development of methemoglobinemia and hemolysis. The acetylated metabolites are pharmacologically inactive [8].

In normally healthy subjects, symptoms of cyanosis begin to appear when the level of MHB is around 15%. Headaches, tachycardia, fatigue, weakness and dizziness appear at levels of 30–40%. Hypoxia leading to acidosis, paralysis, arrhythmias, convulsions and coma are present at 60% and death at 70–80% [9]. The severity of the patient’s methemoglobinemia is relative to the patient’s Hb level.

Many scientific authors in the past have suggested that exposure to dapsone metabolites results in an acceleration of the aging process of normal erythrocytes which in turn increases splenic sequestration and consequent breakdown [10]. L. Ciccoli and M. Ferrali in their study published in 1999 showed that acute intoxication of laboratory rats with aniline and dapsone compounds resulted in a marked increase in the content of free iron and methemoglobin within erythrocytes. Sub chronic administration of the same compounds resulted in marked iron overload in the spleen and the kupffer cells of the liver. Splenic weight was markedly increased and the free iron pool in both the liver and spleen were also increased further indicating increased erythrocyte breakdown in the spleen [11].

The primary treatment in cases of acquired methemoglobinemia is to stop the offending agent. A decision to hospitalized patients and use specific therapeutic agents is made based on the degree of symptoms as well as the level of methemoglobin. The best described pharmacological therapies for methemoglobinemia are methylene blue and vitamin C as reducing agents and cimetidine as an inhibitor of the N-hydroxylation of dapsone to dapsone hydroxylamine which causes methemoglobinemia.

In life threatening circumstances treatment of methemoglobinemia, intravenous methylene blue is considered to be the treatment of choice [12]. When methylene blue is unavailable high doses of intravenous vitamin C can be used [13]. Blood transfusions and hyperbaric oxygen have also been used in some cases. Since cimetidine works slowly it is not useful for acute dapsone associated methemoglobinemia.

For outpatient treatment of acute methemoglobinemia, oral methylene blue and vitamin C are the primary options. Cimetidine has mostly been studied for chronic use to improve the therapeutic/toxic ratio to dapsone and decrease the level of dapsone induced methemoglobinemia [14].

4. Conclusion

Although methemoglobinemia is a well-known risk of dapsone exposure we report a case that suggests that splenectomy can interact with dapsone to further increase the risk methemoglobinemia. We believe that our patient did not develop methemoglobinemia despite being on dapsone for many years because her spleen was able to remove older more susceptible erythrocytes from the circulation leaving the more robust younger erythrocytes which were able to prevent MHB formation because of their adequate enzyme levels. With the splenectomy the number of older erythrocytes in the peripheral circulation increased and resulted in an accumulation of MHB leading to low oxygen saturations. Once recognized, her dapsone was immediately stopped and she was started on vitamin C. 3 days later, at her follow up clinic visit, she was noted to have oxygen saturations close to 100% on room air. She was later placed on atovaquone for continued Pneumocystic jiroveci prophylaxis.

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