

Unexpected findings in the routine histopathological examinations of appendectomy specimens

A retrospective analysis of 1,970 patients



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Unexpected findings in the routine histopathological examinations of appendectomy specimens. A retrospective analysis of 1,970 patients

INTRODUCTION: Diseases and tumors of the appendix vermiformis are very rare, except for acute appendicitis. This study aimed to examine rare findings in the histopathologic examinations of specimens of patients undergoing appendectomy due to the diagnosis of acute appendicitis.

METHODS: The files of 1,970 patients undergoing appendectomy due to the diagnosis of acute appendicitis between March 2012 and March 2016 were retrospectively investigated. Rare findings were found in 59 (3%) patients, and these were evaluated in detail. Patients' age, gender, pathology reports, and post-operation follow-ups were recorded.

RESULTS: The rare histopathological findings of 59 patients were examined. Of these, 31 were female (52.5%) and 28 were male (47.5%). The average age was 33.1 ± 18.2 years. The unusual findings were as follows: 16 Fibrous obliteration, 11 Enterobius vermicularis, 2 Schistosomiasis, 3 Appendiceal neuroma, 2 Granulomatous appendicitis, 1 Crohn's disease, 3 Chronic appendicitis, 1 Endometriosis, 2 Hyperplastic polyps, 9 Mucinous cystadenoma (+mucosele), 8 Carcinoid tumors and 1 Lymphoma. All of the malignant tumors were localized in the distal end of the appendix and all of the patients were treated with appendectomy. Patients with parasitic diseases also underwent anthelmintic treatment, while chemotherapy was administered to the patient with lymphoma. All of the patients diagnosed with malignancy were alive reported no problems at their follow-ups.

CONCLUSION: Although all of the appendectomy samples were normal macroscopically, data from this study suggest that all specimens should be sent for routine investigation.

KEY WORDS: Appendicitis, Appendectomy, Carcinoid, Mucosele, Endometriosis

Introduction

Acute appendicitis (AA) is one of the most common causes of acute abdomen surgery and appendectomy is

the most commonly performed surgical procedure world-wide. The lifetime frequency of AA is 8.6% in males and 6.7% in females ¹.

The increased incidence of AA, which peaks in young adults in their twenties, is associated with lymphoid development. Lumens obstruction is an effective factor in the formation of AA. However, fecaloid and lymphoid hyperplasia are the most common causes and can cause obstruction in some rare cases ^{2,3}. These hyperplasias include enterobiasis, ascariasis, balantidiasis, taeniasis, actinomycosis, schistosomiasis, amebiasis, trichuriasis, blastocystis hominis, tuberculosis, adenovirus, neurofi-

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broma, carcinoid tumor, goblet-cell carcinoid, primary or secondary adenocarcinoma, cystadenocarcinoma, lymphoma, leukemia, dysplastic changes, endometriosis, granulomatous diseases, gastrointestinal stromal tumor, mucocoele, villous adenoma, tubulevillous adenoma, tubular adenoma, leiomyoma, diverticulitis, eosinophilic granuloma, and neurogenic appendicopathy^{2,3}.

The literature describes different protocols for sending appendectomy specimens for pathological examination. Matthyssens et al. suggested that it is not necessary to routinely send appendectomy specimens unless they raise doubts macroscopically; however, there has not been a consensus regarding whether all specimens should be routinely sent for analysis^{4,5}. On the other hand, some studies have reported that unusual results are becoming more common. Consequently, important pathological findings may be overlooked, which might affect the treatment of some patients⁶. More than half of appendiceal tumors are diagnosed in pathological examination. Moreover, diagnoses such as parasitic infections,

endometriosis and inflammatory bowel diseases can be also made with the evaluation of appendectomy specimens^{7,8}.

In this study, we investigated the frequency of unexpected rare pathologies seen in appendectomy specimens in Adiyaman University Medical Faculty Hospital and compared our results with those reported in the literature.

Methods

This study was approved by the local ethics committee. The files of 1,970 patients who underwent appendectomy with the diagnosis of AA between March 2012 and March 2016 in Adiyaman University Medical Faculty Hospital were retrospectively examined. The patients' age, gender, operative findings, diagnosis of pathology, postoperative results, and follow-ups were recorded. Information on postoperative conditions was recorded through May 2016.

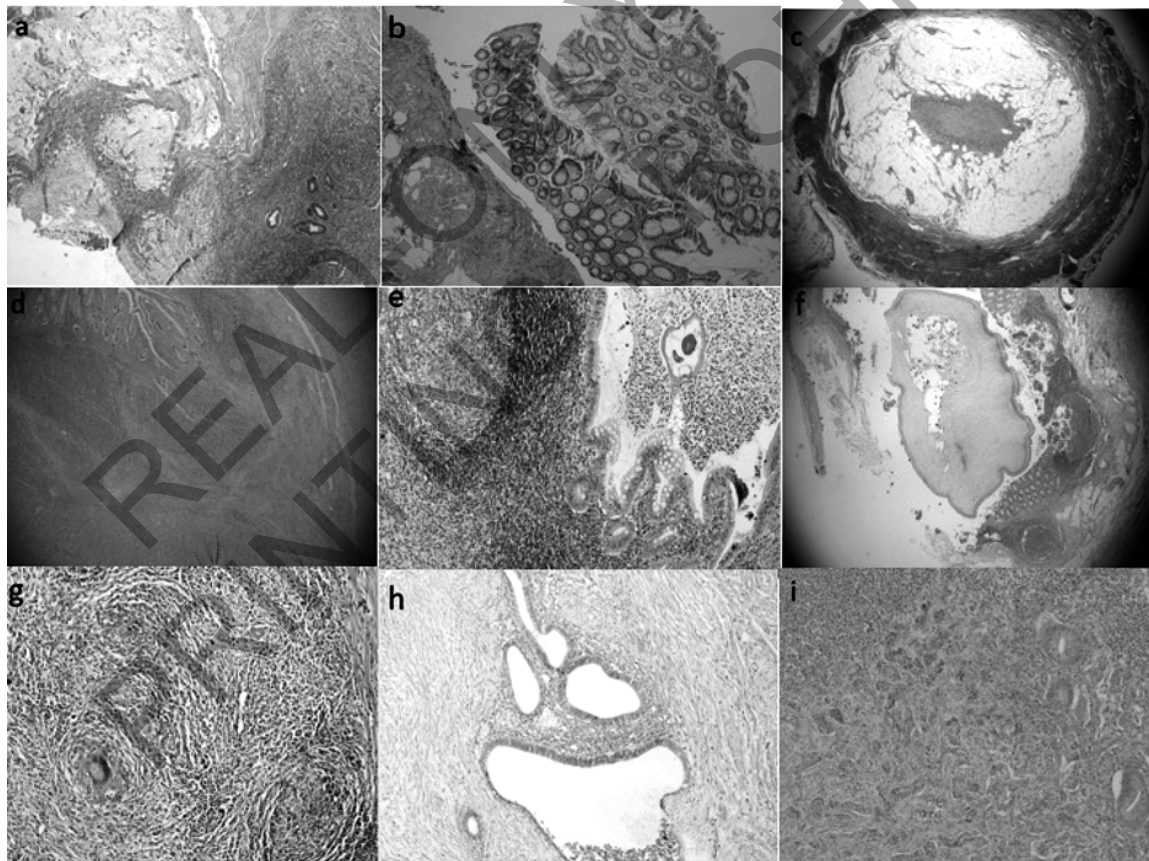


Fig. 1: A) mucocoele, mucin secretion filling the appendiceal lumen (HE x40); B) hyperplastic polyps with serration on the surface developing towards the appendiceal lumen (HE x40); C) neuroma/spindle cells and nerve cells on fibromyxoid surface consisting of fibrous obliteration lumen, lymphoid tissue loss (HE x40); D) B cell lymphoma (HE x20); E) enterobius vermicularis in the appendiceal lumen (HE x200); F) schistosoma haematobium in the appendiceal lumen (HE x40); G) granuloma structures consisting of multinucleated giant cells on the appendiceal wall (HE x200); H) endometriosis, endometrial stroma in the appendix wall, glandular structures with blood components (HE x100); I) carcinoid tumor characterized by uniform cells forming scattered solid islands in the lamina propria and muscularis propria (HE x40).

TABLE I - Distribution of the 59 cases identified as having unusual findings according to etiological causes

Total patients	n = 59
Carcinoid tumor	8
Mucinous cystadenoma (+mucocele)	9
Lymphoma	1
Hyperplastic polyps	2
Granulomatous appendicitis	2
Chronic appendicitis	3
Appendiceal neuroma	3
Fibrous obliteration	16
Schistosomiasis	2
Enterobius vermicularis	11
Endometriosis	1
Crohn's disease	1

There were 1,188 (60%) male patients and 788 (40%) female patients. All of the appendectomy specimens were obtained from appendectomies conducted in our hospital. Histopathological examinations were performed in the hospital's pathology unit. Unusual pathology results after appendectomy were recorded. Appendectomy specimens with unusual findings (n=59, 3%) were re-evaluated by experienced pathologists.

Results

A total of 1,970 patients with the diagnosis of acute appendicitis underwent appendectomy between March 2012 and March 2016 in Adiyaman University Medical Faculty Hospital. The diagnoses of all patients were confirmed via physical examination and laboratory findings. Unusual findings were observed in 59 (3%, 28 male and 31 female) of the patients who underwent appendectomy. The range of age was 3-72 years and the mean age was 33.1 ± 18.2 years. The unusual findings (n=59) were as follows: 16 (27.1%) Fibrous obliteration, 11 (18.6%) Enterobius vermicularis,

2 (3.3%) Schistosomiasis, 3 (5%) Appendiceal neuroma, 2 (3.3%) Granulomatous appendicitis, 1 (1.7%) Crohn's disease, 3 (5%) Chronic appendicitis, 1 (1.7%) Endometriosis, 2 (3.3%) Hyperplastic polyps, 9 (15.2%) Mucinous cystadenoma (+mucocele), 8 (13.5%) Carcinoid tumors and 1 (1.7%) Lymphoma (Fig. 1). The numbers of patients based on etiologic causes are summarized in Table I.

All patients with malignancy had a clinical pre-diagnosis of acute appendicitis. There were no symptoms of carcinoid syndrome in any of the patients, and there was no suspicion of appendiceal tumor in any of the patients preoperatively. The malignant patients were diagnosed by histopathological examination and were sent to undergo treatment and follow-up with an oncologist. Appendectomy was sufficient for all patients. Chemotherapy was additionally administered to the patient with lymphoma. At the time of this manuscript, all patients with tumor are still alive. The mean disease-free follow-up duration was 25.8 months. The clinicopathological features of the tumor cases are summarized in Table II. After establishing diagnosis by histopathologic examination, patients were followed-up with via abdominal ultrasonography, computed tomography, colonoscopy, and hydroxy indoleacetic acid measurements in 24-hour urine samples. All patients were followed-up with once every 3-6 months during the first year. In addition, the patients diagnosed with parasitic infections underwent oral medical treatment.

Discussion

Appendectomy is one of the most commonly performed surgical procedures². Its incidence is quite proportional with lymphoid development, and reaches its maximum level between the end of puberty and the mid-The incidence of acute appendicitis is approximately the same in males and females before puberty; however, its incidence in females is twice that in males after puberty⁹.

TABLE II - Clinicopathological characteristics of 9 patients with primary appendicular tumors

Age	Gender	Diagnosis	Diameter(cm)	Localization	Therapy	Involvement	Follow-up (months)
60	M	Carcinoid tm	0.6	tip	Appendectomy	mucosa	40
18	M	Carcinoid tm	0.4	tip	Appendectomy	mucosa	44
34	F	Carcinoid tm	0.5	tip	Appendectomy	mucosa	25
16	F	Carcinoid tm	0.5	tip	Appendectomy	mucosa	35
8	M	Carcinoid tm	0.7	tip	Appendectomy	mucosa	13
25	M	Carcinoid tm	0.3	tip	Appendectomy	serosa	20
13	F	Carcinoid tm	0.5	tip	Appendectomy	mucosa	21
35	F	Carcinoid tm	0.8	tip	Appendectomy	m.propria	34
45	M	B Lymphoma	2	tip	Appendectomy Chemotherapy	m.propria	26

Obstructions in the lumen are the most important factors causing acute appendicitis. Intraluminal obstruction causes continuous mucus secretion, which leads to increases in pressure. This obstructs the lymphatic drainage, causing the development of edema and mucosal ulceration. The distension of the appendix increases, which results in venous obstruction. Following these events, ischemia and necrosis develop on the appendage wall¹⁰.

Although fecalith and lymphoid hyperplasia are the most common factors causing intraluminal obstruction, some other rare factors have also been identified¹¹⁻¹³. Intestinal parasitic diseases and malignant or benign tumors are the most common unusual pathological findings observed in specimens after appendectomy due to any cause⁹.

Enterobius vermicularis (pinworms, oxyuris) is a parasitic infection that affects nearly 200 million people worldwide. At the end of the 19th century, it was first shown that the localization of *E. vermicularis* on the appendiceal lumen causes appendicitis. Previous studies have shown that the incidence of *E. Vermicularis* is between 0.6% and 3.8% in surgical specimens of patients suspected to have appendicitis¹⁴. These patients should also undergo anthelmintic treatment, as appendectomy only treats the consequences, but not the cause, of disease. *E. Vermicularis* infestation is treated with oral mebendazole, which is repeated in 2 weeks². Similar to the literature, in our current study, 11 (0.6%) patients had oxyuris infestation and were given anthelmintic treatment.

The relationship between AA and schistosomiasis, another parasitic infection, was first identified by Burfield in 1906¹⁵. Schistosomiasis, also known also as bilharziasis, is a rare cause of appendicitis that is seen only in endemic areas. Its prevalence depends on the presence of fecal contamination and snails in the source of drinking water¹⁶. In a study conducted in Nigeria by Gali et al., 2.3% of appendectomy specimens had eggs of this parasite (as determined by histopathological examination)¹⁷. The development of a periappendiceal reaction against the parasite causes its pathophysiology. Inflammation causes structural deformation on the appendage wall, leading to intraluminal obstruction and appendicitis. Schistosomal appendicitis is treated with appendectomy and praziquantel². In our current study, this parasite presented in only 2 (0.1%) appendectomy specimens.

Histopathological examinations of appendectomy specimens have revealed that fibrous obliteration occurs at a rate of nearly 30%. Despite this identification, the majority of the specimens are positive for neurogenic proliferation. Therefore, various definitions, including neurogenic appendicopathy and appendiceal neuroma, have recently been used. Although the mechanism of this pathological formation is not fully known, it is thought to develop secondary to hyperplasia of the neuroendocrine cells. The appendiceal lumen is full of inflammatory cells and fibrous tissue, and therefore, it is fre-

quently accompanied by proliferating neuroendocrine and nerve cells. The differential diagnosis between acute appendicitis and appendiceal neuroma is difficult, and it should be established according to the patients' anamnesis, symptoms, and laboratory and physical examination findings. Most of these cases become incidentally evident with pathological examination in asymptomatic patients^{18,19}. One study reported that fibrous obliteration was found in 57 (65%) of 88 appendectomy specimens with unusual findings³. In our current study, of the appendectomy specimens with unusual findings, there were 16 (27.1%) with fibrous obliteration and 3 (5%) with appendiceal neuroma.

Granulomatous appendicitis can be incidentally found in patients with acute appendicitis. Its incidence is rare, and is reported to be between 0.14% and 0.3% in western societies and between 1.3% and 2.3% in less developed countries^{20,21}. Diagnostic criteria for granulomatous appendicitis are similar to those of the intestinal tract, and include granulomatous inflammation, transmural lymphoid accumulation, and fissure type ulcers. Several infectious and non-infectious factors may cause granulomatous appendicitis.

Granulomatous inflammation of the appendix may also be associated with Crohn's disease and some other conditions, such as systemic sarcoidosis. However, in most cases, it has been incorrectly reported that granulomatous appendicitis is an indicator of Crohn's disease. In fact, only 5% to 10% of patients with granulomatous appendicitis have conditions associated with Crohn's disease developing in other parts of the gastro-intestinal system. Idiopathic granulomatous appendicitis is difficult to distinguish from early stage Crohn's disease, which only affects the appendix. The definitive diagnosis of granulomatous appendicitis requires long-term monitoring and detailed research. It has been reported that infectious agents such as *Yersinia*, *Mycobacterium*, *Blastomycosis*, *Schistosoma*, *Actinomyces*, *Campylobacter*, and *Histoplasma* are responsible for causing granulomatous inflammation of the appendix. The clinical course of these diseases is always changing, and patients often have symptoms of acute appendicitis, such as right lower quadrant pain, fever, nausea, and loss of appetite^{2,20-22}. One of the patients in our current study had granulomatous appendicitis; in this patient, a detailed investigation was performed due to the development of post-operative enterocutaneous fistula and Crohn's disease.

Endometriosis is identified as the presence of endometrial tissue ectopically outside the uterine cavity. Although endometriosis is common in most females of reproductive age, its gastrointestinal localization is rare. Approximately 10% of females with endometriosis have pathologies of the intestinal region classified as external endometriosis. Intestinal endometriosis is mostly observed in the rectum and in the sigmoid colon, and is rarely seen in the appendix. Although appendiceal endometriosis is usually asymptomatic, it sometimes

causes appendicitis, perforation, and invagination. The histopathological diagnosis of appendiceal endometriosis is based on the demonstration of endometrial tissue in the specimen. This condition is often treated with surgery and hormone therapy ^{2,3,14}. In our current study, appendiceal endometriosis was detected in one patient. The patient began medical treatment after consultation with gynecology.

Carcinoid tumor is the most common type of malignant tumor of the appendix, and its incidence is reported to be approximately 60%. In patients undergoing appendectomy, the incidence was found to be between 0.3% and 2.3%. Its incidence in females is 2-3 times that in males. The preoperative diagnosis of carcinoids is quite rare, as they are usually detected incidentally after an appendectomy ^{2,13,23,24}. Approximately 70-95% of carcinoid tumors are <1 cm and are localized at the tip of the appendix. Most of the appendix carcinoids are benign, and metastases of malignant carcinoids are rare. Appendectomy is adequate treatment for malignant tumors with a diameter of <1 cm, since their risk of metastasis is almost zero. The risk of metastasis increases up to 85% in tumors with a diameter of >2 cm. Therefore, right hemicolectomy should be performed in those with carcinoid tumors of the appendix with a diameter of 2 cm or greater ^{2,11,23,24}.

Consistent with the literature, in our current study, appendix carcinoid tumor was detected in 8 patients (0.4%), and the female/male ratio (4:4) was 1. All of the affected patients presented with signs and symptoms of acute appendicitis. None of these patients showed findings of carcinoid syndrome, and none of these patients needed hemicolectomy.

Extranodal lymphomas are typically observed in the gastrointestinal tract of 35-40% of all extranodal patients. The most frequently affected organs include the stomach, intestine, colon, and esophagus, respectively. The incidence of primary appendix lymphoma is estimated to be between 0.015%- 0.022% of all appendix specimens. Appendix lymphoma is usually seen in those in their twenties and thirties. It clinically behaves like acute appendicitis, and is often diagnosed via histopathological examination following surgery. The most common histopathological type is B-cell lymphoma. Since extranodal lymphomas are rare, there are no defined treatments. In our current study, B-cell lymphoma was detected in just one (0.05%) case. The patient underwent chemotherapy and is in remission; there was no recurrence at follow-up ².

Appendix Mucocele was identified for the first time in 1842. It is an obstructive dilatation of the appendix caused by the accumulation of mucoid material into the appendiceal lumen. The incidence of this lesion is reported to be between 0.2% - 0.7%. Appendix Mucocele has been described as four histopathological types: retention cyst, mucosal hyperplasia, mucinous cyst adenoma, and mucinous cyst adenocarcinoma. Mucoceles are often

asymptomatic and therefore, they are usually identified during appendectomy, laparotomy performed for another reason, or during examination of the surgical specimen. Since variability of its presentation, preoperative diagnosis of Appendix Mucocele is frequently difficult. Abdominal pain is the most common clinical sign. Other findings are abdominal mass, weight loss, nausea and vomiting ²⁵. The standard treatment of appendix mucocele is appendectomy, but right hemicolectomy is necessary in mucinous cyst adenocarcinomas ^{2,26}. In our current study, nine appendectomy specimens were reported as mucinous cystadenoma (+ mucocele). All patients had abdominal pain, two had vomiting and nausea, none of these patients showed findings of abdominal mass and weight loss. Appendectomy was sufficient in all of these cases.

Since mucinous cyst adenomas are highly associated with colon and ovarian malignancies, postoperative follow-ups of our cases were conducted using computed tomography, ultrasonography, and colonoscopy ¹⁴.

Appendix hyperplastic polyps (AHP) are rare, and their actual incidence is unknown. These polyps are typically small and have similarities with hyperplastic polyps, which can be seen anywhere in colon. Although AHP can present with symptoms of acute appendicitis, it is usually detected incidentally. Such polyps are significantly associated with adenocarcinoma in any part of the colon. Therefore, the presence of mucosal hyperplasia findings in appendectomy material is an indication that further detailed research should be conducted to eliminate colorectal cancer ²⁷. In our current study, hyperplastic polyps were found in the appendectomy specimens of two patients with acute appendicitis. There were no symptoms of malignancy in these cases.

Although AA is the most common pathology affecting the appendix, chronic or recurrent appendicitis can also be seen. Chronic inflammatory changes up to 5%, infiltrated by both lymphocytes and plasma cells on serous and muscular layers, can be seen in the specimens of patients who underwent appendectomy. Chronic inflammation of the appendix is determined based on the presence of lymphocytic and eosinophilic infiltration, fibrosis, and granulomatous and foreign body reaction. Since this rare pathology creates a dilemma for clinicians in its diagnosis and treatment, there are often delays in its diagnosis. Chronic appendicitis does not display the classic signs of acute appendicitis, and therefore, its diagnosis should be established with histopathological examination. Chronic appendicitis should also be considered in the differential diagnosis of patients with recurrent or chronic right lower quadrant pain. Computed tomography is the best test for its diagnosis, and appendectomy can be an effective treatment for these patients ²⁸. In our current study, of the three patients reported as having chronic appendicitis, two had a history of recurrent abdominal pain and one had chronic abdominal pain.

Conclusion

Although lymphoid and fecaloid hyperplasia are the most common causes of acute appendicitis, other unusual causes should also be considered. These unusual causes may be overlooked if specimens do not undergo histopathological evaluation. These overlooked causes may prevent full therapy of the disease, and therefore, we suggest that all appendectomy specimens undergo histopathological evaluation.

The most common unusual findings in appendectomy specimens are parasites and benign or malignant tumors. Appendectomy is not sufficient therapy in parasitic diseases; in these cases, anti-parasitic treatment should be performed. While appendectomy is curative in cases with benign tumors, additional surgery may be necessary in those with malignant tumors, based on the characteristics of the mass. Therefore, overlooked malignant lesions may cause further medical, social, and legal problems. In conclusion, all appendectomy materials should undergo routine histopathological investigation due to unexpected and unusual findings, even in cases where the appendectomy materials are macroscopically normal.

Riassunto

È molto raro il riscontro di tumori ed altre patologie dell'appendice vermiforme al di fuori dell'appendicite acuta. Ci si è proposti con questo studio di ricercare rari reperti nello studio istopatologico di appendici asportate in caso di appendicite acuta. Sono state studiate retrospettivamente le cartelle cliniche di 1.970 pazienti sottoposti ad appendicectomia per appendicite acuta tra il marzo 2012 e marzo 2016, con il risultato di individuare rari reperti in 59 pazienti, pari al 3%, e questi sono stati studiati in dettaglio, prendendo nota di età, genere, dati patologici e decorso postoperatorio.

Sono stati dunque esaminati i reperti istopatologici dei 50 pazienti, di cui 31 donne (52,5%) e 28 uomini (47,5%). L'età media è risultata di 33.1 ± 18.2 anni.

I reperti non usuali sono stati i seguenti: 16 oblitterazioni fibrose, 11 elmintiasi da *Enterobius vermicularis*, 2 da *Schistosoma*, 3 neuromi appendicolari, 2 appendiciti granulomatoze, 1 morbo di Crohn, 3 appendiciti croniche, 1 endometriosi, 2 polipi iperplastici, 9 cistadenomi mucinosi con mucocele, 8 Carcinoidi ed 1 Linfoma.

Tutti i tumori maligni erano localizzati all'estremità distale dell'appendice, e tutti i pazienti erano stati trattati con appendicectomia. Quelli affetti da patologia parassitaria erano stati sottoposti a trattamento antielmintico, mentre i pazienti affetti da linfoma erano stati sottoposti a chemioterapia.

Tutti i pazienti cui era stata diagnosticata una patologia maligna erano vivi al follow up senza particolari problemi.

Sebbene tutti i reperti anatomopatologici delle appendici asportate apparivano normali macroscopicamente, i dati di questo studio suggeriscono che tutte le appendici asportate debbano essere sottoposte alle indagini di routine.

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