Fatal carboplatin-induced immune hemolytic anemia in a child with a brain tumor

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Abstract: Drug-induced immune hemolytic anemia (DIIHA) is an uncommon side effect of pharmacologic intervention. A rare mediator of DIIHA, carboplatin is an agent used to treat many pediatric cancers. We describe here, the first case of fatal carboplatin induced DIIHA in a pediatric patient and a brief review of the literature. Our patient developed acute onset of multi-organ failure with evidence of complement activation, secondary to a drug induced red cell antibody. Early recognition of the systemic insult associated with carboplatin induced hemolytic anemia may allow for future affected patients to receive plasmapheresis, a potentially effective therapy.

Keywords: hemolytic anemia, carboplatin, glioma, complement fixation, drug-induced hemolysis

Case

An 11-year-old female was being treated for low-grade astrocytoma with carboplatin and vincristine. The patient was also receiving levothyroxine for central hypothyroidism, ondansetron for chemotherapy-induced nausea, omeprazole for gastrointestinal reflux, and trimethoprim-sulfamethoxazole for Pneumocystis jirovecii pneumonia prophylaxis. Notably, she was not receiving any steroids. On day 15 of cycle five (carboplatin dose number 22), the patient reported acute lower back pain prior to receiving chemotherapy. Her physical exam was unremarkable. She had a stable macrocytic anemia and normal platelet count (Table 1). Thought to be of musculoskeletal origin, the back pain resolved with hydromorphone and ibuprofen. Vincristine 2 mg (max dose) and carboplatin 294 mg (175 mg/m²) were administered. She developed abdominal pain, diarrhea, chills, and tachypnea within approximately 8 hours of chemotherapy administration. The following morning, upon arrival at the local emergency room, she was afebrile, tachycardic, hypertensive, tachypneic, and hypoxicemic. She had diffuse abdominal tenderness, delayed capillary refill time, and a normal neurologic exam. She had worsening anemia (with rouleaux formation but without schistocytes) and carboplatinemia. Transfusion support and broad-spectrum antibiotics were initiated. She was started on continuous positive airway pressure, and remained alert and interactive.

Possible explanations of the patient’s acute presentation include; hemolytic uremic syndrome (HUS), atypical HUS, viral hepatitis, autoimmune hemolytic anemia, sepsis with disseminated intravascular coagulation (DIC), and toxic exposure. Concurrent with this patient’s presentation, there was an epidemic of HUS occurring in her community. She denied similar exposures to those reported by the affected patients.
Review of the peripheral smear did not demonstrate the typical significant schistocytosis found in HUS. Furthermore, stool cultures were negative. While the patient presented acutely with multi-organ failure, she was not febrile and did not have the characteristic distributive shock associated with bacterial sepsis. Blood culture at the time of admission grew non-typable *Haemophilus influenzae*; repeat cultures after 24 hours of cefepime were negative. It seemed that her severe illness could not be primarily attributed to this positive culture because she was not neutropenic, non-typeable *H. influenzae* is not typically associated with severe infection, and the culture cleared quickly with appropriate antibiotics.

Computed tomography (CT) of the chest, abdomen, and pelvis done on hospital day 2, demonstrated a small right pleural effusion, multi-focal nodular ground glass and tree-in-bud opacities in both lungs concerning for atypical infections or diffuse alveolar injury, hepatic steatosis versus edema, and edematous kidneys. An endotracheal aspirate culture grew *Aspergillus*. As she was not neutropenic and had not been on steroids previously, this appeared to be consistent with laboratory contaminant. Furthermore, her chest CT did not reveal the typical findings associated with invasive pulmonary aspergillosis. Serum viral studies were negative except for Epstein–Barr virus (EBV polymerase chain reaction: 320 copies/mL). Serum cortisol was normal at 46 µg/dL. Acetaminophen level was less than 10 µg/mL.

While undergoing dialysis on hospital day 2 the patient complained of severe headache, became lethargic, and required intubation. Her pupils became fixed and dilated. Head CT demonstrated diffuse cerebral and cerebellar edema (Figure 1). An external ventricular drain was placed. Approximately 40 hours into the hospitalization, she had no brain or brainstem activity. She was pronounced dead 64 hours after initial presentation to our hospital.

The temporal relationship between the patient’s acute deterioration and the administration of carboplatin and

![Figure 1](https://www.dovepress.com/)

**Figure 1** An axial, non-contrast enhanced view of the brain shows severe diffuse cerebral and cerebellar edema.

**Notes:** The normal definition between gray and white matter tissue is poor because of the edema. The quadrigeminal and ambient basal cisterns (white arrows) are no longer seen due to upward transtentorial herniation. The fourth ventricle (black circle) is not seen as edematous cerebellum displaces the CSF. The cystic (asterisk) and calcified suprasellar mass is seen.
Fatal carboplatin induced hemolytic anemia

Marani et al described a 44-year-old female developing hemolytic anemia following carboplatin administration. Interestingly, her hemolysis did not worsen with additional doses. Dacha et al described a 72-year-old female who developed acute onset intravascular hemolysis during infusion of carboplatin and subsequently died of multi-organ failure. In our patient, carboplatin-dependent antibodies were identified. The clinical

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picture and laboratory evidence support the pathophysiologic mechanism of drug-dependent immune hemolytic anemia resulting in complement fixation and intravascular hemolysis prompting a systemic inflammatory response, resulting in acute multi-organ failure and death.

Conclusion

Although uncommon, DIIHA is often responsive to drug withdrawal and supportive care. Select drugs have been implicated in a more serious, often fatal form of DIIHA. Here we report the second case of fatal carboplatin-induced immune hemolytic anemia, the first in a pediatric patient. Despite its rarity, DIIHA must be included in the differential diagnosis of any patient receiving platinum-based chemotherapy that presents with overt hemolysis, sudden changes in serum chemistry values, or unexplained back pain. Along with supportive care, clearing the offending antibodies via plasma exchange may control the underlying cause and prevent the brisk and efficient complement fixation that characterizes this form of severe DIIHA. Due to the rapidity of clinical deterioration, plasma exchange was not performed in this case.

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Disclosure

The authors have no conflicts of interest to disclose.

References