RESEARCH PAPER

UNEXPECTED PATHOLOGICAL LESIONS OF APPENDIX: AN ANALYSIS OF 3000 SURGICAL SPECIMENS FROM SRI LANKA

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Abstract

Background: Unexpected pathological lesions are not infrequent findings in surgical specimens of appendix. Appendiceal malignancies are commonly encountered as incidental lesions.
Objective: To analyze the unexpected appendiceal pathological lesions encountered in surgical specimens in a sample of Sri Lankan patients.
Methods: A retrospective review of 3000 consecutive appendicectomy specimens and appendices in colectomy specimens received at the Department of Pathology, Faculty of Medicine, University of Peradeniya from 2001 to 2014.
Results: There were 2907 appendicectomy specimens and 93 colectomy specimens with an appendix. In appendicectomy specimens, there were 9 (0.3%) primary neoplasms of which 8 were malignant, 2 (0.06%) secondary carcinoma deposits, 7 (0.24%) endometriosis, 7 (0.24%) granulomatous inflammation, 2010 (69.1%) acute appendicitis and the rest (30%) were unremarkable. In the appendices of colectomy specimens, there were 4 (4.3%) primary neoplasms, all of which were malignant, 7 (7.5%) secondary carcinoma deposits, 1 (1.1%) granulomatous inflammation, 11 (11.8%) acute appendicitis and the rest (75.2%) were unremarkable. Of the 3000 specimens, 13 (0.4%) had a primary appendiceal neoplasm: 9 (0.3%) mucinous neoplasms, 3 (0.1%) NET G1 (carcinoids) and 1 (0.03%) sessile serrated adenoma. Of the mucinous neoplasms, 1 was an adenoma, 3 were low grade appendiceal mucinous neoplasms and 5 were adenocarcinomas. Caseous tuberculoid granulomata were present in 5/8 (62.5%) granulomatous appendicitis.
Conclusions: The commonest unexpected finding in the appendicectomy sample was primary malignant tumours (0.3%) and the commonest malignant tumour group was mucinous neoplasms. Secondary adenocarcinoma is the commonest pathology in the appendices of colectomy specimens. Most granulomatous appendicitis cases were suggestive of tuberculosis.

Key words: Appendix, appendicitis, incidental pathology, mucinous neoplasms, granulomatous appendicitis

Introduction

Unexpected pathological lesions in surgical specimens of appendix, removed for suspected acute appendicitis and with colectomy specimens, are not infrequent. The most clinically significant finding of such lesions is appendiceal neoplasms. Acute appendicitis, precipitated by increased intraluminal pressure by the tumour, could reveal such lesions at an early stage. Published case series have demonstrated that the incidence of primary appendiceal malignancies in appendicectomy specimens ranged from 0.1% to 1.4% [1-4]. Despite the relatively low prevalence, these tumours comprise a clinically significant group of

appendiceal lesions due to their poor prognosis. Furthermore, according to the surveillance, epidemiology and end results (SEER) database, appendiceal adenocarcinoma has shown a 2.6 fold rise over the past 30 years[3].

Although neuroendocrine tumours were the most well recognized incidental neoplasms of the appendix, mucinous neoplasms of the appendix are increasingly being recognized and in some published series these are the commonest primary appendiceal tumour group[2,3]. The group mucinous neoplasms of the appendix comprises a spectrum of lesions: adenoma, low grade appendiceal mucinous neoplasm (those with questionable stromal invasion) and mucinous adenocarcinoma (those with unequivocal stromal invasion). Mucinous adenocarcinoma of the appendix is known to infiltrate the peritoneal surface replacing the peritoneal cells with tumour cells. It causes copious production and accumulation of mucus within the peritoneal cavity. This is an intractable stage with available treatment options and is known as pseudomyxomaperitoneii (PMP). Although a neoplasm diagnosed as an adenoma should not show malignant behaviour, the entire spectrum of mucinous neoplasms has been reported to be associated with PMP[5]. However, the risk of PMP with mucinous adenoma is low and most reported cases have been associated with "ruptured mucinous adenoma" which may have represented mucinous adenocarcinoma with deceptive stromal invasion. The reason for this controversy is that the predictors of malignant behavior in mucinous neoplasms, in the absence of unequivocal destructive invasion, are not fully determined. These tumours usually have mild cytological atypia and notorious to have deceptive stromal invasion patterns. Therefore, currently there are no universally accepted diagnostic criteria for mucinous tumours with equivocal morphological features. Mucinous neoplasms with questionable stromal invasion have been named in many ways in different classifications, as low grade appendiceal mucinous neoplasm (LAMN), mucinous tumours of uncertain malignant potential, mucinous tumours of low malignant potential and borderline tumours of the appendix. LAMN is the presently recommended term by the World Health Organization (WHO) 2010 tumour classification[6].

Appendiceal neuroendocrine tumours include carcinoid tumors, goblet cell carcinoids and mixed neuroendocrine – adenocarcinoma. Lymphomas and mesenchymal malignancies are less commonly encountered malignant appendiceal neoplasms. Benign mucosal lesions include hyperplastic polyps, diffuse mucosal hyperplasia and sessile serrated adenoma. Common non neoplastic incidental lesions include granulomatous appendicitis, parasitic infestations and endometriosis.

The frequency and the clinico-pathological profile of incidental appendiceal lesions in Sri Lanka have not been published. Therefore, we conducted the present study to analyze the appendiceal pathological lesions encountered in surgical specimens in a sample of Sri Lankan patients.

Materials and methods

This study is a retrospective review of 3000 consecutive appendicectomy specimens and appendices included in right hemicolectomy and total colectomy specimens, received at the Department of Pathology, Faculty of Medicine, University of Peradeniya, from 2001 to 2014. Histology of mucinous tumours were reviewed and reclassified according to WHO 2010 tumour

classification, as mucinous adenoma, LAMN and mucinous adenocarcinoma[6]. Presence of intraperitoneal mucin collections was recorded when indicated in the request form.

Results

There were 2907 appendicectomy specimens and 93 right hemi colectomy and total colectomy specimens which included an appendix. The mean age of the appendicectomy sample was 25.3 ± 14.1 years and 1572 (54%) were males. The mean age of the colectomy sample was 46.3 ± 19.8 years and 37 (39.8%) were males.

In the appendicectomy sample, the indication for surgery was suspected acute appendicitis in 2490 (85.7%), suspected appendicular mass in 38 (1.3%) and laparotomy performed for other reasons in 33 (1.1%); the indication was not mentioned in 346 (11.9%). In the colectomy sample, indications for surgery were, malignancy elsewhere in the colon: 44 (47.3%), acute abdomen or suspected obstruction: 26 (28%), familial adenomatous polyposis: 3 (3.2%), appendicular masses: 2 (2.2%) and other reasons: (19.2%).

Grossly, in the appendicectomy specimens, there were 11 (0.4%) masses, 3 (0.1%) mucoceles, 1585 (54.5%) with features of inflammation only and 1308(45%) were unremarkable. In the colectomy specimens, 3(3.2%) were appendicular masses, 1(1.1%) was a mucocele, 5(5.4%) were with features of inflammation and in 84(90.3%) the appendix was unremarkable.

Microscopically, in the appendicectomy specimens, 9 (0.3%) had a primary neoplasm of which 8 were either frankly malignant or had malignant potential (**Table 1**), 2 (0.06%) secondary carcinoma deposits, 7 (0.24%) endometriosis, 7 (0.24%) granulomatous inflammation and 2010 (69.1%) acute appendicitis; the rest (30%) were unremarkable. Four appendices with granulomatous inflammation had typical caseous tuberculous granulomata. Of these, two had the disease predominantly on the appendiceal serosa associated with peritoneal tuberculosis, one had associated ileo-caecal tuberculosis and the other was confined to the appendix. Only one patient was clinically suspected as having tuberculosis pre-operatively. In the rest, one had xanthogranulomatous appendicitis and the other two cases had non necrotizing granulomata associated with acute suppurative appendicitis in appendicular masses. Twenty five (1.2%) appendices had nematodes in the lumina and identified as *Enterobius vermicularis*. Eighteen (72%) of those with nematode infestation were less than 24 years in age.

Microscopically, in the 93 appendices of colectomy specimens, 4 (4.3%) had a primary neoplasm, all of which were malignant (**Table 1**), 7 (7.5%) had secondary carcinoma deposits, 1 (1.1%) granulomatous inflammation which was consistent with tuberculosis associated with ileal tuberculosis and 11 (11.8%) had acute appendicitis; the rest (75.2%) were unremarkable. None had evidence of nematode infestation. Correlations of gross appearances of appendices with microscopy in appendicectomy and colectomy specimens are given in **Tables 2 and 3**.

Of the 3000 specimens, 13 (0.4%) had a primary appendiceal neoplasm: 9 (0.3%) mucinous neoplasms, 3 (0.1%) neuroendocrine tumours grade 1 (NET G1) (formerly known as carcinoid tumour) and 1 (0.03%) sessile serrated adenoma. The mean age of those with a primary appendiceal neoplasm was 47.8 ±19.2years. The presentation patterns of these tumours are given in the **Table 1**.

Table 1. Clinical presentation patterns of primary appendiceal neoplasms

Type of neoplasm	Type of surgery			Clinical presentation		
	Total	Appendicec.	Colectomy	Incidental	Mass	Other
Mucinous neoplasms						
Adenoma	1	1	0	1	0	0
LAMN	3	2	1	2	1	0
Adenocarcinoma	5*	3	2	3	1	1**
Neuroendocrine tumours						
NET G1 (Carcinoid)	3	3	0	3	0	0
Others						
Sessile serrated adenoma	1	0	1	1	0	0
Total	13	9	4	10	2	1

LAMN, low grade appendiceal mucinous neoplasm, NET G1, neuroendocrine tumour grade 1
*Four were mucinous adenocarcinomas, one was unclassified.
**Presented as an abdominal wall fistula and later found to have an appendiceal mass

Table 2. Correlation of gross appearances of appendices with microscopic features in appendicectomy specimens

Gross app	Microscopic diagnosis					
	Total	Neoplasm*	Acute Inflam	Granuloma inflam	Other non neoplastic	Unremarkable Non specific
Mass	11	1	5	3	0	2
Mucoceole	3	2	0	0	0	1
Inflammed	1585	2	1346	2	1	234
Unremarkable	1308	6	659	2	6	635
TOTAL	2907	11	2010	7	7	872

*Two secondary carcinomas

Table 3. Correlation of gross appearances of appendices with microscopic features in colectomy specimens

Gross app	Microscopic diagnosis					
	Total	Neoplasm*	Acute inflam	Granuloma	Other non neoplastic	Unremarkable/ non specific
Mass	3	1	2	0	0	0
Mucoceole	1	1	0	0	0	0
Inflammed	5	0	2	0	0	3
Unremarkable	84	9	7	1	0	67
Total	93	11	11	1	0	70

*Seven secondary carcinomas

Of the mucinous neoplasms, 1 was an adenoma, 3 were LAMN and 5 were adenocarcinomas. Of the adenocarcinomas, four were mucinous type and one was unclassified. Gross appearances of these tumours were as follows, 3 had masses, 4 had thickened walls, 1 was ruptured with mucus on the serosa and 1 showed inflammation only. One had localized mucin in the right pelvic peritoneal cavity at the time of surgery.

None had synchronous ovarian tumours or secondary tumour deposits elsewhere. The mean age of the patients with mucinous neoplasms was 54.5 ± 14.05 years and 7 (78%) were females.

All neuroendocrine tumors present were NET G1 (carcinoid tumours) and they were incidental findings in appendicectomy specimens performed for suspected acute appendicitis (Table 1). The mean age of patients with carcinoids was 21.3±0.6 years and 2 (66.7%) of them were females.

Of the appendiceal tumours of the colectomy specimens, 7 were secondary carcinomas, of which 5 were direct invasions of caecal adenocarcinoma while two were deposits from adenocarcinoma elsewhere in the colon. Of the primary tumours, three were mucinous adenocarcinomas while the other was a sessile serrated adenoma.

Discussion

The most common pathology in appendicectomy specimens was acute inflammation and this was the only pathology in 69% specimens (Table 2). In colectomy specimens, acute inflammation was present only in 11.8% (Table 3). Acute inflammation of the appendix is commonly precipitated by factors that increase its intraluminal pressure, such as mucosal lymphoid hyperplasia in children, faecaliths, tumours and parasites. Therefore, acute appendicitis could be a secondary manifestation of the incidental lesions. Even in the absence of inflammation obstruction of the appendiceal lumen can produce colicky pain mimicking acute appendicitis.

The most important group of unusual findings in the appendicectomy sample is primary appendiceal malignancies which had a prevalence of 0.3% (**Table 1**). In published series the frequency of primary appendiceal malignancies ranged from 0.1% to 1.4%[1,4]. In the colectomy specimens there were 3.2% with primary appendiceal malignancies. All malignancies in our series were of epithelial type and included, 5 adenocarcinomas, 3 LAMN and 3 NET G1 (carcinoid tumours). Of these tumours, 73% (8/11) were incidental findings during surgery or detected at pathological examination of appendicectomy specimens of patients suspected of acute appendicitis. The rest were present in colectomy specimens performed for right iliac fossa mass and exploration of an anterior abdominal wall sinus (**Table 1**).

Malignant mucinous neoplasms, which comprised 23% LAMN and 38.5% adenocarcinoma, were the largest primary tumour group in this series. In many published series mucinous neoplasms were the commonest group of primary appendiceal tumours[2,3]. The main complications of appendiceal mucinous neoplasms are pseudomyxomaperitoneii (PMP) and distant metastasis.

PMP is described as accumulation of mucin and mucinous epithelial cells within the peritoneal cavity secondary to peritoneal spread of a mucinous neoplasm[6]. PMP is most commonly due to spread from an appendiceal mucinous neoplasm and very occasionally from mucinous carcinoma from other sites, especially from colon[2,6,7].

When PMP is associated with ovarian mucinous neoplasms, almost always the primary tumour is present in the appendix[5,8]. Low grade PMP is usually associated with LAMN and high grade PMP with appendiceal mucinous adenocarcinoma[7]. Twenty percent prevalence of PMP had been reported among those with appendiceal mucinous neoplasms and the risk was highest for mucinous adenocarcinoma and lowest for

mucinous adenoma[2,5]. Most reported cases of PMP with mucinous adenomata are found to be "ruptured adenomata" which may have fulfilled the criteria for LAMN according to current WHO classifications. The median time between diagnosis of the primary mucinous tumour and development of PMP have been shown to be 2 years; however this period can be as long as more than 20 years[2]. In our series, there was only one subject, who had a mucinous adenocarcinoma, with localized involvement of the right pelvic peritoneum at the time of surgery. The clinical significance of localized PMP is not yet determined with certainty due to paucity of studies available[5]. In the present study, follow up data is not available.

Coexistence of mucinous neoplasms of appendix with similar lesions in the ovary has been reported in many studies[5,9,10]. While some argue that these are synchronous independent tumours, the currently favoured opinion is that almost always these are primary appendiceal tumours with metastatic deposits in the ovary. In our series, none of the mucinous tumours had a detectable ovarian pathology.

Mucocele of the appendix is a common gross manifestation of mucinous neoplasms[11]. However, mucocele is a descriptive term used for a distended appendix filled with mucus and could have a non-neoplastic aetiology as well. In our series[3,4] mucoceles were associated with mucinous neoplasms, two LAMNs and one mucinous adenocarcinoma and the other was a non neoplastic retention mucocele. The other gross manifestations of mucinous neoplasms, in our series, included two adenocarcinomas as masses and one adenocarcinoma and one LAMN as irregular thickening of the wall. In one adenocarcinoma, inflammatory features were predominant and in the adenoma appendix was grossly unremarkable. However, LAMN has also been reported in grossly unremarkable appendices[5]. The mean age and the female predominance in mucinous neoplasms in the present study are consistent with the published literature[6].

The most common neuroendocrine tumour type in the appendix is NET G1 (carcinoid tumour) which has low grade malignant behaviour with a low risk of metastasis. As observed in our series, these tumours are often incidental findings in younger age groups[6]. The frequency of NET G1 in appendicectomy specimens range from 0.02-0.9% [4,12-15]. In our series, all neuroendocrine tumours were NET G1, the frequency of which was 0.1% and constituted 23% of all primary appendiceal tumours. All were incidental findings in externally unremarkable appendices.

Apart from acute inflammation, the benign conditions encountered in our series were granulomatous inflammation and endometriosis. Granulomatous inflammation was present in 0.2% (7/2907) of appendicectomy specimens and 1% 1/93 of appendices in colectomy specimens. Prevalence of granulomatous inflammation is known to vary geographically, it is 0.4% in a Western country, 0.3% in a Middle Eastern country and 2.4 to 2.9% in a South Asian country[16-19]. Causes of granulomatous appendicitis include infectious causes such as tuberculosis and Yersinia, interval appendicectomy, Crohn disease, foreign body related, idiopathic and sarcoidosis. The aetiology of granulomatous appendicitis too shows geographical variations and in endemic regions tuberculosis is a common cause and is the reason for higher prevalence of granulomatous appendicitis[18,19]. In some series from India, almost all cases of granulomatous appendicitis had a histological picture consistent with tuberculosis[18]. In our series, 57% 4/7 had

tuberculous appendicitis and three of them were associated with either peritoneal or ileo-caecal tuberculosis. In the West, Yersinia infection has been recognized as the commonest infectious cause of granulomatous appendicitis[21,22]. Furthermore in Western countries, most of the "previous idiopathic" appendicitis cases are considered to be either due to Yersinia infection or interval appendicectomy[21]. Crohn disease is no longer recognized as a common cause of granulomatous appendicitis and isolated Crohn disease in the appendix, without the involvement of the rest of intestinal tract, is no longer considered a cause[20,21]. It is now accepted that, in countries where tuberculosis is non endemic, the majority of granulomatous inflammation in the appendix is due to prolongation of the acute inflammatory process associated with interval appendicectomy or due to recurrent attacks of acute appendicitis[20,21]. In our series, only two cases fulfilled criteria of interval appendicitis /recurrent attacks.

Of the females who underwent appendicectomy 0.5% had endometriosis. All, except one, did not have associated acute appendicitis, indicating that the abdominal pain in these women may have been due to endometriosis.

Conclusions

The main unexpected findings in the appendices were the neoplasms, granulomatous inflammation and endometriosis. These findings were consistent with those of the rest of the world. The commonest unexpected finding in the appendicectomy sample was primary malignant tumours (0.3%) and the commonest malignant tumour group was mucinous neoplasms (low grade appendiceal mucinous neoplasms and mucinous adenocarcinomas). The majority of the tumours were incidental findings. Secondary adenocarcinoma was the commonest pathology in the appendices of colectomy specimens. As observed in other tuberculosis endemic countries, the commonest cause for granulomatous appendicitis was tuberculosis.

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Author Contributions

DLPD, KD and DNKB collected data and performed literature survey; SW and DLPD analyzed the data and wrote the paper;
SW and NVIR performed the histological analysis of appendiceal neoplasms.

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