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Diagnostic Dilemma: A Presentation of Chest Pain in a Patient with Ehlers-Danlos and Klinefelter Syndromes

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Abstract

We describe a young man with Ehlers-Danlos syndrome and Klinefelter syndrome who presented with acute chest pain, syncope, and transient bilateral weakness, and underwent urgent evaluation for life-threatening vascular and neurologic processes. His heritable connective tissue and endocrine disorders heightened the physiologic risk of disease and diagnostic concern. Following comprehensive exclusion of existing pathology, the acute presentation was attributed to functional neurologic disorder, arising from the interaction of psychological stressors and neurobiological dysfunction. This case report highlights how complex medical histories can both complicate and warrant exhaustive evaluation, while also contributing to functional and symptomatic presentations.

Introduction

Chest pain is one of the most common complaints in emergency medicine, accounting for over six million annual visits in the United States [1]. Causes range from benign musculoskeletal pain to life-threatening aortic, embolic, or coronary events, requiring clinicians to prioritize rapid exclusion of life-threatening causes [2,3]. In younger adults, cardiovascular pathology is less prevalent, yet diagnostic diligence is critical, particularly when patient-specific risk factors are present.

Rare heritable and endocrine disorders such as Ehlers-Danlos syndrome (EDS) and Klinefelter syndrome (KS) are independently associated with increased vascular and thromboembolic risk. EDS is a rare heritable and heterogeneous group of collagen disorders, in which certain subtypes increase major artery fragility and susceptibility to pathologies such as aortic dissection [4]. Klinefelter syndrome (KS) is a chromosomal disorder of sexual differentiation that results in hypogonadism and hyperestrogenism, which predispose this population to a 4- to 6- fold increase in venous thromboembolism (VTE) and cardiovascular mortality [5]. However, in patients in whom both disorders are present, excess caution to rule out acute pathology is warranted.

Functional neurologic disorder (FND), historically termed *conversion disorder*, can be characterized by motor, sensory, or consciousness disturbances that are inconsistent with recognized neurologic pathology [6]. Often, a combination of psychological and neurobiological factors precipitates FND presentation. Psychological factors include, and are not limited to, stress, attentional dysregulation, and stimuli that are perceived as threatening, which can contribute to presentation. From the neurobiological perspective, it has been noted that brain network dysfunction, altered metabolic demand, and neuronal connectivity within different anatomical areas of the brain help contribute to specific symptomatic presentation [6,7]. When presentations mimic life-threatening causes in patients with a predisposing medical history, diagnostic reasoning becomes particularly complex.

This report describes a young man with EDS, KS, and Gilbert syndrome who presented with acute chest pain and syncope. The case highlights how a patient's past medical history helped shape diagnostic probability, precipitate patient anxiety, and heighten physiologic response, which in turn ultimately produced a functional manifestation.

Case Presentation

A 22-year-old man with EDS vascular type, KS managed with long-term testosterone therapy, and Gilbert syndrome presented to the emergency department (ED) with sudden-onset chest pain, bilateral upper and lower extremity motor weakness, and a syncopal event.

He first developed acute substernal chest pain while driving, describing the sensation as

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"someone reaching into my chest and squeezing my heart." Before that, he had been working in the heat. Concomitant with his chest pain, he experienced shortness of breath, blurry vision, dizziness, nausea, and non-bloody emesis. He pulled over his vehicle and called emergency medical services. While waiting, he sequentially developed bilateral upper then lower extremity motor weakness and suffered a syncopal episode. He recalled awakening in the ambulance en route to our hospital's ED. He noted that this was the first time such an event had occurred.

On arrival, the patient was afebrile and hemodynamically stable. We performed a physical examination and noted a mild interarm blood pressure difference (112/50 mm Hg right, 127/61 mm Hg left) but no murmurs or pulse deficits. Of note, the patient was only able to move his thumbs but was unable to move any other fingers. However, the weakness was quickly resolved within hours during re-evaluation.

In addition to KS treated with supplemental testosterone injections every 14 days, EDS, and Gilbert syndrome, the patient's medical history included major depressive disorder, for which he received counseling and medication, but stopped taking medication on his own accord. Additionally, the patient reported a 5-year history of electronic cigarette use, consumption of alcohol socially, and use of over-the-counter erectile dysfunction medication. The erectile dysfunction medication was acquired through an online retail service that provided generic phosphodiesterase-5 inhibitors, potent vasodilators like sildenafil, tadalafil, and vardenafil [8]. The patient was uncertain which specific medication he used.

A complete metabolic panel revealed hypophosphatemia (0.6 mg/dL), mildly elevated creatinine (1.24 mg/dL), total bilirubin 1.2 mg/dL, and mild hyperglycemia (127 mg/dL). His complete blood count returned with results within normal limits. Cardiac troponin results were negative, and the results of an electrocardiogram showed a normal sinus rhythm with possible left bundle branch block. The patient's chest radiograph was unremarkable. Subsequently, the ED initiated electrolyte replacement.

Given his presentation and past medical history, there was concern for acute aortic dissection. Stroke protocol was activated to evaluate the patient's weakness and syncope. Computed tomography (CT) angiography of the head, neck, thoracic, and abdominal aorta revealed no dissection, aneurysm, or large-vessel occlusion. CT and magnetic resonance imaging (MRI) of the brain and spine with and without contrast showed no acute ischemia, demyelination, or structural abnormalities. Our internal medicine service requested a neurology consultation for evaluation and assistance with care management.

The neurology consultant documented an NIHSS (National Institutes of Health Stroke Scale) score of 18/42 significant for a moderate stroke (in which higher scores indicate increased severity of a stroke) and performed a physical exam, during which the patient was ambulating, thereby demonstrating motor competency. The absence of structural abnormalities observed via CT and MRI imaging made vascular etiologies of his symptoms less likely. Given the results of the patient's physical exam and imaging, FND or panic-related syncope were deemed the most appropriate explanations. The patient remained neurologically intact and hemodynamically stable throughout hospitalization. He was counseled on the benign findings, encouraged to cease his tobacco consumption, and discharged home on hospital day 3 with instructions to follow up with his primary care physician and therapist.

Discussion

This case illustrates the diagnostic and cognitive uncertainty that arises when rare heritable disorders intersect with functional presentations. The alarming initial presentation of acute chest pain with bilateral upper and lower extremity motor weakness justifiably prompted emergent evaluation for aortic dissection, pulmonary embolism, acute coronary syndrome, and stroke. Considering the patient's past medical history and increased risk of significant vascular pathology, urgent and thorough cardiac examinations and investigations were essential. Compounded onto his medical history, his concurrent use of e-cigarettes, over-the-counter vasodilators, and alcohol further exacerbated the cardiovascular risk of events or disease [9]. Physicians must remain vigilant of the intricate interplay between the human psyche and body, which can help explain symptomatic presentations when thorough investigations provide no physiological causes of pathologies.

Ehlers-Danlos syndrome is a heterogeneous group of collagen disorders affecting approximately 1 in 5000 individuals [4,10]. Depending on the collagen type affected, EDS is inherited in either an autosomal dominant or autosomal recessive pattern. EDS Type IV, also referred to as vascular EDS, as seen in our patient, predominantly affects blood vessel tensile strength, predisposing major arteries to vascular fragility, and, more uncommonly, autonomic instability [10,11]. Vascular EDS arises from *COL3A1* mutations and carries a 25% risk of major vascular events, including dissection, aneurysm, or rupture of vessels, by age 20; there is an 80% lifetime risk of major cardiac events, and a median survival age of 48 years [4,12]. Such high rates of morbidity and mortality motivate an aggressive diagnostic approach when patients with EDS present with chest or back pain, even when hemodynamically stable on presentation [12]. Beyond structural manifestations, EDS frequently involves neurovisceral dysregulation, similar to a bridge spanning connective tissue pathology, autonomic dysfunction, and emotional regulation [11,13]. Orthostatic intolerance, palpitations, and transient weakness are commonly reported and may overlap with functional or psychogenic phenomena, blurring the distinction between physiologic and psychosomatic causes [11,13].

Klinefelter syndrome is a chromosomal disorder of sexual differentiation resulting in either the 47 XXY genotype, occurring in 1 in 600-650 live male births, or the rarer 48 XXXY genotype, occurring in 1 in 50,000 live male births [5]. Existence of an additional chromosome dysregulates production of the seminiferous tubules and Leydig cells, which in turn causes hypogonadism and hyperestrogenism. Hypogonadism in KS contributes to metabolic syndrome, dyslipidemia, and hypercoagulability, conferring a 4- to 6-fold increased risk of VTE and elevated cardiovascular mortality [5,14-17]. Treatment for this condition is testosterone replacement therapy (TRT), which may be linked to VTE risk itself [16]. As such, given the patient's presenting symptoms, his concurrent KS further intensified the likelihood for high-risk vascular catastrophe, such as pulmonary embolism, and warranted expeditious and thorough cardiopulmonary investigation [5,14-17].

When clinical presentation involves syncope and neurologic deficits, such as motor weakness, it is imperative for clinicians to quickly and accurately rule out major cerebrovascular accident [18,19]. The essential components in identifying the existence and

location of a stroke include CT imaging, MRI imaging, NIHSS, continuous monitoring, and focused neurologic exam [18,19]. In this case, after structural pathologies were excluded by comprehensive imaging and laboratory testing, FND was deemed to be the cause of the patient's neurological presentation. FND is a common and often disabling condition impacting 50/100,000 people per year [3,6]. Diagnostic requirements focus on at least 1 altered voluntary motor or sensory function, the exclusion of alternative diagnoses, and the magnitude of deficit impact on diminished social activities, occupational activities, or activities of daily living [20]. This patient's pattern of symptoms, including abrupt onset, bilateral upper and lower extremity weakness, rapid resolution, and neurologic inconsistencies, aligned with a psychophysiologic cascade, where the somatic sensation of chest pain and psychologic stress of a possible major pathologic catastrophe synergized [6,20]. The patient's inherited disorders provided legitimate grounds for alarm, yet his symptomatic appearance may have been induced, or exacerbated, by the heightened autonomic response from emotional stress or panic. This integration of functional and physiologic processes is best conceptualized as a spectrum rather than a dichotomy, where the causal agent of symptomatic presentation is a mixture of both processes. Currently, there are no known effective treatments targeted to FND; however, symptom reduction and management can be accomplished through education about the disease, antidepressants, and cognitive behavioral therapy [3,7].

Ultimately, this case demonstrates how a complex previous medical history can simultaneously obscure and inform diagnosis. The presence of high-risk comorbidities in a patient with serious symptoms appropriately mandated comprehensive testing, yet recognition of functional overlay was crucial for accurate diagnosis and effective counseling. As physicians, it is important to recognize how anchoring bias (fixating on one etiology over another) and premature closure (accepting benign explanations too early) can both threaten diagnostic accuracy and patient safety with missed pathology [21]. While extensive imaging and laboratory testing results showed no structural or metabolic concerns, the backdrop of comorbid life-threatening conditions warranted thorough and timely investigation. Integration of vigilance with diagnostic humility ensured patient safety, therapeutic clarity, and psychological reassurance [22].

Conclusion

This case showcases the diagnostic challenge of distinguishing functional from life-threatening disease in the setting of high-risk comorbidities. The coexistence of Ehlers-Danlos and Klinefelter syndromes increases physiologic vulnerability and psychological stress, resulting in a presentation that intertwines body and mind. Although careful diagnostic evaluation showed no answers, the diagnosis of FND allowed the patient to be properly counseled on the management of his symptoms. This case shows the importance of diagnostic diligence in modern internal medicine, where the coexistence of rare genetic disorders and functional presentations may frequently overlap.

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