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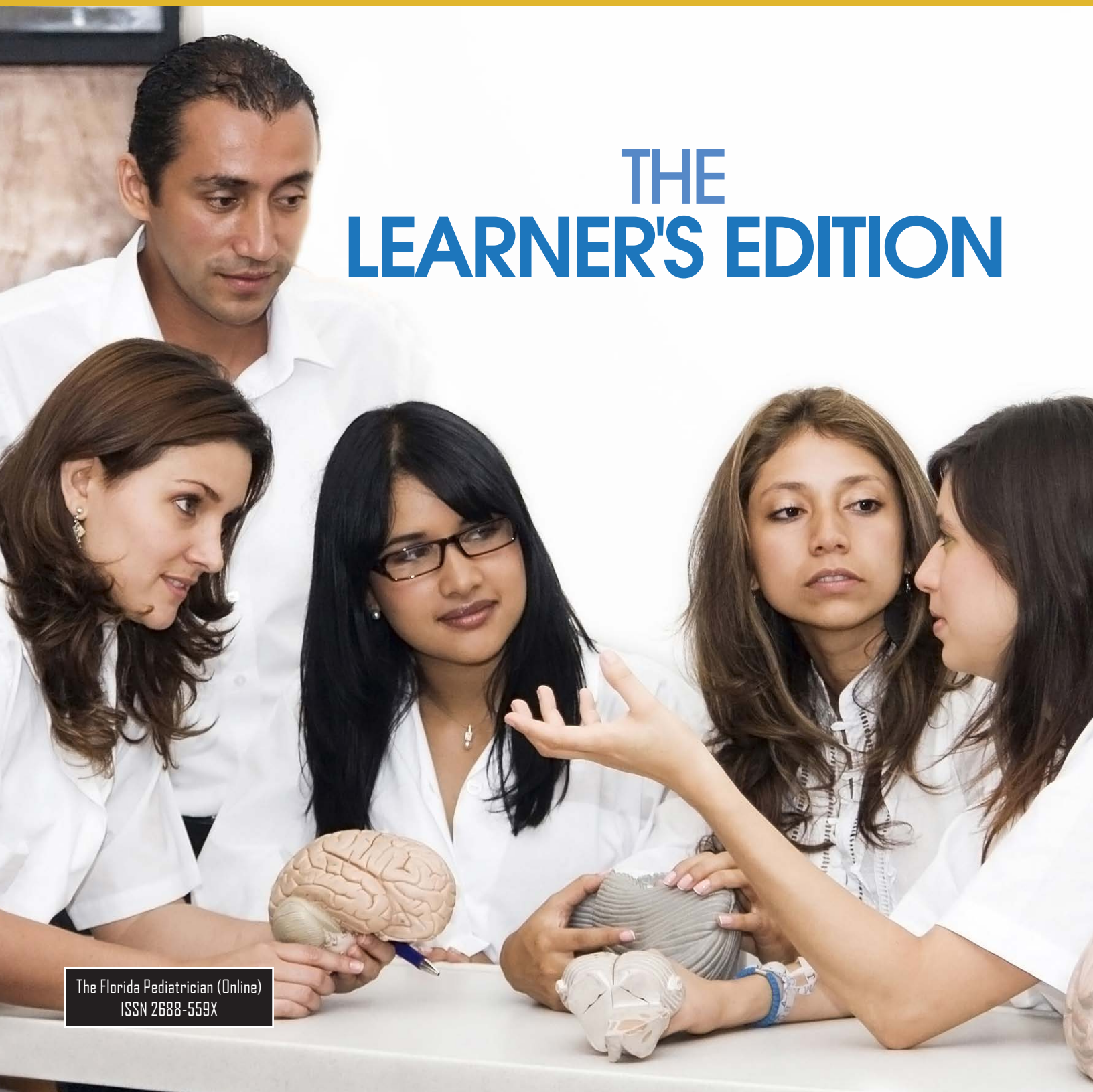

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Editor's Note

Dear Colleagues,

There is light at the end of the tunnel, but we are still in the tunnel.

It has been a year since the Coronavirus pandemic began… and it has been tough for all of us. But we do have the vaccine at the end of the tunnel. The vaccine is a HUGE light, but we all must remember that we are still in the tunnel. We need to continue to work hard to get out of this very dark tunnel safely.

While the vaccine is our only hope, we must continue to follow the other preventive efforts that many of us have so faithfully done for the past 13 months. We still must wear masks. We still must practice social distancing. We still must avoid large gatherings of people and smaller gatherings if we do not know everyone's vaccine status.

We have three safe and efficacious vaccines, and, finally, the vaccines are available to anyone who is eligible. We are immunizing millions of people every day.

Vaccines are only useful if people get the vaccines!

Vaccine hesitancy is becoming a major issue. It is very discouraging that only about 50% of the healthcare workforce is willing to take the vaccine. We should be leading the charge on getting everyone vaccinated.

Let me address some issues that have recently been discussed around the vaccines. First is the "Vaccine Passports." We are using vaccine passports in many other situations already, for example mandatory vaccinations for children to attend schools, mandatory influenza vaccinations required by many healthcare organizations, and mandatory yellow fever vaccinations to visit some countries. Mandatory vaccines are typically provided free of cost to recipients. However, travelers usually have to pay for the tourism related vaccinations. Currently, there are just not enough Coronavirus vaccines available to immunize everyone, and there are significant inequities with regards to access to the vaccines. In addition, the vaccine is under Emergency Use Authorization (EUA) by the FDA, and it is not clear that a product under EUA can be legally mandated. I believe, at some point in time, there might be a mandatory requirement for Coronavirus vaccines in some situations, such as healthcare organizations and long-term care facilities among others. I am sure this will be an area of significant debate in the future.

Then there is the question of herd immunity. In the history of medicine, no disease has been eradicated, eliminated, or controlled without use of vaccines. Eradication of smallpox, elimination of poliomyelitis, and the control of many other diseases, including diphtheria, tetanus, pertussis, and measles, is the direct result of vaccines. To control the Coronavirus pandemic, we have to immunize enough people to achieve herd immunity. In my humble opinion, herd immunity will be achieved once 90%-95% of the population is immunized.

Then there is the question of vaccinating children. We must vaccinate children because children do get the Coronavirus infection, and we must protect children from it. The Coronavirus disease can be serious and even fatal in children, but the vaccine will also prevent the dreaded Multisystem Inflammatory Syndrome in Children (MIS-C). Finally, we will never reach herd immunity without vaccinating children.

Pediatricians are well positioned to be an effective part of the vaccination administration infrastructure since we have been doing it for decades. However, we must be fairly compensated for providing this essential service. Furthermore, we must vaccinate the entire family, not just the children.

At the present time, our focus should be immunizing anyone eligible who wants to be immunized and convincing those on the fence that the Coronavirus vaccine is safe and effective. Aggressive education campaigns targeting individuals and communities most at risk of infection, serious disease, and high mortality must begin as soon as possible.

Mobeen H. Rathore, MD, CPE, FAAP, FPIDS, FSHEA, FIDSA, FACPE
Editor, The Florida Pediatrician

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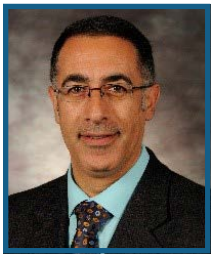

CASE REPORT

Knowing Too Much, but Understanding Too Little: Making Sense of Genotype-Phenotype Correlation in Modern Day Medicine

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In as early as 1960, gene-linked causes of heart disease were proposed to the greater scientific community.[1] Time and time again since, multigenerational familial studies have identified genetic variation hypothesized to lead to cardiomyopathy and sudden cardiac death. This has often led to characterizing these mutations contained within one family as pathogenic. Variation, regardless of location or functional consequence, was deemed causative.

At the turn of the century, scientific endeavors to better understand the human genome were underway and near completion. These efforts were believed to lead to a better understanding of genetic variation and genotype to phenotype correlations. What we failed to foresee was the conundrum that followed, *knowing too much, but understanding too little*. Mutations with conflicting interpretations of pathogenicity, variants of undetermined significance, and benign mutations previously proven to be pathologic muddle our understanding of genetic interpretation. Furthermore, with the introduction of large variant data in the form of genetic population databases, mutations previously reported to be causative of disease were found in seemingly ostensibly healthy individuals. With increasing numbers of individuals with identified mutations, cohorting those with mutations has directly contradicted previously accepted phenotypical tendencies derived from multigenerational family studies. In addition, functional studies in animal models frequently contradicted each other, further increasing confusion within the scope of cardio-genomics.[2,3]

A prime example is variation within the Troponin Complex. Initial studies were concerned with finding any variation of the genome at specific locations. Once those were found, it became well established that variation in the Troponin complex (TNNT2-encoded Tropinin T, TNNI3-encoded Troponin I, and TNNC1-encoded Troponin C) were highly likely to lead to cardiomyopathy. However, large population databases, like the GnomAD database, exhibit that even in seemingly healthy individuals, variation in the Troponin complex exists.[4] How could a healthy individual have variation at a location where proven pathogenic mutations have been found? This would go against all scientific certainty that location of variation determines functional changes and thus, phenotype. We found ourselves with too much information, but no tools for interpretation. As such, it is not surprising that much scrutiny is being exercised regarding claiming causation when variation is identified in a cardiomyopathy patient.

Efforts within the genetic community are underway to address these exact issues. Landstrom et al. have proposed a novel approach to mapping frequencies from pathologic cohorts against those from the general population with rare variation and proved utility in identifying areas of heightened gene penetrance and pathogenicity.[5-7] Large population studies have also exhibited tendencies for certain variations to prove more pathologic than others. Theoretically, radical mutations, or those that cause deletions and "frame-shift" changes, are more likely to cause large changes in amino acid sequences. Furthermore, theories that "more" mutation leads to "more" phenotype, although not always true, is frequently the case in cardiomyopathy. In other words, compound heterozygosity, homozygosity, double heterozygosity, and even de novo mutations have been linked with more malignant phenotypes.[7-10]

In response to this explosion of genetic information, the American College of Medical Genetics (ACMG) released a document outlining guidelines for variant interpretation in 2015.[11] It recommends classifying variants by categorizing pathogenic or benign evidence, from supporting evidence (the lowest power) to very strong evidence (the highest power). This includes evidence from population, computational/predictive, functional, segregation, de novo, and allelic data. By identifying evidence for a variant, we are then able to categorize that variant as Pathogenic, Likely Pathogenic, Benign, Likely Benign, or of Uncertain Significance. Although this is highly useful in variant interpretation, much of the evidence may be interpreted subjectively and thus, this mode of interpretation will always be prone to bias.

Regardless, with this new wave of genetic data, clinicians and residents, such as myself, are still left puzzled. Are variants of undetermined significance truly permissible? Should we expect more malignant phenotypes in those with "pathologic" mutations? How can we, as clinicians, make any solid conclusions from genetic testing? I believe the answer is we cannot always make definite conclusions, but we may be able to make reasonable inferences based on recommendations. As such, we should move away from calling variants "mutations" and should make a strong effort to classify variants based on ACMG criteria, which should translate into clinical relevance. Also, taking advantage of data we currently have is essential. Genetic studies have given us insight into the importance and function of significant genes in the genome. Furthermore, those with more than one variation, radical variation, and non-inherited variation may be at an increased chance of disease. Although much of what is in the middle, in the form of post-translational modifications for instance, may always remain obscure, we can make reasonable predictions about how variation within vital locations in the gene may affect gene function. And, statistically, proven pathogenic mutations within vital domains will always more than likely present with a predictable phenotype.

Although I am still fairly early in my medical career, it has become evident to me that this is not an issue solely relevant to cardio-genomics. It is also an issue in every other pediatric subspecialty. Therefore, any genetic variation should not be immediately brushed aside. We must look at these findings as scientists, understanding that this variation may be causative, but also may likely be incidental. As a pediatrician, being able to predict a child's clinical future, in the setting of conditions as severe as sudden cardiac death and debilitating cardiomyopathy likely leading to end-stage heart failure as well as avoiding reassuring parents and preventing undue stress due to incidental variations found on a chromosomal microarray, may seem like a lofty goal at present, but I hope will be an achievable reality in the not too distant future.

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TRAINEE ARTICLE

Long Term Psychosocial Outcomes of Childhood Cancer Survivors

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INTRODUCTION

Survivors of childhood cancer are at risk for numerous long-term adverse effects on their health and quality of life. Some are followed in survivorship clinics, developed to screen for long-term cancer or treatment-related health outcomes. However, many survivors may not have the opportunity to do so due to limited availability of these clinics. As a result, primary care providers may be the only clinician the patient sees on a yearly basis. As primary care providers we can help improve outcomes for survivors by being aware of the specific risks, remaining vigilant in screening for them, and by providing early intervention where possible.

Social determinants of health are increasingly recognized as important factors for health outcomes across all patient populations, and are very important for childhood cancer survivors. We discuss some of these factors including education, economic stability, community and social context, and health care systems. We also explore other psychological issues which can impact health outcomes including mental health disorders, risky behaviors, and fatigue/sleep problems.

The Children's Oncology Group generated long-term follow-up guidelines for survivors of childhood, adolescent, and young adult cancers based on the consensus of a panel of experts.[1] Screening for psychosocial issues is recommended for all survivors, regardless of the type of cancer or treatment received. The guidelines are intended to be implemented two or more years following completion of therapy. The document is available at survivorshipguidelines.org; this article is based on the October 2018 version. Health Links, available for each topic, provide information and handouts suitable for patients and families. We list the current recommendations.

EDUCATIONAL PROBLEMS

Recommendation: *yearly psychosocial assessment with attention to educational and/or vocational progress; refer as indicated to school liaison to facilitate acquisition of educational or vocational resources; refer as indicated for neuropsychological evaluation*

One study used parental reports to compare educational difficulties in cancer survivors versus age matched controls. Survivors were significantly more likely to have repeated a grade (21% vs. 9%) or have other educational or school problems (46% vs 23%). They were also more likely to be participating in special education programs (20% vs 8%) or programs for learning disabilities (19% vs 7%).[2]

Studies show that survivors diagnosed during the adolescent young adult (AYA) period are less likely than sibling controls to have attained post-high school education.[3] Assessment of a subset of neuroblastoma survivors showed increased risk for psychological impairment. Psychological impairment was associated with increased use of special education services during childhood or adolescence and lower adult education attainment.[4] Referrals for early educational interventions and supportive services are essential to maximize their academic and social success.

UNDER-EMPLOYMENT/UNEMPLOYMENT

Recommendation: *yearly psychosocial assessment*

Survivors are significantly less likely than siblings to be employed. Those with central nervous system (CNS) or bone cancer, ≥30 Gy cranial radiation, or age under 4 years at diagnosis are at a particularly increased risk.[5] Kirchhoff et al. reported that survivors with impaired health have a nearly 8-fold higher rate of health-related unemployment than physically healthy survivors.[6] Survivors are also more likely to be unemployed but seeking work than siblings, indicating they could benefit from assistance in job-seeking.[7] Additionally, female survivors are less likely to work in professional or managerial positions if they have limitations in task efficiency, emotional regulation, and memory. Male survivors who have problems with somatization, memory, or task efficiency are more likely to be unemployed.[6] Addressing these underlying attention and cognitive issues could improve the patients' overall quality of life and career achievements.

SOCIAL WITHDRAWAL AND DEPENDENT LIVING

Recommendation: *yearly psychosocial assessment with attention to social withdrawal*

Kunin-Batson et al. reported that survivors are more than twice as likely as siblings to live dependently. The risk was increased in those with CNS tumors or leukemia. Risk was also increased in patients using neuroleptic, anticonvulsant or psychostimulant medication and in those with attention and processing speed problems, poor physical functioning, depression, or of racial/ethnic minority.[8]

Survivors were 1.7 times as likely as siblings to report antisocial behaviors. These behaviors included having trouble getting along with or being disliked by other children.[9] In a study of survivors diagnosed during the AYA period, survivors were significantly less likely than siblings to be married. Survivors diagnosed prior to the AYA period were also less likely to be married and less likely to be living independently.[3]

LIMITATIONS IN HEALTHCARE ACCESS

Recommendation: *yearly psychosocial assessment with attention to healthcare and insurance access; potentially consider social work consultation*

Brinkman et al. categorized survivors into three classes based on their health-related concerns and motivations.

- The "worried" class reported the highest levels of worries, health concerns and extrinsic motivation, but the lowest level of intrinsic motivation.
- The "self-controlling" group had the lowest concerns about current or future health problems, but were highly intrinsically motivated for self-care, and placed little value on medical check-ups.
- The "collaborative" group showed intermediate scores across all domains.

Overall, the worried class was most likely to complete follow-up health screening as recommended, and the self-controlling class was least likely.[10] Recognizing these subtypes may help identify survivors who are at high risk for not completing follow-up as recommended.

MENTAL HEALTH DISORDERS

Recommendation: *yearly psychosocial assessment with attention to depression, anxiety, post-traumatic stress and suicidal ideation; potentially consider psychological consultation in patients with emotional difficulties related to cancer experience; potentially consider psychotropic medications; potentially consider evaluation of parent for post-traumatic stress*

Overall, survivors were 1.5 times more likely than siblings to report depression or anxiety symptoms, including feeling worried/fearful/anxious or unhappy/sad/depressed.[9] AYA survivors reported greater emotional distress, anxiety, depression, and somatization than siblings. They also self-reported high rates of problems with task efficiency, emotional regulation, and memory.[3]

Brinkman et al. reported that survivors tend to fall into four categories of mental health symptoms:

1. No symptoms,
2. Externalizing – headstrong behaviors and attention deficit,
3. Internalizing – anxiety, depression, peer conflict, social withdrawal and attention deficit;
4. Global – increased symptoms across all domains.

Among survivors who received cranial radiation therapy, approximately 1/3 experienced internalizing and none experienced externalizing symptoms. For survivors who did not receive cranial radiation therapy, approximately 1/6 experienced externalizing symptoms with a small percentage experiencing internalizing or global symptoms.[11]

Tonorezos et al. used a baseline exercise question and long-term symptom questionnaires, and demonstrated an association between vigorous exercise and less psychological burden and cognitive impairment. Survivors who completed 9 metabolic equivalent (MET) hours per week (approximately 20 minutes of vigorous exercise 3 times per week) had a lower prevalence of depression and somatization. Those who completed 15-21 MET-hours per week self-reported better task completion, organization, and working memory.[12]

RISKY BEHAVIORS

Recommendation: *yearly psychosocial assessment*

Compared to siblings, survivors of childhood cancer reported similar rates of tobacco, alcohol and illicit drug use, and similar rates of risky sexual behaviors, such as not using protection or having multiple partners.[13] However, because survivors are at increased risk for adverse physical and mental health outcomes, as well as second cancers, they should be educated about risky behaviors.

FATIGUE/SLEEP PROBLEMS

Recommendation: *yearly psychosocial assessment; potentially consider screening for physical sources of fatigue, such as anemia, sleep disturbances, nutritional deficiencies, cardiomyopathy, pulmonary fibrosis, hypothyroidism, or other endocrinopathy; potentially consider referral to specialties such as endocrinology, sleep medicine center, or nutrition as indicated; potentially consider referral to psychology for behavioral intervention for emotional difficulties contributing to sleep and fatigue*

Daniel et al. investigated a randomly selected subset of survivors and siblings who completed a sleep survey. Survivors were more likely than siblings to report poor sleep efficiency (<85% of time in bed spent asleep), daytime sleepiness, snoring, and use of supplements and medications to aid in sleeping. Cranial or neck radiation was associated with delayed sleep onset (>30 minutes to fall asleep 3 time per week).[14]

CONCLUSION

As children transition from a cancer patient to a cancer survivor they continue to face adverse effects, both physical and mental, as a result of their disease and treatment. Many patients and families may wish to put these difficult times behind them at this time, but as healthcare providers we must remain vigilant for the presence of adverse effects. Ultimately many of these patients will lead relatively normal lives compared to healthy peers and many report high levels of life satisfaction. However, as reflected by the guidelines and research studies, survivors are at increased risk for specific adverse outcomes. As their primary care providers, we must be aware of the relevant risks they face, and take the opportunity for early identification and intervention. These initiatives may be crucial to ensure optimal outcomes for survivors of childhood cancer.

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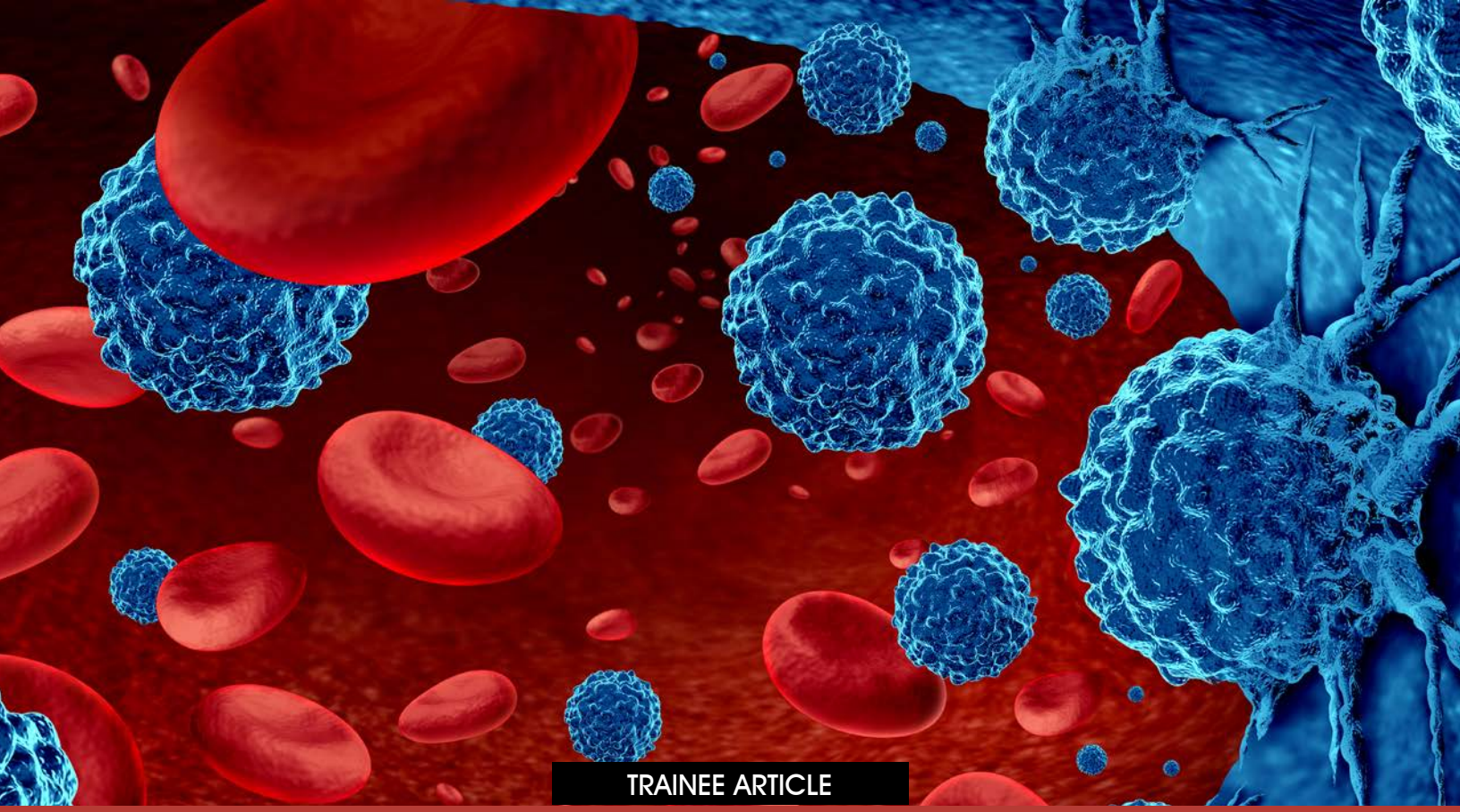

TRAINEE ARTICLE

Symptomatic Hypercalcemia as a Rare Presentation of Leukemia in an Adolescent Male

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ABSTRACT

We present a case of symptomatic hypercalcemia as the presentation of leukemia in a teenage male. He presented with a serum calcium level of 13.9 mg/dL associated with nausea, vomiting, constipation, abdominal pain, and leg pain. He had no abnormality in his WBC count or presence of peripheral blast cells. After an extensive evaluation he was ultimately diagnosed with B-cell ALL based on bone marrow biopsy. Chemotherapy was initiated, and his hypercalcemia was managed with IV fluids, bumetanide, calcitonin, and pamidronate. Hypercalcemia of malignancy is well described in adults, but its prevalence in pediatric cancer patients is only about 0.5-1.5%. While hypercalcemia among pediatric patients is rare, it is important for the general pediatrician to recognize the symptoms and guide their work-up based on a broad differential diagnosis, considering malignancy as an important potential cause.

INTRODUCTION

Calcium plays an essential role in many biologic processes and organ systems including cardiac muscle contraction, nerve conduction, and strengthening bones and teeth to name a few. Calcium homeostasis is maintained by a delicate interplay between the parathyroid gland, the kidney, and skeletal factors.[1-3] The pathophysiology of hypercalcemia is often related to a disturbance in one of these three systems. "Hypercalcemia is defined as a serum calcium concentration that is greater than two standard deviations above the mean", which can vary based on age specific normal values.[2] Additionally, serum calcium levels need to be interpreted in the context of age, as well as the albumin concentration and acid-base status, all of which can alter calcium binding.[2] The clinical presentation of hypercalcemia is a spectrum ranging from an asymptomatic incidental finding to abdominal pain, constipation, lethargy, seizures, psychiatric symptoms, and in severe cases, acute renal failure or pancreatitis.[2]

Hypercalcemia can pose a diagnostic challenge to practicing pediatricians as it is not commonly encountered, and symptoms may be non-specific. Primary hyperparathyroidism and malignancy are the most common causes of hypercalcemia in adults (>90% of cases), but as a cause for hypercalcemia in children only accounts for <5%.[2] Hypercalcemia in children is more likely to be PTH-independent and can be due to a variety of genetic and acquired causes.[1,2] Thus, the differential diagnosis can be quite broad and a systematic approach to diagnosis is required. We present a unique case of an adolescent male who presented with symptomatic hypercalcemia secondary to acute lymphoblastic leukemia (ALL).

PATIENT PRESENTATION

The patient is a previously healthy 13-year-old male who presented to the emergency department (ED) with 5 days of abdominal pain, nausea, vomiting, constipation, and decreased oral intake. The patient's mother reported that he had significant fatigue and lost about 10 pounds over a 2-month period. For the past 6 weeks he also had multiple bone and joint pains lasting for several days at a time and then self-resolving. At the time of presentation, he complained of right ankle pain for one week.

His vital signs were normal for age. He appeared as a thin male with a BMI of 16 (10th percentile for age). His cardiorespiratory, HEENT, and neurological exams were normal. His abdomen was full but non-tender with good bowel sounds and without hepatosplenomegaly. He had no palpable lymphadenopathy. Pain with active and passive range of motion of the right ankle was demonstrated, but with no swelling, redness, or warmth. There was no bony tenderness elsewhere.

He was found to have a serum calcium of 13.9 mg/dL at his pediatrician's office, which precipitated the ED evaluation, where a repeat calcium was 12.6 mg/dL with an ionized calcium of 1.74 mmol/L. He was admitted to the hospitalist service with initial consultations to nephrology and endocrinology. A broad differential diagnosis was considered, divided into parathyroid and non-parathyroid mediated causes (Table 1). Additional work-up is summarized in Table 2. In summary, he was found to have hypercalcemia with suppressed parathyroid hormone (PTH), hypercalciuria, mild acute kidney injury, and mild anemia and thrombocytopenia.

PARATHYROID MEDIATED	NON-PARATHYROID MEDIATED
Primary hyperparathyroidism • Hyperplasia • Adenoma/Carcinoma • MEN type 1 and 2A	Hypervitaminosis D • Excessive intake • Granulomatous Diseases (e.g., Sarcoidosis, Tuberculosis, Cat Scratch Disease)
Familial hypocalciuric hypercalcemia	Medications • Thiazide diuretics • Lithium • Theophylline • Excessive vitamin A
Tertiary Hyperparathyroidism of Renal Failure	Hypercalcemia of Malignancy • Paraneoplastic PTHrp secretion • Bone Tumors • Osteolytic bone metastases • Leukemia • Other malignancies associated with release of inflammatory mediators
	Endocrinopathies • Hyperthyroidism • Pheochromocytoma • Adrenal insufficiency
	Milk-alkali syndrome (excess calcium ingestion, e,g., Tums)
	Immobilization
	Liver Disease
	Inborn Errors of Metabolism
	Chronic Inflammation

Table 1: Differential Diagnosis for Hypercalcemia in Children and Adolescents

LABORATORY TEST	PATIENT'S VALUE	REFERENCE RANGE
WBC count	5.21 x103/μL	4-10.5x103/μL
Differential		
% lymphocytes	48.1%	
% monocytes	3.2%	
% neutrophils	45.9%	
% eosinophils	2.2%	
% basophils	0.6%	
% blasts	0	
Hemoglobin	11.4g/dL	12.5-16.1g/dL
Hematocrit	32.4%	36-47%
Platelets	123 x103/μL	150-450 x103/μL
MCV	83.1 fL	78-95 fL
Total Serum Calcium	12.6 mg/dL	8.8-10.6 mg/dL
Ionized Calcium	1.74 mmol/L	1.15-1.35 mmol/L
Serum Creatinine	1.11 mg/dL	0.42-0.81 mg/dL
BUN	15 mg/dL	7-17 mg/dL
Urine calcium excretion	25.6 mg/dL	
Urine calcium to creatinine ratio	0.39	
Parathyroid Hormone (PTH)	2	11-74
PTHrp	0.6	<2
Vitamin D,25-OH	29 ng/mL	30-100 ng/mL
Vitamin D 1,25-OH	<8 pg/mL	30-83 pg/mL
Vitamin A	47 mcg/dL	26-72 mcg/dL
TSH	3.1 UIU/mL	0.5-4.5 UIU/mL
AM Cortisol	13.1 μg/dL	4.5-22.7 μg/dL
ESR	17 mm/hr	0-15 mm/hr
CRP	<0.5 mg/dL	<1 mg/dL
LDH	437	470-750IU/L
Uric Acid	7.4	2.7-6.7mg/dL

Table 2: Laboratory Evaluation – Abnormal Values are highlighted

The etiology of his hypercalcemia, however, remained unclear and given the persistent right ankle pain with mild cytopenias hematology/oncology was consulted about 3 days into the admission. An x-ray of the right ankle revealed an abnormal lucency of the metaphysis of the distal tibia and fibula with subtle periosteal reaction. An MRI of the lower extremities was then obtained to further investigate this finding and revealed a marrow replacement process of the tibia and fibula (Figure 1). He underwent bone marrow biopsy which showed B-cell ALL with 64% blasts.

He was started on chemotherapy and his hypercalcemia was managed with IV fluids, loop diuretics (bumetanide), calcitonin, and pamidronate. His calcium trended down nicely after initiation of treatment (Figure 2). He is currently in remission and doing well without the need for additional medications aside from his maintenance chemotherapy.

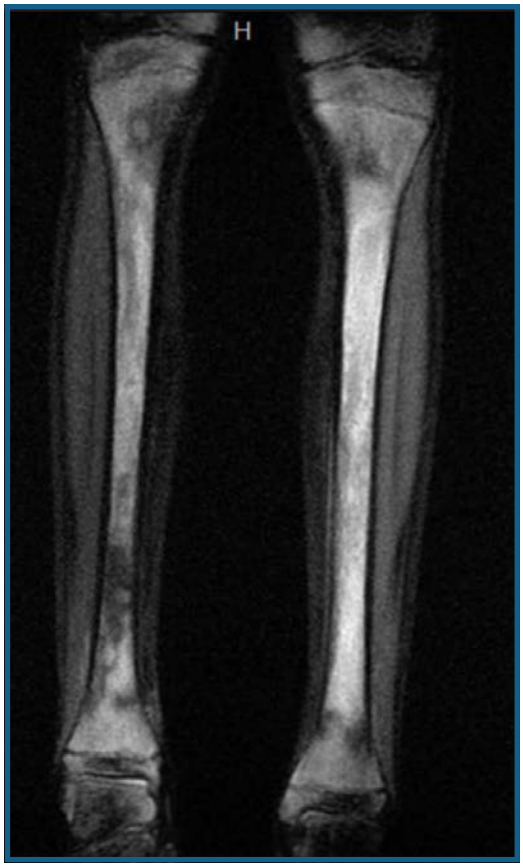

Figure 1: MRI bilateral lower extremities
Marrow replacement process involving the tibias and fibulas

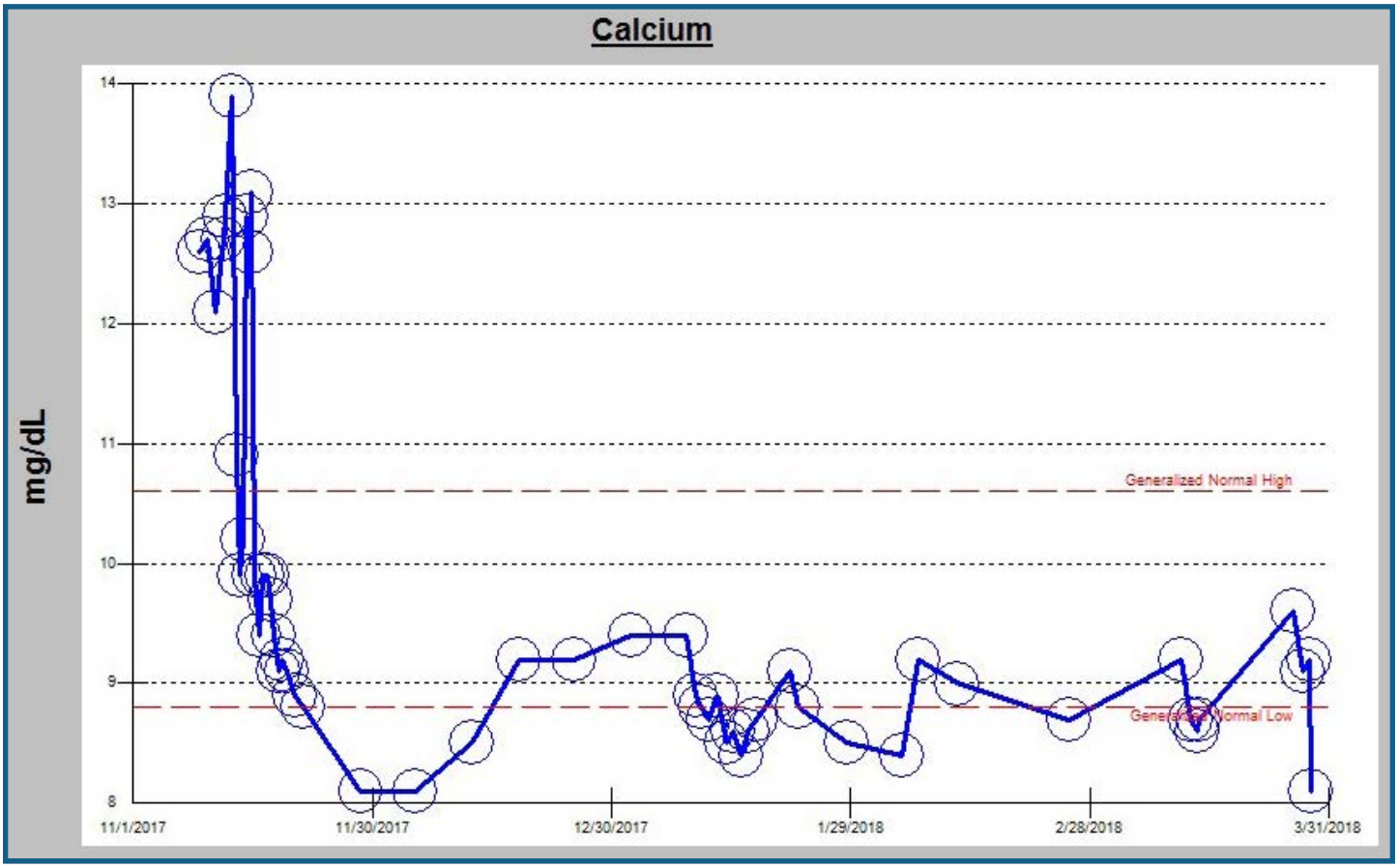

Figure 2: Calcium trend

DISCUSSION

Hypercalcemia is a rare presentation of pediatric malignancies with an overall estimated prevalence of 0.5-1.5%.[4] It has been reported in a variety of malignancies including leukemia, lymphoma, neuroblastoma, and rhabdomyosarcoma, among others.[1] The pathogenesis is hypothesized to be related to PTHrp secretion from tumor cells, altered osteoclastic activity by inflammatory mediators (including TNF-alpha, TNF-beta, IL-6, and TGF-B), osteolytic metastases, and increased activated vitamin D.[1,3,5] In our patient, since the PTHrp was negative, the hypercalcemia was suspected to be secondary to increased osteoclast activity mediated by inflammatory cytokines.

The literature on management of hypercalcemia in pediatric malignancies is limited to case reports and case series. In general, the main principles for treatment of acute hypercalcemia include hydration, prevention of bone resorption, and ultimately treating the underlying cause, the malignancy in this case.[3] Since the cancer is driving the hypercalcemia initiation of chemotherapy is effective, although with delayed response. In addition to aggressive rehydration, several pharmacologic agents have been utilized including loop diuretics (ex. furosemide), which increase calcium excretion, bisphosphates and calcitonin, which inhibit osteoclastic activity.[2] Bisphosphate use has shown promising results to manage acute symptomatic hypercalcemia in this population.[6-9] One case series of 8 children treated with an IV infusion of the bisphosphonate pamidronate showed a rapid decline in serum calcium level within 48 hours.[6] Additionally, Inukai et al, reported in their case series of 22 children with leukemia associated hypercalcemia that children who received bisphosphonate therapy experienced a more rapid normalization of serum calcium level and renal function compared to those that did not receive bisphosphonate therapy.[10]

For patients who require a more rapid decrease in their serum calcium level bisphosphonate therapy may not suffice. Calcitonin can be utilized to drop the calcium level more quickly, with a peak response of 12-24 hours.[3] While the initial response is rapid, repeated administration is not effective due to downregulation of calcitonin receptors and resultant tachyphylaxis.[3] In case reports of pediatric ALL with symptomatic hypercalcemia a combination of bisphosphonates and calcitonin was effective and safe for treatment of hypercalcemia.[11,12]

Malignancy associated hypercalcemia by itself has not been shown to impact overall prognosis in leukemia patients.[10] Although it may not impact overall prognosis, it is important to recognize as it can be associated with significant symptomatology or co-morbidities. Further studies are needed to better understand this rare complication and optimize its treatment. While hypercalcemia among pediatric patients is rare, it is important for the general pediatrician to recognize the symptoms and guide their etiologic evaluation based on a broad differential diagnosis, considering malignancy as an important potential cause.

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TRAINEE ARTICLE

Chronic Idiopathic Urticaria in a Young Male

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ABSTRACT

Chronic idiopathic urticaria (CIU) is defined as urticaria, angioedema, or both that occurs without a known trigger and persists for greater than 6 weeks. CIU is a relatively common hypersensitivity disorder in childhood. Treatment is difficult as up to half of patients don't respond to traditional medications for urticaria. CIU can have a significant impact on quality of life, including increased rates of psychiatric disorders that often are untreated or unrecognized. Here we present a case report of a patient suffering from both CIU and anxiety where the urticaria was unresponsive to second generation antihistamines but improved with the tricyclic antidepressant, doxepin.

KEY WORDS

Chronic idiopathic urticaria, anxiety, doxepin

INTRODUCTION

Urticaria is defined as transient, pruritic wheals surrounded by an erythematous base that typically last less than 24 hours.[1,2] An estimated 20% of people will experience an episode of urticaria at some point in their lifetime, but chronic urticaria, lasting a minimum of 6 weeks, is reported to have a point incidence of 0.1-0.3% of children, with some estimates as high as 1.8%.[3,4,5] The types of chronic urticaria are differentiated by the trigger associated with the disease (such as heat, cold, pressure, vibratory, cholinergic, contact, or aquagenic), however an estimated 75% of patients with chronic urticaria have no specified trigger, termed chronic idiopathic urticaria (CIU).[2] Of those cases termed CIU, there may be an underlying autoimmune mechanism in up to 50% of cases[5,6], leading many to subgroup CIU into truly idiopathic and autoimmune mediated. The treatment of CIU is very challenging due in part to an unclear etiology in many cases. One study reports the mean time to resolution of CIU in children at approximately 20 months, while another study indicates approximately 9 months.[5,8] Additionally, the often unpredictable and

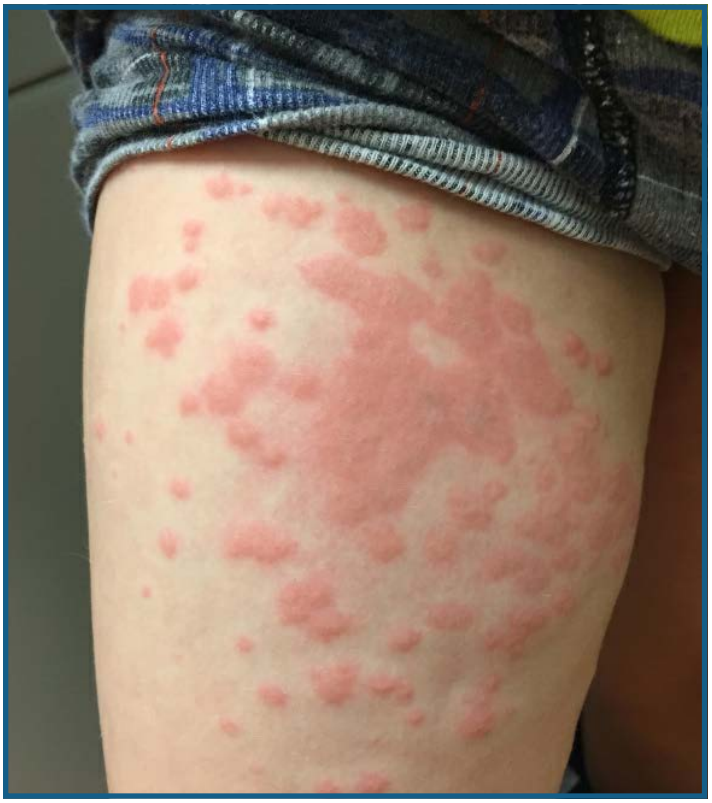
variable nature of episodes can lead to a sense of loss of control in patients, with many reporting decreased quality of life due in part to fatigue, sleep disturbances, pain, self-imposed social restrictions, and emotional turmoil.[9,1,2,10] This disease also has an impact on mental health, with higher levels of stress reported, along with increased incidence of psychiatric disorders, most notably anxiety and depression.[10,11] Here we present a case report of a patient suffering from CIU and anxiety whose symptoms of urticaria were unresponsive to second generation antihistamines but improved with the tricyclic antidepressant, doxepin.

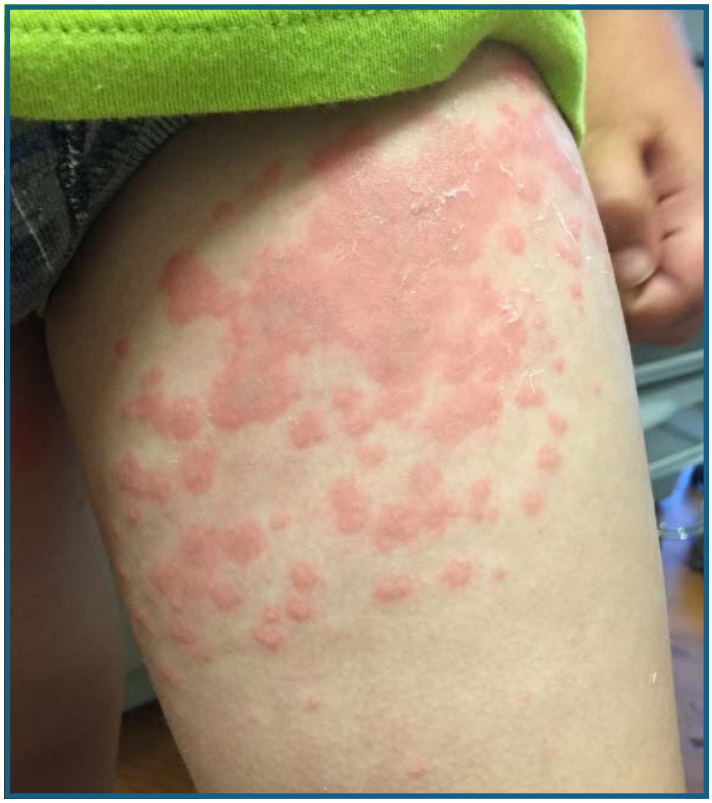
CASE REPORT

A 7-year-old male with a past medical history of asthma, eczema, and allergic rhinitis presented to the clinic with recurrent episodes of transient, erythematous, pruritic, blanchable wheals that were increasing in frequency over the last year. The patient has a family history of systemic lupus erythematosus in his mother, and extensive history of asthma, allergy, and eczema on his paternal side, including his father. The patient's first episode of wheals occurred across the hands, neck, and back after administration of ibuprofen following a tonsillectomy. Due to the timing and lack of other symptoms or sick contacts, the rash was determined to be consistent with allergic reaction. The patient was given an antihistamine and instructed to stop ibuprofen.

Approximately 6 months later, the patient experienced another episode of hives, which resolved with diphenhydramine treatment over a 10-day period. Two months following that episode, he presented to the emergency department with a 3-day history of wheals mostly on the trunk, legs, and face that did not respond to diphenhydramine or loratadine. With no new contacts or medications, and no fever or difficulty breathing, he was diagnosed with urticaria of unknown etiology and given prednisone 20 mg in the morning and 10 mg in the evening for 3 days. Lesions cleared within 1 day of administration of the steroid.

Over the next 3 months, the patient's mother noticed an increased frequency of hives, now occurring weekly. Of note, the hives had become persistent following a diagnosis of molluscum contagiosum with a superimposed *Staphylococcus aureus* infection 3 months ago. Additionally, the hives were now unresponsive to antihistamines, requiring low-dose steroids on two separate occasions. While there was no location predilection, the rash most commonly occurred over the patient's medial thighs and flexural areas. There were never symptoms of angioedema, gastrointestinal issues, breathing difficulties, joint pain or swelling, or sleep disturbances. The patient's mother did not notice correlation of recurrence of the hives with the common triggers of heat, cold, exercise, or compression. At the time of presentation at our clinic, the patient was currently taking loratadine 10 mg every morning and hydroxyzine HCl 5 mg every evening along with applying desonide 0.05% ointment during recurrence of hives, as prescribed by his pediatrician. The patient was also taking albuterol and beclomethasone for his asthma, as well as montelukast 4 mg nightly for his allergic rhinitis and asthma. A consult to UF Health Dermatology and a pediatric allergist was placed by his pediatrician to rule out other systemic disorders due to the increasing severity.





At this time, the patient presented with edematous erythematous wheals of variable size and shape diffusely across his body that were blanchable and warm to touch. Several lesions across the patient's thigh had faded to purple. While diagnosed with chronic urticaria, the differential for the cause of his chronic urticaria included urticarial vasculitis and hypocomplementemic urticarial vasculitis due to the presence of bruising following the resolution of some wheals. Other causes of chronic urticaria were eliminated based on history, including aquagenic urticaria, cholinergic urticaria, cold urticaria, delayed-pressure urticaria, dermatographic urticaria, exercise induced urticaria, solar urticaria, and vibratory angioedema.

Laboratory studies for a chronic urticaria panel were drawn including total IgE, C1, C2, C3, C4, and CH-50, along with Tryptase, CBC and differential, and ESR, all of which were normal. Due to the patient's history of allergic rhinitis, an ImmunoCAP® to environmental triggers was also performed, with negative results. As the episodes of wheals had increased in frequency and duration while on his current medication, he was started on cetirizine 5 mg every morning and 5 mg nightly along with continuing hydroxyzine 5 mg nightly and loratadine 10 mg every morning.

Upon further consultation, the mother noted persistent bruising on areas where wheals had resolved, resulting in a consult to pediatric rheumatology to rule out a vasculitic cause of his urticaria. He was also started on doxepin 35 mg every evening in place of the hydroxyzine. As the hives were improving, the dose of doxepin was changed to 50 mg every night as needed for breakthrough symptoms while continuing the cetirizine 5 mg twice a day.

Based on the history, physical presentation, and lab reports, a diagnosis of chronic idiopathic urticaria without clinical signs of urticaria vasculitis was made. As 40% of children with chronic idiopathic urticaria may develop an autoantibody to IgE, further blood tests were recommended for the future. Additionally, a thyroid panel including TSH, free T4, thyroglobulin antibody, and thyroid peroxidase, was ordered to evaluate for autoimmune thyroid disease as a cause for his urticaria, as thyroid autoimmunity can occur in up to one-third of patients.[1] The patient was continued on loratadine once a day, doxepin at night, cetirizine twice a day, and hydroxyzine as needed, with a plan that if the disease is not well controlled by this regime, cyclosporine would be considered the next-line agent for treatment.

DISCUSSION

With only 30-55% of patients achieving spontaneous remission within 5 years[12], urticarial symptoms have been shown to have a profound impact on everyday life for patients. Notably, more than 50% of patients report experiencing problems with daily living[2], citing issues of fatigue, pain, and itching, as well as emotional upset, withdrawal from social activities, and worsening performance in school.[9,13,12] Multiple studies have also shown an association between stress, psychiatric comorbidities, and CIU.[11,12] Therefore, while typically considered a dermatologic disorder, some physicians are now considering CIU to be a psychodermatological disorder due to the important role mental health and the stress response plays in the course of the disease.[14,15] Patient studies report that 81% of patients with CIU believed their illness was due to stress[11], with the unpredictable nature of episodes and difficulty in treatment mentioned as detrimental factors to the psychological well-being of patients.[15] The most common psychiatric diagnoses in CIU patients are depression, anxiety, and somatoform disorders, with as many as one-half of patients experiencing a psychiatric comorbidity.[10,11] Pediatric patients seem particularly vulnerable to developing concurrent emotional or behavioral difficulties due to stress because of underdeveloped coping strategies.[16] One study in children with CIU found that 70% had psychiatric comorbidities, indicating higher levels than the 49% and 60% that have been found in adult studies.[17] This study also showed that children diagnosed with CIU who had a previous stressful life event had a higher frequency of psychiatric disorders, possibly indicating that children with CIU may be prone to stress and thereby psychiatric disorders, or that stressful life events can serve as a trigger for already susceptible children.[17]

Treatment has always been a tenuous task for clinicians treating CIU as about half of patients fail to respond to traditional doses of H1-receptor antagonists and sometimes require up to four times the labelled dose.[18] Traditionally, treatment involves using second generation antihistamines as first line therapy with refractory cases using H2-antihistamines, anti-leukotrienes, immunosuppressive drugs, and anti-IgE antibody.[19] However, due to the discussed psychological associations, treatment with agents such as doxepin that have both antihistamine and antidepressant properties may be beneficial to consider. In our patient, doxepin was the treatment option that proved to provide the biggest relief from symptoms after resistance to the typical first line of anti-histamines. Doxepin has been shown to be a beneficial therapy for difficult to treat CIU since 1986[20], with two double-blind studies showing doxepin as more effective in clearing lesions than diphenhydramine in difficult to treat CIU.[18,20] While it is a tricyclic antidepressant, the major effect of doxepin as a treatment for CIU is thought to be due to the potent antagonism of H1 and some H2 receptors.[18] In light of the association of CIU with psychiatric disorders however, what has yet to be considered is the effect of doxepin acting as a tricyclic antidepressant on the psychiatric comorbidities of those with CIU. However, the use of doxepin needs to be both carefully considered and monitored, as all antidepressants have a FDA black-box warning for increased risk of suicidal thinking and behavior in children with major depressive disorder and other psychiatric disorders.

As more research indicates the association between psychiatric disorders, stress, and CIU, the use of agents such as doxepin may be considered sooner in these patients, in conjunction with the standard regime of antihistamines and steroids. Only one study[22] was found that used psychotropics in conjunction with antihistamines, therefore, more research is needed in order to determine the effect of appropriate psychiatric interventions as a more integrated approach may be necessary in children and parents trying to manage CIU. Furthermore, other psychological therapies outside of medication may be considered as well. While no studies have indicated a causal role of stress or psychiatric comorbidities in urticaria development at this point, one meta-analysis concerning adult patients reported a beneficial effect of psychological interventions across other skin conditions, including atopic dermatitis, that similarly have a large impact on quality of life.[23] Even though multiple studies have mentioned the association between psychological comorbidities and CIU, no rigorous studies were found that examined whether more intensive psychological interventions led to improved outcomes in pediatric patients with CIU, indicating an important potential area of treatment that has yet to be addressed.

CONCLUSION

At this point in time, the lack of research into the association between CIU and psychological health constrains our understanding of this disease, even more so in the pediatric population. While the evidence is still uncertain as to whether psychological factors are a cause or result of CIU, the high prevalence in patient populations indicates they may play an important role in the disease process and should be taken into account in terms of management and treatment of CIU. Therefore, the use of agents such as doxepin that have both immunological and psychiatric modes of action may be beneficial to consider in CIU. Additionally, an interdisciplinary effort that also includes psychiatric management may be beneficial for the treatment of CIU and further research is needed to better determine appropriate psychiatric interventions.

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CASE REPORT

Dyspnea on Exertion... An Asthma Masquerader!

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ABSTRACT

Children with asthma should not be exercise-limited and consulting with an expert is recommended if symptoms remain uncontrolled. We present a case of severe pulmonary hypertension (PH) that was misdiagnosed with asthma for several years based on dyspnea on exertion. We emphasize the role of the pediatrician in providing asthma education to the families – as well as to the patients with asthma to improve the quality of life of patients and avoid missing fatal diagnoses with detrimental outcomes that masquerades asthma.

CASE PRESENTATION

Our patient is a 13-year-old African American girl who was diagnosed with asthma for several years (almost five years) prior to presentation to our institution. Her diagnosis was based on dyspnea on exertion, and she was treated with inhaled β-agonist as needed for her symptoms. Following involvement in a minor motor vehicle accident as a passenger in the back seat, she presented to the emergency department with left-sided chest pain. Physical exam showed weight: 32 kg (< 3rd), temperature: 97.7F, heart rate: 89 bpm, respiratory rate: 23 breaths per minute, oxygen saturation 85% on room air and blood pressure: 100/75 mmHg. Chest examination was positive for decreased air entry bilaterally and signs of respiratory distress with mild suprasternal retractions. There was no evidence of trauma on the chest wall. Cardiac exam with single loud S2 and normal pulses. Musculoskeletal exam was positive for clubbing of the fingers and toes and kyphoscoliosis. The rest of the exam including the abdomen, skin, and genitourinary systems was unremarkable. Due to the above respiratory findings, a chest radiograph was performed and revealed severely enlarged pulmonary arteries suggestive of elevated pulmonary artery pressure. A Computed tomography (CT) [Figure-1] of the chest confirmed this finding with moderate-severe airway compression at the level of mid-distal trachea and ruled out interstitial lung disease and abnormal pulmonary venous system. An echocardiogram showed severely decreased right ventricular (RV) systolic function, severely dilated pulmonary artery, and tricuspid valve regurgitation with jet peak gradient consistent with elevated RV pressures, all suggestive of chronic severe PH. The patient was admitted to the pediatric cardiac intensive care unit and immediate therapy was started

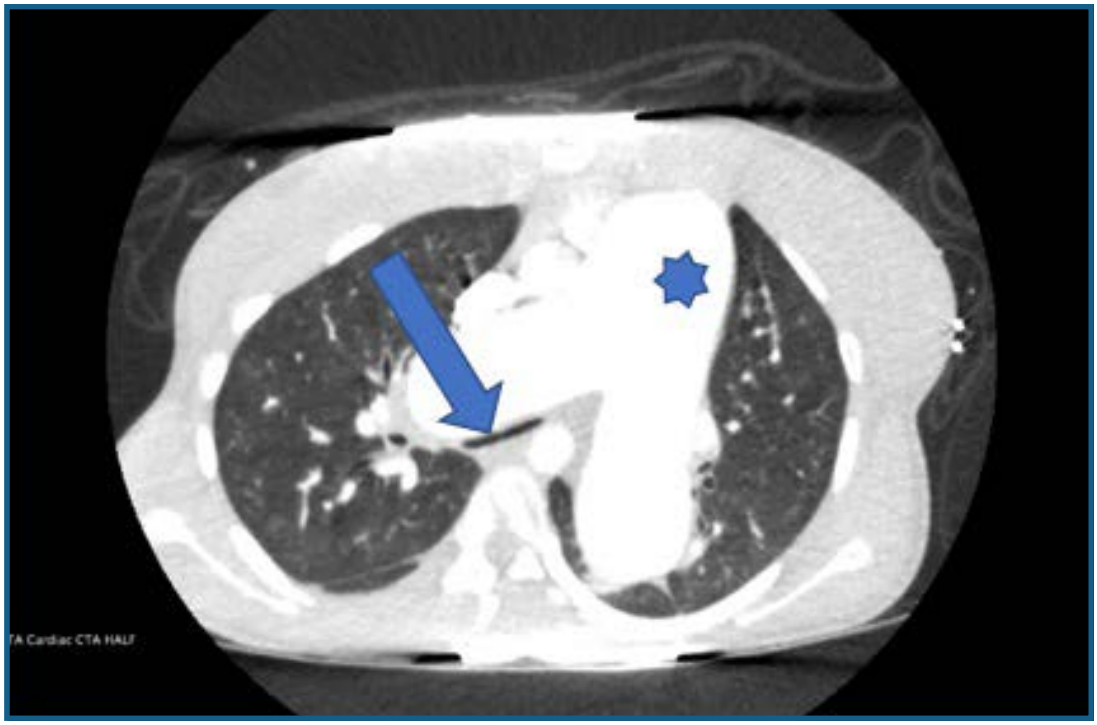

Figure 1: CT scan of the chest with IV contrast showing severely dilated pulmonary artery (star) with evidence of airway compression (arrow).

SIX MINUTE WALK TEST	
Gender	Female
Age	13
Indication/Diagnosis	PAH
Supplemental Oxygen	Y
O2 Flow (L/M)	4
O2 Device	Nasal Cannula
Baseline SPO2 %	92
Baseline Dyspnea	0
Baseline Fatique	0
Baseline Heart Rate	112
Baseline BP	92/54
End Of Test SPO2 %	83
End Of Test Dyspnea	3
End Of Test Fatique	3
End Of Test Heart Rate	145
End Of Test BP	104/70
Stopped Or Paused Before 6 Minutes	Y
Reason For Stopping	Other
Total Distance Walked In 6 Minutes (Ft)	259
Total Distance Walked In 6 Minutes (M)	78.94

Figure 2: 6-Minute-Walk test showing extreme limitation of physical activity

with Oxygen (FiO2 100%), inhaled nitric oxide and milrinone infusion. Following stabilization, right heart catheterization (RHC) confirmed severely increased pulmonary artery pressure at 90 mmHg and supra-systemic RV pressure at 120 mmHg with negative acute vasoreactivity test. PH-targeted therapy was started including treprostinil infusion, ambrisentan, and tadalafil. Comprehensive PH workup including autoimmune and thromboembolic diseases was negative. PH genetics revealed a mutation of unknown significance in the KCNK3 gene. Functional classification with 6-minute walk test was severely impaired [Figure-2]. Severe (Class IV) Primary PH was diagnosed, and the patient is currently being evaluated for lung transplantation.

DISCUSSION

Asthma clinical practice guidelines recommend medical history and physical examination to establish the diagnosis of asthma and determine the presence of episodic airflow limitation.[1] Spirometry is recommended to confirm the diagnosis of asthma in children > 5 years of age, and more advanced pulmonary function tests are currently available at specialized pulmonary centers for children younger than 5 years, including impulse oscillometry and measurement of airway resistance.[2] Imaging is not recommended in the initial diagnostic process or in severe exacerbations unless complications are expected or in the exclusion of other comorbid conditions such as the use of chest X-rays to rule out pneumothorax. However, evidence is available to highlight the utilization of lung imaging in chronic management of the disease.[3] An example is the use of computed tomography (/CT) scans of the chest to aid in the diagnosis of conditions that might be associated with chronic severe asthma, such as bronchopulmonary aspergillosis, eosinophilic pneumonia and eosinophilic granulomatosis with polyangiitis.[4] In addition, growing research is now focusing on identifying specific radiological measures (including airways diameter and geographic hyperinflation on CT scans) to assess severe asthma and correlate that with pulmonary function test findgins, hoping to identify a unique group of patients who may benefit from certain therapies in the future.[3] The lack of evidence of airflow limitation or failure to respond to initial therapy mandates considering alternative diagnoses and early consultation with a pediatric pulmonary specialist.

Our patient was misdiagnosed for several years, and her exercise limitation was incorrectly attributed to asthma. Her physical exam findings including the severely decreased weight and the presence of clubbing as well as her echocardiogram findings of impaired RV systolic function affirm the long-standing history of her condition.

Exercise is a well-recognized major trigger for asthma, and many patients seek medical advice due to experiencing dyspnea on exertion. However; activity should not be limited in asthma patients, and goals of treatment should include symptom-control and improvement of the quality of life for asthma patients as highlighted by the National Asthma Education and Prevention Program (NAEEP expert panel report-3)[1] and the Global Initiative of Asthma Guidelines (GINA).[5] In our case, the limited understanding of the pathophysiology of the disease, and the lack of understanding of the goals of asthma therapy, lead to the serious misconception by the patient as well as her family that patients with asthma "cannot exercise" which consequently resulted in acceptance of her limited endurance and reduced physical capacity.

There is general agreement that asthma education has positive outcomes on symptom control as well as on other outcomes, including the rate of hospitalization and ER visits for asthma, unscheduled doctors' visits, costs and improvement in quality of life[6], with better outcomes for programs that provided self-management skills. As a result, repeated assessment of families' and patients' perceptions of the disease is an integral component of asthma care visits. The pediatrician is encouraged to utilize educational tools and strategies to deliver the information at different levels of health literacy to caregivers; an example is asthma action plans that became an essential part of a pediatric asthma visit. Other tools of education include more interactive learning that incorporates either individual or group learning.

PH is rare in pediatrics and is associated with considerable morbidity and mortality that can affect all age groups from the newborn period to infancy and childhood. Symptoms of PH are commonly nonspecific[7], and the diagnosis may be missed in the early disease stages. Exertional dyspnea and progressive fatigue are the most frequent complaints in the older child. Special considerations should apply to the child with exertional dyspnea that is not responding to asthma management and a lower threshold for investigating the child with uncontrolled asthma is recommended with early referral to a specialist.

CONCLUSION

Pediatricians are encouraged to educate patients and caregivers about asthma and utilize the widely available variable tools and strategies to provide an understanding of the expected symptoms, disease progression, and goals of care.

Timely referral to a specialist is mandatory when symptoms remain uncontrolled. PH is rare in pediatrics but with considerable mortality and morbidity and should be considered in pediatric cases of dyspnea on exertion.

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TRAINEE ARTICLE

Severe Necrotizing Pneumonia and Persistent Bacteremia in a Teenager with a History of Vaping

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INTRODUCTION

After being introduced into the market in 2004, electronic cigarette (e-cigarette) use has gained immense popularity worldwide as a safe alternative to cigarettes.[1] This trend has become especially prominent among the youth, with an estimated 4.9% of middle school and 20.8% of high school students reported having used e-cigarettes in 2018.[2] Vaping devices contain 4 basic components: a cartridge or a pod to hold e-liquid or e-juice, a heating element known as an atomizer, a battery and a mouthpiece used to inhale the vapor.[3] The most popular form of vaping among teenagers is JUUL®, a vaping device shaped like a small USB flash drive. A JUULpod is made from loose tobacco leaves and contains 2 ml of liquid nicotine (59 mg/0.7 ml of liquid) which is equal to one pack of cigarettes.[4]

Although long term health effects of vaping have largely remained unknown, vaping and e-cigarette use has been associated with a recent national outbreak of acute or subacute life-threatening respiratory illness, later termed e-cigarette or vaping-associated lung injury (EVALI). Initially recognized in the summer of 2019, there have been a total of 2,409 hospitalized EVALI cases with 52 deaths reported to the Centers for Disease Control and Prevention (CDC) as of December 10, 2019.[5] Vitamin E acetate is strongly linked to the EVALI outbreak. It has been found in product samples tested by FDA and state laboratories and in patient bronchoalveolar-lavage samples tested by CDC from geographically diverse states. Vitamin E acetate has not been found in bronchoalveolar-lavage fluid of people that do not have EVALI.[6]

EVALI is a diagnosis of exclusion and patients usually present with non-specific symptoms including shortness of breath (85%), cough (85%), nausea (66%) and vomiting (61%).[7,8] While the working case definition of EVALI specifically excluded individuals with microbiologically confirmed infections, there is mounting data suggesting a relationship between viral and bacterial infectious etiologies and EVALI that remains to be elucidated. Here, we present the case of an adolescent boy with a history of frequent vaping who developed severe necrotizing staphylococcal pneumonia and persistent bacteremia in the setting of influenza B infection. We go on to propose that his vaping increased his susceptibility to infection while also increasing the virulence of the infection itself.

CASE DESCRIPTION

A previously healthy 15-year-old Caucasian boy presented to his primary care provider with cough and a one-day history of fever (maximum of 106.3°F). He was diagnosed with a viral illness and discharged home. Over the next 3 days, he developed nausea, vomiting, diarrhea, and fatigue. He was taken to an emergency center where a throat swab was positive for influenza B, chest X-ray was consistent with a viral infection, and he was discharged home. Oseltamivir was not prescribed, as it had been greater than 72 hours since the onset of his symptoms.

Over the next 3 days, he worsened and returned to the emergency center where he was found to have dehydration, electrolyte disturbances, lactic acidosis and pre-renal azotemia. He received intravenous fluids and ceftriaxone and was transferred to the children's hospital for further management. Soon after his admission to the general floor he developed respiratory distress and was subsequently transferred to the pediatric intensive care unit (PICU) where he was placed on bilevel positive airway pressure (BiPAP) for acute hypoxic respiratory failure. He reported vaping JUUL® flavored nicotine pods: 1-2 per day for the last 2 years. He denied vaping THC or any other substance use. A repeat chest X-ray was concerning for development of bacterial pneumonia. A chest computed tomography (CT) scan showed significant bronchiectasis and bilateral areas of dense opacities consistent with necrotizing pneumonia (Figure 1). Sputum and blood cultures were positive for oxacillin-resistant *Staphylococcus aureus* (ORSA) susceptible to vancomycin, clindamycin, linezolid, gentamicin, and trimethoprim-sulfamethoxazole. He received vancomycin through a peripherally inserted central catheter (PICC). However, his blood cultures remained positive for the following 10 days while his antibiotic regimen was escalated to also include gentamicin, linezolid, and ceftaroline. Once the blood cultures were negative, antibiotics were deescalated and his PICC was removed. He was weaned off BiPAP to high flow nasal cannula and then to room air. He was switched to oral antibiotics upon transfer to the floor. Prior to discharge, he was counseled on the dangers of vaping and nicotine use and he agreed to quit. He was discharged home after a 22-day hospital stay. After discharge, the patient continued to receive oral antibiotic therapy (mainly as oral clindamycin) for 3 more weeks thus completing a total of 46 days of antibiotics (37 days of treatment after his first negative blood cultures).

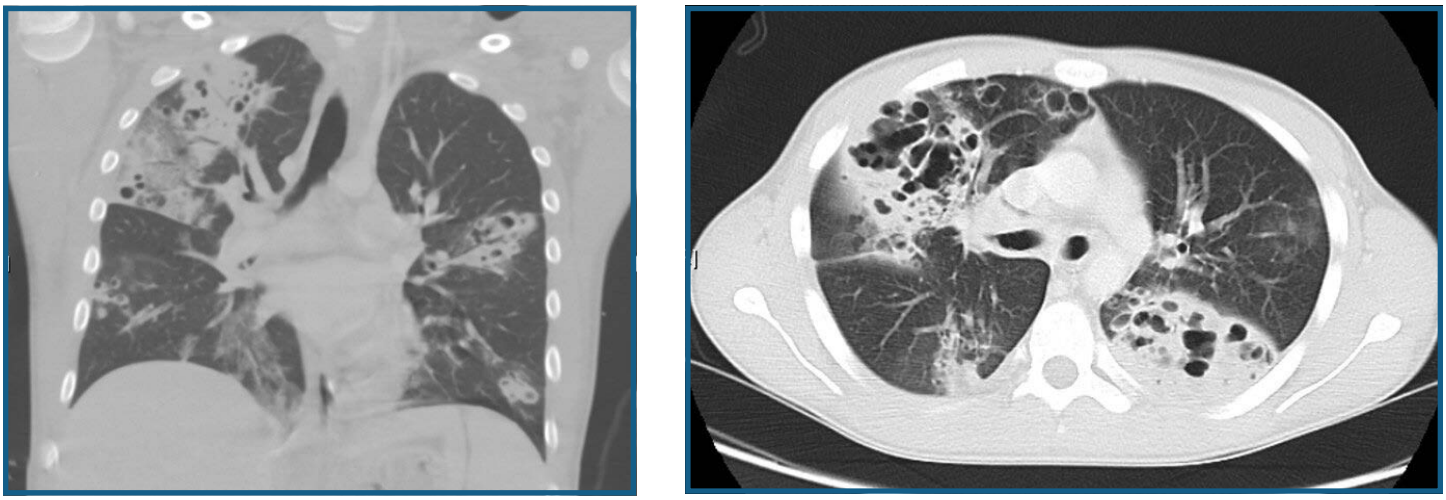

Figure 1: Computerized tomography (CT) scans of the chest demonstrating multifocal areas of dense opacification surrounding large cystic spaces throughout the lung lobes. Some of these may be filled with debris or mucous.

Two weeks after discharge, on follow up in the pediatric infectious diseases clinic, he reported some shortness of breath and was still found to have wheezing and crackles in both lung fields posteriorly. A repeat chest X-ray showed improvement with some residual necrotizing pneumonia. Four weeks later, he continued to experience shortness of breath on moderate exertion but had a normal lung exam.

DISCUSSION

Severe respiratory illness and lung injury related to vaping has been well documented, however its relationship to viral and bacterial infections is not well described. The case of this adolescent who vaped nicotine through a vape pen several times daily for about 2 years and developed influenza B and severe ORSA necrotizing pneumonia with bacteremia contributes to our understanding. Secondary bacterial co-infection is relatively common in adolescents infected with influenza.[9] A population based analysis on influenza and bacterial coinfection demonstrated bacterial coinfection in 2% of children hospitalized with

influenza between 2003 and 2010.[10] *Staphylococcus aureus* accounted for 28% of these infections, and was the second most common bacteria after *Streptococcus pneumoniae*, which accounted for 35%.[10] Although *S. aureus* colonizes the nares in about 50% of the population, it infrequently acts as a primary infectious agent in the development of community acquired pneumonia.[11] The suggested mechanism for secondary staphylococcal infection involves disruption of the lung epithelial barrier with impairment of mucociliary clearance. Additionally, there is modulation of the host immune response leading to increased host susceptibility to subsequent bacterial infection.[11]

Patients who develop bacterial pneumonia secondary to influenza can either present with abrupt worsening of clinical status, clinical deterioration after initial improvement or recurrent fever one to two weeks after recovering from the viral illness. In murine models, infection was seen to most commonly develop 7 days post-viral infection.[12] However, bacterial infection was observed as early as 3 days post-viral infection in those with enhanced susceptibility prior to initial viral infection.[12] The patient described here experienced an abrupt worsening of his clinical status about 4 days after first experiencing symptoms and 1-2 days after testing positive for influenza B. This suggests that he was at increased susceptibility for developing secondary bacterial infection prior to contracting influenza B. We propose that his frequent vaping increased his susceptibility to secondary bacterial pneumonia. Vaping and e-cigarette use alter the structure and function of lung epithelial cells and decreases both the number of cilia and ciliary beat frequency.[13] This causes impairment of mucociliary clearance in the lung leading to increased risk for bacterial infection. Furthermore, an in vivo study showed that mice exposed to e-cigarette aerosols for two weeks had impaired bacterial clearance when compared to mice exposed to air. An effect partially attributed to reduced phagocytosis by alveolar macrophages.[14] Therefore, this patient's vaping may have led to both direct epithelial damage impairing bacterial clearance as well as alveolar macrophage dysfunction reducing his host defenses.

Since the patient had not received a seasonal influenza vaccine, it is difficult to speculate whether his frequent e-cigarette use increased his risk for contracting influenza. However, in a recent study, mice exposed to e-cigarette aerosol had higher viral titers in the lung and higher rates of viral induced illnesses and death than unexposed mice.[15] Vaping use may have increased the virulence of our patient's influenza infection contributing to the severity of his initial presentation, including a markedly high fever of 106.3°F.

Necrotizing pneumonia usually follows infection by particularly virulent bacteria.[16] We propose that this patient's vaping led to the development of a more virulent infection capable of producing a necrotizing pneumonia through the direct effect of nicotine aerosols on both bacterial virulence and host defenses. A study in mice involving ex vivo exposure to e-cigarette vapor showed that *S. aureus* became more virulent when exposed to e-cigarette vapor, potentially by inducing biofilm formation, invasiveness, and resistance to antimicrobial peptides.[15] Vaporized nicotine has also been shown to decrease glutathione levels, which plays a key role in maintaining oxidant induced epithelial cell lung function.[17] Decreased glutathione levels in the lung leads to increased oxidative stress which in turn increases the severity of bacterial lung infections through direct cellular damage and impairment of signaling pathways.[18] Multiple studies have also shown statistically significant increases in lung inflammation after exposure to e-cigarette aerosols, even with short-term exposure, through various mechanisms including increased endothelial permeability and increased production of pro-inflammatory cytokines.[15,19,20]

Vaping has been associated with necrotizing pneumonia in a case report of a previously healthy girl who developed *Fusobacterium necrophorum* infection of her lung without having any traditional predisposing conditions. The girl described had a history of vaping "several times each hour" for about 9 months' time. The authors propose that her vaping was the predisposing factor for her developing the infection.[21]

Further research on the association between vaping-induced injury to the lung and predisposing the host to severe infection is warranted. Our case can help increase awareness among providers of the dangers of vaping in teens, both directly on the lungs but also contributing to development of more severe infections.

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