DOI: 10.38103/jcmhch.78.2

Case Series

SIX CASES OF APPENDICEAL CANCER: LITERATURE REVIEW, DIAGNOSIS AND TREATMENT

Tran Nguyen Ha[1], Phan Thi Hong Duc[1], Luong Hoang Tien[1]✉

[1]Internal Medicine of Breast, Gastroenterology, Hepatology, Urology Department, Ho Chi Minh City Oncology Hospital

Received:
23/02/2022
Revised:
17/3/2022
Accepted:
25/03/2022
Corresponding author:
Luong Hoang Tien
Email:
dr.hoangtienluong@gmail.com
Phone: 0907889176

ABSTRACT

Appendiceal cancer is a very rare disease. Based on 6 cases of appendiceal cancer who were admitted to the Internal Medicine of Breast, Gastroenterology, Hepatology, Urology, Department, Oncology Hospital of Ho Chi Minh City from September 2019 to March 2021, we evaluate the available literature review about diagnosis and treatment of appendiceal cancer. Four out of 6 cases were diagnosed with stage IV disease, only 1 case was in stage II, and 1 case with undermined stage. All cases were treated with Capecitabine-based chemotherapy, 5 out of 6 were treated with Capecitabine and Oxaliplatin combination, while the other was treated with Capecitabine monotherapy. We didn't use hyperthermic intraperitoneal chemotherapy in any of those cases because of technical limitations at Ho Chi Minh City Oncology Hospital. Up to the time of reporting, all 6 cases are being monitored for survival.

Keywords: *Appendiceal cancer, diagnosis, chemotherapy.*

I. INTRODUCTION

Cancer of the appendix is very rare, and there are many heterogeneous forms of the disease. Therefore, early diagnosis and treatment is also a clinical challenge. Based on 6 cases diagnosed at Ho Chi Minh City Oncology Hospital, we re - evaluate the literature overview, diagnosis, and treatment of patients with appendiceal cancer. McCusker et al classified malignant appendiceal tumors into the following histopathological categories: epithelial mucinous tumors, neuroendocrine tumors, goblet cell tumors, composite carcinoid, lymphomas, sarcomas, and adenocarcinomas. 65% of which are neuroendocrine tumors, the remaining 20% are adenocarcinomas (mucinous adenocarcinoma, signet ring, or non - mucinous) [1]. Reports suggest that signet ring cell and poorly differentiated carcinoma have a much worse prognosis than other histopathological forms.

Patients often are presented with abdominal pain like appendicitis, intermittent pain, pain in the right iliac fossa [2]. In addition, there may be abdominal distension, loss of appetite, digestive disorders, nausea, vomiting, bowel obstruction, and fever may be present. In advanced stages, patients may have mucus in the peritoneal cavity, severe abdominal pain, weight loss, anemia, umbilical hernia, inguinal hernia, and in some rare cases, intestinal obstruction may occur. Diagnosis by computed tomography (CT), magnetic resonance (MRI), ultrasound and colonoscopy, and cancer markers CEA, CA19-9, CA12-5 help evaluate the response to treatment and prognosis. Appendiceal cancers stain positive for CK20 (100%) and negative for CK7 (71%). In addition, the MUC5AC gene mutation and the DPC4 mutation were positive in 86% and 100%, respectively [3]. When conducting gene expression profile analysis, Levine found that high gene expression profile predicts poor prognosis (regardless of grade, physical condition, age, and PCI score) [4].

In terms of treatment, appendectomy is the primary treatment in locally staged appendiceal cancer. For low - grade appendiceal mucinous

tumors with peritoneal nodular metastases, surgery remains controversial. Survival of this group is 3 years (100%), 5 years (86%), 7 years (60%) and 10 years (45%) [5]. In those patients diagnosed with non - mucinous adenocarcinoma (NMAC), mucinous adenocarcinoma (MAC) and signet ring cell carcinoma (SRCC), chemotherapy significantly improved cancer - specific and overall survival [6]. Adjuvant chemotherapy with a 5-FU and Oxaliplatin regimen is given when the disease is at high risk, such as poorly differentiated (signet ring cell), lymph node metastasis, and tumor rupture. For low - grade, well - differentiated disease without high - risk factors (similar to colorectal cancer), adjuvant chemotherapy is not required. If peritoneal metastasis is presented, cytoreductive surgery is chosen, followed by intraperitoneal chemotherapy (HIPEC) [7]. Preoperative chemotherapy only has a 29% of response, and 50% continues to progress even after chemotherapy [8]. Follow-up plans are similar to colorectal cancer.

II. CASES SERIES

2.1. Patient characteristics

Table 1: Patient characteristics

Gender	Age		N (%)
	< 60	60	
Male	0	1	1 (17%)
Female	3	2	5 (83%)
Total	3 (50%)	3 (50%)	6

The median age of this group was 54.5. There was 1 patient with hypertension, and 1 patient with impaired glucose tolerance.

5 patients were admitted to the hospital because of abdominal pain in the right iliac fossa, 1 patient was admitted to the hospital because of a palpable pelvic mass and no pain.

2.2. Clinical and pathological characteristics

1 patient was diagnosed at stage II, accounting for 17%. 4 patients were diagnosed at stage IV, accounting for 66%, and 1 patient had an undetermined stage disease.

Table 2: Tumor markers

Patient	CA 19-9 (U/ml)	CEA (ng/ml)	CA 12-5 (U/mL)
1	Not indicated	24	56.7
2	11.7	1.6	34.6
3	9.49	1.57	22.4
4	620	29.4	Not indicated
5	12.1	1.5	Not indicated
6	23.4	7.7	43.1

All six patients were tested for CEA, in which two patients had high levels compared to 2.5ng/ml cut-off. In five patients who were tested for CA 19-9, we observed that one patient had absurdly high level of this tumor marker, which is 620 U/ml. For CA 12-5, four out of six were tested, in which two was noted to have slightly increase levels.

Table 3: Imaging results

Features	Ultrasound	Computed tomography (CT)
Pelvic and hypogastric mass	3 (50%)	4 (67%)
Mucinous fluid in the abdominal cavity	4 (67%)	4 (67%)
Diffuseperitoneal lesions	1 (17%)	1 (17%)

All 6 patients had a negative colonoscopy.

Tumor sizes assessed post-surgery are: 3cm, 5cm, 6cm, 12cm, 20cm, respectively. In which, 1 case could not evaluate the tumor size. The most frequent metastatic site was the peritoneum (60%). The other metastatic sites were ovarian and uterine metastasis, with 1 case each.

Table 4: Pathological classification

Pathological classification	N (%)
Low-grade appendiceal mucinous neoplasms (LAMN)	3 (50%)
Mucinous adenocarcinoma grade 1	1 (17%)
Poorly differentiated mucinous adenocarcinoma	2 (33%)

We performed immunohistochemical staining for 2 cases. Both cases had CDX2 expression (+) and normal expression of MLH1, MSH2, MSH6, PMS2 (MSS).

2.3. Treatment

Table 5: Treatment

	Type of treatment	N (%)
Surgery	Appendectomy and omentectomy	1 (17%)
	Appendectomy, ometectomy, and oophorectomy	2 (33%)
	Appendectomy	1 (17%)
	Bypass surgery	1 (17%)
	Exploratory laparotomy - Biopsy	1 (17%)
Chemotherapy		
	Capecitabine - Oxaliplatin	5 (83%)
	Capecitabine monotherapy	1 (17%)

III. DISCUSSION

At our department, only 6 cases were recorded within 18 months (from September 2019 to March 2021). According to McCusker's study, female patients with appendiceal mucinous tumors accounted for 51% to 62% [1,9], and according to Nutu's, the median age was 64 [9], whereas in our reports, 5 out of 6 patients were female (83%). In the group of patients we observed, there were 3 patients < 60 years old, and 3 patients 60 years old, with a median age of 60 [1]. This is also consistent with the documented literature and also because in adults, the highest cancer incidence is also in this age group. Clinical presentation is usually asymptomatic or nonspecific symptoms [10]. Regarding the reason for admission, 5 out of 6 patients had pain in the right iliac fossa, and the disease was detected only through laboratory tests. The remaining 1 patient was completely pain-free, and was admitted to the hospital because of a palpable pelvic mass. For these patients, 2 cases (33%) were diagnosed with appendiceal mucinous tumor pre - surgery, 3 cases (50%) were misdiagnosed with ovarian tumor. Thus, this is also consistent with the literature according to the study of Carr et al., because 32% of patients were misdiagnosed pre-surgery [11]. The misdiagnosis may be due to the atypical and imaging features on abdominal CT scans and abdominal ultrasound, making it difficult to differentiate tumors from the ovaries or from the appendix. Therefore, we can only make an accurate diagnosis during surgery and after the pathological results are available. All six patients underwent colonoscopy, but all had negative tests, while the literature reported that 13% to 42% of appendiceal cancer patients had concurrent colorectal tumors [9,12].

Most of our patients were diagnosed with stage IV disease (accounting for 66%), only 1 case was detected at stage II (17%), and 1 patient could not be staged. This is comparable with other reports, in which 53.2% of the disease was detected at stage IV, and 26.3% was at the early stage. The most common site of metastasis in our group of patients was peritoneum (60%), other sites were uterine metastases (20%) and ovarian metastasis (20%), no other metastatic sites outside the abdomen were recorded. This is consistent with previous reports of other authors: 53.2% peritoneal metastases and 55% ovarian metastases [12].

We only had immunohistochemical staining for 2 cases, in which both cases had caudal type homeobox 2 (CDX-2) positive, and normal expression of MLH1, MSH2, MSH6, PMS2. This is similar When compared to 22 LAMN patients of Yiyan's study, the immunohistochemical showed the same pattern of cytokeratin 7 (CK7) negative, cytokeratin 20 (CK20) positive, and CDX-2 positive [13].

In addition, tumor biomarkers such as CEA, CA19-9 and CA 12-5 are used to monitor the response to treatment. Among our 6 cases, 1 patient had unresectable stage, who underwent exploratory laparotomy and biopsy, and were presented with very high CA19-9 level (620 U/ml). This tumor marker level did not decrease even after chemotherapy, therefore it can be inferred that this patient would have much worse progression free survival (PFS), despite the fact that the histopathological type of this patient is mucinous adenocarcinoma grade 1 [12,14].

Regarding treatment, our stage II patient underwent right hemicolectomy. This patient received adjuvant chemotherapy thereafter, due to high - risk factors such as tumor rupture during surgery and poorly differentiated mucinous adenocarcinoma. The remaining cases were

appendectomy, omentectomy, removal of metastatic organs such as ovaries, uterus, and then chemotherapy. All 6 of our patients received chemotherapy, in which 5 patients received chemotherapy with Capecitabine - Oxaliplatin and 1 patient received Capecitabine monotherapy. According to the literature, adjuvant treatment after optimal surgery has proven to achieve great benefit in terms of overall survival [15].The 5 - year overall survival was 100% for appendiceal mucinous carcinoma and 62% for peritoneal pseudmyxoma [16]. However, due to the short observation period, we could not assess the overall and disease-free survival of these patients.

Besides, at Ho Chi Minh City Oncology Hospital, we have not performed intraperitoneal chemotherapy (HIPEC) due to technical limitations. However, HIPEC has been shown to be beneficial in terms of PFS in patients with diffuse peritoneal appendiceal cancer.

IV. CONCLUSION

Appendiceal mucinoma is a rare, heterogeneous group of tumors with an increasing incidence. Treatment of appendiceal tumors is mainly based on stage and histopathology. Low-grade tumors are treated with resection at the early stage, or cytoreductive surgery and HIPEC in the advanced stage. High-grade tumors may opt for surgery and HIPEC, with or without preoperative chemotherapy. Adjuvant chemotherapy for high-risk patients such as tumor rupture, poorly differentiated carcinoma, and lymph node metastasis.

REFERENCES

1. McCusker ME et al. Primary malignant neoplasms of the appendix: A population- based study from the surveillance, epidemiology and end-results program, 1973-1998. Cancer. 2002; 94:3307-3312.
2. Sugarbaker PH. New standard of care for appendiceal epithelial neoplasms and pseudomyxoma peritonei syndrome, Lancet Oncol. 2006;7:69-76.
3. Ji H, et al. Cytokeratins 7 and 20, Dpc4, and MUC5AC in the distinction of metastatic mucinous carcinomas in the ovary from primary ovarian mucinous tumors: Dpc4 assists in identifying metastatic pancreatic carcinomas. Int J Gynecol Pathol. 2002;21:391-400.
4. Levine EA, et al. Prognostic molecular subtypes of low-grade cancer of the appendix. J Am Coll Surg 2016; 222:493-503. 5. Pai RK, et al. Appendiceal mucinous neoplasms: Clinicopathologic study of 116 cases with analysis of factors predicting recurrence. Am J Surg Pathol. 2009;33:1425-1439.
5. Nutu OA, M.Q.A., Manrique Municio A, Justo Alonso I, Calvo Pulido J, García-Conde M, Tumores mucinosos del apéndice: incidencia, diagnóstico y tratamiento quirúrgico. Cir Esp. 2017. 95: p. 321-327.
6. Leiting, J.L., et al., The impact of HIPEC vs. EPIC for the treatment of mucinous appendiceal carcinoma: a study from the US HIPEC collaborative. International Journal of Hyperthermia, 2020. 37(1): p. 1182-1188.
7. Wang, G., Q. Li, and W. Chen, Chemotherapy in the treatment of different histological types of appendiceal cancers: a SEER based study. BMC Cancer. 2021. 21(1): p. 778.
8. Mehmet Sitki Copur, M., Allison M. Cushman-Vokoun, MD, PhD, James Padussis, MD, Whitney Wedel, MD, Caleb W. Schroeder, MD, Daniel J. Herold, MD, Nicholas Lintel, MD, Adam J. Horn, MD, Mucinous Adenocarcinoma of the Appendix With Histologic Response to Neoadjuvant Chemotherapy: Review of Histologic and Clinical Spectrum of Epithelial Neoplastic Mucinous Lesions of the Appendix. ONCOLOGY. 2021. 35(6): p. 335-340.
9. Carr NJ et al, Epithelial non- carcinoid tumors and tumor-like lesions of the appendix. A clinicopathologic study of 184 patients with a multivariate analysis of prognostic factors. Cancer. 1995;75:757-768.
10. Glasgow, S.C., et al., The American Society of Clon and Rectal Surgeons, Clinical Practice Guidelines fo the Management of Appendiceal Neoplasms. Diseases of the colon & rectum. 2019. 62: p. 1425-1438.
11. Lu, Y., et al., Clinicopathological Features of Low-Grade Appendiceal Mucinous Neoplasms Confined to the Appendix. Frontiers in Oncology. 2021. 11.
12. Chen W, Ye JW, Tan XP et al. A case report of appendix mucinous adenocarcinoma that recurred after additional surgery and a brief literature review. BMC Surg. 20, 182 (2020).
13. Hoehn RS et al. Current Management of Appendiceal Neoplasms. American Society of Clinical Oncology Educational Book. 2021(41): p. 118-132.
14. Dulskas A et al. Long-Term Outcomes after Surgery for Appendiceal Mucinous Tumours. Visceral Medicine. 2018. 34(2): p. 151-155.