

# Fatal *Streptococcus pneumoniae* Sepsis in a Patient With Celiac Disease-Associated Hyposplenism

Madhu M. Ouseph, MD, PhD<sup>1</sup>, Malorie Simons, MD<sup>2</sup>, Diana O. Treaba, MD<sup>1</sup>, Evgeny Yakirevich, MD, DSc<sup>1</sup>, Peter H. Green, MD<sup>3</sup>, Govind Bhagat, MD<sup>3</sup>, Steven F. Moss, MD<sup>2</sup>, and Shamlal Mangray, MBBS<sup>1</sup>

<sup>1</sup>Department of Pathology and Laboratory Medicine, Alpert Medical School of Brown University and Rhode Island Hospital, Providence, RI

<sup>2</sup>Division of Gastroenterology, Alpert Medical School of Brown University and Rhode Island Hospital, Providence, RI

<sup>3</sup>College of Physicians and Surgeons of Columbia University and New York-Presbyterian Hospital, New York, NY

## ABSTRACT

We present a 59-year-old male with poorly controlled celiac disease (CD) and fatal *Streptococcus pneumoniae* sepsis, describe the morphologic findings, and stress the need for monitoring splenic function and pneumococcal vaccination in these patients.

## INTRODUCTION

Celiac disease (CD) is an autoimmune disorder of the small intestine affecting 0.6%-1.0% of the population worldwide. Although physical and functional splenic atrophy, hyposplenism, and their profound clinical implications have been reported in CD, these remain largely underrecognized without any clear guidelines for monitoring splenic function in the United States. In the absence of prior reports on morphological changes, the causes of splenic atrophy remain speculative.

## CASE REPORT

A 59-year-old white male smoker with a prior history of CD had a witnessed cardiac arrest. He reportedly complained of feeling ill on waking up and later developed numbness of his hands and incomprehensible speech before collapsing. The initial rhythm identified by emergency medical services was asystole. Advanced cardiac life support was unsuccessful.

The patient was diagnosed with CD in 2008 after presenting with chronic abdominal pain, intermittent diarrhea, and weight loss. At diagnosis, he had anti-tissue transglutaminase (anti-tTG) immunoglobulin A (IgA) antibodies 74 U/mL and antiendomysial IgA titer 1:320 accompanied by classic histopathologic features including severe villous atrophy, increased intraepithelial lymphocytes, crypt hyperplasia, and lamina propria lymphoplasmacytosis on duodenal biopsy (Figure 1). At current presentation, he had poor dietary compliance, anti-tTG IgA antibody 89 U/mL, and antiendomysial IgA titer 1:160.

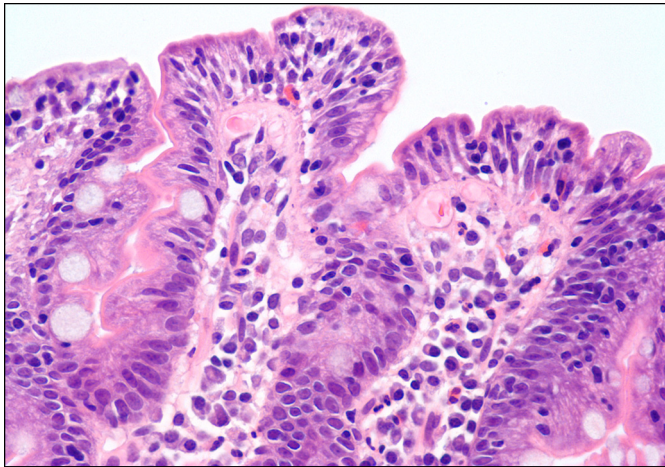
Further review of his history revealed that computed tomography in 2006 and 2009 showed a diminutive spleen with a calcification suggestive of old infarction (Figure 2). His blood counts from June 2008 onward showed thrombocytosis (platelet count,  $526 \times 10^9/L$ ) and peripheral blood smears from January 2007 onward were remarkable for red blood cell anisopoikilocytosis with target cells, schistocytes, acanthocytes, Howell-Jolly bodies, basophilic stippling, and Pappenheimer bodies, consistent with hyposplenism.

ACG Case Rep J 2016;3(4):e140. doi:10.14309/crj.2016.113. Published online: October 12, 2016.

**Correspondence:** Shamlal Mangray, MBBS, Department of Pathology and Laboratory Medicine, Alpert Medical School of Brown University and Rhode Island Hospital, Providence, RI 02903 (SMangray@Lifespan.org).



Copyright: © 2016 Ouseph et al. This work is licensed under a Creative Commons Attribution-NonCommercial-NoDerivatives 4.0 International License. To view a copy of this license, visit <http://creativecommons.org/licenses/by-nc-nd/4.0>.



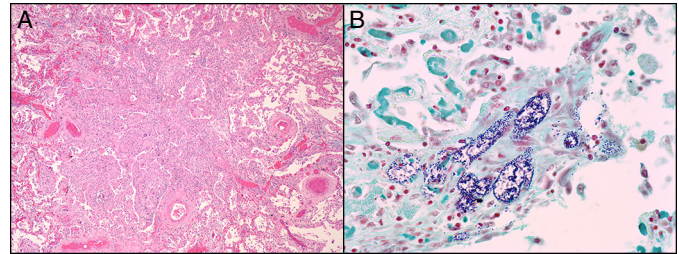
**Figure 1.** Duodenal mucosa showing severe villous atrophy, crypt hyperplasia, and intraepithelial lymphocytic infiltrates, consistent with diagnosis of CD (hematoxylin and eosin, 400x).

Additional history included chronic obstructive pulmonary disease, hyperlipidemia, hypertension, coronary artery disease, gastroesophageal reflux disease, peptic ulcer, depression, anxiety, osteoarthritis, avascular necrosis of the left hip, osteoporosis, and scoliosis. A history of opioid dependence and recreational marijuana use was also documented.

Postmortem examination of the lungs demonstrated severe emphysematous change and patchy pneumonia, most marked in the left lower lobe with microabscesses with Gram-positive cocci, correlating with lung and blood cultures positive for *Streptococcus pneumoniae* (Figure 3). The spleen was markedly atrophic (21 g; normal, 125-195 g) with normal vasculature, depletion of the white pulp, and gross and microscopic features of prior hemorrhage (Gamna-Gandy changes; Figure 4). Vasculitis was absent. Immunohistochemistry showed that



**Figure 2.** Computed tomography from 2009 showing splenic calcification consistent with prior infarct.



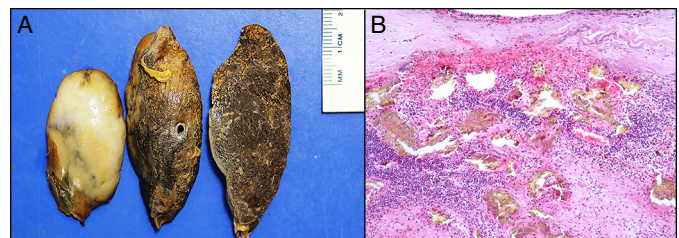
**Figure 3.** (A) Section from left lower lung lobe showing pneumonia (hematoxylin and eosin, 40x) and (B) multiple intravascular and intraparenchymal collections of gram positive cocci (gram stain, 400x).

lymphoid aggregates in the white pulp were composed of CD20+ B lymphoid cells, whereas CD3+ and bcl-2+ T cells were present in the periarteriolar regions and red pulp. Some of the B-lymphoid aggregates had reactive germinal centers (bcl-6+, bcl-2-, CD20+). Polymerase chain reaction of formalin-fixed paraffin-embedded splenic tissue was negative for T-cell receptor- $\gamma$  rearrangement. Mesenteric lymph nodes were reactive without cavitory changes.

Evaluation of the duodenum was limited by autolysis, but the villi appeared blunted on microscopy. Refractory CD Type II was ruled out by normal CD8 immunostaining (85% of CD3+ intraepithelial lymphocytes were CD8+) and detection of polyclonal products by T-cell receptor- $\gamma$  rearrangement polymerase chain reaction on his initial biopsy and autopsy tissue.<sup>1</sup> A sickle cell screening test was negative, and hemoglobin electrophoresis showed denatured hemoglobin A 1.2%, hemoglobin A 96.7%, and hemoglobin A2 2.1%. Blood drug screening was positive for cannabinoids.

**DISCUSSION**

Causes of hyposplenism include congenital asplenia, physical loss/injury, infarctions, infiltrative diseases, engorgement, and involvement in systemic diseases.<sup>2</sup> Celiac disease is a less recognized cause of hyposplenism, estimated at 20% prevalence by hematologic and radiologic parameters in patients with mild CD controlled on diet and up to 80% prevalence in patients with uncontrolled or complicated CD.<sup>2,3</sup> The cause of



**Figure 4.** (A) Gross appearances of spleen (weight 21 g) with apparent atrophy and capsular as well as parenchymal fibrosis; and (B) section from spleen demonstrating areas of fibrosis, hemosiderin pigmentation, and calcification consistent with Gamna-Gandy changes (hematoxylin and eosin; 100x).

hyposplenism in CD is unclear but is hypothesized to result from reticuloendothelial atrophy secondary to either loss of lymphocytes or circulating immune complexes, supported by rare occurrence of cavitating mesenteric lymph nodes with hemorrhagic necrosis.<sup>4</sup> The spleen functions that are critically lost include those related to phagocytosis of unopsonized particles, antibody production, and activation of the alternative complement pathway.

Hyposplenism increases the risk of fulminant and fatal septicemia by encapsulated organisms (*S. pneumoniae*, *Haemophilus influenzae*, and *Neisseria meningitidis*) by approximately 4-fold in CD patients compared to the general population.<sup>2</sup> The risk for *Capnocytophaga canimorsus* and *Babesia* infections is also increased.<sup>2</sup> Population-based studies from the United Kingdom and Sweden have demonstrated higher incidence of pneumococcal infection in CD patients.<sup>5,6</sup> Incidence might be higher in patients with comorbidities similar to our patient. Up to 20% of community-acquired pneumonias are associated acute cardiac events, which explains the unique presentation of our patient.<sup>7</sup>

The degree of hyposplenism in CD correlates with the severity of duodenal mucosal atrophy.<sup>8</sup> Although splenic function might show improvement after initiation of a gluten-free diet, the overall progression is unaltered and irreversible even with strict adherence to gluten-free diet, especially once splenic atrophy occurs.<sup>2,9</sup> Splenic size as estimated by (99m)Tc-labelled sulphur colloid scintiscans and computed tomography correlates well with splenic function and hematologic parameters in patients with CD.<sup>10,11</sup> Splenic Gamna-Gandy changes have never been reported in CD. Without a history of trauma or vasculitis/vasculopathy, they may be due to splenic infarcts attributable to a hypercoagulable state in CD resulting from autoantibodies, thrombocytosis, hyperhomocysteinaemia, methylenetetrahydrofolate reductase mutations, and protein C and S deficiency due to vitamin K deficiency.<sup>12,13</sup> It is noteworthy that our patient had history of avascular necrosis of the left hip, akin to what is seen in sickle cell disease, but underlying steroid treatment for chronic obstructive pulmonary disease cannot be excluded.

Whether routine evaluation of splenic function should be a part of the management of CD is controversial, but the risk of infections, especially overwhelming postsplenectomy infections, with mortality of up to 70%, warrants screening and preventive measures.<sup>14,15</sup> Determining the percentage of pitted erythrocytes by phase interphase microscopy is considered a good screening test for these patients along with a confirmatory (99m)Tc-labelled, heat-altered, autologous erythrocyte clearance or (99m)Tc-labelled sulphur colloidal scintigram.<sup>2</sup> However, these tests are not readily available. An elevated platelet count in any CD patient should raise suspicion for hyposplenism, and follow-up peripheral blood smears for Howell-Jolly bodies or target cells and splenic size evaluation

should be performed.<sup>2,16,17</sup> Although Howell-Jolly bodies are not accurate in quantitation of splenic function, their presence is universal in patients with a degree of hyposplenism sufficient to cause overwhelming postsplenectomy infections.<sup>2,16,17</sup>

Currently, the British Society of Gastroenterology recommends routine pneumococcal vaccination for all CD patients regardless of their splenic function, although the efficacy of this approach is unclear due to poor adherence to this guideline.<sup>18,19</sup> Although it is known that CD patients can be effectively immunized even in the presence of hyposplenism, no clear guidelines for monitoring or management of splenic function in CD exist in the United States.<sup>20</sup> Although the Advisory Committee on Immunization Practices recommends pneumococcal vaccination for patients with diagnosed hyposplenism,<sup>21</sup> without guidelines for routine evaluation of splenic function in CD, these patients are excluded. This case underscores the need for monitoring splenic function in CD or adopting the European approach of vaccination of susceptible CD patients. Furthermore, in unexplained cases of hyposplenism, laboratory workup should also include serologic testing for CD.

## DISCLOSURES

Author contributions: MM Ouseph and M. Simons wrote the manuscript. All authors reviewed, edited, and approved the final manuscript. MM Ouseph is the article guarantor. MM Ouseph and M. Simons contributed equally.

Financial disclosures: None to report.

Informed consent was obtained from the deceased patient's next of kin.

Received January 23, 2016; Accepted April 15, 2016

## REFERENCES

- Rubio-Tapia A, Kelly DG, Lahr BD, Dogan A, Wu TT, Murray JA. Clinical staging and survival in refractory celiac disease: A single center experience. *Gastroenterology*. 2009;136(1):99-107; quiz 352-3.
- Di Sabatino A, Carsetti R, Corazza GR. Post-splenectomy and hyposplenic states. *Lancet*. 378(9785):86-97.
- Di Sabatino A, Rosado MM, Cazzola P, et al. Splenic hypofunction and the spectrum of autoimmune and malignant complications in celiac disease. *Clin Gastroenterol Hepatol*. 2006;4(2):179-86.
- William BM, Corazza GR. Hyposplenism: A comprehensive review. Part I: Basic concepts and causes. *Hematology*. 2007;12(1):1-13.
- Thomas HJ, Wotton CJ, Yeates D, Ahmad T, Jewell DP, Goldacre MJ. Pneumococcal infection in patients with coeliac disease. *Eur J Gastroenterol Hepatol*. 2008;20(7):624-8.
- Ludvigsson JF, Olen O, Bell M, Ekblom A, Montgomery SM. Coeliac disease and risk of sepsis. *Gut*. 2008;57(8):1074-80.
- Musher DM, Rueda AM, Kaka AS, Mapara SM. The association between pneumococcal pneumonia and acute cardiac events. *Clin Infect Dis*. 2007;45(2):158-65.
- Corazza GR, Frisoni M, Vaira D, Gasbarrini G. Effect of gluten-free diet on splenic hypofunction of adult coeliac disease. *Gut*. 1983;24(3):228-30.
- Marsh GW, Stewart JS. Splenic function in adult coeliac disease. *Br J Haematol*. 1970;19(4):445-57.



10. Robinson PJ, Bullen AW, Hall R, Brown RC, Baxter P, Losowsky MS. Splenic size and function in adult coeliac disease. *Br J Radiol.* 1980; 53(630):532-7.
11. Mallant M, Hadithi M, Al-Toma AB, et al. Abdominal computed tomography in refractory coeliac disease and enteropathy associated T-cell lymphoma. *World J Gastroenterol.* 2007;13(11):1696-1700.
12. Lerner A, Blank M. Hypercoagulability in celiac disease—an update. *Autoimmun Rev.* 2014;13(11):1138-41.
13. Dickey W, Ward M, Whittle CR, et al. Homocysteine and related B-vitamin status in coeliac disease: Effects of gluten exclusion and histological recovery. *Scand J Gastroenterol.* 2008;43(6):682-8.
14. Di Sabatino A, Brunetti L, Carnevale Maffe G, Giuffrida P, Corazza GR. Is it worth investigating splenic function in patients with celiac disease? *World J Gastroenterol.* 2013;19(15):2313-8.
15. Schwartz PE, Sterioff S, Mucha P, Melton LJ 3rd, Offord KP. Postsplenectomy sepsis and mortality in adults. *JAMA.* 1982; 248(18):2279-83.
16. Corazza GR, Ginaldi L, Zoli G, et al. Howell-Jolly body counting as a measure of splenic function. A reassessment. *Clin Lab Haematol.* 1990; 12(3):269-75.
17. Brigden ML. Detection, education and management of the asplenic or hyposplenic patient. *Am Fam Physician.* 2001;63(3):499-506, 508.
18. Ciclitira PJ, Dewar DH, McLaughlin SD, Sanders DS. The management of adults with coeliac disease. 2010. Available from <http://www.bsg.org.uk/sections/small-bowel-nutrition-articles/bsg-guidance-on-coeliac-disease-2010.html>.
19. Khan J, Jennings A, Subramanian S. OC-021 a retrospective audit of pneumococcal & influenza vaccination in coeliac disease. *Gut.* 2013;62 (suppl 1):A9-10.
20. McKinley M, Leibowitz S, Bronzo R, Zanzi I, Weissman G, Schiffman G. Appropriate response to pneumococcal vaccine in celiac sprue. *J Clin Gastroenterol.* 1995;20(2):113-6.
21. Tomczyk S, Bennett NM, Stoecker C, et al. Use of 13-valent pneumococcal conjugate vaccine and 23-valent pneumococcal polysaccharide vaccine among adults aged  $\geq 65$  years: Recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR Morb Mortal Wkly Rep.* 2014;63(37):822-5.