Are there specific endosonographic features in Crohn's patients with perianal fistulae?

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Abstract

Both 2-dimensional and 3-dimensional endoanal ultrasounds have been shown to be accurate in the definition of the anatomy of complex fistulae-in-ano in patients with perianal Crohn's disease. Recently, a Crohn's Ultrasound Fistula Sign (CUFS) has been suggested as a discriminating feature of perianal Crohn's disease as has the presence of fistulous debris and fistular bifurcation. We blindly assessed 197 patients (39 Crohn's fistulae and 158 cryptogenic fistulae) to determine if these signs differentiated fistula types. The incidence of CUFS in Crohn's cases was 17/39 (43.6%) and in cryptogenic cases was 4/158 (2.5%) (P<0.0001). The sensitivity, specificity, positive and negative predictive values and accuracy for CUFS were 43.6%, 97.5%, 80.9%, 87.5% and 86.8%, respectively. The presence of debris and fistula bifurcation in evaluable cases had a high specificity (87.2% and 81.8%, respectively) but poor sensitivity. The kappa values for or against CUFS, debris and bifurcation in Crohn's cases between 2 observers blinded to the diagnosis were 0.85, 0.72 and 0.93, respectively and in cryptogenic fistulae were 0.89, 0.85 and 0.80, respectively. The kappa values of an agreed consensus for CUFS in Crohn's disease, cryptogenic fistulae and overall with a third observer with no ultrasound experience were 0.62, 0.85 and 0.77, respectively. The presence of CUFS differentiates Crohn's-related from cryptogenic fistulae-in-ano with a high level of agreement for this sign between experienced and inexperienced observers blinded to the underlying diagnosis.

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1. Introduction

In a number of cases of Crohn’s disease, the first manifestation may be in the form of perianal fistulae.\(^1,2\) A variety of clinical findings are indicative of perianal Crohn’s disease including fleshy skin tags, cavitating ulcers and complex abscesses and fistulae, with a range of specific disease activity and classification systems.\(^3\)–\(^6\) The natural history of perianal Crohn’s disease differs from that of anal fistulae of cryptoglandular origin where the accuracy of preoperative imaging,\(^7\) in particular, enhanced magnetic resonance (MR) imaging, provides in some complicated and recurrent cases, a gold standard for outcome following surgery.\(^8\) MR imaging has also been shown to be discriminating of underlying fistula type.\(^9\) Three-dimensional endoanal sonography has shown a high accuracy for the determination of the anatomy of complex perianal fistulae\(^10\) and for the delineation of the site of the internal fistula opening.\(^11\) Recently, some have used specific endoanal ultrasonographic features to separate Crohn’s-related from cryptogenic anal fistulae with Zawadzki et al. suggesting that the presence of a hypoechoic rim with a surrounding hyperechoic region around abscesses and fistulae is a specific ultrasonographic sign of Crohn’s disease.\(^12\) This sign has been designated the Crohn’s Ultrasound Fistula Sign (or CUFS) and may represent a peri-fistula inflammatory process specific to Crohn’s disease. Further, Blom et al. have suggested that on 3-dimensional endosonography, that Crohn’s fistulae are more often bifurcating in structure, are wider than cryptogenic fistulae and tend to contain more hyperchoic debris.\(^13\) They have postulated that these fistula-specific features correlate with overall disease activity.\(^14\) This study aims to determine if 3-dimensional ultrasonographic criteria previously described are pathognomonic of Crohn’s fistula-in-ano.

2. Patients and methods

Between January 2010 and March 2012, 214 patients with perianal sepsis were assessed with 3-dimensional endosonography at the Chaim Sheba Medical Center Israel. This center acts as a tertiary referral coloproctology and inflammatory bowel disease service. All cases of Crohn’s disease were confirmed histologically with perianal fistula biopsy, enteric or colonic biopsies at endoscopy or from prior resectional specimens. All cases were examined with a ProFocus ultrasound machine (Bruel-Kjaer Medical Herlev, DK) equipped with a 2050 13 MHz rotating probe. Patients were examined by one of 3 clinicians who had a minimum of 10 years’ experience performing 3-dimensional endosonography and who performed >100 ultrasounds per annum. All 3-dimensional volume datasets were all stored on computer and were blindly analyzed retrospectively by 2 of the ultrasonographers (AZ and DC) without knowledge of the diagnosis. Discordant results were re-analyzed for a final agreed consensus on the presence or absence of CUFS. To assess whether an untrained observer without endoanal ultrasound experience could detect CUFS, a further blinding was created against the accepted diagnosis using one our colorectal residents (NH).

Fig. 1 shows a 3-dimensional image of a CUFS fistula and a cryptogenic fistula without evidence of the CUFS sign, highlighting the ultrasonographic distinguishing features between the two fistula types.

As a secondary study, a blind assessment of the presence of fistula bifurcation or secondary extension and determination as to whether the fistula was filled with hyperechoic debris was made between the 2 experienced observers on post-processing of the 3-dimensional datasets. An example of each ultrasound feature is shown in Figs. 2 and 3, respectively. All patients undergoing ultrasound with perianal Crohn’s disease were incorporated onto an electronic database permitting retrieval of the basic clinical information including, age, gender, duration of perianal Crohn’s disease, the presence of associated enteric Crohn’s disease and its duration, the history of prior anal and/or abdominal procedures, the history of prior biologic therapy and a calculation of a simplified perianal Crohn’s Disease Activity Index (PCDAI) as reported by Hughes.\(^3\) The duration of fistula symptoms and the history of prior anal surgery were recorded for the cryptogenic fistula group.
3. Statistics

Dichotomous variables were compared using the Chi-square and Fisher’s exact test where appropriate. Blinded comparisons of the presence of an agreed consensus CUFS status between the 2 experienced ultrasonographers and the observer not proficient in ultrasound were reported as sensitivity, specificity, positive and negative predictive values and accuracy. P values less than 0.05 were considered significant. Inter-observer agreement was determined using the Cohen kappa statistic.

4. Results

The study was approved by the local hospital Institutional Review Board. Of the Crohn’s disease group, (a total of 50 patients), 2 patients were excluded as review of the final histology showed ulcerative colitis, 4 cases were excluded because of anal canal distortion precluding endoanal ultrasonography, a further patient was not analyzed as a 3D dataset was missing, 3 patients were excluded because they had a rectovaginal fistula and one patient was not included because perianal disease was inactive. Analysis was therefore conducted on 39 evaluable cases. Of the cryptogenic group, (a total of 164 patients), 6 cases were excluded because 3 had inactive disease with normal endosonography, one had a rectovaginal fistula, one had a missing 3D dataset and one was a child with a cryptogenic perianal fistula where transperineal sonography only was performed. Cryptogenic fistulae were registered if there were no associated endoscopic or clinical features suggestive of underlying inflammatory bowel disease and where available if fistula histology was non-specific.

Thirty-nine patients with Crohn’s disease were analyzed (20 females, 19 males; mean age 40.5 years, range 16–79 years) and compared with 158 patients with cryptogenic fistulae (mean age 49 years; range of 23–80 years). Of the Crohn’s patients, the anatomic distribution was ileocolic in 6, colonic in 7 and mixed small bowel and colonic in 2 cases. Seventeen patients had isolated perianal disease with 7 Crohn’s cases definitively being diagnosed at the time of ultrasonography where colonoscopy and ileoscopy were indicated after performance of the ultrasound. Of these patients endoscopic and magnetic resonance enterography (MRE) work-up of the small and large bowel showed Crohn’s disease in all cases (3 ileocelecal disease and 4 colonic disease). The mean duration of cryptogenic fistulae was 2.97 months (range 0.25-68 months) with the mean number of operations being 1.23 (range 1–7). Most cryptogenic fistulae were not subjected to routine histology, although no features of Crohn’s disease were found in any patient designated with a cryptogenic fistula during follow-up (mean 14 months; range 2–48 months).

Table 1 shows the demographic features of patients with Crohn’s disease and with cryptogenic fistulae. Cases where the diagnosis was left blank by the observers were regarded as unevaluable. Table 2 shows the consensus findings between the 2 experienced observers in the diagnosis of CUFS for patients with Crohn’s disease and cryptogenic fistulae (197 cases evaluable). In the Crohn’s patients, there were 3 discordant cases. These 3 cases were discussed between the 2 experienced observers with each regarded as negative providing consensus agreement for the ultrasound diagnosis of CUFS in 17/39 cases (43.6%). In the cryptogenic cases there was one discordant case which was agreed to be negative resulting in a CUFS incidence of 4/158 (2.53%) cases (P<0.0001). Follow-up of these ‘CUFS-like’ cases showed that one had a recurrent fistula of 4 years duration who had undergone 5 separate anal procedures without relief. The other 3 cases had a fistula history of between 1–3 months. No patient had endoscopic evidence of Crohn’s disease.

Of 188 evaluable cases, the agreed incidence of debris within a fistula for Crohn’s disease and cryptogenic disease was 5/39 (12.8%) vs. 5/149 (3.4%), respectively (P=0.05) and for a bifurcating fistula between the 2 types of fistulae (190 patients evaluable) of 9/39 (23.1%) and 7/151 (4.6%), respectively (P=0.034). After agreement between the 2 observers, of the total patient group, the sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) and accuracy of the CUFS sign was 43.6%, 97.5%, 80.9%, 87.5% and 86.8%, respectively.

The presence of debris in evaluable cases resulted in a sensitivity, specificity, PPV, NPV and accuracy of 3.4%,
87.2%, 50%, 19.2% and 20.7%, respectively. The presence of a bifurcating fistula tract in evaluable cases resulted in a sensitivity, specificity, PPV, NPV and accuracy of 5.9%, 81.8%, 56.3%, 17.2% and 20.5%, respectively. Tables 3a and 3b show the inter-observer agreement for the CUFS, debris and bifurcating signs in Crohn's and cryptogenic cases, respectively where these could be evaluated. The kappa value for or against CUFS, debris and bifurcation in Crohn's cases was 0.85, 0.72 and 0.93, respectively showing substantial agreement for these individual signs. That for or against CUFS, debris and bifurcation in cryptogenic fistulae was 0.89, 0.85 and 0.80, respectively also showing a high level of agreement. The kappa value of an agreed consensus for CUFS in Crohn's disease, cryptogenic fistulae and overall with a third observer with no ultrasound experience was 0.62, 0.85 and 0.77, respectively (Table 4).

It has been suggested by Sloots et al.\textsuperscript{15} that in cryptogenic fistulae, fistula ramification is more common in recurrent cases when compared with never-operated patients. In the Crohn's cohort, bifurcation of fistulae (9 cases) was detected in 6 patients who had no prior perianal surgery. In those where there was no bifurcation, (30 cases), 15 patients had previously undergone anorectal procedures. In the cryptogenic group, where bifurcation was demonstrated (7 cases), 6 patients had not previously undergone anal surgery whereas in those where bifurcation was not detected (144 cases), 102 patients presented with never-operated fistulae.
5. Discussion

This study shows that the presence of a Crohn’s Ultrasound Fistula Sign (CUFS) is a feature of Crohn’s but not cryptogenic anal fistulae (P<0.0001). The presence of CUFS in patients without a diagnosis of Crohn’s disease was predictive of Crohn’s as a final diagnosis. There was high inter-observer agreement amongst experience ultrasonographers for the diagnosis (or diagnostic exclusion) of CUFS with a moderate sensitivity but a high diagnostic specificity, PPV, NPV and accuracy. A non-experienced observer on manipulation of the 3-dimensional datasets showed a moderate level of agreement particularly if the CUFS sign was not present. Other reported ultrasonographic features of Crohn’s disease; namely the presence of intra-fistular debris or track bifurcation had low diagnostic sensitivity but high specificity for a diagnosis of Crohn’s disease.

Confirmation of perianal Crohn’s disease was histologically based, although it accepted that frequently cryptogenic fistulae were not histologically confirmed. During follow-up of this latter group, no cases of unexpected Crohn’s disease were detected, where the mean preoperative duration of fistulous disease was very short in comparison with the Crohn’s disease cohort. By comparison with the only available CUFS study in perianal Crohn’s disease, our results have lower diagnostic sensitivity where Zawadski et al. found CUFS in 69% of Crohn’s cases. As in their study we found on follow-up that CUFS-positive cases ultimately had an endoscopic diagnosis of Crohn’s disease although our study proportionally had more isolated perianal Crohn’s patients perhaps suggesting a different pattern of disease progression. The diagnosis of CUFS will also be affected by the inherent prevalence in subgroups examined of isolated perianal disease and by the natural history of such disease progression. Equally, biases in ultrasonographic referral pattern will result where in some series only patients treated surgically will be referred whereas in other reports most patients with perianal manifestations receive ultrasound referral. Different results may also occur with different-aged patients where those Crohn’s patients less than 40 years of age are at greater risk for the development of perianal disease as are different racial subgroups. A higher incidence of referred patients with pre-existing colorectal as opposed to ileocolic disease will also affect the likelihood of attendant perianal disease and whether the perianal disease precedes other sites of bowel involvement. Further, the differential incidence of CUFS may also reflect the possibility of different subsets of Crohn’s patients also having coincident cryptogenic anal fistulae. The finding of CUFS on endoanal sonography would suggest that further investigation of the gastrointestinal tract (by colonoscopy and either CT or magnetic resonance enterography) would be mandated. The sign is relatively straightforward to diagnose on the manipulation of 3-dimensional datasets where a third inexperienced observer was readily able to diagnose when the sign was present and particularly when it was absent. In this respect, the performance of 3-dimensional ultrasound and the saving of appropriate representative datasets based on the fistula anatomy is a specific skill, however, once saved, reliable post-processing of the dataset voxel to diagnose CUFS requires minimal skills.

The finding of hyperechoic debris within a fistula or bifurcation of a complex fistula was a feature of Crohn’s disease with good specificity but relatively poor sensitivity. These findings were less common than reported by Blom et al. although in their work they used the presence of debris,

<table>
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<th>Table 3b</th>
<th>CUFS, debris and bifurcation diagnoses: inter-observer agreement (cryptogenic cases).</th>
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<tr>
<td>Observer 1</td>
<td>Yes  No  Total</td>
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<tr>
<td>Observer 2</td>
<td>Yes 4  No  4  Total 4</td>
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<td></td>
<td>Yes 1  No 153  Total 154</td>
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<td>Total 5 153 158</td>
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Debris diagnosis: inter-observer agreement (in evaluable cases) (Kappa =0.85)

| Observer 1 | Yes  No  Total |
| Observer 2 | Yes 6 1 7  Total 7 |
|          | No 1 141 142 |
|          | Total 7 142 149 |

Bifurcation diagnosis: inter-observer agreement (in evaluable cases) (Kappa =0.80)

| Observer 1 | Yes  No  Total |
| Observer 2 | Yes 7 2 9  Total 9 |
|          | No 1 141 142 |
|          | Total 8 143 151 |

Table 4 | Inter-observer agreement between inexperience observer and agreed experienced consensus for CUFS in Crohn’s and cryptogenic cases. |
<table>
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<tr>
<td>CUFS Crohn’s cases</td>
<td>Inexperienced observer</td>
</tr>
<tr>
<td>Agreed Yes 12 4 16</td>
<td></td>
</tr>
<tr>
<td>Consensus No 3 20 23</td>
<td></td>
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<tr>
<td>Total 15 24 39</td>
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<tr>
<td>(Kappa =0.62)</td>
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| CUFS cryptogenic cases | Inexperienced observer |
| Agreed Yes 3 1 4  |
| Consensus No 151 151  |
| Total 3 152 155*  |
| (Kappa =0.85) |

*3 patients were not considered evaluable by the independent inexperienced observer

| CUFS all cases | Inexperienced observer |
| Agreed Yes 15 5 20  |
| Consensus No 3 171 174  |
| Total 18 176 194  |
| (Kappa =0.77). |
fistula bifurcation and a width of the fistula exceeding 3 mm in diameter as combined discriminating features of perianal Crohn’s disease. In their study, the presence of 2 or more criteria discriminated for Crohn’s disease and correlated with a higher disease activity index, a greater number of prior fistula operations and a greater incidence of prior biologic therapy. These features were used to separate different types of Crohn’s fistulae which were more or less likely to respond to simple manoeuvres such as seton insertion where diseases was generally more active and complicated as opposed to those cases with one or none of the features more likely to have relatively inactive disease and be treated by more conventional procedures traditionally reserved for cryptogenic fistulae. Our study approached this aspect in a different way initially to determine the value of these signs which appeared less predictive of the diagnosis rather than as discriminatory features of different types of Crohn’s fistulae. Further, as post-processing measurements could not be made on 3-dimensional datasets, fistula width could not be accurately determined. It has been suggested by Sloots and colleagues that fistula ramification is uncommon in never operated cases of cryptogenic fistulae and that this may be an iatrogenic feature more of recurrent surgery. This view has also been suggested by Eisenhammer where more complicated fistulae, particularly suprasphincteric fistulae, did not occur in patients who had not previously undergone anorectal surgery for sepsis. In our cryptogenic cohort, fistula bifurcation was uncommon and most cases presented in never operated patients. By contrast, in the Crohn’s patients, half of those without bifurcation had previously undergone anorectal surgery.

Both CUFS and the ancillary features of fistula debris and bifurcation, probably represent deep chronic inflammatory activity of the fistula tract or of perianal disease as a whole although histologic correlation is awaited if these signs are confirmed in other series. These ultrasound distinguishing features of perianal Crohn’s disease remain to be validated where it is known that clinical examination can underestimate the extent of disease. The presence of these Crohn’s-related features would more likely mandate biopsy of certain perianal fistulae and the endoscopic evaluation of selected patients. Future studies will better define the natural history of different forms of perianal disease when ultrasonographically defined along with other correlates of disease activity, the clinical course and the indications for novel surgical procedures.

Conflict of interest

The authors declare in this publication that there is no conflict of interest.

References


