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WALL PLURISTRATIFICATION: A FURTHER ULTRASONOGRAPHIC SIGN OF ACUTE APPENDICITIS

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Abstract

Aim of the study was evaluate new US signs, other than the already known, that are positive correlated with histophatological results and that can improve diagnostic accuracy, in case of normal maximal outer diameter, absence of periappendicular fluid or clinical doubts

Our study is based on the diagnosis of appendicitis only with the use of UltraSonography. 373 Patients underwent UltraSonography exam, performed by 2 radiologists not sharing information between them and without knowing laboratories and clinical parameters. Out of 373, we retrospectively analyzed UltraSonographic findings related to 102 Patients who had positive pathological specimens. No one had perforated appendicitis.

For each patient, we evaluated age, sex, maximal outer diameter, ColorDoppler positivity, periappendicular free fluid and pattern stratification (from 1 to 4 layers). Statistical analysis was performed by Matlab statistical toolbox version 2008 (MathWorks, Natick, MA, USA) for Windows at 32 bit.

The most frequent stratification pattern is HYPO-HYPER-HYPO ($p<0.0001$) and is indipendent from maximal outer diameter.

Four kinds of pluristratification (HYPO-HYPER-HYPO, HYPO-HYPER-DIS, HYPO-HYPER and HYPO-DIS) have statistically significative inverse correlation with fluid presence ($p< 0.0001$).

In absence of fluid the presence of these stratification pattern can allow an appendicitis diagnosis.

The pattern stratification has no positive correlation with age or sex and is indipendent from ColorDoppler evaluation.

In conclusion, indipendently from age and sex of patients when clinical suspicion of appendicitis, expecially when maximal outer diameter and ColorDoppler signal are not conclusive and periappendicular free fluid is not present, secondary evaluation of pattern stratification can be done.

This new sign could help not only radiologists during emergency procedures, but also surgeons and clinicians in case of doubts and to further standardize the exam.

***Keywords**: abdominal pain, appendicitis, ultrasonography.*

Introduction

Acute Appendicitis (AA) is one of the most frequent reasons of acute abdomen in pediatric and young-adult population but can manifest in elderly patients, also. Excedingly rare in Asia and Africa, it is more common in western countries as well as in African Americans etnies, thus proving its dietary origin rather than genetic. In U.S.A., the lifetime risk of appendicitis is higher for males (8.6%vs.6.7 %), even if the risk of undergoing appendectomy is much higher for females (12%vs.23%), most often occurring before 30-year-old. Diagnosis is essentially clinical, supported by laboratory data and imaging, but confirmed only by surgical excision. The classical pain evolution described by Murphy occurs in only 50-60% of patients, while 30-45% have atypical clinical presentation. Therefore, imaging plays a crucial role to avoid useless appendectomies. According to the American College of Radiology, enhanced-CT is the most accurate technique in patients with right low quadrant (RLQ) pain, but ultrasonography (US) is suggested as first-line examination due to low radiation exposure, followed by CT in inconclusive cases [1 – 3].

Previous-published papers underline CT supremacy versus US in terms of sensitivity and diagnostic accuracy [4]; contrary, "there is no significant difference in predictive values of CT and sonography" [5]. Further studies indicate well-performed US such useful as CT in suspected AA [6], according to graded compression an excellent specificity both in children and adults. For this reason, additional CT is unnecessary if AA is precisely diagnosed on US [7, 8].

In a pediatric meta-analysis, Zhang et al. assessed that US, CT and MRI have almost the same diagnostic accuracy [9], endorsing US as the gold-standard in children.

Although much has been already stated on the role of US in AA, to our knowledge no study focused on appendicitis walls echogenicity and the resulting stratification type has been published, yet [10].

In some cases, clinical and laboratory exams orient to an appendicitis, even if a negative radiological exam could create (legal) problems if a surgical complication occurs.

Then, the analysis of about one hundred of patients with histological proven appendicitis could help to define further ultrasonographic signs in the diagnosis also in case of regular maximal outer diameter, absence of peri-appendicular fluid or in case of clinical suspicion.

Methods

Between January 2010 and December 2016, 373 patients with right lower quadrant pain and suspected for acute abdomen underwent abdominal US with the graded compression technique using Esaote MyLab Class C with convex (3.5-5 MHz) and linear (4-13 MHz) probes.

Two radiologists (18y and 10y experience in abdominal US imaging and blinded to each other) analyzed retrospectively all images filed in PACS archive.

US examination was performed at different timing and when radiologists matched, surgical consulting was obtained. Together with graded compression, some modalities to improve appendix visualization were taken, as described in previous published papers [11].

During US examination gallbladder, right kidney, right side of the colon and pelvis were explored to exclude possible causes of RLQ pain other than appendicitis. Intussusception, Meckel diverticulum, abdominal hernia, diverticulitis, Amyand hernia, ileopsoas abscess, omental infarction, ovarian cyst, testicular torsion, nephrolithiasis, cholecystitis, chronic pancreatitis, gastroenteritis and inflammatory bowel disease were also excluded [12–15].

When appendix was not immediately visualized despite all above-mentioned operations/precautions, a new US was performed after short time (6-12-36 h), until appendix was sufficiently evaluated by both radiologists [16, 17].

Patients and imaging analysis

In all patients with proven histological result of appendicitis, these features were analyzed:

Age, sex, maximal outer diameter (MOD), ColorDoppler positivity, peri-appendicular free fluid, appendiceal wall stratification (no. of layers and echogenicity: hypo, hyper, disomogeneous).

Statistical analysis

The statistical analysis was performed by Matlab statistical toolbox version 2008 (MathWorks, Natick, MA, USA) for Windows at 32 bit. Data are presented as number and percentages for categorical variables and continuous data were expressed as mean ± standard deviation (SD), unless otherwise specified. The chi-square test and Yates's continuity correction or Fisher's exact test, were performed to compare the differences between two percentages or proportions for unpaired data and multiple comparison chi-square test with residual analysis and Z-test were performed to compare the differences among more percentages or proportions and to locate the higher or lowest significant differences into group. Univariate and multivariate linear correlation analyses were performed. In addition the test on Pearson's linear correlation coefficient R was performed with T-Student test, under null hypothesis of Pearson's linear correlation coefficient R=0. All tests with p-value <0.05 were considered as significant. To define a statistical analysis on correlation among layers, we changed the qualitative variable layer in quantitative variable, assigning at different layer a score according to sonographic appearance: NO ECHO/*echogenicity absence*=0, HYPO=1, HYPER=2, DIS=3.

Results

Of 373 patients included in the study for right lower abdominal quadrant pain or acute abdomen suspicious, 102 had surgery confirmation of acute appendicitis.

53.92% were females, 46.18% were males; patients had a mean age of 23yo (SD ±14), age range 4- 86 yo.

From the analysis of wall layers, we could distinguish four classes, as shown in Table 1 and Graph 1.

The most frequent patterns were those composed by triples HYPO-HYPER-HYPO (p-value<0.0001) (**FIG.1,2**) and HYPO-HYPER-DIS (p-value=0.0041) (**FIG.3,4**).

Instead, the less frequent were the patterns composed by pairs: HYPO-HYPER (p-value=0.0056) and HYPER-HYPO (p-value=0.0294) and the single layer: HYPER (p-value=0.0021) and DIS (p-value=0.0021). Subsequently, we considered a multiple linear correlation among layers composition, i.e. *Stratification Patterns,* with *age*, *sex*, *maximal outer diameter* and *liquid presence* between the horns. In order to do this *layers composition* and *liquid presence* were represented with experimental probability distribution, such as that: 1=presence and 0=absence, while for variable *sex* we considered male=1 (success) and female=0 (failure). Eventually, for Doppler variable, we assigned a value into range (0-4), where 0=no vascularization and 4=maximum vascularization. In Table 2, we observed that all patterns with four layers were negatively correlated both univariate and multivariate analysis with variable *Sex*. The highest frequent pattern with three layers (HYPO-HYPER-HYPO) was positively correlated both univariate and multivariate analysis with variable *Liquid presence* and the lowest frequent pattern with three layers (HYPER-HYPO-DIS) was negatively correlated both univariate and multivariate analysis with variable *Sex*. Conversely, the other triple layer composition (HYPO-HYPER-DIS) was negatively correlated both univariate and multivariate analysis with variable *Liquid presence.* Patterns with two layers (HYPO-HYPER and HYPO-DIS) were positively correlated both univariate and multivariate analysis with variable *Sex* (i.e. HYPO-HYPER and HYPO-DIS (**FIG.5, 6**) were present most in gender males in comparison to females) and negatively correlated both univariate and multivariate analysis with variable *Liquid presence*. In the end the patterns with one layer (HYPER and DIS) were negatively correlated both univariate and multivariate analysis with variable *Sex.* Subsequently we considered a multiple linear correlation among each layer with *age*, *sex*, *MOD* and *liquid presence* between the horns.

Discussion

The paper deals with the radiological approach to patients with RLQ pain by considering wall stratification on US ("hypo-hyper-hypo" and "hypo-hyper-dis" pattern) even when MOD is smaller than its ambiguous cut-off. Starting from 1986 [18]**,** the trend to distinguish between primary signs[ζ] and secondary signs has endured and the MOD cut-off of 6mm has never changed, over the years. In 1994, Jeffrey proposed to measure appendix from outer wall to outer wall, with examination inconclusive with multiple measurements 5-to7mm. In 2004, Prendergast arranged the optimal cut-point to 7mm rather than 6mm [19-21]. In the meanwhile, Hussain and other authors reported that "appendix diameter greater than 6mm under compression is the most accurate US finding with high positive predictive value for diagnosis of AA" [22]. Anyway, a normal appendix can be visualized with an outer diameter >6mm due to fecal material within the lumen as showed by Simonovsky, thus considering that some early appendicitis may resolve spontaneously when confined to the appendiceal tip [23]. All patients in our series showing hypo-hyper-hypo pattern (5), hypo-hyper-dis (21), hyper-hypo-dis (8) or hypo-dis pattern (13), MOD cut-off ≥6mm was respected.

Furthermore, if applying this criterion to our series, 6 patient with histological-proved AA would have been lost at diagnosis because of MOD smaller than 6mm (4 showing HYPO-HYPER-HYPO stratification, 2 among them featuring CD signal. Therefore, MOD alone risks to increase false negatives and could be misleading for the AA diagnosis. More researches underlined the pivotal role of secondary signs [24, 25].

In 2000th, Birnbaum purposed that AA should be diagnosed in case of incompressible appendix with a transverse outer diameter ≥6mm and presence of secondary signs, such as parietal thickening and peri-appendiceal fat hyperechogenicity are proposed. Simonovsky, who analyzed the maximal thickness of a single layer in 1200 patients with US graded compression, introducing a cut-off for appendiceal maximal mural thickness of ≥3mm associated to SSs, i.e. appendicolith or fluid presence [26].

Xu et al. counted the hyperechoic peri-appendiceal fat among the layers with the peri-appendiceal fluid and mural hyperemia as a true positive sign of AA (differential vs lymphoid hyperplasia) *[18]*. The trend to assess mural thickening rather than MOD alone is explained by Je, postulating the value of 5.7mm for MOD and 2.2mm for mural thickening [27]. In recent years, also a pediatric research by Goldin suggested highest sensitivity (98.7%) and specificity (95.4%) for MOD ≥7mm or wall thickness >1.7mm, thus making US diagnostic accuracy for appendicitis closer to CT in terms of sensitivity and specificity [28, 29].

Compared with other imaging modalities, such as CT, US has the great value of reading between the layers of bowel wall (hypoechoic lamina propria and the echogenic submucosa) [17]. Therefore, MOD alone should not be considered as the most accurate criterion in US AA diagnosis, but together with other US variables, overall incompressibility and wall thickness. This is the reason why, we propose the stratification pattern (hypo-hyper-hypo or hypo-hyper-dis) as the main tool for US diagnosis, independently from MOD cut-off.

Our study points out the role of MOD versus others specific parameters such as the ones already assessed (wall thickening/free fluid).

The main limitation to this study was the single-center nature. Moreover, patients in our series never underwent CT, thus limiting comparison of US and CT findings and their possible matching [30].

Despite the target appearance has already been described in previous papers, this study shows how important and specific is the stratification pattern among US findings even in the absence of secondary signs, free abdominal fluid and/or increased appendiceal outer diameter.

Conclusion

In conclusion, independently from age and sex of patients with clinical suspicion of appendicitis, especially when maximal outer diameter and ColorDoppler are not conclusive and peri-appendicular free fluid is not present, secondary evaluation of pattern stratification can be done.

The most frequent pattern that can orient to a surgical procedure is a three layers pattern (hypo-hyper-hypo), followed by three less frequent wall composition:

- Hypo – hyper – disomogeneous
- Hypo-hyper
- Hypo – disomogeneous.

These signs could help not only radiologists during emergency procedures, but also surgeons and clinicians that often perform abdominal ultrasonography and can help to standardize the procedure.

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Table 1. Distribution of the pattern of stratification (no of layers and echogenicity of each layer) and their percentage.

	No. of layers	ECHOGENICITY	no	%
	1	DIS	1	0,98
		HYPER	1	0,98
	2	HYPER-HYPO	4	3,92
		HYPO-DIS	13	12,75
		HYPO-HYPER	2	1,96
	3	HYPO-HYPER-DIS	21	20,59
		HYPER-HYPO-DIS	8	7,84
		HYPO-HYPER-HYPO	47	46,08
	4	HYPO-HYPER-HYPO-HYPER	5	4,90
TOT			102	

Table 2. Univariate and multivariate linear correlation analysis between Maximal Outer Diameter, Doppler, Liquid presence, Age and Sex with Stratification patterns.

Linear correlation analysis	Univariate analysis	Multivariate analysis
Parameters: layers composition	R (p-value)	Multiple linear correlation coefficient = 0.685
HYPO-HYPER-HYPO-HYPER / Age	0.016 (0.873)	$R_{partial}$ = -0.052; p-value = 0.607
HYPO-HYPER-HYPO-HYPER / Sex	**-0.669 (< 0.0001)***	**$R_{partial}$ = -0.675; p-value <0.0001 ***
HYPO-HYPER-HYPO-HYPER / MOD	0.131 (0.189)	$R_{partial}$ = 0.072; p-value = 0.483
HYPO-HYPER-HYPO-HYPER / Doppler	0.078 (0.433)	$R_{partial}$ = 0.103; p-value = 0.315
HYPO-HYPER-HYPO-HYPER / Liquid presence	-0.064 (0.523)	$R_{partial}$ = 0.139; p-value = 0.172
		Multiple linear correlation coefficient = 0.643
HYPO-HYPER-HYPO / Age	-0.044 (0.659)	Rpartial = -0.049; p-value = 0.632
HYPO-HYPER-HYPO / Sex	0.127 (0.205)	Rpartial = -0.055; p-value 0.589
HYPO-HYPER-HYPO / MOD	-0.130 (0.194)	Rpartial = -0.098; p-value = 0.337
HYPO-HYPER-HYPO / Doppler	0.179 (0.072)	Rpartial = 0.139; p-value = 0.173
HYPO-HYPER-HYPO / Liquid presence	**0.627 (< 0.0001)***	**Rpartial = 0.611; p-value <0.0001 ***
		Multiple linear correlation coefficient = 0.425
HYPO-HYPER-DIS / Age	0.091 (0.365)	Rpartial = 0.097; p-value = 0.343
HYPO-HYPER-DIS / Sex	-0.030 (0.765)	Rpartial =-0.089; p-value 0.382
HYPO-HYPER-DIS / MOD	0.087 (0.383)	Rpartial = 0.051; p-value = 0.619
HYPO-HYPER-DIS / Doppler	-0.142 (0.156)	Rpartial = - 0.105; p-value = 0.304
HYPO-HYPER-DIS / Liquid presence	**-0.393 (< 0.0001)***	**Rpartial = -0.389; p-value = 0.0001 ***
		Multiple linear correlation coefficient = 0.710
HYPER-HYPO-DIS / Age	0.154 (0.121)	Rpartial = 0.132; p-value = 0.195

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HYPER-HYPO-DIS / Sex	**-0.677 (< 0.0001)***	**Rpartial = -0.694; p-value <0.0001 ***
HYPER-HYPO-DIS / MOD	0.141 (0.157)	Rpartial = 0.068; p-value = 0.508
HYPER-HYPO-DIS / Doppler	-0.075 (0.454)	Rpartial = - 0.118; p-value = 0.245
HYPER-HYPO-DIS / Liquid presence	-0.0163 (0.871)	**Rpartial = 0.231; p-value = 0.0219 ***
		Multiple linear correlation coefficient = 0.698
HYPO-HYPER / Age	-0.118 (0.239)	Rpartial = -0.094; p-value = 0.358
HYPO-HYPER / Sex	**0.472 (< 0.0001)***	**Rpartial = 0.626; p-value <0.0001 ***
HYPO-HYPER / MOD	-0.056 (0.574)	Rpartial = -0.015; p-value = 0.882
HYPO-HYPER / Doppler	-0.041 (0.683)	Rpartial = 0.016; p-value = 0.213
HYPO-HYPER / Liquid presence	**-0.373 (0.0001) ***	**Rpartial = -0.574; p-value <0.0001 ***
		Multiple linear correlation coefficient = 0.711
HYPO-DIS / Age	-0.036 (0.719)	Rpartial = -0.026; p-value = 0.801
HYPO-DIS / Sex	**0.235 (0.0174) ***	**Rpartial = 0.494; p-value <0.0001 ***
HYPO-DIS / MOD	0.080 (0.425)	Rpartial = 0.110; p-value = 0.283
HYPO-DIS / Doppler	-0.122 (0.223)	Rpartial = -0.074; p-value = 0.466
HYPO-DIS / Liquid presence	**-0.584 (<0.0001) ***	**Rpartial = -0.676; p-value <0.0001 ***
		Multiple linear correlation coefficient = 0.136
HYPER-HYPO / Age	-0.077 (0.443)	Rpartial = -0.058; p-value = 0.573
HYPER-HYPO / Sex	0.104 (0.297)	Rpartial = 0.094; p-value = 0.355
HYPER-HYPO / MOD	-0.076 (0.448)	Rpartial =- 0.047; p-value = 0.644
HYPER-HYPO / Doppler	-0.0164 (0.879)	Rpartial = -0.013; p-value = 0.897
HYPER-HYPO / Liquid presence	0.0144 (0.886)	Rpartial = -0.012; p-value = 0.910
		Multiple linear correlation coefficient = 0.506
HYPER / Age	0.023 (0.819)	Rpartial = -0.049; p-value = 0.629
HYPER / Sex	**-0.477 (< 0.0001)***	**Rpartial = -0.476; p-value <0.0001 ***
HYPER / MOD	0.19\ (0.055)	Rpartial = 0.164; p-value = 0.106
HYPER / Doppler	-0.006 (0.952)	Rpartial = -0.024; p-value = 0.814
HYPER / Liquid presence	-0.034 (0.734)	Rpartial = 0.116; p-value = 0.255
		Multiple linear correlation coefficient = 0.225
DIS / Age	-0.001 (0.991)	Rpartial = -0.024; p-value = 0.814
DIS / Sex	**-0.210 (0.0346) ***	**Rpartial = -0.214; p-value =0.0348 ***
DIS / MOD	0.059 (0.559)	Rpartial = 0.037; p-value = 0.716
DIS / Doppler	0.044 (0.659)	Rpartial = 0.039; p-value = 0.702
DIS / Liquid presence	0.003 (0.976)	Rpartial = 0.057; p-value = 0.579

R = Pearson's linear correlation coefficient; * = significant test; R_partial = the partial correlation coefficient is the coefficient of correlation of the variable with the dependent variable, adjusted for the effect of the other variables in the model

Graph 1. Graph showing that the most frequent patternis the presence of 3 layers with hypo-hyper-hypo stratification followed by hypo-hyper-disomogeneous

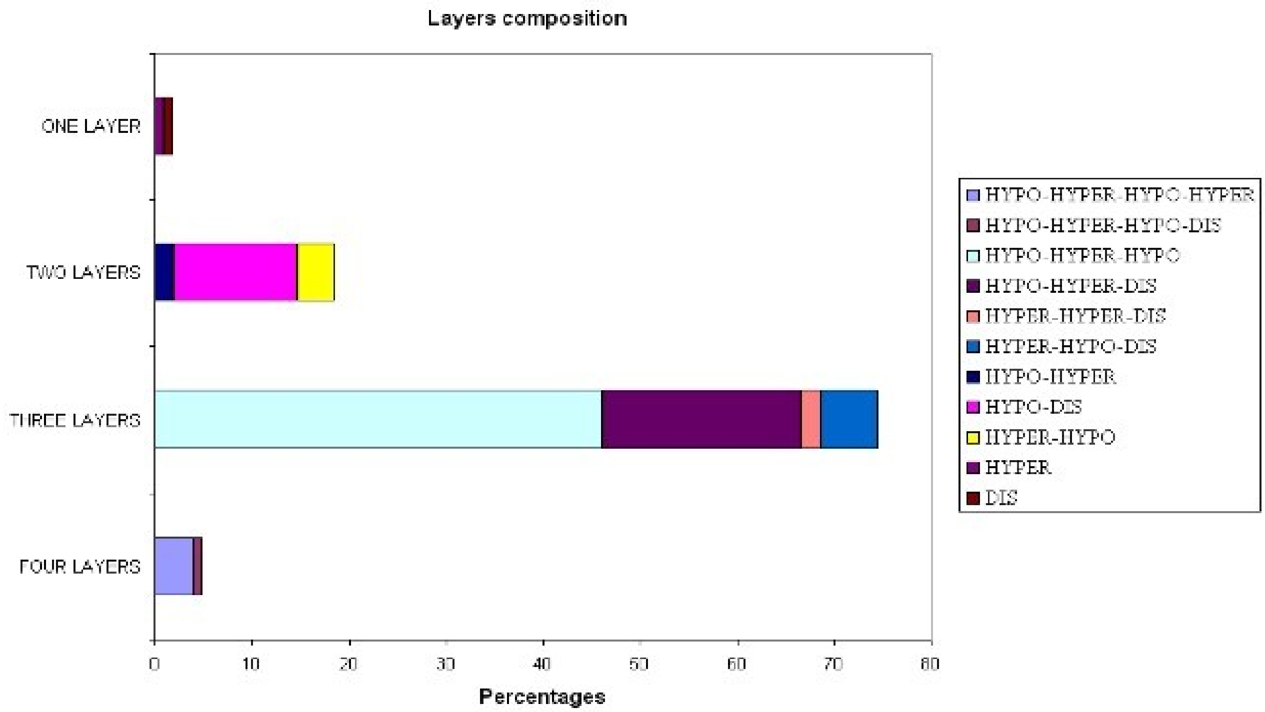

Figure 1. a-b

Female, 15 yo; MOD: 3 mm; stratification pattern: Hypo-Hyper-Hypo; Color-Doppler ** .

Figure 2. a-b-c
Male, 18 yo; MOD: 11.8 mm; stratification pattern: Hypo-Hyper-Hypo.

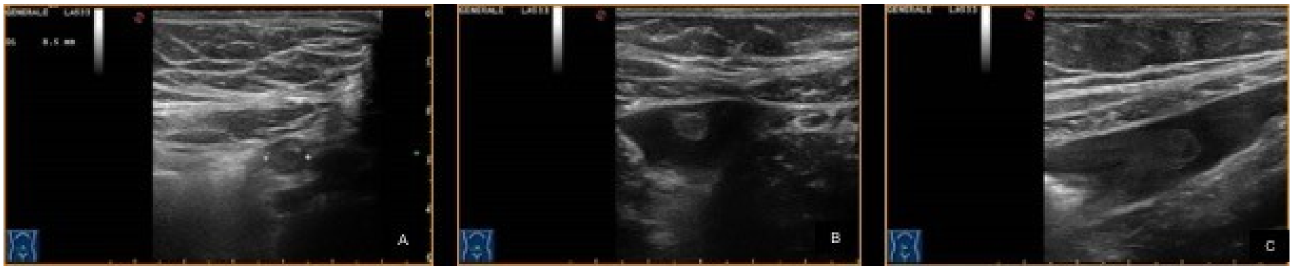

Figure 3. a-b-c
Male, 21 yo; MOD: 17 mm; stratification pattern: Hypo-Hyper-Dis.

Figure 4. a-b-c-d
Female, 6 yo; MOD: 7.6 mm; stratification pattern: Hypo-Hyper-Dis; Color-Doppler ***; SWE + .

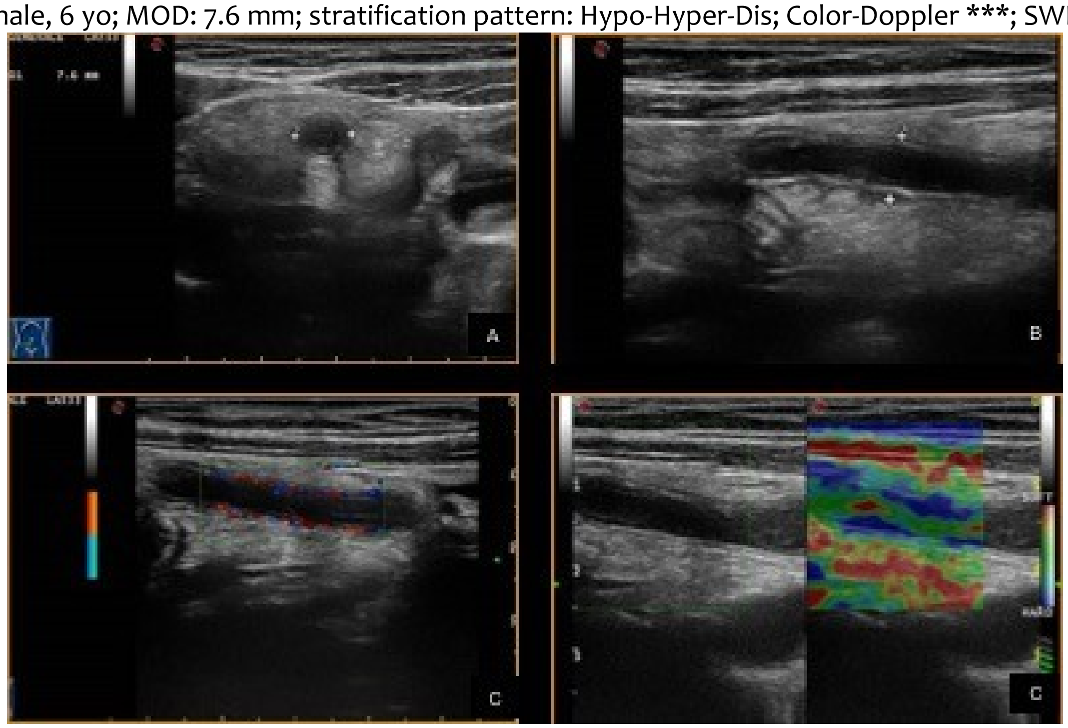

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Figure 5. a-b-c
Male, 18 yo; MOD: 18 mm; stratification pattern: Hypo-Dis; appendicolith 15 mm.

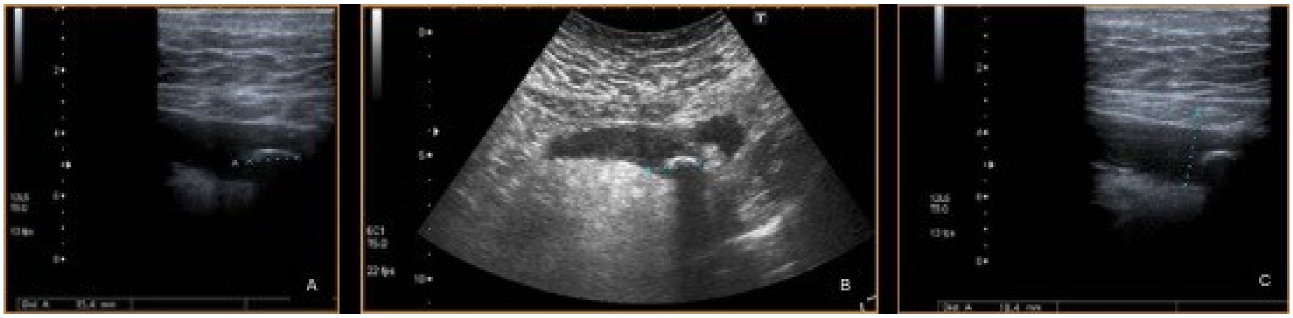

Figure 6. a-b-c-d
Male, 18 yo; MOD 11.8 mm; stratification pattern: Hyper-Hypo-Dis; Color-Doppler **** .

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