“Pistachio” and “Avatar” Green-Blue Discoloration of the Brain

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As per Journal Policies, ethical approval was not required for this manuscript

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“Pistachio” or “avatar” green-blue discoloration of the brain is a phenomenon associated with methylene blue administration. Methylene blue, an inhibitor of nitric oxide synthase and guanylate cyclase, is used as an adjunct treatment in many medical conditions. Prior to the arrival of chloroquine and more recent drugs, one of its main uses was in the treatment of malaria. Now, it is typically used to treat shock that is refractory to more conventional medical therapy. Other indications are to increase partial oxygen pressure in patients with hepatopulmonary syndrome, treat anaphylaxis, as a therapy for ifosfamide-induced encephalopathy, reduce oxidized hemoglobin in methemoglobinemia, and prevent postoperative vasoplegic syndrome in cardiopulmonary bypass patients, a condition characterized by low systemic vascular resistance and high cardiac output. Methylene blue also has many uses as a medical dye, including localization of abnormal parathyroid glands, marking lesions of the intestinal lumen during intraoperative endoscopy, and for sentinel lymph node localization in breast cancer patients. Clinically documented adverse effects of methylene blue include greenish-blue urine and bluish discoloration of skin and mucosa (1).

This green-blue discoloration of the brain and serosal surfaces was discovered in a hospital autopsy case of a 68-year-old man who was admitted for abdominal pain and distention following a robotic assisted laparoscopic prostatectomy with pelvic lymph node dissection three days prior. During his short hospital stay, he was diagnosed with impending sepsis, treated with methylene blue, taken to the operating room for exploratory laparotomy, and found to have diffusely edematous and dilated loops of bowel. His condition worsened, he was admitted to the intensive care unit in critical condition, and died three days following admission.

Autopsy revealed green discoloration of many of the patient’s organs following exposure to air, including: the brain (**Images A and B**), the pleural surface of the chest plate and rib cage (**Image C**), the lungs, the heart, and the kidneys and perinephric fat (**Image D**). Formal examination of the central nervous system two weeks later showed green staining of the superficial neocortex, caudate, and thalamus (**Images E and F**) and superficial cerebellar folia (**Image G**). Microscopically, there was no pigmentation identi-

fied to account for the green discoloration observed grossly. Additional postmortem findings included fibrin thrombi within pulmonary vessels suggestive of disseminated intravascular coagulation, pulmonary aspiration, a 100 mL right-sided subdural hematoma likely secondary to coagulopathy, and extensive necrosis and transmural hemorrhage of the bowel wall.

Standard forensic pathology teaching instills in its students that green discoloration of the brain and body is most often secondary to decomposition and, in rare cases, due to hydrogen sulfide poisoning (2). The association between methylene blue administration and turquoise to green discoloration of organs has only recently been recognized and documented by a small number of case reports and series in the medical literature. Tan and Rodriguez documented greenish-discoloration most pronounced in the heart and brain with milder discoloration of retroperitoneal and perirenal fat in three autopsy cases of death due to sepsis (3). They hypothesized that the discoloration occurs when the colorless metabolite leukomethylene blue is oxidized to methylene blue upon exposure to molecular oxygen in air. Warth and colleagues investigated the chemistry behind methylene blue discoloration by using tandem mass spectrometry (LC/MS/MS) to quantify methylene blue and its metabolites, Azure A and Azure B, in different tissues (kidney, heart, liver, lung, blood) of a 72-year-old man who died of septic shock (4). They found the highest levels of methylene blue and its metabolites within the myocardium, followed by lesser amounts in the lung, kidney and liver. Of note, the distribution of methylene blue levels within the various tissues/organs in the previously mentioned study correlates with the pattern of visualization of tissue/organ involvement seen in the autopsy case. Prayson and Douglas reported four cases of methylene blue discoloration of brain; surfaces turned a green-blue hue upon exposure to air and when bisected freshly, revealed a similar discoloration of the cerebral gray matter approximately 30-45 minutes later (5). The white matter showed no abnormal discoloration. Lummus et al. attempted to preserve the pigmentation histologically in one autopsy case by using various fixation procedures (6). Only with Bouin

fixative was a single microscopic focus of faint linear blue intraluminal discoloration identified within a leptomeningeal proximal spinal cord vessel.

In contrast to methylene blue, the discoloration seen in hydrogen sulfide poisoning affects all internal organs and only the brain in rare cases. The brains are all green, but vary in hue from blue-green, greenish-purple, blackish-green to dark green (2). While in decomposition cases, in addition to the green discoloration of organ there will also be readily evident external signs of putrefaction, such as marbling, bloating, skin slippage, and purge fluid. Other differential diagnoses that are more common and must be considered include purulent leptomeningitis or bile-pigment staining in regions of blood-barrier breakdown in the setting of systemic hyperbilirubinemia/jaundice. Although both of these entities are typically more green in color than blue-green and would not appear upon exposure to air, these entities are much more likely to be encountered than discoloration due to methylene blue.

Methylene blue associated brain discoloration is an unusual entity that although rare, must be kept in mind in cases when one encounters a green-blue discolored brain.

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