Pathologic Quiz Case

A 64-Year-Old Man With Hematuria, Intracranial Hemorrhage, and Severe Coagulation Abnormalities

Dax Kurbegov, MD; Jun Teruya, MD, DSc; Lawrence Rice, MD

A 64-year-old man with a history of depression presented with 2 days of gross hematuria. Shortly after admission, he developed severe headache and became unresponsive. Past history was otherwise significant for hip surgery 9 months earlier with postoperative prophylactic warfarin. He had been off warfarin and all other medications for 6 months.

An emergent head computer tomographic scan showed a large left subdural hematoma with midline shift. Laboratory evaluation showed hemoglobin of 9.9 g/dL, hematocrit of 29%, white blood cell count of 9200/μL, and platelet count of 252 000/μL. The prothrombin time (PT) and activated partial thromboplastin time (aPTT) were markedly prolonged at 62.6 seconds (normal range, 10.3–13.4 seconds) and >100 seconds (normal range, 22.9–37.5 seconds), respectively. The international normalized ratio (INR) was 25. Results of liver and renal function studies were normal.

To correct the coagulopathy, vitamin K and fresh frozen plasma were administered (Table 1). This allowed surgical evacuation of the hematoma, with improvement in neurologic status and cognition. Despite multiple doses of vitamin K and multiple transfusions of fresh frozen plasma, the PT and aPTT remained moderately elevated. A 1:1 mix of patient plasma with normal plasma fully corrected the PT and aPTT at 0, 30, 60, and 90 minutes. Fibrin-split products were normal at less than 10 μg/mL, and D-dimer was 0.88 μg/mL (normal range, 0–0.40 μg/mL). Fibrinogen was 652 mg/dL (or 19.2 μmol/L; normal range, 200–450 mg/dL), and thrombin time was 17.1 seconds (normal range, 15–20 seconds).

What is your diagnosis?

Table 1. Course of Coagulation Tests and Treatments

Hospital Day	Laboratory Parameters*			Interventions	
	PT	aPTT	INR	Fresh Frozen Plasma	Vitamin K
1	62.6	>100	25	6 units	30 mg IV
2	19.5	38.8	1.6	2 jumbo	10 mg IV
3	18.5	39.2	1.5	2 jumbo	10 mg IV
4	19.1	. . .	1.7	2 regular	. . .
6	20.9	. . .	1.7	2 regular	. . .
7	21.6	. . .	1.8	1 jumbo	. . .
8	21.2	. . .	1.8	. . .	. . .

* PT indicates prothrombin time; aPTT, activated partial thromboplastin time; INR, international normalized ratio; and IV, intravenously.

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From the Department of Medicine, Section of Hematology/Oncology, Baylor College of Medicine at The Methodist Hospital (Drs Kurbegov and Rice), and the Departments of Pathology, Pediatrics and Medicine, Baylor College of Medicine at Texas Children's Hospital (Dr Teruya), Houston, Tex.

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Corresponding author: Lawrence Rice, MD, Department of Medicine, Section of Hematology/Oncology, Baylor College of Medicine at The Methodist Hospital, 6565 Fannin, MS 902-Main, Houston, TX 77030 (e-mail: lrice@bcm.tmc.edu).

Pathologic Diagnosis: Long-Acting Warfarin-like Rodenticide Toxicity

The diagnosis of long-acting warfarin-like rodenticide ingestion was suspected based on the markedly prolonged coagulation tests, the partial response to therapy, the long duration of the coagulopathy, and the absence of likely alternatives. On questioning, the patient admitted to frequently handling rat poisons and not wearing gloves or washing his hands afterwards. He denied ingestion, curiously adding, ''My wife would kill me if she knew about this'' (see below).

Further studies included measurement of the vitamin K–dependent factors II and VII, both low at 56% each, performed on hospital day 3 after vitamin K and fresh frozen plasma therapies. The non–K dependent factor V was 110% (and fibrinogen was elevated). Coagulation tests subsequently normalized on large doses of oral vitamin K (30 mg orally twice daily). Serum warfarin levels were negative, but serum levels of superwarfarin rodenticides came back at highly toxic levels (brodifacoum 34 ng/mL and difenacoum 32 ng/mL). A psychiatric consultant judged the patient not actively suicidal and arranged ongoing outpatient care. Prior to discharge, the patient's wife discovered a bottle of superwarfarin rodenticide hidden in the patient's shaving kit.

An immediate clue to the diagnosis in this case was the extreme prolongation of the PT and aPTT. An international normalized ratio of more than 6 is vanishingly rare with acquired coagulation disorders other than vitamin K deficiency or vitamin K antagonism (unintentional warfarin overdose being the most common cause). With milder degrees of vitamin K deficiency or vitamin K antagonist overdose, a clue to diagnosis can be disproportionate prolongation of PT compared to aPTT, but the discriminatory value of this finding is lost when deficiency is more severe. Vitamin K deficiency is often diagnosed by the response to empiric vitamin replacement and can be confirmed in the laboratory by measuring 2 vitamin K–dependent coagulation factors (usually II and VII, as they have the longest and shortest half-lives) and comparing to a nondependent factor (usually V). The differential diagnosis of acquired coagulation disorders (acquired abnormalities of PT and/or aPTT) is a limited one (Table 2). In this case, liver disease was excluded by clinical and laboratory findings. Vitamin K deficiency was unlikely in the absence of underlying problems associated with deficiency, and this and warfarin overdose were excluded by the incomplete response over time to vitamin K administration. Other acquired coagulation disorders were excluded by the incubated mixing study, the disseminated intravascular coagulation screen (and normal platelet count), and the thrombin time.

Because of rodents' widespread acquired resistance to warfarin, the 4-hydroxycoumarin derivatives brodifacoum and difenacoum are now the most commonly used rodenticides. They act by the same mechanism as warfarin but are 100 times more potent and have much longer serum and tissue half-lives.[1,2] Coagulation factors II, VII, IX, X, and other vitamin K–dependent proteins require gamma-carboxylation of glutamic acid residues to be biologically active (to be able to bind calcium on the surface of platelet-derived phospholipid plugs and to participate in clotting reactions). In the carboxylation reaction, the cofactor vitamin K is converted to an inactive vitamin K-2,3-epoxide. Active vitamin K is regenerated by epoxide reductase enzymes, which are blocked by warfarin and its analogs.[3] The limited availability of active vitamin K produces a bleeding diathesis.

Table 2. Causes of Acquired Coagulation Disorders

1. Liver disease (synthetic failure and acquired dysfibrinogenemia)
2. Vitamin K deficiency
3. Disseminated intravascular coagulation (and rare primary fibrinolysis)
4. Circulating inhibitors/anticoagulants
5. Drugs and toxins
6. Others (rare or special situations), eg, factor X deficiency with amyloidosis, dilutional, hypothermia

Superwarfarin ingestion merits consideration in patients presenting with bleeding and coagulopathy, given the wide availability, high potency, prolonged action, and therapeutic implications. Annual human exposures to superwarfarins have been steadily increasing and reached 17 100 reports to the American Association of Poison Control Centers in 2002.[4] While 89% of ingestions were by children younger than 6 years, the 3 reported fatalities occurred in adults; there were also 40 medical ''major outcomes'' (life-threatening illness and/or significant residual disabilities). The higher complication rate in adults probably reflects larger amounts ingested and different motives, which may be suicidal (612 cases in 2002), homicidal, instances of Munchhausen syndrome, or mistakes and accidents.

Pediatric patients who have ingested small amounts can be managed as outpatients.[5] The management of superwarfarin toxicity is similar in many ways to the management of standard warfarin toxicity because of the common mechanism of action. Adults on warfarin who experience life-threatening hemorrhage should be treated with intravenous vitamin K and prothrombin complex concentrates to replace the vitamin K–dependent factors.[6] Early fresh frozen plasma can also be used to supplement vitamin K therapy. In cases of superwarfarin toxicity, vitamin K is typically needed in high doses (often 40–125 mg daily), titrated to keep the PT near normal.[7,8] As a result of delayed clearance of the superwarfarins, vitamin K therapy must be continued for months—serum elimination half-lives of 36 days in humans and 120 days in dogs have been reported.[7,9] Plasmapheresis would not be effective because of lipid solubility with deposits in fatty tissue and the liver. Awareness and suspicion for this problem, leading to appropriate confirmatory tests and therapy, can be life-saving with superwarfarin ingestions.

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