

Is Submucosal Lipomatosis of the Appendix Vermiformis Really a Rare Entity? Apendiks Vermiformisin Submukozal Lipomatozisi Gerçekten Nadir Bir Antite Mi?

Gizem AY HALDIZ¹ ¹Department of Medical Pathology, Şanlıurfa Training and Research Hospital, Şanlıurfa, TÜRKİYE

Abstract

Background: Acute appendicitis (AA) is the most common surgical emergency in patients who visit the emergency department with abdominal pain. In some of the patients who were operated with a prediagnosis of AA, lymphoid hyperplasia, fecalitis, enterobius vermicularis, carcinoid tumor, or adenoma are determined without transmural inflammation in microscopic examination. 'Submucosal lipomatosis' is also another entity that has been rarely reported in appendix localization. In this study, we aimed to determine the frequency and severity of submucosal fatty tissue (SFT) in appendectomy specimens and identify risk factors.

Materials and Methods: 293 appendectomy specimens were evaluated retrospectively. The amounts of SFT (A0: None, A1: Isolated adipocytes (Mild), A2: Small adipocyte groups (Moderate), A3: Prominent adipocyte groups (Marked), A4: Severe adipocyte groups that narrow the lumen (Severe)) and the groups that were created according to the amounts of SFT (Group 1: Cases with A1,2,3,4, group 2: Cases with A2,3,4, group 3: Cases with A3,4) were determined in hematoxylin-eosin sections.

Results: 91.47% of the cases had different amounts of SFT. Amounts of SFT were mild in 23.89%, moderate in 46.76%, marked in 18.09%, and severe in 2.73%. All of the cases without SFT were in pediatric age. It was observed that the amount of SFT increased with increasing age ($p<0.05$). As 68% of the cases without SFT were female, male predominance was observed in cases with SFT. There was a correlation between male gender and increase in the amount of SFT ($p<0.05$). AA wasn't determined in 26,28% of the cases. The AA rate in the group without SFT (20%) was marked lower than group 1 (78,73%), group 2 (82,32%), and group 3 (83,87%) ($p<0.05$). The most prominent increase in AA rate was between the group without SFT and group 1 which was the most sensitive group to the amount of SFT. When group 1,2,3 were compared, no significant increase in the AA ratio was found.

Conclusions: The presence of SFT in the appendix is a common condition. Age increase and male gender are risk factors for the accumulation of SFT. Because of SFT accumulation increases the risk of AA, it would be logical to classify it as mild/moderate/marked/severe, and accept it as 'Submucosal lipomatosis'.

Key Words: Appendicitis, Appendix, Lipomatosis

Öz

Amaç: Akut apandisit (AA) karın ağrısı ile acil servise başvuran hastalarda en sık saptanan cerrahi acildir. AA ön tanısı ile opere edilen hastaların bir kısmının mikroskopik incelemesinde transmural inflamasyon eşlik etmeksizin lenfoid hiperplazi, fekalit, enterobius vermicularis, karsinoid tümör veya adenom saptanır. 'Submukozal lipomatosis'te apendikte nadiren bildirilen bir diğer antitedir. Bu çalışmada apendektomi spesmenlerinde submukozal yağlı doku (SYD) varlığının sıklığını ve şiddetini belirlemeyi, risk faktörlerini tanımlamayı amaçladık.

Materyal ve Metod: 293 apendektomi spesmeni retrospektif olarak incelenmiştir. Hematoksilen-eozin kesitlerde SYD miktarları (M0: Yok, M1: İzole adipositler (Hafif), M2: Küçük adiposit grupları (Orta), M3: Belirgin adiposit grupları (Belirgin), M4: Lümeni daraltan adiposit grupları (Şiddetli)) ve SYD miktarlarına göre oluşturulan gruplar (Grup 1: M1,2,3,4 olan olgular, grup 2: M2,3,4 olan olgular, grup 3: M3,4 olan olgular) belirlenmiştir.

Bulgular: Olguların %91,47'sinde değişik miktarlarda SYD mevcuttur. SYD miktarları olguların %23,89'unda hafif, %46,76'sında orta, %18,09'unda belirgin, %2,73'ünde şiddetlidir. SYD içermeyen olguların tamamı pediatik yaş grubundadır. Yaş arttıkça SYD miktarının arttığı görülmüştür ($p<0,05$). SYD içermeyen olguların %68'i kadinken, SYD içeren olgularda erkek hakimiyeti izlenmiştir. Erkek cinsiyetle SYD artışı arasında korelasyon bulunmuştur ($p<0,05$). Olguların %26,28'inde AA saptanmamıştır. AA oranları SYD içermeyen grupta (%20), grup 1 (%78,73), grup 2 (%82,32) ve grup 3'e (%83,87) göre belirgin düşüktür ($p<0,05$). AA oranında en belirgin artış SYD içermeyen grup ile SYD miktarına en hassas olan grup 1 arasındadır. Grup 1,2,3 karşılaştırıldığında AA oranlarında anlamlı artış belirlenmemiştir.

Sonuç: Apendikte SYD varlığı sık görülen bir durumdur. Yaş artışı ve erkek cinsiyet SYD birikimi için risk faktörüdür. SYD birikiminin AA riskini arttırması sebebiyle hafif/orta/belirgin/şiddetli olarak sınıflandırılarak 'Submukozal lipomatosis' kabul edilmesi mantıklı olacaktır.

Anahtar Kelimeler: Apandisit, Apendiks, Lipomatosis

Corresponding Author / Sorumlu Yazar

Dr. Gizem AY HALDIZ

Şanlıurfa Eğitim ve Araştırma Hastanesi,
Patoloji bölümü, Yenice Mahallesi,
63250, Eyyübiye, Şanlıurfa,
TÜRKİYE

E-mail: gizemayhaldiz@hotmail.com

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Introduction

Appendix vermiformis is a blind bowel extension that is located in the cecum approximately 2 cm away from the ileocecal valve (1). Acute inflammation of the appendix is the most common surgical emergency (3.80%) in patients who are examined in the emergency department with abdominal pain (5.76%) (2).

Different scoring systems (Alvarado, AIR, AAS, RIPASA) that include symptoms, physical examination findings, laboratory values for diagnosis, and guideline (Jerusalem) for patient management have been established. If acute appendicitis (AA) is supported by radiology, appendectomy is recommended for patients with high risk (3). There are differences in consensus about performing the appendectomy when the appendix has a normal macroscopic appearance at the surgery. When one group argues that macroscopy can't override histopathological examination and appendectomy should be performed, the other group argues that unnecessary surgery should be avoided because of similar morbidity rates that were observed in negative appendectomies (6,3%) and uncomplicated positive appendectomies (6.9%) (4).

Although the etiology of AA isn't clearly known, obstruction of the lumen, bacterial infections, genetic, and environmental factors are blamed (5). In 36% of the patients operated with a pre-diagnosis of AA, lymphoid hyperplasia, fecalitis, enterobius vermicularis, carcinoid tumor, or adenoma were determined without transmural inflammation in microscopic examination of the appendix (4). 'Submucosal lipomatosis' is another entity that has been rarely reported in patients who were followed up or operated with pre-diagnosis of AA (6-9).

The histological layers of the gastrointestinal segments are mucosa, submucosa, muscularis propria, and serosa from inside to outside. The submucosa consists of loose connective tissue which contains blood and lymph vessels, nerve fibers belonging to the submucosal plexus, lymphoid follicles, and inflammatory cells (1). The entity called 'Submucosal lipomatosis/lipohyperplasia/lipomatous hypertrophy' is the increase of submucosal fatty tissue (SFT). It is different from lipoma that is the most common mesenchymal tumor of the colon by lack of capsule (10). It is observed in the cecum, ascending colon, sigmoid colon, transverse colon, rectum, and descending colon with decreasing rates (11). Appendix localization is rare for this entity. 'Submucosal lipomatosis of the appendix' was described histopathologically by Antonci in 1956 at first (6,8). Afterward, it has been reported as rare case reports.

On radiological imaging techniques, thickening of the appendiceal wall which is in favor of fatty tissue without periappendiceal inflammation, fluid accumulation, or lymphadenopathy is suspicious for the diagnosis (6). Hypodense homogeneous thickening (7,8) between -80 to -120 HU on CT, high intensity in T1 and T2 weighted sequences

on MRI and decreasing intensity in fat suppression sequence support fatty tissue infiltration (8). Preoperative diagnosis is important as it prevents unnecessary surgery and reduces morbidity.

Significant fatty tissue isn't expected in the submucosa of the appendix. However, varying amounts of SFT are observed in most of the appendectomy specimens by microscopic examination. We aimed to determine the frequency and severity of SFT in appendectomy specimens and identify risk factors. In this way, we hope to obtain more clear data about 'Normal histologic structure' and the diagnosis of 'Submucosal lipomatosis'.

Materials and Methods

330 appendectomy specimens that were sent to the pathology laboratory of Şanlıurfa Training and Research Hospital between 01.06.2022- 01.01.2023 were determined by scanning the pathology report archive. All clinical information and macroscopic findings were obtained from the pathology reports. The hematoxylin-eosin (H&E) sections that were prepared for routine pathological examinations were re-evaluated by one pathologist in a Nikon Eclipse E200 microscope in terms of SFT and AA. 37 cases in which the appendix wall couldn't be evaluated completely due to intense inflammation or necrotic changes were excluded.

When English literature was reviewed, no decisive SFT amount was found for the diagnosis of submucosal lipomatosis in the appendix. Therefore the criteria which was established for this study were used for evaluation. The amounts of SFT (A0: None, A1: Isolated adipocytes (Mild), A2: Small adipocyte groups (Moderate), A3: Prominent adipocyte groups (Marked), A4: Severe adipocyte groups that narrow the lumen (Severe)) (Figure 1A-E) and the groups that were created according to the amounts of SFT (Group 1: Cases with A1,2,3,4, group 2: Cases with A2,3,4, group 3: Cases with A3,4) were determined in HE sections. Cases that included at least one polymorphonuclear leucocyte in muscularis propria were accepted as AA in HE sections. When SFT started to cause AA, it was considered pathological, thus the sensitivity and specificity of the groups were calculated.

Data was analyzed by using SPSS Statistics (Version 23.0). Shapiro-Wilk test was used to determine the normality of the data. The Man-Whitney U test was used to compare two independent groups. The Kruskal-Wallis H test was used to compare more than two independent groups. The Bonferroni test was used to determine the source of the difference. The relationship between categorical variables was analyzed by the chi-square and Fisher's exact tests. $P < 0,05$ was considered statistically significant. Local ethics committee approval was obtained.

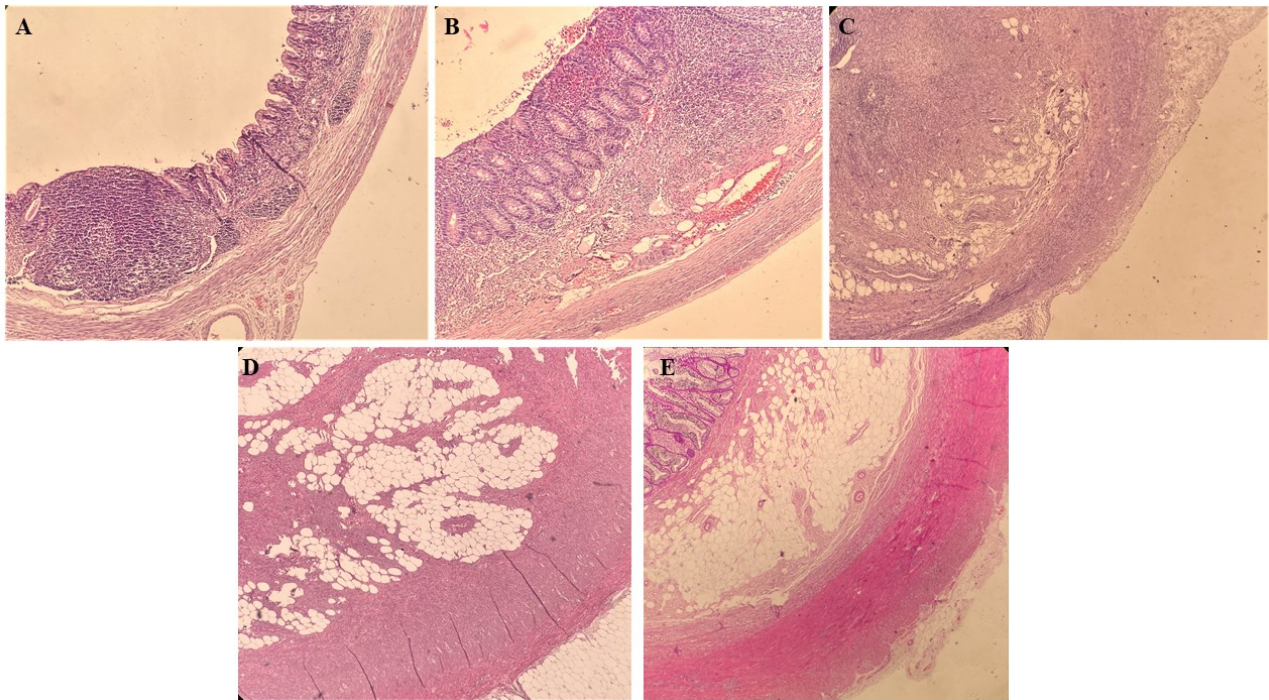


Figure 1. Amounts of the submucosal fatty tissue. **A:** None (H&E; x40). **B:** Isolated adipocytes (Mild) (H&E; x100). **C:** Small adipocyte groups (Moderate) (H&E; x40). **D:** Prominent adipocyte groups (Marked) (H&E; x100). **E:** Adipocyte groups that narrow the lumen (Severe) (H&E; x40).

Results

293 cases were included in our study. Clinical, macroscopic, and microscopic findings of the cases were given in Table 1. The groups that were created according to the amounts of SFT were given in Table 2. The relationships between the amounts of SFT with clinical and macroscopic

findings were given in Table 3.

The relationships between the amounts of SFT and the groups that were created according to the amounts of SFT with AA were given in Table 4. The sensitivity and specificity of the groups were given in Table 5.

Table 1. Clinical, macroscopic, and microscopic findings of the cases

			n	%
Age	Minimum	0		
	Maximum	79		
	$\bar{X} \pm Ss$	18,19±13,79		
Operating clinic	Pediatric surgery		179	61,09
	General surgery		114	38,91
Gender	Female		121	41,30
	Male		172	58,70
Complaint	Abdominal pain		285	97,27
	Cronic constipation		8	2,73
Appendix length	Minimum	0,5 cm		
	Maximum	13 cm		
	$\bar{X} \pm Ss$	6,34±1,87cm		
Appendix diameter	Minimum	0,2 cm		
	Maximum	3 cm		
	$\bar{X} \pm Ss$	0,93±0,48cm		
AA*	-		77	26,28
	+		216	73,72
SFT*	A0	None	25	8,53
	A1	Isolated adipocytes (Mild)	70	23,89
	A2	Adipocytes forming small groups	137	46,76
	A3	Prominent adipocyte groups (Marked)	53	18,09
	A4	Adipocyte groups narrowing the lumen (Severe)	8	2,73

AA: Acute appendicitis, SFT: Submucosal fatty tissue, *: It was determined by histopathologically, \bar{X} : Arithmetic mean, Ss: Standard deviation, n: Number, %: Percentage

Table 2. The groups which that were created according to the amounts of SFT

		n	%
Group 1	The cases with A1,2,3,4	268	91,47
Group 2	The cases with A2,3,4	198	67,58
Group 3	The cases with A3,4	62	21,16

n: Number, %: Percentage

Table 3. The relationships between the amounts of SFT with clinical and macroscopic findings

Amount of the SFT*		A0 n(%)	A1 n(%)	A2 n(%)	A3 n(%)	A4 n(%)	P Value
Age	Minimum	0	0	4	8	13	0,001
	Maximum	30	44	79	60	64	
	Median	0	10	15	27	33	
	$\bar{X}\pm Ss$	2,64±6,52	11,64±8,86	20,09±13,56	26,77±11,65	34,75±14,15	
Operating clinic	Pediatric surgery	25 (13,97) (100,00)	58 (32,40) (82,86)	80 (44,69) (58,39)	15 (8,38) (28,30)	1 (0,56) (12,50)	0,001
	General surgery	0 (0,00) (0,00)	12 (10,53) (17,14)	57 (50,00) (41,61)	38 (33,33) (71,70)	7 (6,14) (87,50)	
Gender	Female	17 (14,05) (68,00)	31 (25,62) (44,29)	57 (47,11) (41,61)	15 (12,40) (28,30)	1 (0,82) (12,50)	0,001
	Male	8 (4,65) (32,00)	39 (22,67) (55,71)	80 (46,51) (58,39)	38 (22,09) (71,70)	7 (4,08) (87,50)	
Appendix length	Minimum	1,5 cm	0,5 cm	3,0 cm	3,0 cm	5,0 cm	0,001
	Maximum	8 cm	10 cm	11 cm	13 cm	9 cm	
	Median	3,5 cm	6,5 cm	6,0 cm	7,0 cm	7,0 cm	
	$\bar{X}\pm Ss$	4,11±1,89cm	6,34±1,67cm	6,60±1,81cm	6,68±1,68cm	6,69±1,33cm	
Appendix diameter	Minimum	0,2 cm	0,3 cm	0,5 cm	0,5 cm	0,6 cm	0,001
	Maximum	1,2 cm	3 cm	3 cm	2 cm	2,30 cm	
	Median	0,4 cm	0,8 cm	1,0 cm	1,0 cm	1,0 cm	
	$\bar{X}\pm Ss$	0,45±0,25cm	0,92±0,52cm	0,98±0,48cm	1,03±0,39cm	1,09±0,52cm	

SFT: Submucosal fatty tissue, *: It was determined by histopathologically, \bar{X} : Arithmetic mean, Ss: Standard deviation, n: Number, %: Percentage

Table 4. The relationships between the amounts of SFT and the groups with AA

AA*		(-) n(%)	(+) n(%)	P value
SFT	A0	20(80) (25,97)	5(20) (2,31)	0,001
	A1	22(31,43) (28,57)	48 (68,57) (22,22)	
	A2	26(18,98) (33,77)	111(81,02) (51,39)	
	A3	8 (15,09) (10,39)	45(84,91) (20,83)	
	A4	1 (12,5) (1,30)	7(87,5) (3,24)	
Group 1	0	20 (80) (25,97)	5(20) (2,31)	0,001
	1,2,3,4	57 (21,27) (74,03)	211 (78,73) (97,69)	
Group 2	0,1	42(44,21) (54,55)	53 (55,79) (24,54)	0,001
	2,3,4	35(17,68) (45,45)	163(82,32) (75,46)	
Group 3	0,1,2	67 (29) (87,01)	164(71) (75,93)	0,041
	3,4	10(16,13) (12,99)	52(83,87) (24,07)	

AA: Acute appendicitis, SFT: Submucosal fatty tissue, *: It was determined by histopathologically, n: Number, %: Percentage

Table 5. The sensitivity and specificity of the groups

	Sensitivity*	Specificity*
Group 1	97,69%	25,97%
Group 2	75,46%	54,55%
Group 3	24,07%	87,01%

* When the SFT starts to cause AA it is considered pathological.

Discussion

Prevalence of the colonic submucosal lipomatosis has been reported as 0.2%. (9,11). In the ileocecal valve, moderate lipomatosis has been observed in 40% of the cases, and severe lipomatosis in 14% of the cases (12). In most of our cases (91.47%), we determined different amounts of SFT in the appendix. The SFT amount was prominent in 18.09% of the cases, and severe enough to narrow the lumen in 2.73%. These fatty tissues were often around thick-walled vascular structures (Figure 2A-B). In some sections, subserosal fatty

tissue was observed to reach the submucosa by dividing the muscularis propria along the vessels (Figure 3A-B). This appearance may lead to the hypothesis that the SFT accumulation originates from subserosal fatty tissue. Due to the subserosal fatty tissue amount didn't take part in our parameters, this hypothesis should be supported by further studies.

Colonic or ileocecal submucosal lipomatosis has been usually reported between 50-70 years old (11,12).

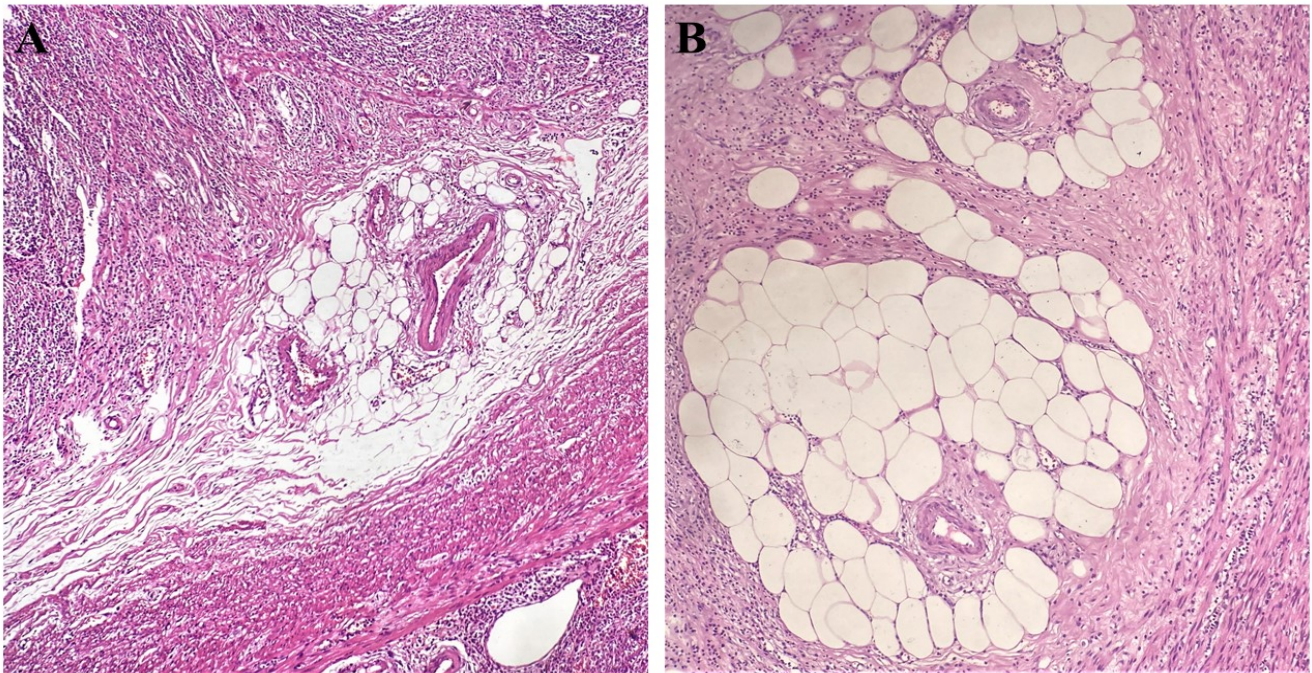


Figure 2. Submucosal fatty tissue around thick-walled vascular structures (H&E; x100)

It has been associated with high body weight (10,12). In our study, all of the cases without SFT were observed in the pediatric age and the amount of SFT increased steadily as the mean age increased ($p < 0.05$). It was thought that this situation might be caused by the increase in body mass index, blood lipids and other systemic diseases with increasing age.

Colonic or ileocecal submucosal lipomatosis has been associated with the female gender in previous studies (11,12). However, we determined female predominance in cases without SFT. Male predominance was observed in cases with SFT. There was a correlation between male gender and the increase in the amount of SFT ($p < 0.05$). It was thought that this situation might be caused by the accumulation of adipose tissue around visceral organs in the male gender and the effect of estrogen on fat metabolism in the female gender. Our study is the first study to investigate gender in appendix localization for this entity.

The amount of SFT increased steadily as the mean diameter and length of the appendix increased ($p < 0.05$). However, this was thought to be due to the fact that all of the cases without SFT were in pediatric age and the length and diameter of the appendix increased with age like other organs. It

is also usual for the diameter of the appendix to thicken when the amount of SFT increases. Şanlı et al. presented 50 years old male patient who was examined in the emergency department with acute abdominal pain. They observed thickening of the appendix wall caused by fatty tissue on CT without periappendiceal inflammation findings or lymphadenopathies. The case was accepted as lipomatosis. Oral intake was stopped. He was followed up by hydrating and then discharged without appendectomy (6). Imaging techniques can detect wall thickening of the fat component (6-8) and unnecessary surgery can be prevented when other findings of acute appendicitis don't accompanied.

In the study of Borekci et al., the fat containing ileocecal thickness was found statistically significantly higher on CT in patients with AA (13). Also in our study, when the amount of SFT increased in the appendix wall, AA rates increased regularly and AA wasn't observed in most of the cases without SFT (80%) ($p < 0,05$). Patients who were examined in the emergency department with severe abdominal pain and were operated with a prediagnosis of AA were the majority of our study (97.27%). We didn't observe AA in some of them (26,28%). However, in most of the cases without AA

(74.03%), different amounts of SFT were observed. This situation was thought that some SFT might be a component of normal histologic structure. Even if we accept a small amount of SFT without inflammation as a normal histological component, this situation showed that SFT may be symptomatic whether or not it causes inflammation. The appendix wall that is getting enlarged and stretched might cause abdominal pain without inflammation. It also should be kept in mind that the appendix wall might be stretched for another

concomitant reason or some of these cases might have inflammation in unsampled parts of the appendix. If we accept SFT as pathological when it starts to cause inflammation in the appendix wall, group 1 had the highest sensitivity but low specificity about catching AA. Group 1 was the most sensitive group to the amount of SFT. When the amount of SFT that accepted pathological rose (Group 2,3), specificity increased but sensitivity decreased. As a result, when group 1,2,3 were compared, the increase in the AA ratios wasn't found significant.

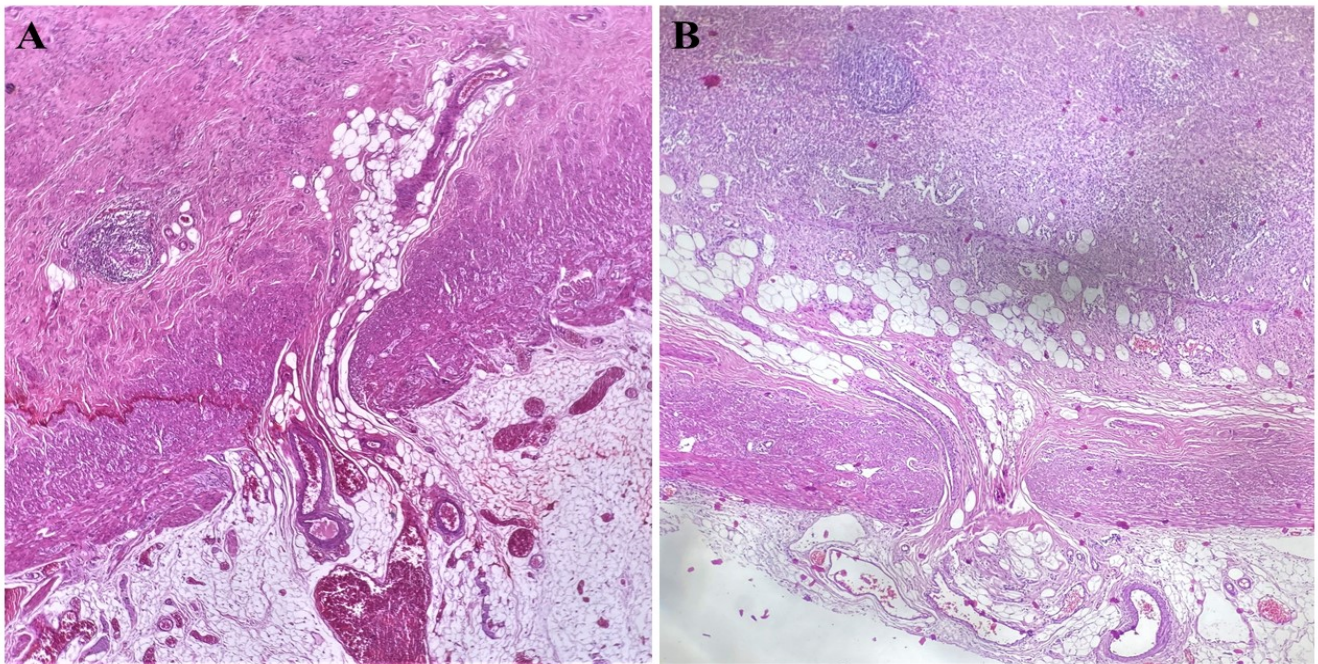


Figure 3. Submucosal fatty tissue along the vessels from subserosa to submucosa (H&E; x40)

In conclusion, the presence of SFT in the appendix is a common condition. Age increase and male gender are the risk factors for SFT accumulation. Any amount of SFT is increased the risk of AA, and it would be logical to classify it as mild/moderate/marked/severe like our study, and accept it as 'Submucosal lipomatosis'. We must add that further studies with non-symptomatic control groups that have similar age-gender ratios may be more useful to understand the normal histological structure.

Ethical Approval: The study was conducted as a result of the decision of Harran University Clinical Research Ethics Committee (HRÜ23.06.14)

Author Contributions:

Concept: G.A.H.

Literature Review: G.A.H.

Design : G.A.H.

Data acquisition: G.A.H.

Analysis and interpretation: G.A.H.

Writing manuscript: G.A.H.

Critical revision of manuscript: G.A.H.

Conflict of Interest: The authors have no conflicts of interest to declare.

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