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Selected Topics: Oncological Emergencies

PULMONARY EMBOLISM CAN BE NAUSEOUS: A CASE REPORT AND REVIEW OF D-DIMER USE IN PEDIATRIC ONCOLOGY PATIENTS

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☐ **Abstract—Background: Pulmonary embolism (PE) is a very common presentation in the emergency department (ED). Despite being life-threatening, PE is preventable if diagnosed and managed early, especially in high-risk patients like pediatric oncology patients. A negative D-dimer has a high negative predictive value and can rule out PE in low-risk patients; however, it does not lower post-test probability enough and should be coupled with further diagnostics in high-risk patients. Case Report: We describe the case of a 14-year-old girl known to have acute lymphoblastic leukemia and presented to the ED with persistent nausea and vomiting only, which was exacerbated by exertion. She had previously presented to the ED 1 week earlier for the same complaint, with a nonrevealing physical examination. At that time, the patient was worked up for nausea and vomiting and received symptomatic treatment. An electrocardiogram (ECG) during that presentation showed normal sinus rhythm. During this presentation, ECG showed new ST segment depressions from V1 to V6 in addition to an S1Q3T3 pattern. This, coupled with the exacerbation of her initial symptoms, triggered further investigations. Computed tomography angiography (CTA) of the chest was performed and showed a right lower lobe segmental pulmonary artery embolus. Why Should an Emergency Physician Be Aware of This?: This case highlights the importance of having a high level of suspicion for PE, especially in pediatric oncology patients and specifically in hematologic malignancies. Although our patient's presentation, examination, and laboratory results were not concerning initially, CTA of the chest showed a PE. We are addressing this particular topic to increase the awareness of emergency physicians of cases like this, as PE can have an unusual presentation and missing such a diagnosis can be fatal.** © **2019 Elsevier Inc. All rights reserved.**

☐ **Keywords—d-dimer; exertion; nausea; oncology; palpitations; pediatrics; pulmonary embolism; vomiting**

INTRODUCTION

Venous thromboembolism (VTE), including deep vein thrombosis and pulmonary embolism (PE), is the third most common cause of cardiovascular mortality after myocardial infarction and cerebrovascular accidents (1). The main predictors for VTE are a history of thromboembolism or prothrombotic state, prolonged immobilization, advanced age, obesity, malignancy and pregnancy (2–4). Patients with PE present with myriad signs and symptoms, ranging from being completely asymptomatic to being critically ill. Therefore, physicians should maintain a high clinical suspicion for PE, as it may be fatal if not diagnosed and managed early (5,6). In fact, 30% of patients with PE who do not receive adequate treatment within appropriate time limits die compared to 8% of those that do receive adequate treatment (7). A typical patient with a PE presents with chest pain, dyspnea, tachycardia, hypoxemia, and shock, all of which are nonspecific (4).

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As means to aid timely diagnosis in the light of this clinical variability, Wells criteria and Geneva scores are now used to rule in thromboembolic accidents (4). The PE Rule-Out Criteria, on the other hand, is used to rule out thromboembolic accidents (4). However, the use of these assessment tools has only been validated in adults.

In PE, a D-dimer level is usually elevated (8). A negative D-dimer result helps in ruling PE out, as it has a high negative predictive value (NPV) (ie, a negative D-dimer rules out PE), especially in hemodynamically stable, low-risk patients. Nonetheless, there are a lot of false-positives (ie, a positive D-dimer in a patient that has no PE) yielding a low positive predictive value, mainly in advanced age, malignancy, and inflammation. Pulmonary angiography, however, is the gold standard for diagnosis of PE. However, pulmonary angiography is contraindicated in patients with renal impairment and difficult to perform in critically ill patients and extremes of age (9–12). Ventilation-perfusion lung scanning can be used in patients with contraindications for pulmonary angiography (9,10).

With the advancement in pediatric care and increase in life expectancy of pediatric oncology patients, VTE incidence in this patient population continues to increase, making them prone to substantial morbidity and mortality (13,14). In fact, pediatric oncology patients are among the largest populations that suffer from VTE, which is seen in 2.1–16% of children with cancer (15–18). This rate was found to be higher when screening for asymptomatic VTE (18,19). According to a study published in 2007, children with cancer are 25 times more likely to develop VTE compared to children without cancer (1.52/1,000 person-years vs. 0.06/1,000 person-years, respectively) (20). Moreover, the incidence of VTE seems to vary with different types of cancer, with incidence rates of 0.9%, 8.1%, and 4.0% in leukemia/lymphoma, soft tissue sarcoma/bone tumors, and other sites, respectively (20).

VTE in the pediatric population is due mostly to a state of both inherited and acquired hypercoagulability. In fact, cancer itself puts children in a prothrombotic state. In children with acute lymphoblastic leukemia (ALL), a malignancy of the bone marrow where early lymphoid precursors multiply and replace the normal hematopoietic cells, the prothrombotic state can be attributed to the increased coagulation and diminished fibrinolysis (prior to any treatment), increased thrombin formation, as well as the remarkable release of cytokines and clotting factors by diseased cells (21–23). Moreover, in malignancies that exert a mass effect, the prothrombotic state is the result of blood stasis. Similarly, mediastinal masses in children with lymphoma exert a prothrombotic state via the compression of veins in the upper limb (24). In renal tumors, however, vascular invasion increases the risk for VTE.

Other risk factors include a genetic predisposition, disease-related factors (eg, inflammatory state, hypercoagulable state, and mass effect), and treatment-related factors (eg, central venous catheters [CVCs], surgery, and chemotherapy) (25). Most pediatric oncology patients have indwelling CVCs for administration of chemotherapeutic agents and nutritional support. CVC is the most widely known factor linked to VTE in pediatric oncology patients. In fact, the rate of symptomatic CVC-related VTE is 2.6–36.7% compared to asymptomatic CVC-related VTE of 5.9–43% (25–27). Also, cancer treatment carries an augmented risk of thrombosis. Treatment of ALL imposes changes in both the quality and the quantity of hemostatic proteins (22). For example, L-asparaginase used in the management of ALL is a known factor in the literature. Further prothrombotic risk factors in this population include infections in the immunocompromised and immobility (22).

CASE REPORT

Here we present the case of a 14-year-old girl known to have ALL and on maintenance chemotherapy (methotrexate), who presented to our ED on February 9, 2019 with waxing and waning nausea and vomiting of 2 weeks' duration, which was severely exacerbated by exertion.

One week prior to this presentation, the patient's nausea and vomiting worsened significantly, such that the patient could not tolerate any oral intake (liquids or solids), leading to her presentation to our ED on February 2, 2019. At the time, she did not have chest pain, dyspnea, tachypnea, tachycardia, or palpitations. Her workup came back negative with normal amylase, lipase, liver functions tests, and brain imaging. Electrocardiogram (ECG) was done and showed normal sinus rhythm. The patient's nausea and vomiting were attributed to chemotherapy and she was admitted to the hospital for symptomatic treatment with intravenous fluids and antiemetics. After experiencing an improved appetite, the patient was discharged home February 6 on symptomatic treatment.

On February 9, she returned to the ED with progressively worsening nausea and vomiting. This time her nausea and vomiting were associated with minimal palpitations on exertion and mild back pain. She has had three episodes of nonbilious, nonprojectile vomiting per day since she was discharged from the hospital. The vomiting was not related to meals. The patient denied fever, chest pain, dyspnea, tachypnea, chills, sick contacts, recent surgery, history of thrombophilia, or history of recent travel. Family and social history were unremarkable as well. Figure 1 provides a timeline of the patient's presentations.

In the ED, the patient had a temperature of 37.1°C, blood pressure of 96/51 mm Hg, pulse of 106 beat/min,

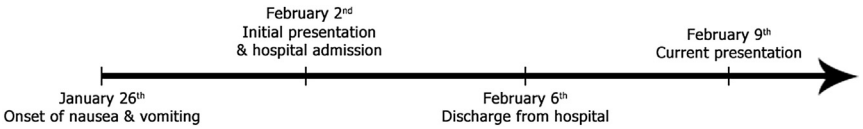

Figure 1. Timeline showing the patient's presentations.

respiratory rate of 14 breaths/min, and oxygen saturation of 100% on room air. Thus, her vital signs were insignificant, with the exception of a slightly increased pulse rate (normal pulse rate for this age group is around 70–100 beats/min) (Table 1). On physical examination, the patient appeared to be fatigued and dysphoric, but the rest of the examination was nonrevealing.

Significant laboratory results included an abnormal complete blood count, with a low white blood cell count of 2000/mm^3 and low hemoglobin of 9.6 g/dL (Table 2). These were consistent with chemotherapy-induced cytopenias. The D-dimer levels were measured and came back negative. An ECG done in the ED showed new ST segment depressions with an S1Q3T3 pattern. The worsening clinical picture and ECG findings led us to have a computed tomography angiogram (CTA) of the chest performed on our patient. CTA revealed a filling defect in the segmental pulmonary artery of the posterior segment of the right lower lobe, indicating a right lower lobe segmental pulmonary artery embolus.

The patient was given enoxaparin in the ED and admitted to the hospital. After being anticoagulated for a period of 48 h, the patient returned to her baseline. Given that other possible causes for nausea and vomiting were felt less likely and that symptoms completely resolved after initiation of anticoagulation, the patient's nausea and vomiting were then attributed to an underlying chronic PE, which could also explain the patient's initial presentation 1 week earlier.

DISCUSSION

This is, to our knowledge, the first report of a patient with PE that presented with only nausea and vomiting on exertion. The case presented delineates the importance of having a high level of suspicion for PE in oncologic pediatric patients with atypical presentations, especially those with liquid tumors.

This patient's initial presentation with nausea and vomiting upon exertion with the absence of chest pain, dyspnea, and hypoxemia, in addition to a negative D-dimer, made the diagnosis of PE unlikely. Nonetheless, the worsening symptoms on exertion coupled with the new ECG changes (new ST depressions and S1Q3T3 pattern), minimal palpitations, and acute-onset back pain raised the concern for possible PE. Given these findings, further workup was initiated, leading to a conclusive diagnosis of PE.

The pathophysiology of nausea in PE has not been discussed in the literature. It may be due to the right heart strain from the embolus causing backflow and hepatic congestion with stretching of Glisson's capsule, leading to a triad of abdominal pain, nausea and vomiting (28). Abdominal pain was not reported by our patient and her liver enzymes were within normal ranges. In the literature, however, many other atypical presentations were described, including abdominal pain (epigastric pain and right upper quadrant pain), symptomatic bradycardia, pleuritic chest pain, back pain, syncope, as well as jerky movements (29–38).

Having established the importance of early detection and management of PE on improving outcomes in a subset of patients that already have multiple comorbidities, including the malignancy, the role of D-dimer needs to be further emphasized. As mentioned, D-dimers have a high sensitivity and NPV and can thus be used to rule out PE (39). In patients with hematologic and oncologic diseases, however, D-dimer levels seem to be less precise (40). A retrospective study, done in the University of Texas MD Anderson Cancer Center, included all patients who presented between May 2009 and November 2015 and were tested for D-dimer levels coupled with a CTA of the chest were included. Those that were later diagnosed with PE, but negative D-dimer levels were noted. Of the 8023 cancer patients, 14% were found to have PE. Only 35 PE patients had normal D-dimer level. Of these, 26 were found to have acute PE and the remaining 9 had subacute/chronic PE. Of the 26 with acute PE, 13

Table 1. The Patient's Vitals in the Emergency Department

Vitals	Blood Pressure (mm Hg)	Temperature (°C)	Heart Rate (Beats/Min)	Respiratory Rate (Breaths/Min)	Pulse Oximeter (%)
1	96/51	37.1	106	14	100
2		37.3	125		100
3	109/63	36.9	103	20	99

Table 2. The Patient's Laboratory Results

Laboratory Tests	Values	Reference Range
CBC with differential		
Adjusted WBC (/mm^3)	2000 (low)	4000–11,000
RBC (million/mm^3)	2.68 (low)	4–6.5
HGB (g/dL)	9.6 (low)	12–18
Neutrophils (%)	88 (high)	40–65
Lymphocytes (%)	10 (low)	25–40
ANC (/mm^3)	1700	1600–7200
D-Dimer (ng/mL)	187	≤ 255
Lipase (U/L)	61 (high)	13–60
Alkaline phosphatase (IU/L)	78	20–385
Alanine transaminase (IU/L)	27	0–50
Aspartate transaminase (IU/L)	24	0–50
Troponin (ng/mL)	0.005	0–0.03
BUN (mg/dL)	6 (low)	8–25
Creatinine (mg/dL)	0.4 (low)	0.5–1

ANC = absolute neutrophil count; BUN = blood urea nitrogen; CBC = complete blood count; HGB = hemoglobin; RBC = red blood cell; WBC = white blood cell.

had hematologic malignancies (eg, lymphoma or leukemia). It is also important to note that the majority (66%) were found to have subsegmental/segmental PE. Despite being unusual (3%), cancer patients with negative D-dimers can have positive radiologic proof of PE (CTA of the chest) (40).

As we discussed previously, malignancy is a risk factor for VTE; consequently, PE is more common in those with cancer compared with the general population (41). Therefore, when a patient with high risk for PE presents to the ED, it is crucial that he or she undergo comprehensive clinical assessment together with laboratory and radiologic investigations in order not to miss a diagnosis of PE (42).

To classify a patient as high, moderate, or low risk, there are established tools (21,43). If a patient is at a low or moderate risk for developing PE, negative D-dimers are adequate to exclude PE. On the contrary, high-risk patients with negative D-dimers need to undergo further investigations. Moreover, recent studies continue to prove a weak role of D-dimers in excluding PE in the setting of hematologic malignancies (44,45).

Studies have repeatedly emphasized the adequacy of a D-dimer test for safely ruling out PE in non–high-risk patients (46,47). In our patient, D-dimer levels came back negative. However, given that our patient was at high risk for PE, it was only reasonable for her to undergo CTA, which in turn came back as positive for PE. Accordingly, we suggest that in high-risk patients, D-dimer levels should always be coupled with further tests, such as CTA, to avoid missing a diagnosis of PE.

WHY SHOULD AN EMERGENCY PHYSICIAN BE AWARE OF THIS?

The scenario we presented described an interesting case of a 14-year-old patient with a history of ALL, who presented to the ED with exertion-related nausea and vomiting and was later found to have PE. Despite having a high NPV, D-dimers should be coupled with further testing in high-risk patients. We are addressing this particular topic to increase the awareness of emergency physicians of cases like this, as missing such a diagnosis can be fatal, especially in the setting of hematologic and oncologic diseases.

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