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Factor V Leiden Thrombophilia in a Female Collegiate Soccer Athlete: A Case Report

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Objective: To raise awareness among health care providers caring for an active population to an uncommon genetic mutation that increases the risk for a potentially fatal venous thromboembolism.

Background: A 19-year-old previously healthy female collegiate soccer athlete complained of coughing and progressively decreased exercise tolerance, which were attributed to a recent illness and lack of sleep. Later that evening, she complained of dyspnea and pleuritic pain and was referred to the emergency department. Bilateral pulmonary emboli were identified with computed tomography, and a hypercoagulable panel revealed that the patient was heterozygous for the factor V Leiden mutation.

Differential Diagnosis: Pneumonia, pneumothorax, pericarditis, pleuritis, gastroesophageal reflux disease, pulmonary embolism.

Treatment: Intravenous heparin therapy was initiated immediately in the emergency department. This was followed by inpatient anticoagulant therapy for 5 days and outpatient anticoagulant therapy for an additional 12 months. During this time, the patient was unable to participate in soccer drills or return to competition and was limited to conditioning activities due to the risk of increased bleeding time.

Uniqueness: Documented cases of pulmonary embolism in a young athletic population are rare and are usually associated with genetic risk factors. Factor V Leiden is a relatively uncommon genetic mutation that dramatically increases the risk for venous thromboembolism. Although the fatality rate in this population is low, fatality is preventable if the condition is recognized early and managed properly.

Conclusions: Athletes should be encouraged to communicate with their athletic trainers regarding any changes in health status or medication usage. When an athlete presents with nonspecific symptoms such as dyspnea and chest pain, athletic trainers should consider the possibility of pulmonary embolism. A high degree of suspicion results in early diagnosis and treatment and may prevent a fatal event.

Key Words: deep venous thrombosis, pulmonary embolism, vascular disease, APC resistance

Thrombophilia is the term used to describe the genetic or developmental propensity to form abnormal blood clots. Factor V Leiden (FVL) is a genetic form of thrombophilia named for a specific mutation and is the most common cause of inherited coagulation disorders.[1] Although thrombolytic events are generally associated with an older population, cases of fatal and nonfatal venous thromboembolism in a young athletic population have been documented.[2–5] Most fatalities seem to occur in untreated patients because of unrecognized pulmonary embolism (PE). This risk obviously presents a concern for every health care provider caring for an athletic or active population. We present the unique case of a young, apparently healthy female collegiate soccer athlete who was unaware that she had FVL and who sustained a PE, a life-threatening condition. This case also demonstrates the importance of obtaining a complete and thorough medical history and of continued communication with our athletes.

HISTORY AND CHIEF COMPLAINT

A healthy 19-year-old collegiate female soccer athlete presented to her team's athletic trainer with initial complaints of decreased exercise tolerance and a cough while warming up for an away competition. On the day before the competition, the patient had traveled for approximately 5 hours on the team bus before arriving at the host city. She had no preexisting cardiovascular or pulmonary conditions and, to the knowledge of the medical staff, was not on any medications. The patient stated that the symptoms had actually begun 3 days earlier, but they did not seem out of the ordinary; she attributed the decreased exercise tolerance to stress and lack of sleep and the cough to a recent illness. Because the patient was experiencing fatigue and having difficulty participating in the team warm-up, the coach decided to hold her out of competition that day. She had no other remarkable signs or symptoms at that time and remained asymptomatic throughout the rest of the day and the return trip. She was instructed to report to the athletic training facility the next morning for reevaluation. However, later that evening, when the team returned home, the patient began to experience dyspnea and lower left pleuritic pain and was immediately referred to the emergency department.

CLINICAL EVALUATION

At the emergency department, the patient did not report any personal or family history of cardiovascular or pulmonary conditions. She was unaware of a family history of PE, deep venous thrombosis (DVT), or genetic risk factors for thrombophilia. She reported starting an oral contraceptive (OC) approximately 1 month earlier for treatment of endometriosis, although she had not notified the athletic training staff of these changes in her health

Table 1. Patient's Prescribed Medications at Hospital Discharge

Medication (Generic Name)	Dosage	Classification
Coumadin (warfarin)[a]	2.0 mg/d	Anticoagulant
Levaquin (levofloxacin)[b]	750 mg/d	Antibiotic
Lortab (hydrocodone and acetaminophen)[c]	5/500 mg prn	Narcotic analgesic

[a] Bristol-Myers Squibb, Princeton, NJ.
[b] Ortho-McNeil-Janssen Pharmaceuticals, Raritan, NJ.
[c] Amneal Pharmaceuticals, Hauppage, NY.

status and medication use. No other medications were reported. Upon assessment, the patient initially complained of pain during deep breathing only, yet this progressed to include pain with shallow breathing as well. Her vital signs were normal, her lungs were clear to auscultation, and she had no clinical signs of lower extremity DVT. A 12-lead electrocardiogram, complete blood count, and chemistry panel were also unremarkable. Chest radiographs suggested no obvious acute infiltrates, effusion, pneumothorax, or other abnormalities. Her prothrombin time (PT), activated partial thromboplastin time (APTT), and international normalized ratio (INR) were within normal ranges, but she had a markedly elevated D-dimer concentration of 16.45 mg/L (normal range = 0.43–1.10 mg/L). The elevated D-dimer concentration indicates the possibility of a thromboembolytic event but does not indicate the cause.[6] Diagnostic ultrasound of the right lower extremity showed no evidence of DVT. However, a computed tomography (CT) scan of the thorax demonstrated bilateral lower lobe pulmonary emboli with evidence of left lower lobe infarction. In addition, genetic testing revealed that the patient was heterozygous for FVL and activated protein C (APC) resistant.

DIFFERENTIAL DIAGNOSIS

The initial presentation of decreased exercise tolerance and cough were nonspecific and initially attributed to lack of sleep and recent illness. The addition of dyspnea and pleuritic pain suggested the possibility of pneumonia, pneumothorax, pericarditis, pleuritis, gastroesophageal reflux disease, or pulmonary embolism. Gastroesophageal reflux disease was included as a possible diagnosis because the patient reported a history of gastric irritation after meals. Although it was not ruled out by any of the diagnostic or laboratory tests, gastroesophageal reflux was not suspected to be the cause of her symptoms. Pneumonia, pneumothorax, pleuritis, and pericarditis were ruled out via laboratory tests and radiographs. The D-dimer concentration and CT results were used to diagnose the pulmonary emboli, and a hypercoagulable panel identified the FVL mutation and APC resistance.

TREATMENT

The patient was initially administered intravenous Toradol (Mylan Pharmaceuticals Inc, Morgantown, WV), a nonsteroidal anti-inflammatory drug, because the initial screening and laboratory studies suggested a possible pneumothorax. However, once she was diagnosed with bilateral pulmonary emboli, Toradol was discontinued, and intravenous weight-based heparin was administered for anticoagulation. She was then admitted to the hospital for continued anticoagulant therapy and observation. Her 5-day inpatient treatment continued with intravenous Coumadin (warfarin; Bristol-Myers Squibb, Princeton, NJ) therapy for anticoagulation and a proton pump inhibitor (Protonix, Pfizer, New York, NY) to help reduce gastric irritation. During this time, she no longer experienced dyspnea, but she continued to have intermittent pleuritic pain, which was controlled with Lortab (hydrocodone and acetaminophen; Amneal Pharmaceuticals, Hauppage, NY). Once her PT, APTT, and INR values remained at therapeutic levels, the patient was released from the hospital under the care of an internist for continued anticoagulation therapy. She was prescribed oral Coumadin for continued anticoagulation and a narcotic analgesic for pain as needed (Table 1). She was also prescribed an antibiotic to protect against potential pneumonia because she was coughing more than usual and had a mildly elevated temperature at discharge. The patient was released from the hospital and instructed to avoid anti-inflammatory medications and schedule an appointment with her gynecologist to discuss an alternate treatment for her endometriosis.

The patient returned to class 3 days after discharge and began noncontact soccer activities 2 weeks later. She continued to struggle with decreased exercise tolerance and had to adjust her exercise participation accordingly. Anticoagulation therapy continued for approximately 1 year; because of the risk of increased bleeding time, contact drills and competitive activities were prohibited. Since that time, the patient has discontinued therapy and returned to playing recreational soccer. She has had no development of DVT or recurrence of PE.

DISCUSSION

Blood coagulation involves a complex series of interactions among proteases, enzymes, and cofactors that lead to the generation of thrombin and the formation of a fibrin-rich clot. However, the clot formed at the end of the coagulation cascade only plays a temporary role and must be removed when normal tissue structure and functions are restored. Factor V is a protein found in the blood that acts as a cofactor in the conversion of prothrombin to thrombin. Once sufficient fibrin has been formed, APC inactivates factor V, helping to stop the clot from growing any larger than necessary. Patients with FVL have a mutation in the gene for factor V, making it resistant to the action of APC. Thus, APC cannot easily stop FVL from making more fibrin. Once the coagulation process begins, it turns off more slowly than in people with normal factor V. Therefore, having FVL results in a condition known as APC resistance.[1] Other inherent factors that can increase the risk for thromboembolic events are deficiencies in protein C, protein S, and antithrombin. Factor V Leiden is

the most common genetic risk factor for thrombophilia. It has a remarkably high prevalence in Caucasian populations, with an average frequency of 2% to 15%, and is rare in people of Asian or African descent.[7] Our patient is Caucasian and was heterozygous for the FVL gene mutation, which means she inherited a copy of the FVL gene from 1 parent and a copy of the normal factor V gene from the other parent. Thus, she has about 50% each of normal factor V and abnormal FVL in her blood. The medical staff was unaware of this condition, as the patient had never been tested for FVL before her PE. This circumstance is not uncommon because the first indication of FVL is usually a thromboembolic event that occurs at a young age. Heterozygous FVL increases the risk for this type of event by 5- to 7-fold.[1] The initial identification of FVL has also been made during autopsy after fatal PEs.

Pulmonary emboli and DVT are clinical presentations of venous thromboembolism that share the same predisposing factors, and in most cases, PE is a consequence of DVT. The incidence of PE is low in the high school, collegiate, and professional athletes more commonly cared for by athletic trainers and increases with age. When PE does occur in younger patients, it is usually attributed to coagulopathy or some other risk factor.[8] In addition to the inherent factors mentioned earlier, hypercoagulopathy can develop as a result of OC use, particularly during the first year of treatment.[9,10] Healthy women using OCs have a 3- to 4-fold increased risk of developing a DVT or PE compared with women who do not take OCs. Women with FVL who take OCs have about a 35-fold increased risk of developing a DVT or PE compared with women without FVL and those who do not take OCs.[1] Our patient was not using an OC before the season started, and thus, the medication was not listed on her medical history. She began OC use during the season but failed to report this to the medical staff. Had the medical staff been aware that the patient was heterozygous for FVL and using an OC, her initial symptoms would have raised a higher level of suspicion for PE. Smoking is also a risk factor for hypercoagulability,[11] but our patient was not a smoker.

The hypercoagulability associated with FVL and OC use is 1 component of the Virchow triad that describes 3 broad categories of risk factors for thrombosis. The other 2 components are venostasis and injury or inflammation of the vessel walls.[12] Demanding athletic events can contribute a number of these risk factors to the development of DVT and PE in athletes. Therefore, in addition to her hypercoagulability, our patient was exposed to many other contributing factors, including repetitive microtrauma, endothelial damage, and dehydration during training and competition.[13]

It is well understood that blood is hypercoagulable after an acute bout of strenuous exercise (for review, see El-Sayed et al[14]), and dehydration can play a role. A massive PE was reported[2] in a high school wrestler after significant episodes of weight loss secondary to fluid restriction and sweating. He did not have any inherent risk factors, but he had undergone rapid dehydration twice in 1 week and had lost 12% of his body weight. It was suggested that the trauma from a wrestling match may have also contributed. Trauma occurs frequently in the athletic population, and many times immobilization and surgery are indicated treatments.

Table 2. Predisposing Factors for Venous Thromboembolism[17]

Strong predisposing factors (odds ratio > 10)
Fracture (hip or leg)
Major general surgery
Major trauma
Spinal cord injury
Moderate predisposing factors (odds ratio = 2–9)
Arthroscopic knee surgery
Malignancy
Oral contraceptive therapy
Pregnancy/postpartum
Previous venous thromboembolism
Thrombophilia
Weak predisposing factors (odds ratio < 2)
Bed rest > 3 d
Immobility due to sitting (prolonged bus or air travel)
Increasing age
Laparoscopic surgery
Obesity
Pregnancy/antepartum
Varicose veins

In addition, training and competition are commonly followed by periods of inactivity and immobility while traveling to and from or recovering from an athletic event. Each of these factors can independently affect venostasis. Campbell et al[15] noted that 20% of patients experienced DVT or PE after a short period of immobilization, whereas travel preceded the occurrence in 9%. The risk of venous thromboembolism after surgery is highest during the first 2 weeks after surgery but remains elevated for 2 to 3 months.[16] Asymptomatic PE is common in the postoperative phase, particularly in patients with asymptomatic DVT.[17] Although our patient did not have a recent surgery or period of immobilization, she became symptomatic after long bus rides.

Recognizing PE outside the hospital setting can be very challenging and presents a significant clinical problem: Most adverse outcomes and fatalities seem to occur in untreated patients because the thromboembolism goes unrecognized.[18] The likelihood of PE increases with the number of predisposing factors present, so awareness of these factors is essential (Table 2).[19] The presence of 1 or more of the risk factors mentioned earlier should increase suspicion and lower the threshold for physician referral. Prodromal signs and symptoms of PE are based on hemodynamic instability and compensatory mechanisms to correct that instability.[12] These signs and symptoms generally represent clinical manifestations of impaired pulmonary gas exchange and low cardiac output and include dyspnea, pleuritic chest pain, tachypnea, and tachycardia. Unfortunately, they are inconsistent and often nonspecific. Furthermore, the onset of symptoms appears to be even more gradual in a younger population.[8] Other signs and symptoms, such as cough, hemoptysis, palpitations, wheezing, and rales, may result from PE but can also result from concomitant illness or injury. Freeman[20] found that no symptom or physical finding had a high positive predictive value for diagnosing PE. However, dyspnea and pleuritic pain seem to be the most common symptoms.[21–23] Stein et al[22] reported that dyspnea, tachypnea, or pleuritic pain was present in 92% of patients with PE. Pleuritic pain was more frequent than hemoptysis, and cough, when present, was usually nonproductive. It is interesting to note that dyspnea

on exertion only was observed in 16% of their patients. Similarly, Ozsu et al[23] observed that dyspnea was the most frequent symptom in patients with PE and that 91% of patients presented with at least 1 respiratory symptom.

Regardless of symptoms, misdiagnosis and mistreatment were common. Courtney and Kline[21] found that acute dyspnea, altered mental status or syncope, and a calculated shock index greater than 0.8 (pulse divided by systolic blood pressure) formed a clinical triad that identified a massive PE. In those with massive PEs, all 3 factors were present in 29.7% and 2 factors were present in 56.8%. The researchers suggested that the clinical presentation is generally prolonged enough to allow for identification before cardiovascular collapse. They also indicated that identifying this clinical triad could provide a recognizable prodrome for massive PE, which would speed the diagnosis and increase the effectiveness of treatment. However, submassive PE presents a greater challenge for detection because they often go unrecognized and can precede the onset of a massive PE by several weeks.[24] The presence of other illnesses can also mask PE and delay diagnosis.[23] Our patient initially presented with decreased exercise tolerance and a cough, which were easily attributable to other conditions. In a similar case[3] involving a collegiate gymnast, the initial symptoms were chest and upper abdominal pain alone. Clinical prediction rules have been developed to aid in the diagnosis of DVT and PE,[25] yet even with CT and other current diagnostic tests, approximately 15% of PEs are diagnosed only after death.[26]

The initial therapy for PE is primarily aimed at life-saving restoration of flow through occluded pulmonary arteries and at preventing potentially fatal early recurrences. It is well accepted that anticoagulant therapy reduces the risk of death and of recurrent embolism. Our patient was treated with the common protocol of heparin for 4 to 5 days, followed by warfarin to maintain anticoagulation. Heparin is generally administered until a target INR value has been achieved. The extended treatment period with warfarin appears to vary by physician preference. It has been suggested that little, if any, advantage is gained by increasing the duration of anticoagulation beyond 3 months and that any possible advantage would need to be judged against the increased risk of fatal and nonfatal hemorrhage associated with longer-duration treatment.[15] Despite this, our patient's anticoagulation therapy was continued for a period of 1 year. Because she suffered a PE, she is at greater risk for another PE or DVT; however, her FVL does not seem to add to that risk.[27] Although no cure or direct treatment currently exists for FVL, some patients with FVL and other risk factors who sustain a DVT or PE are treated lifelong with anticoagulant therapy. This treatment would not be possible for an athlete who wishes to remain competitive, as even minor trauma could result in prolonged bleeding and hypovolemic shock. Instead, an athlete should be counseled about reducing or eliminating other risk factors. For example, the importance of proper hydration should be emphasized when the athlete returns to training and competition. Frequent breaks to stretch the legs are recommended when traveling long distances. Occasionally walking up and down the aisle of the bus or plane or the use of compression sleeves can help to reduce the risk. In addition, the athlete may require temporary anticoagulant treatment during periods of particularly high risk, such as after trauma, major surgery, or immobilization, even though more time away from competition would be required.

CONCLUSIONS

Athletic trainers should encourage athletes to report any changes in their medical condition, symptoms, and medication use throughout the year and not only at the preparticipation examination. Female athletes should report changes in their OC use to provide the medical staff with a complete medical history. The key to managing PE and other thromboembolic events is early detection and early anticoagulation therapy. Health care professionals working with an athletic population must be aware of the signs and symptoms of PE, as well as any athletes with predisposing factors, so that early detection and hospital referral can be made. It is also important that those diagnosed with thrombophilias understand the effect of the condition on their future health care, including obstetric, gynecologic, and cardiovascular implications. Thus, those with a family or personal history of clotting episodes should be considered for further evaluation to identify thrombophilia.

REFERENCES

1. Ornstein DL, Cushman M. Factor V Leiden. *Circulation*. 2003; 107(15):e94–e97.
2. Croyle PH, Place RA, Hilgenberg AD. Massive pulmonary embolism in a high school wrestler. *JAMA*. 1979;241(8):827–828.
3. Kahanov L, Daly T. Bilateral pulmonary emboli in a collegiate gymnast: a case report. *J Athl Train*. 2009;44(6):666–671.
4. Moffatt K, Silberberg PJ, Gnarra DJ. Pulmonary embolism in an adolescent soccer player: a case report. *Med Sci Sports Exerc*. 2007; 39(6):899–902.
5. Tao K, Davenport M. Deep venous thromboembolism in a triathlete. *J Emerg Med*. 2010;38(3):351–353.
6. Fedullo PF, Tapson VF. The evaluation of suspected pulmonary embolism. *N Engl J Med*. 2003;349(13):1247–56.
7. De Stefano V, Chiusolo P, Paciaroni K, Leone G. Epidemiology of factor V Leiden: clinical implications. *Semin Thromb Hemost*. 1998; 24(4):367–379.
8. Arima M, Kanoh T, Takagi A, Tanimoto K, Oigawa T, Matsuda S. Clinical features of acute pulmonary thromboembolism in younger patients. *Circ J*. 2003;67(4):330–333.
9. Dietrich JE, Hertweck SP. Thrombophilias in adolescents: the past, present and future. *Curr Opin Obstet Gynecol*. 2008;20(5):470–474.
10. Farmer RDT, Lawrenson RA, Todd JC, et al. A comparison of the risks of venous thromboembolic disease in association with different combined oral contraceptives. *Br J Clin Pharmacol*. 2000;49(6):580–590.
11. Goldhaber SZ. Risk factors for venous thromboembolism. *J Am Coll Cardiol*. 2010;56(1):1–7.
12. English JB. Prodromal signs and symptoms of a venous pulmonary embolism. *Medsurg Nurs*. 2006;15(6):352–356.
13. Parker B, Thompson PD, Kriz P, d'Hemecourt P. Deep vein thrombosis in athletes: risks of racing and resting. *AMAA J*. 2010; 23(1):7–9.
14. El-Sayed MS, El-Sayed Ali Z, Ahmadizad S. Exercise and training effects on blood haemostasis in health and disease: an update. *Sports Med*. 2004;34(3):181–200.
15. Campbell IA, Bentley DP, Prescott RJ, Routledge PA, Shetty HGM, Williamson IJ. Anticoagulation for three versus six months in patients with deep vein thrombosis or pulmonary embolism, or both: randomised trial. *BMJ*. 2007;334(7595):674.

16. Kearon C. Duration of venous thromboembolism prophylaxis after surgery. *Chest*. 2003;124(6 suppl):386S–392S.
17. Geerts WH, Code KI, Jay RM, Chen E, Szalai JP. A prospective study of venous thromboembolism after major trauma. *N Engl J Med*. 1994;331(24):1601–1606.
18. Kline JA, Hernandez-Nino J, Jones AE, Rose GA, Norton HJ, Camargo CA Jr. Prospective study of the clinical features and outcomes of emergency department patients with delayed diagnosis of pulmonary embolism. *Acad Emerg Med*. 2007;14(7):592–598.
19. Anderson FA Jr, Spencer FA. Risk factors for venous thromboembolism. *Circulation*. 2003;107(23):I9–I16.
20. Freeman L. Pulmonary embolism in a 13-year old boy. *Pediatr Emerg Care*. 1999;15(6):422–424.
21. Courtney DM, Kline JA. Identification of prearrest clinical factors associated with outpatient fatal pulmonary embolism. *Acad Emerg Med*. 2001;8(12):1136–1142.
22. Stein PD, Beemath A, Matta F, et al. Clinical characteristics of patients with acute pulmonary embolism. *Am J Med*. 2007;120(10):871–879.
23. Ozsu S, Oztuna F, Bulbul Y, et al. The role of risk factors in delayed diagnosis of pulmonary embolism. *Am J Emerg Med*. 2011;29(1):26–32.
24. Torbicki A, Perrier A, Konstantinides S, et al. Guidelines on the diagnosis and management of acute pulmonary embolism. *Eur Heart J*. 2008;29(18):2276–2315.
25. Tamariz LJ, Eng J, Segal JB, et al. Usefulness of clinical prediction rules for the diagnosis of venous thromboembolism: a systematic review. *Am J Med*. 2004;117(9):676–684.
26. Wood KE. Major pulmonary embolism. *Chest*. 2002;121(3):877–905.
27. Christiansen SC, Cannegieter SC, Koster T, Vandenbroucke JP, Rosendaal FR. Thrombophilia, clinical factors, and recurrent venous thrombotic events. *JAMA*. 2005;293(19):2352–2361.

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