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CASE REPORT

Hyperfibrinolysis during the treatment of rhabdomyosarcoma

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Abstract

Background: Coagulopathies are frequently observed in alveolar rhabdomyosarcoma (ARMS), with disseminated intravascular coagulation (DIC) being the most common presentation. However, hyperfibrinolysis represents a distinct but often overlapping and potentially life-threatening subset of coagulation disorders that requires specific diagnostic and management approaches.

Key Clinical Question: How can clinicians identify hyperfibrinolysis and what are the implications for management?

Clinical Approach: This case report describes a 25-year-old man with metastatic ARMS arising from the prostate who developed persistent gross hematuria one week after initiating chemotherapy. A comprehensive coagulation workup was performed, including assessment of platelet count, prothrombin time, activated partial thromboplastin time, fibrinogen, D-dimer, and fibrin degradation products. Management included repletion of fibrinogen and the use of anti-fibrinolytic agents.

Conclusion: Recognizing hyperfibrinolysis in ARMS patients is crucial for appropriate management. Clinicians should maintain a high index of suspicion for hyperfibrinolysis in ARMS patients presenting with severe coagulation abnormalities, particularly those with prostatic involvement or undergoing chemotherapy. In cases of primary hyperfibrinolysis, antifibrinolytic agents may be considered, whereas they are generally contraindicated in DIC.

KEYWORDS
alveolar rhabdomyosarcoma, ARMS, chemotherapy, coagulopathies, DIC, fibrinogen, fibrinolysis, hematuria, hyperfibrinolysis, prostate, RMS, tranexamic acid, uPA, urokinase-type plasminogen activator, VAC

Essentials

- Alveolar rhabdomyosarcoma (ARMS) is a rare cancer that is frequently associated with coagulopathies.
- In this case, a patient with ARMS suffers bleeding due to excessive fibrin destruction (hyperfibrinolysis).
- The risk factors, laboratory findings, management, and potential mechanisms of hyperfibrinolysis are described.
- Recognition of hyperfibrinolysis and its risk factors is critical to preventing morbidity and mortality in ARMS.

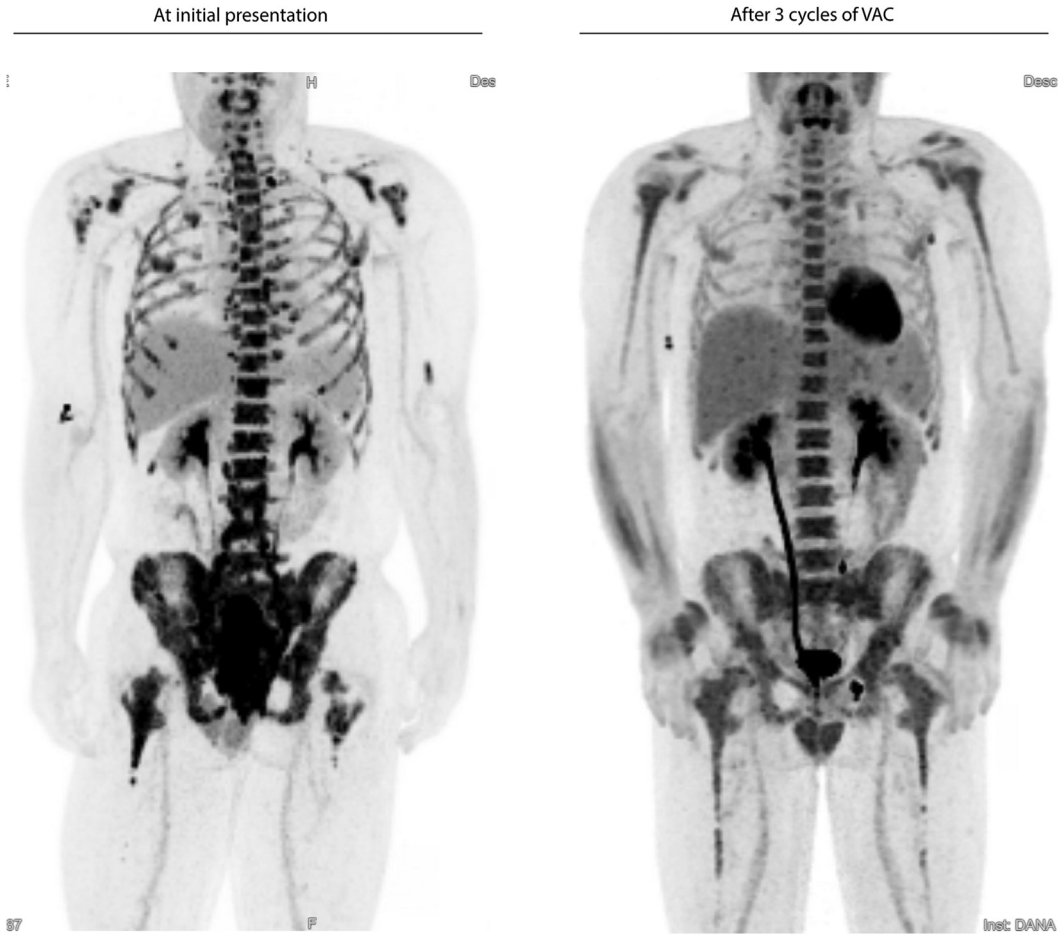

FIGURE Positron emission tomography composite images comparing pretreatment disease burden to disease burden after 3 cycles of starting vincristine, dactinomycin, and cyclophosphamide (VAC). Darker areas indicate sites of high fluorodeoxyglucose avidity, which correlates with sites of malignancy. Images are notable for marked interval improvement with interval resolution of abnormal fluorodeoxyglucose avidity and decreased size of the pelvic mass and sites of disease above and below the diaphragm, as well as decreased avidity of the marrow.

1 | INTRODUCTION

Rhabdomyosarcoma (RMS) is a rare and aggressive soft tissue sarcoma that originates from skeletal muscle progenitor cells. Alveolar RMS (ARMS) is a subtype of RMS characterized by gene fusion, most commonly between *FOXO1* and *PAX3* or *PAX7*; this differs from the other major subtype, embryonal RMS, which is characterized by multiple complex genomic alterations, such as *MYOD1* [1]. Multimodal treatment of high-risk or metastatic RMS involves upfront multiagent chemotherapy, typically vincristine, dactinomycin, and cyclophosphamide (VAC), with consideration of radiation therapy or surgery to primary and metastatic sites [2].

Coagulopathies are anticipated complications of certain cancers, such as RMS. Depending on the balance between procoagulant and anticoagulant forces, coagulation disorders in cancer can manifest as either hypercoagulability or bleeding diathesis. One classically associated coagulopathy is disseminated intravascular coagulation (DIC), wherein systemic activation of coagulation causes consumption of coagulation factors and platelets, resulting in a mix of pathologic thrombosis and hemorrhage. DIC is especially common in cancers such as acute myeloid leukemia, pancreatic adenocarcinoma, and mucin-producing adenocarcinomas [3].

The mechanism of dysregulated coagulation that arises during treatment is not well understood in RMS. Some reports have suggested that DIC and/or hyperfibrinolysis (excessive degradation of fibrin with or without increased clot formation) are frequent and severe, especially in ARMS [4]. Chemotherapy may also affect the coagulation system by causing thrombocytopenia or endothelial damage [5].

Herein, we describe a patient with ARMS who developed severe thrombocytopenia and hyperfibrinolysis after starting chemotherapy and required intensive management to control bleeding. We also review the literature on the epidemiology, pathophysiology, diagnosis, and treatment of coagulation disorders in RMS patients.

2 | CLINICAL PRESENTATION

A 25-year-old man recently diagnosed with metastatic ARMS arising from the prostate presented to the emergency department with persistent gross hematuria 1 week after initiation of chemotherapy.

TABLE Laboratory findings throughout treatment course are shown.

Analyte	Reference range	2 wk PTA	Upon admission	Upon discharge (admit day 6)	6 wk post-discharge
BUN, mg/dL	6-23	22	30	17	23
Creatinine, mg/dL	0.50-1.20	1.38	1.33	1.04	0.78
AST, U/L	<41	34	53	47	25
ALT, U/L	<42	24	49	96	52
Alk phos, U/L	40-129	90	87	111	392
Bilirubin (total), mg/dL	0.2-1.2	0.2	<0.2	0.3	0.3
WBC, K/μL	3.81-8.94	5.9	1.43	7.06	5.34
RBC, M/μL	4.35-5.61	4.94	3.47	2.91	3.15
Hgb, g/dL	12.5-16.3	14.3	10	8.2	9.3
PLT, K/μL	152-440	172	6	107	292
Schistocytes	Absent	Absent	Absent	Absent	Absent
PT, s	11.5-14.5		21	13.5	
PT-INR	0.9-1.1		1.9	1.1	
PTT, s	22.0-36.6		49.6	22.9	
D-dimer, ng/mL	<500		>4000		
Fibrinogen, mg/dL	200-450		<60	455	361
AT3 activity, %	69-127		120		
FII activity, %	50-150		77		
FVII activity, %	50-150		110		
FVIII activity, %	50-150		147		
FIX activity, %	50-150		170		
FX activity, %	50-150		119		
FDP, mcg/mL	<5		>20		

PTA laboratory findings are after rhabdomyosarcoma diagnosis but before starting chemotherapy. Admission laboratory findings are 6 days after starting vincristine, dactinomycin, and cyclophosphamide (VAC). Between admission and discharge, the patient received intravenous fluids, platelets, RBCs, cryoprecipitate, and aminocaproic acid. The patient underwent an additional cycle of VAC 2 weeks after discharge. No further transfusions or aminocaproic acid were given after discharge.

Alk phos, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; AT3, antithrombin III; BUN, blood urea nitrogen; F, factor; FDP, fibrin degradation product; Hgb, hemoglobin; PLT, platelets; PT, prothrombin time; PTA, prior to admission; PT-INR, international normalized ratio; PTT, partial thromboplastin time; RBC, red blood cell; WBC, white blood cell.

One month prior to admission, he had presented to the emergency department with suprapubic pain, polyuria, and dysuria. Staging positron emission tomography showed malignant involvement of the prostate (primary), bladder, peritoneum, multiple lymph nodes above and below the diaphragm, and the bone marrow (Figure). A prostate biopsy was performed with morphology consistent with ARMS. Immunohistochemical staining was positive for desmin, MyoD1, myogenin, and FOXO1. Fluorescence *in situ* hybridization confirmed a PAX3-FOXO1 gene fusion. A ureteral stent was placed to relieve hydronephrosis. At this time, he endorsed no hematuria, and platelets were 172 k/μL (Table).

Several weeks later, he was started on VAC. Shortly thereafter, he developed gross hematuria and returned to the emergency department. He had no personal or family history of coagulopathy and denied any history of easy bleeding or bruising. On clinical presentation, he was afebrile and hemodynamically stable without any localizing signs of infection. Initial laboratories were notable for pancytopenia with profound thrombocytopenia, prolonged prothrombin time (PT) and partial thromboplastin time (PTT), undetectable fibrinogen (Clauss fibrinogen assay; Brigham and Women's Hospital), elevated D-dimer (immunoturbidimetric assay; Brigham and Women's Hospital), and fibrin degradation products (agglutination assay; Quest Diagnostics), absent schistocytes, and normal to increased activity of factor (F)II, FVII, FVIII, FIX, and FX (Table).

A computed tomography scan of his abdomen and pelvis showed significant interval decrease in tumor burden, though worsening of right hydronephrosis. He received 2 units of cryoprecipitate, 3 units of platelets, and 1 unit of red blood cells, as well as a brief course of oral aminocaproic acid. He also underwent ureteral stent upsizing. On day 2 of admission, after these interventions, the PT, PTT, fibrinogen, and

platelets all improved, and hematuria began to abate. He was discharged on hospital day 6 and remained without clinically significant bleeding thereafter.

The abnormal coagulation studies, including fibrinogen level, which was undetectable during the bleeding episode, rebounded and remained normal throughout the following 2 months of follow-up and 2 additional cycles of chemotherapy. He required no further platelet or cryoprecipitate transfusions and no further antifibrinolytic treatments. Interim positron emission tomography scan after 3 cycles of VAC showed significant reduction in size and avidity of all sites of ARMS disease (Figure). He continued VAC treatment with a plan to consolidate with radiation therapy in the coming months.

3 | DISCUSSION

ARMS is a rare diagnosis among adults, and fewer than a dozen cases have been reported of ARMS arising from the prostate [6,7]. This patient's course is also notable for a profound bleeding diathesis with severe depletion of fibrinogen and sparing of other coagulation factors, thrombocytopenia, and rapid and durable improvement with supportive care for coagulopathy and definitive cancer treatment.

Hyperfibrinolysis in RMS patients must be distinguished from DIC and acute liver injury, both of which are common in disseminated cancer and can cause thrombotic and hemorrhagic complications. Differentiating these entities can be challenging as they share common laboratory abnormalities, including prolonged PT and PTT, elevated D-dimer, low fibrinogen, and high fibrin degradation products. However, patients suffering from hyperfibrinolysis, as in this case, have preserved coagulation factor levels and no significant thrombotic microangiopathy. PT and PTT are typically diminished in these patients due to low fibrinogen but rapidly correct with cryoprecipitate infusion, as in this patient. Additionally, hyperfibrinolysis is associated with isolated bleeding, whereas DIC and liver failure can present with both bleeding due to depletion of procoagulant factors and thrombosis due to depletion of anticoagulant factors (ie, proteins C and S). Thrombocytopenia is not a feature of isolated hyperfibrinolysis. In this patient, his low platelets were attributed to chemotherapy-induced marrow suppression, which compounded the bleeding diathesis resulting from excessive fibrinolysis.

Hyperfibrinolysis is a rare but potentially fatal complication of RMS. Although the exact prevalence of hyperfibrinolysis alone in RMS is not known, studies estimate that 10% to 20% of patients with RMS and widespread disease will suffer from coagulopathy secondary to DIC and/or hyperfibrinolysis [8,9]. Factors that are associated with hyperfibrinolysis include large burden of disease, bone marrow involvement, and presence of *PAX3-FOXO1* translocation [4]. The *PAX3-FOXO1* translocation is seen in approximately 50% of ARMS patients and is also associated with a greater risk of bone marrow involvement and poorer prognosis overall [10].

This patient had all 3 of the above factors associated with hyperfibrinolysis. Proactive identification of patients at risk for hyperfibrinolysis is important because it is associated with higher mortality. In a clinical study of soft tissue sarcomas, including RMS, high levels of fibrinolysis markers (D-dimer and plasmin-α2 plasmin inhibitor complex) and coagulation markers (soluble fibrin and thrombin–antithrombin III complex) were predictive of metastasis and poor prognosis, but fibrinolysis markers were more indicative than coagulation markers in predicting advanced disease [11].

Several theories have been proposed to explain the mechanism of hyperfibrinolysis. One theory is that certain PAX target genes transcribed in tumor cells result in elevated coagulation and fibrinolytic activity [4]. Another theory is that fibrinolysis is driven by the production and binding of plasminogen activators by tumor cells. In particular, urokinase-type plasminogen activator receptor is present on RMS cells, localized at sites of cell–cell adhesion, and associated with high metastatic potential [12]. Certain tissues, especially the prostate, are enriched for the urokinase-type plasminogen activator receptor ligand, urokinase-type plasminogen activator (uPA) [13]. Hyperfibrinolysis might thus be triggered by exposure of tumor-bound uPA to plasminogen, occurring with tissue invasion, invasive procedures, or tumor necrosis due to rapid growth or chemotherapy exposure [14].

This patient had all 3 of these potential triggers in the weeks leading up to his presentation. Chemotherapy, such as VAC, may also worsen concomitant bleeding complications. In addition to disrupting tumor architecture and potentially exposing plasminogen activators and tissue factor to the systemic circulation, VAC also causes bone marrow suppression, which reduces the production of platelets and increases the risk of bleeding [15]. Furthermore, VAC can cause kidney damage, which impairs the clearance of plasminogen activators and tissue factor [16].

The management of hyperfibrinolysis in RMS patients depends on the underlying cause and the severity of the clinical manifestations. The mainstay of treatment is the control of the underlying malignancy, either by surgery, chemotherapy, or radiotherapy. Supportive measures include transfusion of blood products, such as platelets and fibrinogen, either as cryoprecipitate or fibrinogen concentrate. Antifibrinolytic agents, such as tranexamic acid or aminocaproic acid, have also been shown to effectively inhibit the fibrinolysis promoted by uPA on RMS cells [12]. These interventions were effective in this patient, but antifibrinolytic agents should be avoided in patients with DIC who have pathologic clot formation [17]. Anticoagulants such as heparin or low-molecular-weight heparin may be indicated to treat thrombosis in DIC, though they have no role in treatment for isolated hyperfibrinolysis [18].

Hyperfibrinolysis is a rare but serious complication of RMS that can cause life-threatening hemorrhage. Hyperfibrinolysis should be distinguished from DIC, which has similar laboratory findings but distinct management. Extensive disease, bone marrow involvement, and *PAX3-FOXO1* gene fusion are associated with higher risk, and tumor-bound uPA may be a disease driver. Though more research is needed to identify targetable risk factors, better awareness of hyperfibrinolysis and its management will improve the care of patients with RMS.

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AUTHOR CONTRIBUTIONS

S.R.T. consulted on clinical management, performed chart review, compiled data and figures, and wrote the manuscript; J.M.C. provided advice and discussion points, consulted on clinical management, and edited the manuscript; V.V. consulted on and subsequently led clinical management, obtained patient consent, and wrote and edited portions of the manuscript.

RELATIONSHIP DISCLOSURE

None of the authors have financial conflicts to disclose.

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