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Systemic hypersensitivity reaction mimicking anaphylaxis after first filgrastim administration in a healthy donor

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Recombinant human granulocyte–colony-stimulating factor (rHuG-CSF) is approved for use to accelerate neutrophil recovery after myelosuppressive therapy and to mobilize hematopoietic progenitor cells from the marrow into the blood to facilitate peripheral blood stem cell (PBSC) collection. Commercially available forms of G-CSF include filgrastim (Neupogen, Amgen, Thousand Oaks, CA) and lenograstim (Granocyte, Chugai, Tokyo, Japan), both of which are manufactured by recombinant DNA technology. Filgrastim is a nonglycosylated *Escherichia coli*-derived 175-amino-acid glycoprotein with an extra N-terminal methionine group, and lenograstim is a Chinese hamster ovary–derived 174-amino-acid glycoprotein with 4% carbohydrate, indistinguishable from native G-CSF. Modest and reversible side effects of rHuG-CSF are common, including bone pain, myalgias, and headache. More severe adverse effects, including splenic rupture, have been described in a handful of healthy donors.¹ Anaphylactoid episodes associated with a first dose of rHuG-CSF in healthy donors have only been reported twice, once after filgrastim and once after lenograstim,^{2,3} although additional reports of hypersensitivity reactions in patients receiving myeloablative therapy are described.^{4,5} In these latter cases, confounding effects of multiple concomitant drugs made attribution of causality uncertain. We describe a second case of severe systemic hypersensitivity reaction mimicking anaphylaxis after filgrastim administration in a healthy donor.

A 17-year-old healthy Haitian female PBSC donor presented to the outpatient clinic to receive her first dose of filgrastim. She had no history of allergies and met all institutional

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criteria for sibling allogeneic stem cell donation. She received 720 mg (10 mg/kg) of filgrastim subcutaneously and remained in the clinic, feeling well, for 75 minutes. Fifteen minutes after leaving (90 min after the filgrastim injection), she developed difficulty breathing and throat tightness. She was transported back to clinic by wheelchair by her mother. Upon arrival, she complained of severe cramping abdominal pain and developed diarrhea with lightheadedness and extreme diaphoresis. She was tachycardic (pulse, 144) and hypotensive (80/40), with normal oxygen saturation and no rash. She rapidly became confused, then unresponsive, with an undetectable blood pressure. Intramuscular epinephrine and intravenous diphenhydramine, ranitidine, methylprednisolone, and saline were given. Her symptoms and vital signs stabilized rapidly and she was admitted for overnight observation, continuing to receive steroids and H1 and H2 receptor blockers every 8 hours. Serum tryptase, measured within 3 hours of the event, and 24-hour urinary *N*-methylhistamine were both within the reference range. She was discharged 30 hours after the incident without further sequelae.

A severe anaphylactoid reaction to filgrastim in a healthy allogeneic donor has only been reported once in the past, 50 minutes after a first drug dose in a 16-year-old granulocyte donor whose symptoms and response to therapy were identical to those in our donor.² Similar reactions have been reported in patients with malignancies after a first or subsequent filgrastim dose, but confounding conditions and medications rendered causality problematic.^{4,5} Prior sensitization to *E. coli* derivatives has been assumed to be the cause of these events, but one case of anaphylaxis after lenograstim has also been reported in a healthy donor,³ so that the inciting immunogen is uncertain. The cause of the reaction could be rHuG-CSF itself or another component of the drug preparation such as polysorbate 80 (Tween 80), which has been implicated in hypersensitivity reactions.⁶ The clinical course and response to therapy in our donor were consistent with an anaphylactoid event. However, laboratory testing with serum tryptase and urinary *N*-methylhistamine provided strong objective data that the reaction was not due to mast cell or basophil activation and degranulation.

Our case serves as a reminder that filgrastim administration may be associated with severe hypersensitivity reactions mimicking anaphylaxis and that such reactions should be treated promptly with antianaphylaxis medications. Initial doses of filgrastim should be given in a monitored medical setting, followed by at least an hour of observation.

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