Methylene Blue “Avatar” Brain

Methylene blue is a safe and effective therapeutic agent used in a variety of different clinical settings, including as treatment for methemoglobinemia, reversing ifosfamide-induced encephalopathy, severe hepatopulmonary syndrome, and as a pressor during catecholamine-refractory septic shock (1). Of more relevance to neuropathologists, it has recently been experimentally tested as a dye in multimodal confocal imaging of brain tumors for intraoperative detection of brain tumors (2), for ischemic/reperfusion injury (3), and, because it seems to prevent aggregation of tau and β-amyloid, as a potential therapeutic agent for neurodegenerative disorders such as Alzheimer disease (4) and Huntington disease (5, 6). As such, neuropathologists may encounter patients at autopsy treated with methylene blue.

Methylene blue generates a clinically innocuous, self-limiting, but striking blue-green discoloration to the urine, skin, and mucosa of treated individuals as a by-product of its use (1, 7, 8). This systemic tissue discoloration is more well known than is discoloration of brain tissues, which, to our knowledge, has only been reported once previously (9). The tissues were reported to transform into a bright blue-green color when the colorless leukomethylene blue molecule undergoes oxidation to methylene blue on exposure to air (9). We share our recent experience with brain tissue discoloration and methylene blue use, capturing the transition from colorless to colorful during a very short time interval at the time of autopsy.

A 20-year-old woman with asthma and surgically repaired coarctation of aorta was transferred to our hospital for refractory respiratory failure, hepatopulmonary syndrome, and possible cirrhosis. Her hospital course was complicated by persistent altered mental status, respiratory failure, acute kidney injury, and hypotension. Hypotension became refractory to catecholamines, necessitating the use of methylene blue to maintain stable pressures and to reduce possible shunting. She succumbed soon after transfer; autopsy demonstrated that her demise was caused by acutely decompensated high-output heart failure with left-to-right shunting from a clinically suspected and autopsy-demonstrated subdiaphragmatic vascular malformation.

On opening the cranial vault, the brain surface quickly transformed on exposure to air to a pale blue-green color (Fig. A) that intensified and darkened even during a short time interval after removal of the brain (Fig. B). The color became particularly striking after formalin tissue fixation (Fig. C). The blue color relatively spared the dura (Fig. C), optic and cranial nerves (Fig. B), and deep white matter on coronal section (Fig. D), contrasting with the intense discoloration in cortical and subcortical gray matter (Fig. D). General autopsy revealed similar, but less intense, blue-green discoloration of skin, fat, fascia, and serosal surfaces (Fig. E).

We extended the work of Prayson and Douglas (9) and attempted to preserve the blue discoloration at the microscopic level by the use of alternative fixation procedures. Despite the use of several tissue alternative fixatives to the usual formalin (100% ethanol, Bouin), the pigmentation was almost completely lost at the time of histologic examination, as previously described (1), leaving only a faint linear bluish discoloration very focally intraluminally within rare blood vessels (Figure, F: arrows, Bouin fixative, proximal spinal cord leptomeninges, hematoxylin and eosin, 100×).

While a curiosity in the case of methylene blue use, discoloration of tissues encountered at autopsy can prompt confusion and concern. Indeed, for forensic pathologists and neuropathologists, discoloration of tissues often suggests the possibility of ingestion of a toxin, and recent cases of patients treated with methylene blue who show systemic tissue discoloration have prompted additional toxicologic testing (7). With the exception of the classic “cherry red” discoloration of systemic and brain tissues with carbon monoxide poisoning, toxins, however, usually produce discoloration limited to the skin or nail beds and do not extend to the CNS.

Berton Roueché immortalized how toxins can produce striking skin discoloration in his tale of a group of New York City men who, in 1944, had inadvertent ingestion of sodium nitrite and developed azure-colored cutaneous changes, entitled “Eleven Blue Men” (10). Agryria caused by silver ingestion is also well known, and although silver sulfide deposits can be found within CNS and peripheral nervous system tissues, it is in very low amounts insufficient to produce gross discoloration of brain tissues (11, 12). Although too numerous to review, other examples of skin discoloration, particularly in sun-exposed areas, include Addison disease, amiodarone use, and hemochromatosis (11). Unlike these compounds, methylene blue diffusely discolors skin.

A number of different medications also produce blue-black discoloration of the fingernails, the most relevant of which for neuropathologists and neuroscience clinicians are zidovudine, antimarial drugs, and gefitinib, a tyrosine kinase inhibitor used to block epithelial growth factor receptor in lung cancer patients (13). Unlike methylene blue use, these are all superficial discolorations not involving the CNS.

Except for the exquisite study by Prayson and Douglas (9), we were only able to identify a single other image of coronal sections of autopsy brain tissue with “bright turquoise discoloration…” illustrated in the Forensic Neuropathology text by Itabashi et al (14). This occurred in a 20-year-old man who succumbed after cleaning the interior of a tanker containing 90% formic acid, with collapse and death 1.5 hours later. The authors could not attribute the brain discoloration to formic acid poisoning. The rarity of blue discoloration in CNS tissues was underscored by these authors who noted that “this was the only case with this specific dramatic color change in the brain encountered in over 20,000 neuropathology consultations performed in this department over the last quarter century” (14).
Prayson and Douglas (9), in the time-honored tradition of assigning pathologic conditions food-related appellations, considered this methylene blue discoloration of the brain to be “pistachio green” (9). In deference to a modern pop movie, we liken this sky blue color to the famous creatures in the movie “Avatar.”

It must be emphasized, however, that, to our knowledge, full neuropathologic examination has not been conducted on Avatar creatures. Hence, there is no FIGURE. (A–C) At autopsy, the calvarium was removed to reveal a pale blue-green brain (A), but this rapidly transformed into a duskier shade of blue (B). After several minutes, the brain surface maintained the blue color, but there was sparing of the dura, cranial nerves, and white matter of the brainstem; this dichotomy between intense blue discoloration of the brain versus sparing of the dura was maintained after formalin fixation, although a more intense turquoise color was now evident (C). (D) Coronal sections showed the striking gray-white matter differences in the discoloration. (E) Within minutes of evisceration at autopsy, the omental fat, muscular fascia, and the serosal surfaces had also transformed into a bright blue color on exposure to air. (F) Despite the use of several alternative fixatives to the usual formalin (100% ethanol, Bouin), the pigmentation was virtually completely lost at the time of histologic examination, as described (9), leaving only a faint linear bluish intraluminal discoloration within rare blood vessels (arrows, Bouin fixative, proximal spinal cord leptomeninges, hematoxylin and eosin, 100×).
scientific evidence to suggest that the blue color of Avatars extended to the CNS—or that their azure beauty was anything other than “skin deep.”

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REFERENCES