

CASE REPORT

Open Access



Delayed cystic fibrosis diagnosis due to presumed celiac disease-A case report from Syria

Yahia Ranjous^{1*}, Abdulrahman Al Balkhi¹, Nazir Alahmad², Ali Asaad² and Ayman Ali²

Abstract

Background This case report describes a cystic fibrosis case after 7 years of a presumed diagnosis of celiac disease without confirming laboratory tests and biopsies. Both cystic fibrosis and celiac disease cause malnutrition, malabsorption, and failure to thrive. Also, the occurrence of cystic fibrosis in celiac disease patients is higher than in the normal population. Therefore, the differentiation between the two diseases might be challenging. This article highlights the reason for the confusion between cystic fibrosis and celiac disease and emphasizes the importance of not skipping the necessary investigations no matter how difficult it is to perform them.

Case presentation This report details the case history of a patient presumed to have celiac disease for 7 years without confirming investigations. He developed multiple respiratory infections and weight loss throughout the 7 years but was only diagnosed with cystic fibrosis after hospitalization for gradual abdominal distension and productive cough. Chest CT showed atelectasis in the right upper lobe, tree-in-bud sign on both sides, and right periumbilical mass with several enlargements in the mediastinal nodes. Ascites paracentesis revealed a high SAAG gradient and low-protein fluid. The sweat chloride test resulted in a chloride level of 90 mEq/L, which confirmed the cystic fibrosis diagnosis. Subsequent genetic testing revealed the rare G85E mutation.

Conclusion This report highlights the potential for diagnostic confusion between cystic fibrosis and celiac disease. Also, it reminds physicians about the importance of taking a detailed medical history and performing the essential investigations no matter how difficult it is to do them. Finally, it emphasizes the need to verify the patient's previous medical history in case there is no official documentation of his case. This should be considered particularly in rural areas in low-income countries where the possibility of medical malpractice should not be forgotten.

Keywords Cystic fibrosis, Celiac disease, Misdiagnosis

*Correspondence:

Yahia Ranjous
yahran2@gmail.com

¹Faculty of Medicine, Damascus University, Damascus, Syria

²Gastroenterology Department, Faculty of Medicine, Damascus University, Damascus, Syria



© The Author(s) 2023. **Open Access** This article is licensed under a Creative Commons Attribution 4.0 International License, which permits use, sharing, adaptation, distribution and reproduction in any medium or format, as long as you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons licence, and indicate if changes were made. The images or other third party material in this article are included in the article's Creative Commons licence, unless indicated otherwise in a credit line to the material. If material is not included in the article's Creative Commons licence and your intended use is not permitted by statutory regulation or exceeds the permitted use, you will need to obtain permission directly from the copyright holder. To view a copy of this licence, visit <http://creativecommons.org/licenses/by/4.0/>. The Creative Commons Public Domain Dedication waiver (<http://creativecommons.org/publicdomain/zero/1.0/>) applies to the data made available in this article, unless otherwise stated in a credit line to the data.

Background

Cystic Fibrosis (CF) is an autosomal recessive disease caused by a mutation in a gene on chromosome 7. This gene encodes a transmembrane protein called CFTR, which functions as a chloride channel [1]. CF is a multi-organ disease that manifests mainly with recurrent pulmonary infections, meconium ileus, malnutrition, and failure to thrive [2]. This disease is relatively rare in the middle east, and the approximate prevalence is about 1 in 30,000 to 1 in 50,000 [3], [4].

On the other hand, celiac disease (CD) is an autoimmune disorder that is triggered by gluten, a protein mainly found in wheat [5]. The main symptoms of CD are diarrhea and malabsorption [6]. Celiac disease prevalence in Syria is about 1.5% [7].

The two aforementioned diseases share similar features and were not distinguished from each other until 1938 [8]. It was noticed then on autopsy that some patients who were supposed to have celiac disease had pancreatic fibrosis [9]. Both CF and CD cause malnutrition, malabsorption, and failure to thrive. Also, the occurrence of CD in CF patients is 2–3 times higher than in the normal population [10]. Moreover, having CD might elevate sweat electrolytes, leading to a false positive CF diagnosis [11]. Therefore, distinguishing between CD and CF could be challenging. These difficulties are more notable in poor areas at times of crisis where necessary investigations are not always available. In this case report, we report a case of a 16-year-old male who was diagnosed with cystic fibrosis after 7 years of a false diagnosis of celiac disease without confirming laboratory tests and biopsies.

Case presentation

A 16-year-old male was diagnosed with celiac disease 7 years ago. This was a clinical diagnosis based on clinical symptoms of steatorrhea and malnutrition. No serology or duodenal biopsy was performed due to the lack of resources at times of crisis. The patient was put on an experimental celiac disease gluten-free diet but he did not adhere to it. During these 7 years, steatorrhea persisted and the child had associated progressive weight loss. Also, he was repeatedly hospitalized for respiratory infections.

At the present time, he was referred to Assad University Hospital after a 2-week history of gradual abdominal distension and fever. He had a productive cough with yellow sputum for ten days and second-grade dyspnea. On the physical examination, the patient had pallor, clubbing, and pitting edema. He weighed 40 kg, his height was 150 cm, and with BMI=17.7 Kg/m². Abdominal examination showed generalized tenderness and shifting dullness. On the lung examination, there was generalized wheezing in the two lungs, prolonged exhalation, and dullness

in the right apex pulmonis. Groin, chest, and armpit hair were absent, with Tanner stage=1. Laboratory evaluation showed: hemoglobin 9.9 g/dL; total protein 5 g/dL; albumin 2.8 g/dL; ALT 81 IU/L; AST 98 IU/L; ALP 320 IU/L; total bilirubin 2 mg/dL; direct bilirubin 1.6 mg/dL; PT 31%; INR 2,4; Total IgA 580 mg/dL; TTG IgA negative. Chest X-ray revealed opacity in the right apex pulmonis with bilateral interstitial alveolar infiltrates. A computed tomography scan (CT) of the abdomen showed a moderate amount of fluid, severe heterogeneity of the hepatic tissue, and a small-sized pancreas with fatty infiltrations. On chest CT, we found atelectasis in the right upper lobe, tree-in-bud sign on both sides, and right periumbilical mass with several enlargements in the mediastinal nodes. Ascites paracentesis showed a high SAAG gradient and low-protein fluid. Esophagogastroduodenoscopy showed esophageal varices <5 mm. Duodenal biopsies did not show atrophy or inflammation. While stomach biopsies showed mild chronic nonspecific inflammation. On bronchoscopy, there were massive purulent discharges that plug the right bronchus. Samples were taken to culture after suctioning the plugging discharges. TTG IgA negative result and negative findings in biopsies ruled out the former presumed celiac disease. The sweat chloride test resulted in a chloride level of 90 mEq/L, which confirmed the CF diagnosis. Steatorrhea improvement with pancreatic enzyme replacement therapy and the small-sized pancreas confirmed exocrine pancreatic insufficiency. Subsequent genetic testing revealed the rare G85E mutation. The patient's health improved with treatment and he was discharged after recovery. Later, he was hospitalized again because of another pulmonary infection, resulting in respiratory failure and death.

Discussion and conclusions

The differentiation between CF and CD can be challenging for many reasons. Firstly, both CD and CF cause malnutrition. Secondly, there is a coexistence possibility of the two diseases [10]. Finally, CD can elevate sweat electrolytes mimicking CF [11]. However, with a precise medical history and investigations, the final diagnosis can be made.

Total IgA and IgA tissue transglutaminase (tTG) should be tested in the serum to diagnose a patient with suspected CD. If the result is positive, then duodenal biopsies are necessary to confirm the diagnosis [12]. Also, HLA genetic testing can be useful in some rare specific cases [13], [14].

On the other hand, the first investigation in suspected CF patients is the sweat chloride test. If the test result is $\geq 60\text{mmol/L}$, then the diagnosis is confirmed. And if it is $\leq 29\text{mmol/L}$, CF diagnosis is excluded. However, further study is required if the result is indecisive between 30 and 59 mmol/L [15].

The coexistence of the two diseases is well-known, and many studies showed a higher prevalence of CD in CF patients [16], [17], [18]. Imrei, M. et al. showed that the CD prevalence in CF patients is about two times higher than in the general population. Therefore, they recommended routine screening for CD in CF patients [19].

The first investigation in suspected CF patients is the sweat chloride test. Thus, many cases that cause abnormality in sweat electrolytes, such as CD, could be diagnosed by mistake as CF [11], [20], [21]. If it is difficult to screen CF patients for CD because of a lack of resources, doctors should at least keep in mind the coexistence of CD and CF and the possibility of a false positive sweat chloride test. Thus, any CF patient whose malnutrition does not get better with CF treatment will be tested for CD and other potential causes [16], [22].

Many mutations can affect the CFTR gene and cause cystic fibrosis [1]. Jarjour RA et al. study about CF mutations prevalence in Syria has shown that the G85E mutation in our patient is relatively rare, with only 4% prevalence in CF patients [23]. This missense mutation causes a replacement of glycine by glutamic acid at amino acid 85 [24]. It is classified as a class II mutation. This reduces CFTR molecules reaching the cell surface because of premature degradation by the endoplasmic reticulum [25]. Clinically, patients with G85E mutation have a more severe phenotype. They have a higher prevalence of pancreatic insufficiency and liver cirrhosis, worse BMI, and more frequent failure to thrive at diagnosis [26].

Our case differs from the previous literature in the absence of CD despite a false diagnosis with it based on clinical features without confirming serum tests and biopsy. The uncommon cystic fibrosis disease which had all the typical clinical features from the beginning was wrongly labeled something else. And finally, when the diagnosis was made, it was too late for the child. The reason for this lack of specialist care could be partially attributed to the war and crisis in Syria that made it difficult to get medical healthcare, especially in rural areas.

In conclusion, this case reminds us of the importance of taking a detailed medical history and checking previous investigations that the patient has done. Essential investigations should not be skipped no matter how difficult it is to do them. Also, it emphasizes the importance of verifying the previous diagnoses that the patient says he has if there were no confirming investigations or official documentation of his previous admittances to hospitals. This should be considered particularly in times of war and crisis. Finally, in places where CD is not routinely screened in CF patients, it should be kept in mind if the patient does not respond properly to CF treatment.

List of Abbreviations

| | |
|-----|-----------------|
| CF | Cystic fibrosis |
| CD | Celiac disease |
| BMI | Body mass index |

Acknowledgements

The authors would like to thank the patient's parents for consenting to publish their son's case.

Author Contribution

YR, AAB, NA AIA, AyA took part in writing the manuscript. All authors read and approved the final manuscript.

Funding

The authors did not receive funding for this paper.

Data Availability

The laboratory tests and imaging results are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

We got written informed consent from the patient's parents to publish this article.

Competing interests

The authors declare that they have no competing interests.

Authors' information

Not applicable.

Received: 20 January 2023 / Accepted: 31 March 2023

Published online: 11 April 2023

References

- Chen Q, Shen Y, Zheng J. A review of cystic fibrosis: Basic and clinical aspects. *Animal Model Exp Med*. 2021 Sep 16;4(3):220–232. <https://doi.org/10.1002/ame2.12180>. PMID: 34557648; PMCID: PMC8446696.
- Radlović N. Cystic fibrosis. *Srp Arh Celok Lek*. 2012 Mar-Apr;140(3–4):244–9. PMID: 22650116.
- Hammoudeh S, Gadelhaq W, Hani Y, Omar N, Dimassi D, Elizabeth, Cynthia, Pullattayil S, Kareem A, Chandra, Prem, Janahi, Ibrahim. The epidemiology of cystic fibrosis in Arab Countries: a systematic review. *SN Compr Clin Med*. 2021;3:1–9. <https://doi.org/10.1007/s42399-021-00756-z>.
- Banjar H, Angyalosi G. The road for survival improvement of cystic fibrosis patients in arab countries. *Int J Pediatr Adolesc Med*. 2015 Jun;2(2):47–58. <https://doi.org/10.1016/j.ijpam.2015.05.006>. Epub 2015 Jun 19. PMID: 30805437; PMCID: PMC6372404.
- Caio G, Volta U, Sapone A, Leffler DA, De Giorgio R, Catassi C, Fasano A. Celiac disease: a comprehensive current review. *BMC Med*. 2019 Jul 23;17(1):142. <https://doi.org/10.1186/s12916-019-1380-z>. PMID: 31331324; PMCID: PMC6647104.
- Adam MP, Everman DB, Mirzaa GM, Pagon RA, Wallace SE, Bean LJH, Gripp KW, Amemiya A, editors, editors. *GeneReviews®* [Internet]. Seattle (WA):University of Washington, Seattle;1993–2023. PMID: 20301295.
- Challor MH, Jouma M, Sitzmann FC, Seferian V, Shahin E. Prevalence of asymptomatic celiac disease in a syrian population sample. *JABMS*. 2004;6:155–60.
- Davis PB, Respir Crit Care Med. Cystic fibrosis since 1938. *Am J*. 2006 Mar 1;173(5):475 – 82. <https://doi.org/10.1164/rccm.200505-840OE>. Epub 2005 Aug 26. PMID: 16126935.
- Andersen DH. Cystic fibrosis of the pancreas and its relation to celiac disease: a clinical and pathologic study. *American journal of Diseases of Children*. 1938 Aug 1;56(2):344 – 99.

10. Fluge G, Olesen HV, Gilljam M, Meyer P, Pressler T, Storrösten OT, Karpati F, Hjelte L. Co-morbidity of cystic fibrosis and celiac disease in scandinavian cystic fibrosis patients. *J Cyst Fibros*. 2009 May;8(3):198–202. Epub 2009 Mar 19. PMID: 19303374.
11. Ruddy RM, Scanlin TF. Abnormal sweat electrolytes in a case of celiac disease and a case of psychosocial failure to thrive. Review of other reported causes. *Clin Pediatr (Phila)*. 1987 Feb;26(2):83–9. <https://doi.org/10.1177/000992288702600205>. PMID: 3802695.
12. Walker MM, Ludvigsson JF, Sanders DS. Coeliac disease: review of diagnosis and management. *Med J Aust*. 2017 Aug 21;207(4):173–178. <https://doi.org/10.5694/mja16.00788>. PMID: 28814219.
13. Raiteri A, Granito A, Giamperoli A, Catenaro T, Negrini G, Tovoli F. Current guidelines for the management of celiac disease: A systematic review with comparative analysis. *World J Gastroenterol*. 2022 Jan 7;28(1):154–175. <https://doi.org/10.3748/wjg.v28.i1.154>. PMID: 35125825; PMCID: PMC8793016.
14. Rubio-Tapia MD1, Hill IDMD2, Semrad CMD3, Kelly CP. MD4; Lebwohl, Benjamin MD, MSS. American College of Gastroenterology Guidelines Update: Diagnosis and Management of Celiac Disease. *The American Journal of Gastroenterology* 118(1):p 59–76, January 2023. | <https://doi.org/10.14309/ajg.0000000000002075>
15. Farrell PM, White TB, Ren CL, Hempstead SE, Accurso F, Derichs N, Howenstine M, McColley SA, Rock M, Rosenfeld M, Sermet-Gaudelus I, Southern KW, Marshall BC, Sosnay PR. Diagnosis of Cystic Fibrosis: Consensus Guidelines from the Cystic Fibrosis Foundation. *J Pediatr*. 2017 Feb;181S:S4–S15.e1. <https://doi.org/10.1016/j.jpeds.2016.09.064>. Erratum in: *J Pediatr*. 2017 May;184:243. PMID: 28129811.
16. Emiralioğlu N, Ademhan Tural D, Hizarcioglu Gulsen H, Ergen YM, Ozsezen B, Sunman B, Saltık Temizel İ, Yalcin E, Dogru D, Ozcelik U, Kiper N. Does cystic fibrosis make susceptible to celiac disease? *Eur J Pediatr*. 2021 Sep;180(9):2807–13. <https://doi.org/10.1007/s00431-021-04011-4>. Epub 2021 Mar 25. PMID: 33765186.
17. Walkowiak J, Blask-Osipa A, Lisowska A, Oralewska B, Pogorzelski A, Cichy W, Sapiejka E, Kowalska M, Korzon M, Szaffarska-Poplawska A. Cystic fibrosis is a risk factor for celiac disease. *Acta Biochim Pol*. 2010;57(1):115–8. Epub 2010 Mar 20. PMID: 20300660.
18. Sahin Y, Erkan T, Kutlu T, Kepil N, Kilinc AA, Cullu Cokugras F, et al. The frequency of celiac disease in turkish children with cystic fibrosis. *Eur J Ther*. 2019;25(1):39–43.
19. Imrei M, Németh D, Szakács Z, Hegyi P, Kiss S, Alizadeh H, Dembrovsky F, Pázmány P, Bajor J, Párniczky A. Increased prevalence of Celiac Disease in patients with cystic fibrosis: a systematic review and Meta-analysis. *J Pers Med*. 2021 Aug;28(9):859. <https://doi.org/10.3390/jpm11090859>. PMID: 34575636; PMCID: PMC8470465.
20. Shaw NJ, Littlewood JM. Misdiagnosis of cystic fibrosis. *Arch Dis Child*. 1987 Dec;62(12):1271–3. <https://doi.org/10.1136/adc.62.12.1271>. PMID: 3435163; PMCID: PMC1778647.
21. Naehrlich L, Bagheri-Behrouzi A, German. CF quality assurance group. Misdiagnosis of cystic fibrosis: experience from Germany. *J Cyst Fibros*. 2013 Jan;12(1):68–73. <https://doi.org/10.1016/j.jcf.2012.06.008>. Epub 2012 Jul 24. PMID: 22835809.
22. Genkova ND, Yankov IV, Bosheva MN, Anavi BL, Grozeva DG, Dzhelepova NG. Cystic fibrosis and celiac disease—multifaceted and similar. *Folia Med (Plovdiv)*. 2013 Jul-Dec;55(3–4):87–9. <https://doi.org/10.2478/folmed-2013-0033>. PMID: 24712288.
23. Jarjour RA, Al-Berrawi S, Ammar S, Majdalawi R. Spectrum of cystic fibrosis mutations in Syrian patients. *Minerva Pediatr*. 2018 Apr;70(2):159–164. <https://doi.org/10.23736/S0026-4946.17.04280-3>. Epub 2015 Jun 4. PMID: 26041005.
24. Chalkley G, Harris A. A cystic fibrosis patient who is homozygous for the G85E mutation has very mild disease. *J Med Genet*. 1991 Dec;28(12):875–7. <https://doi.org/10.1136/jmg.28.12.875>. PMID: 1757965; PMCID: PMC1017167.
25. Veit G, Avramescu RG, Chiang AN, Houck SA, Cai Z, Peters KW, Hong JS, Pollard HB, Guggino WB, Balch WE, Skach WR, Cutting GR, Frizzell RA, Sheppard DN, Cyr DM, Sorscher EJ, Brodsky JL, Lukacs GL. From CFTR biology toward combinatorial pharmacotherapy: expanded classification of cystic fibrosis mutations. *Mol Biol Cell*. 2016 Feb 1;27(3):424–33. <https://doi.org/10.1091/mbc.E14-04-0935>. PMID: 26823392; PMCID: PMC4751594.
26. Decaestecker K, Decaestecker E, Castellani C, Jaspers M, Cuppens H, De Boeck K. Genotype/phenotype correlation of the G85E mutation in a large cohort of cystic fibrosis patients. *Eur Respir J*. 2004 May;23(5):679–84. <https://doi.org/10.1183/09031936.04.00014804>. PMID: 15176679.

Publisher's Note

Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.