Cystic Fibrosis: Unenhanced CT Description of the Appendix in Asymptomatic Adults

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OBJECTIVE. The purpose of this study was to describe the unenhanced CT appearance of the appendix in adults with cystic fibrosis.

SUBJECTS AND METHODS. Among adults with cystic fibrosis undergoing follow-up at our hospital, 71 patients (35 women, 36 men; mean age, 33 years; range, 18–59 years) without a history of appendectomy or current abdominal pain were prospectively included in this study and underwent unenhanced abdominopelvic MDCT. Two readers coded visualization of the appendix, measured the diameter of the appendix, and described the attenuation of its contents in relation to the intestinal wall. They also coded the presence of colonic wall redundancy, pancreatic fatty replacement, and cirrhosis. Lung transplant status and *CFTR* gene mutations were recorded. Analysis of variance, linear regression analysis, Student *t* test, and Pearson test were used.

RESULTS. The appendix was detected in all patients. The mean diameter was recorded as 10.6 ± 3.5 mm. The mean diameter was larger when the appendix contained hyperattenuating material ($p = 0.001$). There was no association between diameter and the other coded CT findings ($p = 0.076$–0.466), transplant status ($p = 0.788$), or *CFTR* mutation ($p = 0.078$). In 75% of the patients, the appendix contained hyperattenuating material with a higher proportion in homozygous Δ*F508* mutation ($p = 0.029$) without any significant effect of the other CT features ($p = 0.056$–0.392), or transplant status ($p = 1.000$).

CONCLUSION. The appendix is larger in adults with cystic fibrosis than in those without it and appears hyperattenuating at unenhanced CT in 75% of patients, more commonly in those with Δ*F508* homozygous mutation.

Keywords: adults, appendix, CT, cystic fibrosis

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As the life expectancy of patients with cystic fibrosis (CF) improves—the predicted median age for survival exceeding 35 years [1]—attention is being turned toward nonpulmonary manifestations of the disease. Abdominal imaging, such as sonography and CT, is therefore increasingly performed for young adults with CF, who frequently report abdominal pain that may have various origins, such as appendiceal disease, including inflammation and abscess formation [2–6]. However, not all abdominal manifestations of CF revealed at imaging require specific treatment, because many of these manifestations correspond to normal appearances in these patients. For example, colonic wall redundancy, which can be misinterpreted as acute colonic disease, has been identified at CT of adult CF patients without acute colonic disease [7].

In people without CF, one of the chief ultrasound and CT diagnostic criteria for acute appendicitis is an increase in appendiceal diameter [8–13]. Sonography has nevertheless shown that in children and very young adults with CF, the appendix can be enlarged yet be considered normal [14, 15]. Differentiating acute appendicitis from chronic distention of the appendix in CF patients is important for avoiding unnecessary appendectomy yet can be challenging [3, 5]. Although the ultrasound appearance of the appendix in CF patients, particularly children, has been described, the CT appearance has not been reported to our knowledge [14, 15]. Moreover, this appearance could differ between adults and children with CF, preventing generalization to adults what has been reported in children. We undertook this study to describe the unenhanced CT appearance of the appendix and its possible associations in adults with CF.

Subjects and Methods

This prospective study was approved by our institutional ethics committee, and written informed consent was obtained from all patients.

Patients

Between June 2010 and October 2011, all 131 CF patients older than 18 years undergoing follow-up at our hospital were asked to participate in this study. The requests were made during a visit to the chest medicine outpatient clinic or during a hospital stay for acute respiratory exacerbation. Exclusion criteria were previous appendectomy (n = 19), previous colectomy (n = 10), abdominal pain or symptoms or signs of acute abdominal inflammatory disease (n = 3), and pregnancy (n = 1). Seven patients who had previously undergone intestinal surgery but were unsure whether they had undergone colectomy or appendectomy were also excluded. Eighteen patients who were not seen at our outpatient clinic or who were not hospitalized during the study period and two patients who died during this period were also excluded. The final study group consisted of 71 patients without symptoms (35 women, 36 men; mean age, 33 ± 10 [SD] years; range, 18–59 years). Patients recruited during their hospital stay for acute respiratory exacerbation were treated by IV antibiotic therapy and underwent abdominal CT on the first day of their stay to reasonably avoid the possible effect of antibiotics on appendiceal and periappendiceal CT features. No patient had undergone a barium or water-soluble contrast study before CT.

CT Examinations

Patients were examined in the supine position with a 64-MDCT scanner (Sensation 64, Siemens Healthcare) under the direct supervision of a board-certified radiologist. A frontal scout-view image was obtained at 80 kVp and 35 mA. This scout-view image was followed by a helical scan from the top of the liver to the upper aspect of the pubis. Individual detector collimation was 0.6 mm; tube rotation time, 0.5 second; and pitch, 1. The default effective tube current–time product was set at 90 mAs and the tube potential at 120 kVp with automatic exposure control (CARE Dose 4D, Siemens Healthcare) switched on. With these parameters, the mean absorbed radiation dose (expressed as volume CT dose index) was 4.0 ± 0.7 mGy (range, 2.8–6.6 mGy), and the mean dose-length product (DLP) was 171 ± 36 mGy · cm (range, 112–289 mGy · cm). With a conversion factor of 0.015 mSv/mGy [16], the corresponding effective dose would be 2.6 ± 0.5 mSv. No patient received enteric or IV contrast material. From the raw data acquired, 2-mm-thick axial sections were reconstructed with a 1-mm interval and a soft-tissue algorithm (B20f, Siemens Healthcare).

Image Analysis

Reconstructed images were stored in a PACS and read at the PACS workstation with real-time multiplanar reformation display (Carestream PACS Client, version 11.1, Carestream Health) on a 3-megapixel liquid crystal display color monitor (Radiforce R31, Eizo Nanao). Readers were authorized to manipulate the window width and level as desired. Two board-certified radiologists with 6 (reader 1) and 13 (reader 2) years of experience in reading abdominal CT scans in routine clinical workflow read the CT images. They were not blinded to the diagnosis of CF.

The readers were first asked to code independently whether the appendix was visible. If the appendix was visible, the readers were asked to perform the following tasks. The first was to measure the maximal transverse outer-to-outer wall diameter of the appendix and its wall thickness, if measurable. The second step was to describe the attenuation of the predominant appendiceal content (gaseous, liquid, calcified, hyperattenuating, or isoattenuating compared with the attenuation of the appendiceal wall or adjacent intestinal walls). Content was considered predominant if it filled more than 50% of the appendiceal lumen. The readers were free to use bone windows settings to discriminate hyperattenuating from calcified content [17]. The third task was to code periappendiceal fat stranding (infiltration and increased attenuation of the immediate periappen-

TABLE 1: CT Findings Coded by Two Readers in Independent Readings

Finding	Reader 1	Reader 2	*p*
Appendiceal and periappendiceal CT features			
Visualization of appendix	71 (100)	71 (100)	1.000
Appendiceal diameter (mm), mean ± SD	10.4 ± 3.3	10.5 ± 3.6	1.000
Visualization of appendiceal wall	59 (83)	62 (87)	0.375
Appendiceal wall thickness (mm), mean ± SD	2.3 ± 1.1	2.3 ± 1.1	1.000
Appendiceal content			0.368[a]
Hyperattenuating	53 (75)	54 (76)	
Isoattenuating	15 (21)	15 (21)	
Gaseous	3 (4)	2 (3)	
Calcified	0 (0)	0 (0)	
Liquid	0 (0)	0 (0)	
Periappendiceal lymphadenopathy	2 (3)	1 (1)	1.000
Periappendiceal fat stranding	1 (1)	2 (3)	1.000
Other cystic fibrosis–related CT features			
Cirrhosis	7 (10)	8 (11)	1.000
Colonic wall redundancy	9 (13)	10 (14)	1.000
Fatty replacement of the pancreas (median severity score)	4	4	1.000[b]

Note—Unless otherwise indicated, data are the frequency of CT findings in a total of 71 patients; data in parentheses are calculated percentages. Also unless otherwise indicated, comparisons between proportions were made by McNemar test.

[a]McNemar-Bowker test.

[b]Wilcoxon test.

diceal fat [11, 18]) and lymphadenopathy (multiple periappendiceal enlarged nodes larger than 5 mm [11]) as present or not.

The readers were also asked to score the severity of fatty replacement of the pancreas according to a 5-point scale [19] (0, normal; 1, less than 25% of the pancreatic volume replaced by fat; 2, 25–50% replaced by fat; 3, 50–75% replaced by fat; and 4, more than 75% replaced by fat) and to record the presence of colonic wall redundancy as described by Webb et al. [7] (inner colonic wall with overlapping folds or with a doubled appearance of the wall independent of colonic haustra) and cirrhosis (nodular hepatic contour, enlarged caudate lobe, enlarged lateral segment of left lobe, atrophy of the right and quadrate lobes, and signs of portal hypertension) [20]. Immediately after each independent reading, readers were asked to report whether they agreed on identifying the same anatomic structure as the appendix. Thereafter they were asked to code in consensus the same features as those coded independently.

Clinical Data Collection

Data were collected by a medical student near completion of medical school who was not involved in image reading. By reviewing the medical charts, he recorded the type of *CFTR* gene mutations (Δ*F508*/Δ*F508*, Δ*F508*/non Δ*F508*, non Δ*F508*/non Δ*F508*, Δ*F508*/unknown, unknown/unknown) and lung transplant status. He also recorded clinical follow-up information to exclude development of acute appendicitis and/or right lower quadrant pain in the month after the CT examination.

Statistical Analyses

Continuous quantitative variables were summarized by mean and SD. Proportions were compared by Pearson, McNemar, and McNemar-Bowker tests. Medians of pancreatic fatty replacement scores according to reader were compared by Wilcoxon test, and appendiceal content by Kruskal-Wallis test. Analysis of variance followed by Sidak multiple comparison tests if appropriate were used to compare the means of the quantitative continuous variables. Mean appendiceal diameter in CF patients was compared with the highest value of mean appendiceal diameter reported in adults without acute appendicitis [21] by Student *t* test of conformity. Linear regression analysis was used to evaluate the relation between diameter and age. Statistical significance for all tests was set at $p < 0.05$. The statistical software used was SPSS Statistics 20 (IBM SPSS).

Results

No patient had right lower quadrant pain during the month after the CT examination.

Appendiceal and Periappendiceal CT Findings

Both readers visualized the appendix in all patients, and both identified the same structure as the appendix in all patients. CT findings coded by the two readers are summarized in Table 1. Because their results were homogeneous without any statistically significant difference between their findings (p = 0.368–1.000), we further considered only the results of their consensus reading for describing the appearance of the appendix and looking for possible associations.

According to consensus reading, the mean appendiceal diameter was 10.6 ± 3.5 mm, statistically significantly greater than the largest mean diameter reported in adults without CF and without acute appendicitis (6.6 mm; $p < 0.001$) [21]. Appendiceal wall was detectable in 62 (87%) patients with a mean wall thickness of 2.3 ± 0.9 mm.

Appendiceal content was interpreted as predominantly hyperattenuating in 53 (75%) patients, isoattenuating in 15 (21%) patients, and gaseous in three (4%) patients. No patient had predominantly calcified or liquid content. Enlarged and hyperattenuating appendixes are shown in Figures 1 and 2. Periappendiceal lymphadenopathy was seen in three (4%) patients, and no patient had periappendiceal fat stranding.

Associations Between Appendiceal CT Findings and Other Features of Cystic Fibrosis

Among the 71 patients included in this study, 28 (39%) had undergone lung transplant. The common Δ*F508 CFTR* mutation was the predominant mutant allele, occurring in 30 (42%) patients who were homozygous for the Δ*F508 CFTR* mutation. Forty-

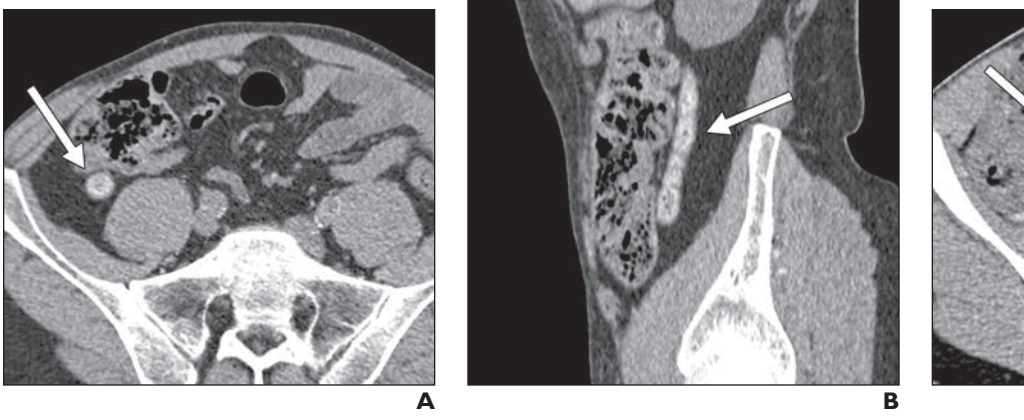

Fig. 1—50-year-old man with cystic fibrosis and no abdominal pain.
Transverse (**A**) and sagittal (**B**) unenhanced CT reformations show enlarged appendix (*arrow*) with hyperattenuating content.

Fig. 2—21-year-old woman with cystic fibrosis and no abdominal pain. Unenhanced oblique CT reformation shows enlarged appendix (*arrow*) with hyperattenuating content in its long axis and visible appendiceal walls.

one (58%) patients were heterozygous for the Δ*F508 CFTR* mutation (35 patients, Δ*F508*/non Δ*F508*; four patients, non Δ*F508*/non Δ*F508*; two patients, Δ*F508*/unknown; and no patient unknown/unknown).

Pancreatic fatty replacement was seen in 59 (83%) patients, 44 of them having the highest severity score. Among all patients, the median severity score of fatty replacement was 4. Cirrhosis was found in seven (10%) patients and colonic wall redundancy in 11 (15%) patients, eight of them (73%) being homozygous for Δ*F508 CFTR* mutation.

Appendiceal diameter was not related to *CFTR* homozygosity, lung transplant status, or other CT findings except appendiceal content (Table 2). The mean diameter was statistically significantly larger when the appendix contained hyperattenuating material than it was when it contained isoattenuating material (11.5 ± 3.4 mm vs 7.9 ± 2.2 mm; $p = 0.001$, Sidak test). Appendiceal diameter was not related to patient age ($p = 0.799$), whereas appendiceal content was: Patients with hyperattenuating appendiceal content were younger (mean age, 31 ± 9 years) than those with isoattenuating (mean age, 39 ± 10 years) and gaseous (mean age, 39 ± 8 years) content ($p = 0.017$). In addition, the proportion of patients whose appendix contained predominantly hyperattenuating material was statistically significantly greater in Δ*F508* homozygous patients than in heterozygous patients (Table 3). Appendiceal content, however, was not related to lung transplant status or other CF-related CT findings (Table 3).

TABLE 2: Mean Appendiceal Diameter as a Function of Genetics, Transplant Status, and Other CT Findings

Characteristic	No. of Patients	Diameter (mm)[a]	*p*
CFTR mutation			0.078[b]
Homozygote	30	11.5 ± 3.1	
Heterozygote	41	10.0 ± 3.6	
Lung transplant			0.788[b]
Yes	28	10.5 ± 3.5	
No	43	10.7 ± 3.5	
Appendiceal content			< 0.001[c]
Hyperattenuating	53	11.5 ± 3.4	
Isoattenuating	15	8.0 ± 2.2	
Gaseous	3	7.5 ± 1.8	
Cirrhosis			0.076[b]
Yes	7	12.8 ± 3.7	
No	64	10.4 ± 3.4	
Colonic wall redundancy			0.466[b]
Yes	11	11.3 ± 2.3	
No	60	10.5 ± 3.6	
Fatty replacement of the pancreas (severity score)			0.357[c]
0	12	10.6 ± 3.9	
1	5	9.4 ± 3.0	
2	5	9.4 ± 2.6	
3	5	8.4 ± 3.1	
4	44	11.2 ± 3.5	

[a]Mean ± SD.
[b]Student *t* test.
[c]Analysis of variance.

TABLE 3: Appendiceal Content as a Function of Genetics, Transplantation Status, and Other CT Findings

Characteristic	Hyperattenuating (*n* = 53)	Isoattenuating (*n* = 15)	Gaseous (*n* = 3)	*p*
CFTR mutation				0.029[a]
Homozygote	27	3	0	
Heterozygote	26	12	3	
Lung transplant				1.000[a]
Yes	21	6	1	
No	32	9	2	
Cirrhosis				0.248[a]
Yes	7	0	0	
No	46	15	3	
Colonic wall redundancy				0.392[a]
Yes	10	1	0	
No	43	14	3	
Fatty replacement of the pancreas (median severity score)	4	4	0	0.056[b]

Note—Data are number of patients unless otherwise indicated.
[a]Pearson chi-square test.
[b]Kruskal-Wallis test.

Discussion

The findings of our study show that a normal appendix in adults with CF is larger than that in adults without CF, that appendiceal content appears hyperattenuating in 75% of CF patients, that appendiceal content is more frequently hyperattenuating in *CFTR* homozygous patients, and that the appendix is visible on unenhanced CT images in adults with CF who do not have abdominal pain or symptoms.

Enlargement of the appendix is one of the most predictive signs of acute appendicitis at both ultrasound and CT [8–13]. The ultrasound finding of asymptomatic enlargement of an uninflamed appendix in children and very young adults with CF has been reported [14, 15]. At CT, in accordance with the findings of the previous ultrasound studies, enlargement of the appendix also should not be considered a criterion for acute appendicitis in adult CF patients, particularly if the appendix contains hyperattenuating material. In adults without CF, periappendiceal fat stranding is the other CT sign highly predictive of acute appendicitis [10–13]. However, we have found that periappendiceal features—fat stranding in particular—are uncommon in CF patients without abdominal pain or symptoms. Periappendiceal fat stranding, therefore, may be a valuable CT criterion for acute appendicitis in CF patients, as previously suggested in ultrasound studies [14, 15].

The possible relation between appendiceal diameter and patient age has been investigated by Menten et al. [14], who found no difference in appendiceal diameter in patients younger than 15 years and those older than 15 years. Similarly, for our patients—all of whom were older than 18 years—patient age was also not related to appendiceal diameter. There was, however, a relation between appendiceal content and age whereby patients with hyperattenuating content were younger than those with any other form of appendiceal content. We also found that the proportion of appendix containing hyperattenuating material was higher in homozygous Δ*F508*/Δ*F508* patients than in heterozygous patients, possibly reflecting the greater expression of disease in these patients. The severity of CF and its rate of progression in the involved organs vary considerably, and the nature of mutations may determine the phenotypic expression of the disease. For example, a strong relation between the severity of the digestive aspect of CF and Δ*F508* mutation, in particular pancreatic insufficiency in homozygous Δ*F508*/Δ*F508* patients, has been reported [22].

The appendix was visualized in all patients, even with the low radiation dose as we used. Joo et al. [23], using low-radiation-dose CT (mean dose-length product, 100 mGy · cm), had an appendix visualization rate ranging from 92.3% to 99.1% in patients without CF. They attributed this high detectability at low-dose CT to use of the sliding-slab averaging technique. We attributed the high detectability of the appendix at unenhanced CT in our study more to the hyperattenuating appendiceal content highlighting the appendix in 75% of our patients.

Other CF-related abdominal CT features were observed with similar frequencies than in previous studies. The exception was the colonic wall redundancy observed in only 15% of our patients. This frequency is quite lower than the 39% reported for adults with CF [3, 5–7, 19]. In addition, the predominant mutant allele in patients with colonic wall redundancy was *CFTR ΔF508*. This finding contradicts the results reported by Webb et al. [7], making the hypothesis of an association between *CFTR* gene mutation and colonic wall redundancy doubtful.

Our study had limitations. First, we did not recruit a control group of patients without CF because we wanted to study rather young adults without abdominal pain or symptoms. We would have had to scan young healthy adults to describe the diameter of the appendix, which is extensively reported, and thus expose them to unnecessary radiation. Consequently, the readers were not blinded to the fact that all included patients had CF, but our results were close enough to homogeneous that blinding the readers presumably would not have had any effect. In addition, the readers could not have been reasonably totally blinded given the spectrum of imaging findings typically present in CF patients. The second limitation was that we did not evaluate the consistency of appendiceal CT features over time. However, such an evaluation would have required repeated CT examinations and the subsequent increase in radiation exposure.

Third, we did not administer any iodinated IV contrast material, so we were unable to evaluate possible appendiceal wall enhancement. Because these patients had no symptoms and were susceptible to renal insufficiency, there would have been increased ethical concerns about administering such contrast material, which would challenge the kidneys. In addition, unenhanced CT performs well for visualizing the appendix and for the diagnosis of acute appendicitis [13, 24–27]. Fourth, the CT appearance of the appendix was not compared with histologic data. However, patients were symptom free, and therefore none underwent unnecessary appendectomy. This is a concern about studies of the normal appendix, as previously reported by numerous authors [15, 21, 24, 28]. We therefore also could not analyze the content of the appendiceal lumen to investigate whether its hyperattenuating appearance could be explained, at least in part, by inspissated mucus.

The last limitation was that we were not able to evaluate the possible effect of oral antibiotics on appendiceal CT features. CF patients are iteratively treated with oral antibiotics, and it is therefore impossible to recruit homogeneous groups of patients taking or not taking antibiotics. However, concerning IV antibiotic therapy, we reduced the possible effects by performing CT examinations on the first day of a hospital stay for pulmonary exacerbation. We therefore can consider the study group close to homogeneous in terms of antibiotic therapy. Interestingly, appendiceal features were not related to lung transplant status and therefore probably not to immunosuppression.

Conclusion

The appendix is larger in CF adults without abdominal pain or symptoms of abdominal inflammatory disease than it is in the population without CF, suggesting that appendiceal enlargement is not a valid CT sign of acute appendicitis in these patients. The appendiceal content appears hyperattenuating in 75% of CF patients and in a higher percentage of those homozygous for Δ*F508* mutation.

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