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Brief Communication

Carcinoma Appendix: A Report of Four Cases and Review of Literature

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Primary appendicular carcinomas are rare and may present either as appendicitis or ruptured appendicitis. Its incidence is 1-2 cases per 100000 people per year in USA.[1] They are generally detected accidentally after appendicectomy; or incidentally on abdominal imaging or during colonoscopy or abdominal surgery.[1] Most common symptom is acute abdominal pain in the right lumbar region. It may be associated with other symptoms like fever, leukocytosis, etc. There classification depends on different histological sub-types. Surgery is the first line of treatment. Most masses in appendix are benign mucoceles or small carcinoids, requiring no further treatment. However, if large carcinoids, lymphoma, adenocarcinoma or neuroendocrine tumor is found, then the line of treatment varies.

Case History

Case 1

A 35-year-old male patientattended the Surgery OPD with the complain of occasional pain abdomen and vomiting. There was no history of fever or loss of weight. Routine blood investigations showed mild leukocytosis and Ultrasoundabdomen showed an appendicular lump. The patient underwent interval open appendicectomy and the excisedappendicectomy specimen which was 5.0×1.5 cm in size with attached mesoappendix, was sent for histopathological examination (HPE). On HPE, the appendiceal mucosa was lined with multilayered dysplastic epithelium with infiltration into mucosa and submucosa. All margins were free of tumor with no evidence of tumor deposits, lymphovascular invasion (LVI) or perineural invasion (PNI). These features were suggestive of Low grade appendiceal mucinous neoplasm (LAMN) (G1, well differentiated tumor) (Stage 1). (**Figure 1**)

The patient was asymptomatic with no specific complaints on follow up. Baseline investigations were found to be within normal limit, with post-op Contrast enhanced computed tomography (CECT) scan of Thorax, Abdomen and Pelvis showing no evidence of any lesion

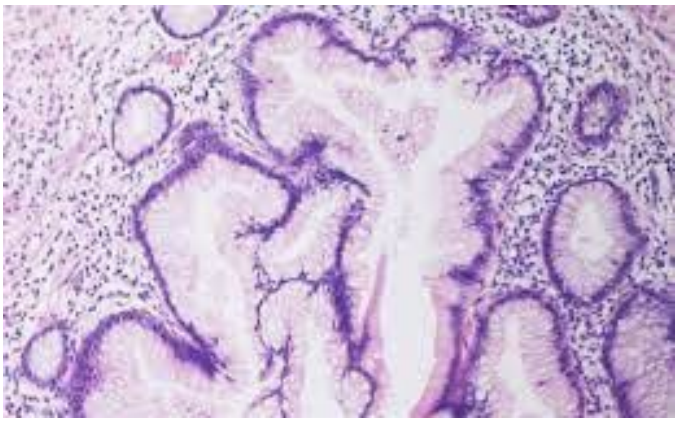

Figure 1: Histopathological report of appendicectomy specimen of Case 1 showing features suggestive of low grade appendiceal mucinous neoplasm (LAMN) (H & E stain).

or distant metastasis. The patient is under regular follow up with no active anti-cancer intervention, and is currently disease free for the past 6 months.

Case 2

A 57-year-old male patient came to the casualty with complains of lower abdomen pain for last 3-4 days, along with vomiting and fever. On local examination, rightlower abdomen was tender with no elevation of local temperature. Routine blood investigations showed marked leukocytosis, with Ultrasound screening of whole abdomen showing features of subacute appendicitis. The patient underwent emergency appendicectomy, and the excisedappendicectomy specimen was 4.5×0.7 cm in size with one cyst present at the tip filled with gelatinous material. On HPE, the appendiceal mucosa was lined with dysplastic epithelium with infiltration into the subserosa and mesoappendix. All margins were free of tumor with no evidence of tumor deposits, LVI or PNI. These features were suggestive of Low grade appendiceal mucinous neoplasm (LAMN) (Stage 2A).

The patient was asymptomatic with no specific complains on follow up. Baseline investigations along with post-op CECT scan of Thorax, Abdomen and Pelvis was found to be within normal limits with no evidence of any lesion or distant metastasis. The patient is on regular follow-up with no active anti-cancer intervention, and is currently disease free for the past 4 months.

Case 3

A 62-year-old male patient attended the Surgery OPD with the complain of lower abdomen pain for the past 10 days, along with occasional melena and constipation. There was no history of vomiting. On local examination, the right side of the abdomen was tender with raised local temperature. Routine blood examination showed marked leukocytosis and anemia. Ultrasound of whole abdomen showed appendicular mass with peri-appendicular fluid collection. The patient was treated with injectable antibiotics, blood transfusion and other supportive care. The patient was planned for right hemicolectomy, but due to the wide spread nature of the disease and the presence of regional lymph nodes, the patient only under went open appendicectomy and omentectomy. The excisedappendicectomy specimen was 5.0×1.0 cm in size with few fibro fatty tissue and was sent for HPE. On HPE, sheets of malignant cells with pleomorphic and hyperchromatic nuclei were seen in the appendiceal epithelium infiltrating up to the serosa. Malignant cells deposits were also seen in the omental tissue. These features were suggestive of colonic type adenocarcinoma (Stage 4A). Postoperative period was uneventful.

The patient attended the OPD at the Department of Radiation Oncology with the HPE report. Routine baseline investigations were done and were within normal limits. CECT scan of whole abdomen showed appendicectomy status with smooth diffuse wall thickening of distal ileum, caecum, and ascending colon; with multiple small mesenteric and pelvic lymphadenopathy. The patient was started on adjuvant chemotherapy with Injection Oxaliplatin and Tablet Capecitabine, three weekly cycles. Post six cycles of chemotherapy the patient is diseases free on imaging and is on regular follow up for the last six months.

Case 4

A 26-year-old male patient attended the Casualty with complains of acute lower abdomen pain for the past three days, along with fever and vomiting. There was no history of weight loss, or altered bowel habits. Routine blood investigations showed marked leukocytosis and Ultrasound screening of abdomen showed features suggestive of acute appendicitis with dilated appendix. The patient underwent emergency appendicectomy and the excisedappendicectomy specimen was 6.0×1.3 cm in size, with lumen obliterated with mucinous material. On HPE, the tumor was infiltrating the muscularis propria and subserosa, with presence of LVI. There was no evidence of PNI and all margins were free of tumor. Mitotic index was 1/10 HPF and Ki 67 labelling index was less than 3%. These features were suggestive of Neuroendocrine tumor of appendix (G1, well differentiated tumor) (Stage 2A). (**Figure 2**)

Post operative period was uneventful. After that the patient was referred to the Department of Radiation Oncology for further management. Baseline investigations were done and were found to be within

normal limit.CECT scan of Thorax, Abdomen and Pelvis showed no evidence of disease or distant metastasis. The patient received adjuvant chemotherapy with Injection Etoposide and Injection Ifosfamide, three weekly cycles, for a total of six cycles. The patient is currently under follow up, without no evidence of disease on imaging, six months post chemotherapy.

Discussion

According to the Surveillance, Epidemiology, and End Results (SEER) database, appendicular carcinoma accounts for 0.4% of all gastrointestinal tumors.[2] According to the AJCC 8th edition, appendicular carcinoma is classified into the following histological types: Adenocarcinoma in situ, Low grade appendiceal mucinous neoplasm (LAMN), Colonic-type adenocarcinoma, Mucinous carcinoma, Goblet cell carcinoma, Neuroendocrine neoplasm or Carcinoid tumors, Signet ring cell carcinoma, Undifferentiated carcinoma, Mixed adeno-neuroendocrine carcinoma, Carcinoma NOS, Lymphoma, Ganglioneuroma, and Benign tumors (Hyperplastic polyp, Cystadenoma, Retention cysts).

Colonic-type adenocarcinoma: It is the most common type of primary appendicular carcinoma, accounting for 60% of all cases. They can arise from pre-existing adenoma.[3] Mean age of diagnosis is 62 to 65 years with slight male predominance.[1] There is no specific staging system for this type of appendicular cancer; with the workup, staging and treatment mirroring that of colon cancer. AJCC, NCCN or ESMO guidelines for colonic cancer can be used for the T staging.

Patients with Tis tumors with negative margins are treated with appendicectomy only. For patients with favorable T1 tumor characteristics, treatment with appendicectomy is sufficient and for unfavorable T1 tumor, additional right hemicolectomy should be considered for adequate staging and resection. For patients with T2 or greater tumors, right hemicolectomy is indicated with dissection of 12 or more lymph nodes for accurate staging. Thus, for patients with Stage 3 disease, adjuvant chemotherapy is recommended in accordance with colon cancer. Adjuvant chemotherapy should also be considered for Stage 2 tumors with high-risk features.

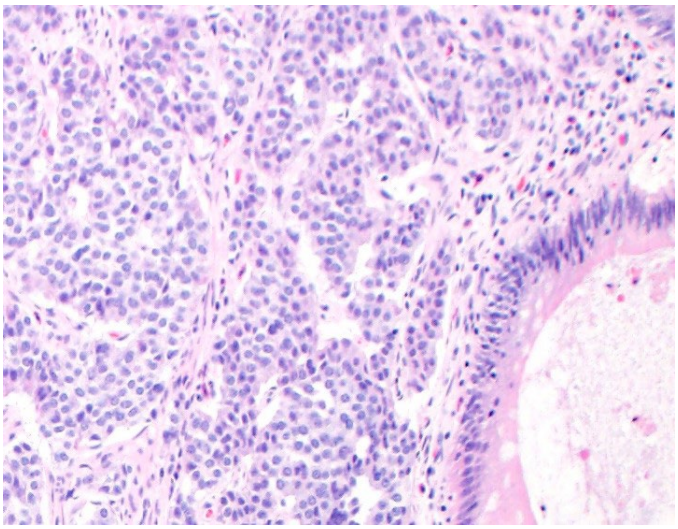

Figure 2: Histopathological report of appendicectomy specimen of Case 4 showing features suggestive of neuroendocrine tumor of appendix (H & E stain).

The rate of distant metastases at the time of presentation is not well known.[4] Surgical resection including metastasectomy of limited liver and lung lesions should be considered for selected patients with appendicular adenocarcinoma.

Mucinous carcinoma / neoplasm: It is both histologically and biologically a distinct entity from colorectal cancer and colonic-type adenocarcinoma of appendix. The mean age of diagnosis is 60 years with no sex predilection. Its grading and staginghave both therapeutic and prognostic implications. They exhibit a wide variety of clinical behavior, ranging from slow growing less aggressive neoplasm to highly aggressive neoplasm. On the basis of AJCC 8th edition, appendiceal mucinous neoplasms are classified into serrated polyp with or without dysplasia, low-grade appendiceal mucinous neoplasm (LAMN), high-grade appendiceal mucinous neoplasm (HAMN), mucinous adenocarcinoma with (≤ 50% cells are signet cells) or without signet ring cells, and mucinous signet ring cell carcinoma (> 50% cells are signet cells).[5]

LAMNs lack infiltrative invasion and are usually well-differentiated (G1, low grade). HAMNs are very rare, and may have high-grade cytology with features of infiltrative invasion. If HAMN is diagnosed than care should be taken to exclude the presence of associated invasive adenocarcinoma.

HAMNs is characterized by its infiltrative nature. The presence of any signet ring cell is another indicator for infiltrative mucinous adenocarcinoma. They are generally localized to the appendix, but can also be advanced with peritoneal deposits. Distant metastases through lymphatic or hematogenous route is rare.

AJCC 8th edition, did significant changes to the staging of appendiceal mucinous neoplasm, mainly for low-grade tumors. The pT1 and pT2 category is not applicable for LAMN, due to a number of features that are unique to it. Thereby, not allowing for proper staging of LAMN using conventional criteria used elsewhere in the GIT.

For patients with disseminated mucinous appendiceal neoplasms, pathological grade is an important prognostic factor. The prognosis and treatment depend on the grade and stage of the disease. Patients with Tis (LAMN) are treated with appendicectomy, with no risk of recurrence. Patients with LAMN T3 and LAMN T4a (with acellular mucin on visceral peritoneum) disease should be considered for regular follow up, due to the risk of developing peritoneal dissemination. For patients with LAMN T4a disease with cellular mucin deposits on visceral peritoneum, the role of additional surgery &/ or Hyperthermic Intraperitoneal Chemotherapy (HIPEC) therapy is unclear.

Patients with HAMN are treated with appendicectomy, butdue to its highly aggressive and disseminating behavior, these patients should undergo oncological resection with right hemicolectomy and evaluation of lymph node status.[6]

Patients with disseminated low-grade (G1, well-differentiated) mucinous neoplasm are treated with Cytoreductive surgery (CRS) and HIPEC.[7] For patients with Stage 4 low-grade mucinous neoplasm, systemic chemotherapy is not effective. For patients with Stage 4 (G2 & G3) mucinous adenocarcinoma, systemic chemotherapy improves overall survival. Patientswith unresectable high-grade (G2 or G3) adenocarcinoma are treated with only chemotherapy.[8]

Goblet cell carcinoma (GCC): It accounts for 14% to 19% of primary appendicular carcinoma.[9] It is a mixed tumor consisting of both epithelial and neuroendocrine elements containing goblet cells. Its prognosis lies between appendiceal neuroendocrine tumors and primary appendiceal adenocarcinoma. The mean age of diagnosis is 52 years, with no sex predilection and no known risk factors.[10] The AJCC 8th edition staging system, classifies GCC on the basis of tumor size, nodal status and metastatic disease.[11] GCC displays a variety of histological features and has the potential to transform into an aggressive adenocarcinoma phenotype.[12]

Patients with tumor < 2 cm having negative surgical margin; and with pT1 or pT2 tumors, are treated with appendicectomy alone.[13] Patients with Stage 3 and selected patients with Stage 2 disease generally require adjuvant chemotherapy. Right hemicolectomy is the most common treatment approach for localized disease, with adjuvant chemotherapy being considered for lymph node positive patients or Stage 3 patients.[14]

Appendicular neuroendocrine neoplasm belongs to a subgroup of neuroendocrine tumor (NET) with a mean age at the time of diagnosis between 38 to 48 years. They are the second most common malignancy of the appendix after adenocarcinoma. The histopathological characteristics of appendiceal NET includes confirmation of neuroendocrine entity by immunohistochemical staining for Chromogranin A, Neuron-specific enolase (NSE) and Synaptophysin; along with Ki67 to determine the tumors proliferative capacity.[15] NET of appendix is usually G1 or G2. The pathology report should include the WHO grading, pTNM staging according to AJCC classification or European Neuroendocrine Tumor Society (ENETS) or both, vascular and lymphatic involvement and the status of any mesoappendix's infiltration.[16]

They generally present with signs and symptoms of acute abdomen, otherwise they are mostly asymptomatic. Carcinoid syndrome is seen in around 10% of patients only. Serum Chromogranin A and Urinary 5-HIAA levels can also be used for diagnosis. The surgical extent depends on the size of the tumor, but as appendiceal NET are diagnosed incidentally on routine appendicectomy, a second surgery is sometimes indicated.

For appendiceal NET < 1 cm, appendicectomy alone is the preferred treatment option, with one exception when the NET is located at the base of the appendix or when the mesoappendix invasion is >3 mm. For tumors > 1 cm but < 2 cm, right hemicolectomy should be considered. For tumors >2 cm, right hemicolectomy with lymph node dissection should be considered, due

to increased risk of lymph node metastases, recurrence and distant metastases.[17] Patients with high-grade tumor (G3), should undergo oncological lymph node dissection, irrespective of the tumor size.

Appendiceal NET <2 cm with R0 resection requires no follow up, but for other appendiceal NET, patients should be advised for long term follow up. For patients with unresectable tumor or unfit for surgery;somatostatin analogues, everolimus and peptide receptor radionuclide therapy may be considered.

Lymphoma: The GIT is the most common site for extra-nodal lymphoma, with stomach being the most common organ involved. Appendicular lymphomas are exclusively Non-Hodgkin's B-cell Lymphoma, especially Burkitt's Lymphoma. The incidence of primary appendiceal lymphoma is 0.015% of appendicectomy specimen,[18] with a median age of onset of 18 years. Patients generally presents with symptoms similar to acute appendicitis.

Postoperative adjuvant chemotherapy is the treatment of choice, with the most commonly used chemotherapy regimen being Cyclophosphamide, Doxorubicin, Vincristine and Prednisolone (CHOP). If the tumor is CD20 positive, Rituximab needs to be added along with CHOP regimen. The combination of CHOP with Rituximab has increased both the event free survival and overall survival.

Conclusion

Primary appendicular carcinomas are rare, and generally detected incidentally on HPE of the appendicectomy specimen. There are four main histological types, with treatment option being considered on the basis of subtype, grading and stage of the tumor. Appendicular carcinoma possesses a challenge, for both diagnosis and treatment. There is no standard line of treatment due to the rarity of the condition. Simple appendicectomy is the treatment of choice for early- stage appendiceal neoplasm, except for mucinous adenocarcinoma. For locally advanced appendiceal neoplasms and mucinous adenocarcinoma, additional surgery with right hemicolectomy and lymph node assessment is required. This article presents a review of four cases diagnosed with appendicular carcinoma, along with a review of literature into the classification, diagnosis, and treatment options available for appendiceal carcinoma.

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