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CASE REPORT

- 1 Celiac sprue - a cryptic disease: A case report

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Celiac sprue - a cryptic disease: A case report

Lisa R Maness

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Abstract

BACKGROUND

Celiac sprue, or celiac disease, is a relatively common disease whereby many are unaware that they have it. It often manifests with symptoms outside of the digestive system. Many health care providers are unaware of the wide variety of symptoms of celiac disease as well as diseases that are associated with it, often delaying diagnosis and treatment.

CASE SUMMARY

The following case indicates an otherwise healthy 20-year-old female who presents with a variety of symptoms and is ultimately diagnosed with shingles, infectious mononucleosis, and celiac disease

CONCLUSION

Although it is known that risk-factors are genetic as well as environmental, much more research is needed to better understand the relationship of potential causes. In addition, continuing education is needed in health care so that more practitioners better understand celiac disease.

Key Words: Celiac disease; Autoimmune disease; Shingles; Infectious mononucleosis; Case report

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Core Tip: More studies are needed that correlate infectious agents such as Epstein-Barr virus and varicella zoster virus to celiac disease (CD). In addition, further in-depth studies on this particular patient, as well as others, may yield more information on immune status of patients with CD. This case and others demonstrate that more health care practitioners should understand that shingles can occur in patients outside of those recommended for vaccination; delaying treatment places patients more at risk. Practitioners also need to better understand CD, its wide range of symptoms, and its relationship to other infectious agents.

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INTRODUCTION

A 21-year-old female on a vegetarian diet was enrolled in graduate school and working at a local supermarket. She had a history of abdominal pain and bloody diarrhea with a colonoscopy several months previously indicating anal fissures and internal hemorrhoids. She visited a family physician complaining of a tingling, itchy rash on the forehead, eyelid, and eyebrow as well as multiple large, swollen lymph nodes in the neck and jaw, as well as fatigue. The family practitioner mistakenly denied shingles, caused by the varicella zoster virus (VZV), but took note of the large lymph nodes and ordered a rapid test for infectious mononucleosis, caused by Epstein-Barr virus (EBV), that initially turned out negative. The patient was referred to a dermatologist for the rashes.

CASE PRESENTATION

Chief complaints

The patient described to the dermatologist feeling a tingling sensation from the right eye to the right side of the scalp, but the physician stated that this could not be shingles due to her young age. Given the option to take a biopsy in order to determine the cause, the patient agreed. During the 2 wk wait for biopsy results, the patient developed symptoms of blurry vision, numbness in the extremities, night sweats, itchy skin, dizziness, headaches, extreme fatigue, bone and muscle pain in the hips, thighs, and arms along with left upper quadrant pain and an increasing number of lymph nodes enlarging.

Personal and family history

She had a history of abdominal pain and bloody diarrhea with a colonoscopy several months previously indicating anal fissures and internal hemorrhoids.

Physical examination

Multiple physicians were seen over several weeks and all claimed that “there is nothing wrong” with the patient. One ordered an X-ray of the left hip and no abnormalities were detected. Others repeated spot tests for infectious mononucleosis, strep throat, and human immunodeficiency virus, all of which were negative. 2 wk later, the biopsy results were positive for VZV. The same dermatologist who denied that it could be shingles then claimed that it was too late for treatment, that treatment for shingles should begin within 48 h.

Within days, the patient went to the emergency department (ED) with continuation of symptoms and increased abdominal, bone, and joint pain; a cat scan was performed on the abdominal area, with no obvious abnormalities, except for enlarged ovarian follicles. An ultrasound was performed on the head and neck soft tissues; several nodes were measured and reported to be “slightly prominent”, one 2.2 cm in length. The spot mono and strep tests were repeated once again and were negative. Complete blood count (CBC), comprehensive metabolic panel, erythrocyte sedimentation rate, thyroid stimulating hormone, and lipase were all normal and pregnancy test was negative. The ED physician noticed the report of follicles in each ovary and discharged the patient with diagnosis of adenopathy and follicular cysts.

The patient visited her OB-GYN within the next several days and he stated that the sizes of the follicles were normal and of no concern. He stated that he believed the patient’s primary problem was intestinal and recommended that she revisit the gastroenterologist. The white blood cell (WBC) count at OB-GYN visit was $3.8 \times 10^3/\mu\text{L}$ with the reference range of $4.0\text{--}11.0^3/\mu\text{L}$. The student quit her part-time job as she was unable to keep up with expectations.

Laboratory examinations

At several subsequent appointments with a family practitioner a month after onset of symptoms, a physician's assistant (PA) ordered tests for rocky mountain spotted fever, lyme antibodies, uric acid, CBC with differential, and EBV antibody profile. She also prescribed acyclovir to address the shingles diagnosis. The WBC count was still $3.8 \times 10^3/\mu\text{L}$ and at this time EBV titers indicated abnormalities. The EBV Ab VCA, IgM was 81.6 (H) with the reference range of 0.0-35.9 U/mL, the EBV Ab VCA, IgG was 225.0 (H) with the reference range of 0.0-17.9 U/mL, and the EBV Nuclear Antigen Ab, IgG was 66.7 (H) with the reference range of 0.0-17.9 U/mL (Table 1). Results indicated that the patient likely experienced an infection from EBV sometime in the past or recent past[1].

The PA referred the patient to an infectious disease physician to discuss the symptoms of infectious mono and shingles as well as leukopenia. The infectious disease specialist suggested to continue resting adequately, have a CBC repeated in 4 wk if lymph node swelling persists, and to reassess the size of the spleen if necessary. The PA referred the patient for a magnetic resonance imaging; the head scan showed no abnormalities. The patient was referred for another ultrasound of the neck to check the lymph nodes and upon noting further enlargement was referred to an Ear/Nose/Throat specialist. This specialist was unable to know for certain the cause of the enlargements as more nodes were enlarging such as in the cheekbone, armpit, neck, and jaw. He felt it was likely due to the combination of viral infections, leaving it up to the patient to decide whether to have a biopsy performed. After a couple of weeks of symptoms not subsiding, the patient decided to have this performed on the largest lymph node just below the jaw; the result was that this was a reactive lymph node. 2 wk later, after declaring that the patient's symptoms were due to EBV and recent shingles, the PA orders celiac disease (CD) panel and Ova and Parasite test in response to patient symptoms of left upper quadrant abdominal pain and fatty, loose, yellow stools. Within a week the CD panel results indicated a t-transglutaminase (tTG) IgA level of > 100 U/mL, with a reference range of 0-3 U/mL (Table 2). The endomysial antibody IgA was positive. The Quantitative IgA level was 137 mg/dL, with the range of 87-352 mg/dL. The patient was referred to her gastroenterologist for upper gastrointestinal endoscopy.

Imaging examinations

An endoscopy was performed and impressions from the test were: Duodenal mucosal changes seen, suspicious for CD. Biopsies were taken and results from the biopsies indicated celiac disease, whereby the patient should be placed on a gluten free diet indefinitely and recommended to have gluten antibody levels checked periodically.

Two months after initial complaints, the patient had greater explanation for the prolonged and multiple symptoms, including swollen lymph nodes, tingling in the scalp, numbness in the extremities, blurry vision, dizziness, headaches, itchy skin, extreme fatigue, bone and muscle pain in the hips, thighs, and arms, and left upper quadrant pain. It is difficult to know which occurred first, which disease led to the others, if any causation, although it is likely that the shingles occurred in response to untreated CD. It is difficult to understand how long the CD was present or if EBV from the past, or recent past, played a role. Over the next year, the patient adhered to a strict certified gluten free diet and the tTG IgA level decreased over time to 73 U/mL 4 mo later, 18 U/mL 8 mo later, and 12 U/mL 15 mo later.

MULTIDISCIPLINARY EXPERT CONSULTATION

The PA referred the patient to an infectious disease physician to discuss the symptoms of EBV and shingles as well as leukopenia. The infectious disease specialist suggested to continue resting adequately, have a CBC repeated in 4 wk if lymph node swelling persists, and to reassess the size of the spleen if necessary.

FINAL DIAGNOSIS

An endoscopy was performed and impressions from the test were: Duodenal mucosal changes seen, suspicious for CD. Biopsies were taken and results from the biopsies indicated celiac disease.

TREATMENT

The patient should be placed on a gluten free diet indefinitely and recommended to have gluten antibody levels checked periodically.

Table 1 Results from Epstein-Barr virus antibody profile

Name	Value	Reference range
EBV Ab VCA, IgM	81.6 H	0.0-35.9 (U/mL), Negative ≤ 36.0 U/mL, Equivocal = 36.0-43.9 U/mL, Positive ≥ 43.9 U/mL
EBV Ab VCA, IgG	225.0 H	0.0-17.9 (U/mL), Negative = 18.0 U/mL, Equivocal = 18.0-21.9 U/mL, Positive ≥ 21.9 U/mL
EBV Nuclear Antigen Ab, IgG	66.7 H	0.0-17.9 (U/mL), Negative ≤ 18.0 U/mL, Equivocal = 18.0-21.9 U/mL, Positive ≥ 21.9 U/mL

EBV: Epstein-Barr virus.

Table 2 Results from celiac disease panel

Name	Value	Reference range
Endomysial antibody IgA	Positive	Negative
t-Transglutaminase (tTG ¹) IgA	> 100 H	0-3 (U/mL), Negative = 0-3 U/mL, Weak Positive = 4-10 U/mL, Positive ≥ 10 U/mL
Immunoglobulin A, Qn, serum	137 H	87-32 (mg/dL)

¹t-Transglutaminase has been identified as the endomysial antigen. Studies have demonstrated that endomysial IgA antibodies have over 99% specificity for gluten sensitive enteropathy.

OUTCOME AND FOLLOW-UP

Over the next year, the patient adhered to a strict certified gluten free diet and the tTG IgA level decreased over time to 73 U/mL 4 mo later, 18 U/mL 8 mo later, and 12 U/mL 15 mo later.

DISCUSSION

Celiac disease description, symptoms, and causes

The National Institute of Diabetes and Digestive and Kidney Diseases estimates that about 2 million people in the United States have CD, many of which have not been diagnosed[2]. CD is described as a chronic digestive immune disorder that damages the villi of the small intestine and other tissues and is triggered by ingesting foods with gluten. Foods that are high in gluten are wheat, rye, and barley and these are common in breads, pasta, and baked goods. In addition, gluten contaminates many other foods and is also present in cosmetics, vitamins, and medicines.

Patients with celiac disease are unable to obtain all of the nutrients the body needs because of damage to the intestine[3]. In addition to pale, fatty, and loose stools, bloating, nausea, vomiting, constipation, and abdominal pain, patients also have many other symptoms since CD is an autoimmune disease and not just an allergy. Patients have malabsorption, weight loss, fatigue, headaches, tingling of the extremities, cognitive impairment, joint pain, nervous system problems, reduced spleen function, itchy skin rashes, anemia, bone loss, and more. Rare complications of celiac disease include cancer of the small intestine, liver damage, and non-Hodgkin's lymphoma[2]. People with CD are more likely to have other immune-related diseases such as thyroid diseases, Sjogren's Syndrome, rheumatic diseases, type 1 diabetes, and others.

Advancements have been made to determine prevalence of celiac among various combinations of HLA genes. Individuals with DQ2.5/DQ2.5 genotype are in the highest risk gradient with a risk of 1:7 [4]. Those with DQ2.5/DQ2.2 are in a 1:10 risk gradient while DQ2.5/DQ8 are in the 1:19 risk gradient. The patient in this case study has a DQ2.2/DQ2.5 genotype, placing her in the 1:10 risk gradient. Individuals with genotypes HLA-DQ are more at risk for celiac disease because these molecules present gluten proteins to T cells[5].

Whereas genotype is one factor that contributes to celiac disease, there are environmental risks as well. It has been suggested that formula feeding in infants, timing of gluten introduction, infectious agents, and gut microbiota may relate to onset of celiac disease[6]. It is generally understood that the pathogenesis of autoimmune diseases is due to an imbalance between T helper 1 and 2 cell responses [7]. The recipe that fuels celiac disease appears to be a mix of genetic predisposition, gluten exposure, reduction of intestinal barrier function, an innate inflammatory response to gluten, an imbalanced gut microbiome, and a faulty adaptive immune response.

Relationship of celiac disease to shingles and infectious mononucleosis

There are a few studies that link CD with shingles and that link CD with EBV. A nationwide cohort study performed in Sweden indicated that CD leads to a 1.62-fold increased risk of VZ over time, even in patients who are less than 60 years of age[8]. There are also cases available for discussion in celiac patient forums that indicate a correlation between the 2 diseases, even in patients who are less than age 50[9]. More studies are needed in other global regions to further determine any correlation between CD and VZ. Delayed treatment of shingles, such as that of the patient in this case, risks further complications such as post-herpetic herpes and blindness[10,11].

It has been shown that a protein known as EBNA2 that is produced by EBV binds to locations along the human genome[12]. The virus is closely associated with celiac disease as well as several other autoimmune diseases, including multiple sclerosis, type 1 diabetes, rheumatoid arthritis, inflammatory bowel disease, and systemic lupus erythematosus. These findings are highly suggestive that EBV plays a role in auto-immunity. There are also numerous cases that specifically link EBV with CD, some of which show the virus actively present within inflammatory cells and enterocytes of those with CD[13, 14]. Much more research on the effects of EBV on CD and other autoimmune diseases is certainly warranted.

CONCLUSION

More studies are needed that correlate infectious agents such as EBV and VZV to CD. In addition, further in-depth studies on this particular patient, as well as others, may yield more information on immune status of patients with CD. This case and others demonstrate that more health care practitioners should understand that shingles can occur in patients outside of those recommended for vaccination; delaying treatment places patients more at risk. Practitioners also need to better understand CD, its wide range of symptoms, and its relationship to other infectious agents.

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