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Review Article

Acute Appendicitis Secondary to Metastatic Malignancy - A Review of 78 Cases in Literature

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Abstract

Background: Acute appendicitis is one of the most common causes of acute abdomen presentation to the emergency department. Appendicectomy is one of the most common emergency operations performed. Appendicitis is attributed to lymphoid hyperplasia or faecolith causing obstruction of the appendiceal lumen. Other causes include helminth infection, primary appendiceal tumours, malignancy, and calculi. Metastatic malignancy causing acute appendicitis is very uncommon. In this article, we review the literature that exists reporting acute appendicitis attributed to metastatic diseases of the appendix, the malignancies that were identified, and the nature of the presentation.

Methods: This study was performed following the Scale for the Assessment of Narrative Review Articles (SANRA)**.** A literature review of existing case reports, abstracts, and studies was performed. PubMed and Google Scholar were used to search for the articles. Several cases were identified using the 'snowball method' where references were used to identify additional published literature.

Results: Seventy-eight cases of acute appendicitis secondary to metastatic malignancies were identified. The most commonly reported metastatic malignancy causing appendicitis were breast, lung, gastric, and prostate. There was a total of n=34 (46%) of individuals with complicated appendicitis, n=40 (54%) with uncomplicated appendicitis, and four cases did not have degree of inflammation documented. The mean age of the patients was 57 years old.

Conclusion: Appendicitis secondary to metastatic disease is a rare entity. This literature review has collated data identifying known primary malignancies that are associated with metastatic disease to the appendix. The most common have been identified as breast, lung, gastric and prostate primary malignancies. The mean age of patients in this review is 57. Patients presented with more complicated disease in comparison to the general population with acute appendicitis without malignancy. While rare, it important to be cognizant to the patient's previous malignancies even after the surveillance period has been completed. In this article we review the literature that exists reporting acute appendicitis attributed to secondary metastatic disease of the appendix, the malignancies that were identified and the nature of the presentation. When considering management of appendicitis, it is important to be cognizant as to whether the patient has had previous malignancies even after the surveillance period is over.

Keywords: Appendicitis; Acute surgery; Appendiceal malignancy; Emergency surgery; Metastatic malignancy; Secondary appendiceal cancer

Introduction

Acute appendicitis is one of the most common causes of acute abdomen presentation worldwide and appendicectomy is one of the most common emergency operations performed. The estimated lifetime risk of appendicitis in 7-8% [1]. Appendicitis is caused by a wide array of pathology ranging from infectious diseases to primary and metastatic malignancy. The most common aetiology is lymphoid hyperplasia or a faecolith causing obstruction of the appendiceal lumen resulting in increased intraluminal pressure. Primary appendiceal malignancies is rare, with an incidence of 0.9% - 1.5% [2,3]. Metastatic disease resulting in acute appendicitis is extremely rare [4,5], with the majority of data coming from published case reports. The relationship between primary colon and primary ovarian cancer with intraperitoneal secondary metastases has been well established, however other malignancies have also been reported. The relationship has been established, however colorectal and ovarian with secondary appendiceal metastases is still considered rare. The aim of this review article is to identify published literature of acute appendicitis cases secondary to metastatic malignancy and rare non-primary tumours causing acute appendicitis. This study aims to highlight the importance of taking a thorough past medical history and being aware of a patient's previous oncological history prior to performing an emergency appendicectomy.

Methods

This study was performed following the Scale for the Assessment of Narrative Review Articles (SANRA) [6]**.** A review of existing published literature including case reports, abstracts, and studies were evaluated. PubMed and Google Scholar were used to search for the published articles. The search terms were "(appendicitis due to metastasis) OR (appendicitis secondary to metastatic)) OR (appendicitis as a result of metastasis) OR (appendicitis secondary to metastases). Several cases were identified via the snowball method where references were used to identify additional literature [7]. Right sided colon cancer causing acute appendicitis cases were excluded given a systematic review and meta-analysis has already been performed confirming the incidence of right sided colon cancer in patients aged over 40 presenting with acute appendicitis is 10 times greater than the risk in the general population [8]. Patient's age, gender, time after cancer diagnosis to appendicitis presentation, degree of inflammation, histopathology, and operation were evaluated. Percentage of Complicated was compared with uncomplicated appendicitis. Complicated appendicitis is defined as perforated, peri-appendicular abscess, and gangrenous [9].

Results

78 cases were identified in the literature and included in this review. The most commonly reported metastatic malignancy causing appendicitis were breast, lung, gastric, and prostate. Table 1 provides a summary of the findings.

Breast

Seventeen cases [10-25] of metastatic breast cancer causing appendicitis were identified. The age of the patients ranged from 35 up to 90 years old, with an average age of 54 years old. 58.8% of the cases were complicated compared to 41.2% of uncomplicated appendicitis. Four cases were metastatic lobular carcinoma [10,12,18,20] and eleven cases were metastatic ductal carcinoma. One patient had ileocecectomy due to findings of dilated ileum intraoperatively along with oedematous appendix [10]. Bilateral oophorectomy was performed on one of the patients because a clinically pathological ovary was identified intraoperatively and it contained metastatic carcinoma [13]. One patient had an open right hemicolectomy as a hard appendiceal mass suggestive of malignancy was discovered [14].

Melanoma

Three cases of metastatic melanoma causing acute appendicitis were found [26,27]. The age ranged from 30 to 70 years old, with a mean age of 51. One of the cases was desmoplastic melanoma with Clark Level V depth of invasion [26]. Case 2 by Kitano et al. [27], had a Breslow thickness of 5.94 mm. Metastatic Melanoma in the appendix was confirmed with positive S-100 on immunohistochemical staining**.** Two of the cases had perforated appendicitis [27].

Lung Cancer

Thirteen cases of lung cancer metastasis causing acute appendicitis were found [28-40]. The age ranged from 44 to 85 years old with mean age of 60 years old. Six had small cell carcinoma [29,30,32,34,35,36], four had adenocarcinoma [28,37,39,40], one had squamous cell carcinoma [38], one had non-small cell lung cancer [33], and one had bronchogenic carcinoma [30]. Of those with documented degree of inflammation showed that nine patients or (82%), had complicated appendicitis [29,31-34,36-39] compared with three uncomplicated [28,35,40] or (27%).

Gastric Adenocarcinoma

Thirteen cases of gastric cancer metastasizing to the appendix causing acute appendicitis were identified [41-53]. The age ranged from 32 to 79 years old. There were 5 males and 6 females. Further data for two cases published more than 25 years ago were unable to be located. Six patients had complicated appendicitis compared to five uncomplicated. Six patients had poorly differentiated gastric adenocarcinoma, two patients had moderate to well differentiated

adenocarcinoma, and two had gastric signet ring cell adenocarcinoma.

Prostate Cancer

Eight cases of metastatic prostate cancer resulting in acute appendicitis were found [54-61]. Patients ranged from 62 to 82 years old, with a mean age of 80 years old. Three patients or 37% had complicated appendicitis compare to five or 62% with uncomplicated appendicitis. Most of the patients had Gleason 7 or greater prostate adenocarcinoma.

Cervical

Two patients were found to have metastatic cervical cancer causing acute appendicitis [62,63]. Both cases were stage Ib cervical cancer on initial diagnosis and both had perforated appendicitis.

Endometroid

Three endometroid causes of acute appendicitis were identified. One patient had metastatic endometrial adenocarcinoma [64]. All three had uncomplicated appendicitis, and one had an open ileocecectomy [65] as the cecum was found to be oedematous and inflamed.

Others

Nineteen other eclectic cases of metastatic malignancy, non-primary appendiceal tumours causing acute appendicitis were identified [66]. There was one low-grade serous ovarian carcinoma metastasis [67] causing perforated appendicitis. The other cases included hepatocellular carcinoma [68], choriocarcinoma of the mediastinum [69] granular cell tumor [70] acute promyelocytic leukemia [71], nasopharyngeal carcinoma [72], non-seminomatous testicular cancer [73], testicular seminoma [74], inflammatory myofibroblastic tumour [75], two cases of Kaposi's sarcoma [76,77] a natural killer cell/ T cell lymphoma [78], two cases of appendiceal schwannoma [79,80], two cases of cholangiocarcinoma [81,82], a case of metastatic gallbladder carcinoma [83,84], and two cases of pancreatic adenocarcinoma [85,86]. In our results, there was a total of 46%(n=34) of individuals with complicated appendicitis, 54%(n=40) with uncomplicated appendicitis, and 4 cases did not have degree of inflammation documented. The mean age of the patients was 57 years old.

Authors	Primary	Age	Sex	Time after cancer diagnosis	Degree of Inflammation of Appendix	Histopathology	Operation, relevant findings
Breast							
Numan Et al [10] **(2019)**	ER+/PR+/HER2 (-) Invasive Lobular Breast Carcinoma	44	F	3 years	No Perforation	metastatic breast cancer	Ileocecectomy, appendicectomy
Burney et al [11] **(1974) Case 1**	Left Breast Carcinoma, unknown type	35	F	2 years	Perforated appendix with large retroperitoneal abscess	Metastatic carcinoma of the breast	Laparotomy, Appendicectomy
Burney et al [11] **(1974) Case 2**	Breast carcinoma, unknown hormone status	73	F	3 years	Perforated appendix	Metastatic carcinoma of the breast	Laparotomy, appendicectomy
Mori et al [12] **(2016)**	ER+/PR+/HER2+ Loss of E-Cadherin Invasive Carcinoma	56	F	3 years	Gangrenous	ER+/PR-/HER2+ / Loss of E-Cadherin Invasive Lobular Carcinoma	Laparoscopic Appendicectomy
Capper et al [13] **(1956)**	Right Breast Carcinoma, unknown hormone status	36	F	n/a	Gangrenous	Metastatic carcinoma in appendix along with metastatic carcinoma in left ovary.	Open Appendicectomy + Bilateral Oophorectomy
Ng et al [14] **(2018)**	ER-/PR+/HER2+ Invasive ductal carcinoma	59	F	Not previously diagnosed	Peri- appendicular abscess	ER-/PR+/HER2+ poorly differentiated metastatic breast carcinoma	Open Right hemicolectomy: Hard appendiceal mass identified during operation
Latchis et al [15] **(1966)**	Left breast infiltrating ductal carcinoma and infiltrating lobular carcinoma, 0/18 nodes	45	F	4 years	No perforation	Metastatic Breast carcinoma to appendix	Open appendicectomy
Khalil et al [16] **(2022)**	ER+/PR+/HER2- T4N2 Grade 3 invasive Ductal Carcinoma	55	F	6 years	Perforated appendix at base	ER+/PR-/HER2 metastatic breast carcinoma	Laparoscopic Caecectomy
De Pauw et al [17] **(2020)**	Ductal carcinoma	64	F	20 years	No Perforation	Weak ER + poorly differentiated ductal carcinoma Metastasis	Laparoscopic Appendicectomy

Dirksen et al [18] **(2010)**	Previously Undiagnosed metastatic breast carcinoma	76	F	Not previously diagnosed	Perforated appendix with surrounding phlegmon	ER+/PR-/HER- lobular type metastatic breast carcinoma	Appendicectomy
Chotai et al [19] **(2018)**	ER-/PR+/HER2+ invasive ductal carcinoma	59	F	Not Previously diagnosed	No Perforation	ER-/PR+/HER2+ metastatic ductal carcinoma	Right Hemicolectomy as hard appendicular mass felt.
Hughes et al [20] **(2022)**	Right breast (ER-/PR-/HER2-) initially. ER+/PR+/HER2-Left Breast invasive lobular carcinoma 2 years later.	51	F	12 years, 10 years	Perforated appendix	ER+/PR+/HER2- semi-differentiated carcinoma (similar to hormone profile of left breast Invasive lobular carcinoma)	Laparoscopic Appendicectomy
Iwamoto et al [21] **(2014)**	ER+/PR+/Her 2- Stage II, T2N1M0 Invasive ductal breast carcinoma	58	F	10 years	No Perforation	ER-/PR-/HER2-/E-Cadherin – metastatic breast carcinoma	Laparotomy with Appendicectomy
Tahara et al [22] **(2015)**	ER+/PR+/HER2+ Invasive Ductal Carcinoma	39	F	6 years	No perforation	ER-/PR-/HER2+ metastatic poorly differentiated carcinoma morphologically consistent with initial breast carcinoma.	Laparoscopic Appendicectomy
Xia et al [23] **(2018)**	Left breast ductal carcinoma	90	F	14 years	No Perforation	Metastatic Breast carcinoma, ductal type, ER+	Laparoscopic appendicectomy
Meenakshi et al [24] **(2021)**	Locally advanced breast carcinoma	59	F	Not previously diagnosed	Abscess	Deposits of ductal carcinoma in appendix	Laparoscopic appendicectomy
Araujo et al [25] **(2018)**	Invasive ductal carcinoma	37	F	Not previously diagnosed	Abscess	Poorly differentiated adenocarcinoma, positive for HER2.	Laparotomy, Appendicectomy, hysterectomy, Left oophorectomy due to ovarian enlargement.
MELANOMA							
Avallone et al [26] **(2021)**	Desmoplastic Melanoma, Clark Level V. No Mutations in BRAF, NRAS,KRAS genes.	73	M	11 Months	No Perforation	S-100 +, 4cm malignant melanoma Tissue morphology similar to original desmoplastic melanoma.	Laparoscopic Appendicectomy
Kitano et al [27] **(2014) Case 1**	Melanoma	30	F	1 year	Perforated	Metastatic melanoma	Laparotomy, appendicectomy
Kitano et al [27] **(2014) Case 2**	Melanoma, Breslow thickness of 5.94mm.	50	M	3 years	Perforated with abscess	Metastatic melanoma positive S-100, MART-1, HMB-45, Tyrosinase	Laparoscopic appendicectomy
Lung Cancer							
Callum et al [28] **(2021)**	Right Lung Adenocarcinoma EGFR+	62	M	Not previously diagnosed	No Perforation	Right Lung adenocarcinoma, EGFR+	Laparoscopic Appendicectomy
Kermidaris et al [29] **(2019)**	Small Cell Lung Cancer	68	M	1 month	Perforated, purulence	Metastatic highly differentiated adenocarcinoma	Laparoscopic Appendicectomy
Murray et al [30] **(1962)**	Bronchogenic Carcinoma	N/A	N/A	N/A	N/A	Metastatic Bronchogenic Carcinoma	N/A

Yunaev et al [31] **(2011)**	Small Cell Lung Carcinoma	68	M	Not previously diagnosed	Perforated gangrenous	Poorly differentiated neuroendocrine carcinoma of lung origin, with features resembling small cell carcinoma of lung.	Open Appendicectomy
Gonzalev-Vela et al [32] **(1995)**	Small Cell Lung Carcinoma	65	M	9 Months	Perforated gangrenous	Metastatic small cell carcinoma	Laparotomy, Appendicectomy
Karadimos et al [33] **(2020)**	Stage 4 Non-small cell lung cancer	56	F	N/A	Perforated	Positive Thyroid Transcription Factor-1 (TTF-1), napsin-A, Cytokeratin 7(CK7), consistent with metastatic primary lung adenocarcinoma.	Laparoscopic Appendicectomy
Goldstein et al [34] **(2004)**	Small cell lung Carcinoma	54	M	N/A	Perforated Tip, gangrenous appendix	Metastatic Small Cell lung cancer, Positive for CK7, CK20 negative, and TTF-1 Positive, confirming metastatic small cell lung cancer	Open appendicectomy
Park et al [35] **(2012)**	Small Cell Lung Carcinoma	51	M	Not previously diagnosed	No perforation	Metastatic small cell carcinoma	Laparoscopic Appendicectomy
Pang et al [36] **(1988)**	Small Cell Lung Carcinoma	47	M	11 months	Perforated appendix	Metastatic small cell neoplastic cell infiltration	Laparotomy, appendicectomy
Haid et al [37] **(1988)**	Metastatic adenocarcinoma of the lung	50	M	1 year	Perforated appendix	Metastatic undifferentiated carcinoma	Open Appendicectomy
Shirashi et al [38] **(2020)**	Squamous cell carcinoma of Lung	85	M	n/a	Perforated appendix, peri-appendiceal abscess.	Metastatic Squamous Cell Carcinoma from lung, p40+	Open appendicectomy
Shiota et al [39] **(2016)**	Lung adenocarcinoma	74	M	15 months	Phlegmonous Appendicitis	Metastatic Lung adenocarcinoma, TTF-1 +, CK7+, Negative CK20.	Laparoscopic appendicectomy
Neto et al [40] **(2017)**	Lung adenocarcinoma	44	M	Not previously diagnosed	Not Perforated	Metastatic Lung Adenocarcinoma, TTF-1+, , CK7 +, negative CK20	Laparotomy, appendicectomy.
Gastric Cancer							
Wang et al [41] **(2021)**	Gastric adenocarcinoma-poorly differentiated	33	F	Not previously diagnosed	Not perforated	Poorly differentiated adenocarcinoma. CEA+, CK7+,CK+,CK20+,CD34+,P40-, ki67(70%), Chromogranin A negative	Laparoscopic Appendicectomy
Mohammadi et al [42] **(2023)**	Gastric adenocarcinoma	79	M	Not previously diagnosed	Had interval appendicectomy 6 weeks after percutaneous drainage of appendiceal phlegmon.	Well-differentiated gastric adenocarcinoma.	Laparoscopic appendicectomy
Lin et al [43] **(2004)**	T3N1M0 Gastric Adenocarcinoma	48	F	2 years	Not perforated	Metastatic Gastric Adenocarcinoma, CEA +, CK-7 +, CK-20 +.	Appendicectomy
Alhadid et al [44] **(2020)**	T3N0Mx Gastric Signet Ring Adenocarcinoma	54	F	N/A	Not perforated	Metastatic poorly differentiated adenocarcinoma	Right Extended Hemicolectomy
Karanikas et al [45] **(2018)**	Gastric Adenocarcinoma	53	M	3 years	Gangrenous Appendix	High Differentiated Adenocarcinoma	Open Appendicectomy

Sakuma et al [46] **(2022)**	Gastric Adenocarcinoma	65	M	2 years	Appendicitis with peri appendiceal abscess	Poorly Differentiated Adenocarcinoma	Laparotomy, Appendicectomy
Goldfarb et al. [47] **(1951)**	Metastatic Gastric Adenocarcinoma	N/A	N/A	N/A	N/A	N/A	N/A
Moller et al [48] **(1984)**	Gastric Cancer	N/A	N/A	N/A	N/A	N/A	N/A
Simpson et al [49] **(2013)**	Moderately differentiated Gastric Adenocarcinoma	73	F	13 Months	Gangrenous inflamed appendix with perforation at base	Metastatic Gastric adenocarcinoma- CK7 +, negative for CK20,CD56, synaptophysin, chromogranin.	Open Appendicectomy
Siddiqui et al [50] **(2020)**	GastricAdenocarcinoma	35	M	N/A	Contained Perforation	Poorly Differentiated carcinoma	Laparotomy , appendicectomy
Ercetin et al [51] **(2015)**	Gastric Signet Ring Carcinoma	32	F	Not previously diagnosed	Not perforated	Metastatic gastric adenocarcinoma	Laparotomy appendicectomy
Tran et al [52] **(2018)**	Gastric adenocarcinoma	63	M	Not previously diagnosed	Perforated	Poorly differentiated Gastric adenocarcinoma	Diagnostic laparoscopy converted to Open
Lovell et al [53] **(2022)**	Poorly differentiated gastric adenocarcinoma	74	F	Not Previously diagnosed	Not Perforated	Poorly differentiated gastric adenocarcinoma staining: Cytokeratin AE1/3 +, CK7+, CDX2+.	Diagnostic Laparoscopy, appendicectomy
Prostate							
Ratanarapee et al [54] **(2010)**	Gleason 5 High Grade Prostate Cancer	62	M	Not previously diagnosed	No Perforation	Metastatic Adenocarcinoma suspected Prostatic, PSA+	Laparoscopic Appendicectomy
Lec et al [55] **(2013)**	T3bN0M0 prostate cancer	71	M	15 years	No Perforation	Metastatic Prostate Adenocarcinoma, PSA+	Laparoscopic Appendicectomy
Christou et al [56] **(2004)**	Prostate Cancer Gleason 9	82	M	14 years	Phlegmonous	Metastatic Prostate Adenocarcinoma, PSA +	Laparoscopic Appendicectomy
Campos et al [57] **(2020)**	Gleason 3+4 Prostate Cancer	64	M	Not previously diagnosed	No Perforation	Metastatic Prostate Adenocarcinoma, PSA +	Probable carcinomatous masses in mesentery proceeded with open Ileocolectomy + End ileostomy
Khan et al [58] **(2018)**	Gleason 9 Prostate Cancer	72	M	6 years	No Perforation	Metastatic Prostate adenocarcinoma, PSA+, NKX3.1+	Laparoscopic Appendicectomy
Numbere et al [59] **(2020)**	Gleason 3+4 Prostate Cancer	66	M	7 years	No Perforation	Metastatic Prostate cancer, PSA +, NKX3.1+	Laparoscopic Appendicectomy
Propst et al [60] **(2021)**	Gleason 7 Prostate cancer T3aN1	70	M	10 years	Perforated Appendix with abscess. Initially conservative management with antibiotics, then represented again with appendiceal mucocele.	Poorly differentiated Metastatic Prostate adenocarcinoma, High Grade Appendiceal Mucinous Neoplasm also found.	Laparoscopic Appendicectomy
Ozyazici et al [61] **(2013)**	Prostate Cancer	72	M	3 years	Gangrenous appendix, perforation	Metastatic Prostate adenocarcinoma. PSA +	Laparoscopic Appendicectomy

Cervix							
Bair et al [62] **(2007)**	Cervical Cancer, Stage Ib	34	F	2 years	Perforated	Metastatic Cervical Cancer	Appendicectomy
Sudirman et al [63] **(2001)**	Cervical Cancer, Stage Ib	43	F	4 Months	Perforated	Metastatic Cervical Cancer	Laparotomy, Appendicectomy
Endometroid							
Ma et al [64] **(2019)**	Endometrial Adenocarcinoma	61	F	3 years	Not Perforated	Endometroid Adenocarcinoma, ER+/PR+/CK7+	Laparoscopic Appendicectomy
Gupta et al [65] **(2020)**	Endometriosis	36	F	Not previously diagnosed	No perforation	Endometrial tissue invasion into deeper layer of appendix-muscularis propria.	Open Ileocecectomy as cecum found to be oedematous and inflamed.
Huang et al [66] **(2015)**	Endometriosis	42	F	N/A	No perforation	Endometrial tissue staining CD10+, CK7+,ER+,PR+	Laparotomy Appendicectomy
Others							
Raman et al [67] **(2023)**	Ovarian Cancer	61	F	5 weeks	Perforated	Low Grade Serous Ovarian Carcinoma	Laparoscopic Appendicectomy
Kim et al [68] **(2008)**	Hepatocellular Carcinoma	50	M	Initial Presentation	N/A	Hepatocellular Carcinoma	Laparotomy, Appendicectomy
Ramia et al [69] **(1998)**	Choriocarcinoma of mediastinum	35	M	Not previously diagnosed	Perforated	Nests of atypical multinucleate and mononucleate trophoblastic cells infiltrating appendix. Immunohistology stain positive of bHCG, Acid Queratine, Queratine 7, Queratine 20, PSA, PAP. Negative for AFP, CEA, S-100.	Laparotomy , Appendicectomy
Zoccali et al [70] **(2011)**	Granular Cell Tumour	19	M	Not previously diagnosed	Peri-appendiceal Abscess	Granular Cell tumour of appendix with acute appendicitis	Laparoscopic Appendicectomy
Rodriquez et al [71] **(2015)**	Acute Promyelocytic Leukemia	43	F	5 days	No Perforation	Appendix infiltrated by leukemic blasts that co-express MPO and CD68, extramedullary malignancy made of immature myeloid cells.	Laparoscopic Appendicectomy
Hsu et al [72] **(1995)**	Nasopharyngeal Carcinoma-T2N3M0	64	M	1 year	No perforation	Poorly differentiated epidermoid carcinomas, positive stain for cytokeratin.	Appendicectomy
Beddy et al [73] **(2006)**	Non-Seminomatous Testicular Cancer	21	M	Not previously diagnosed	No Perforation	Non-seminomatus germ cell tumour of embryonal origin staining, staining positive for CD30, placental alkaline phosphatase, chromosome 12.	Laparotomy, appendicectomy
Sarma et al [74] **(1986)**	Testicular Seminoma	48	M	Not previously diagnosed	No Perforation	Seminoma arising in atrophic undescended testis, with cells invading appendiceal wall causing resulting in appendicitis.	Laparotomy, appendicectomy

Schoonjans et al [75] **(2016)**	Inflammatory myofibroblastic tumour	42	F	Not previously diagnosed	No Perforation	Spindle shaped myofibroblasts found in appendiceal mucosa.	Laparoscopic appendicectomy
Baker et al [76] **(1986)**	Kaposi's Sarcoma	30	M	Not previously diagnosed	No perforation	Kaposi's sarcoma-spindle shaped cells forming Cleft like spaces lined with atypical endothelial cells	Appendicectomy
Meyer-Rochow et al [77] **(2007)**	Kaposi's Sarcoma	25	M	Not previously diagnosed	No perforation	Kaposi's sarcoma -stain positive CD31, CD34- consistent with Kaposi's sarcoma.	Laparoscopic appendicectomy
Tsujimura et al [78] **(2000)**	Primary NK/T Cell Lymphoma	20	M	3 years	Perforated	Diffuse infiltration of lymphoid cells in appendix, immunoreactive for UCHL-1, MT-1, and CD 56	Laparotomy, appendicectomy
Hendriks et al [79] **(2018)**	Appendiceal Schwannoma	82	F	Not previously diagnosed	Perforated	Appendiceal schwannoma	Laparoscopic appendicectomy and partial caecectomy due to thickened appendiceal base.
Kamp et al [80] **(2015)**	Appendiceal Schwannoma	10	M	Not Previously diagnosed	Not Perforated	Appendiceal lumen filled with cellular spindle cell, Antonia A areas, and stained positive for S-100.	Laparoscopic Appendicectomy
Pena-Amaya et al [81] (2022)	Cholangiocarcinoma-Type IV Klatskin Tumor	65	M	Not Previously diagnosed	Not Perforated	Metastatic Cholangiocarcinoma, positive CK7.	Laparoscopic Appendicectomy
Kang et al [82] **(2014)**	Cholangiocarcinoma	87	F	Not Previously diagnosed	Not perforated	Metastatic Cholangiocarcinoma, Positive Ck7, negative CK20 and CDx2.	Laparoscopic appendicectomy, partial caecectomy
Aksade et al [84]	Gallbladder Carcinoma	62	F	4 months	Not perforated	Gallbladder adenocarcinoma	Laparoscopic Appendicectomy
Filik et al [85] **(2003)**	Pancreatic	78	M	Not Previously diagnosed	Not Perforated	Pancreatic	N/A
Gollapudi et al [86] **(2016)**	Pancreatic	67	M	Not Previously Diagnosed	Perforated appendix, peri-appendiceal abscess	Metastatic Pancreatic Adenocarcinoma	Laparoscopic Appendicectomy

Table 1: Summary of Findings of 78 Cases of metastatic malignancy causing acute appendicitis.

Discussion

Internationally, acute appendicitis is the one of the most common reasons for acute abdomen presentation to the emergency room, and one of the most common reasons for emergency surgery. Appendicitis is usually diagnosed clinically where patients typically present with migratory periumbilical to right iliac fossa pain with biochemical results showing leukocytosis, neutrophilia, and elevated c-reactive protein. In equivocal findings imaging is often performed with computed tomography scans having a sensitivity and specificity of 98% in identifying the pathology [86] the other option would be proceeding to diagnostic laparoscopy [87]. The gold standard treatment for appendicitis is appendicectomy for source control. In our study, 46% of the patients had complicated appendicitis. Whilst small numbers, this suggests that the incidence of complicated appendicitis due to metastatic malignancy is higher compared to incidence of appendiceal perforation in non-malignant appendicitis. A prospective cohort study of 1486 patients by Korner et al found the overall appendix perforation rate was 19%, with elderly and small children having the greatest number of perforated appendix [88]. The pathogenesis of appendicitis is described as an appendiceal outlet obstruction due to infection, calculi, appendicoliths, lymphoid hyperplasia, and tumours with subsequent increased luminal pressure of the appendix. This causes small vessel thrombosis, reduced lymphatic flow, ischemia and resultant accumulation of bacteria. Eventually, if not treated early, the appendix wall may rupture due to necrosis [89] . Several randomized controlled trials have investigated conservative management of acute uncomplicated appendicitis with antibiotics [90-93]. One of these, the Appendicitis Acuta (APPAC) trial enrolled 530 patients aged 18 to 60 years with CT confirmed acute uncomplicated appendicitis. In this trial, patients were randomized into two groups: antibiotic vs surgical management. In the antibiotic group, patients received IV ertapenem for 3 days, then 7 days of levofloxacin and metronidazole. The authors found most patients who received antibiotic for uncomplicated appendicitis at the 1 year did not require an appendicectomy [90]. However, managing patients conservatively presenting with acute appendicitis with a background of malignancy is perilous as an appendicitis due to metastatic or recurrent malignancy may be missed. For example, in one of our cases, a 70-year-old male with history of T3N1M0 Gleason 7 prostatic adenocarcinoma presented with contained perforated appendicitis and was managed conservatively with iv antibiotics. Six weeks later he represented with a symptomatic appendiceal mucocele with histology showing metastatic prostatic adenocarcinoma infiltration [60].

In our review, the malignancies with greatest number to metastasize to appendix causing acute appendicitis are breast, lung, gastric, and prostate. The most common site of distant metastases (from most common to least) in invasive breast carcinoma is bone, lung, brain, and liver [94]. Interestingly, there was a greater number of invasive ductal carcinoma metastasis to appendix compared to Invasive Lobular Carcinoma (ILC). In a study by Dixon et al., when compared with ductal carcinomas, lobular carcinomas showed greater tendency for peritoneal, retroperitoneal, and gastrointestinal tract [95,96]. However, from our review of case reports there was greater number of spread to the appendix by invasive ductal carcinoma. For lung cancer, there was a large number of Small Cell Lung Cancer (SCLC) that metastasized to the appendix causing appendicitis. This is in congruent with published data demonstrating SCLC is highly metastatic, and 70% of patients by the time of diagnosis would have had metastatic disease [97]. The most common sites of gastric cancer metastasis are liver, peritoneum, lung, and bone [98]. Prior to proceeding with surgical resection in gastric cancer, a diagnostic laparoscopy is performed to exclude peritoneal metastasis because curative surgery for gastric cancer is only performed if there is no evidence of metastases [99]. In prostate cancer, the greatest distribution of metastatic sites are bone, distant lymph nodes, liver, and thorax [100].

Conclusion

Acute appendicitis secondary to metastatic malignancy is extremely uncommon. The percentage of complicated appendicitis in acute appendicitis due to metastatic malignancy is greater than the percentage of complicated appendicitis not due to metastatic malignancy. It is important to be cognizant of a patient's previous malignancy history when considering management for acute appendicitis.

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