International Journal of Science and Research (IJSR)
ISSN: 2319-7064
SJIF (2022): 7.942

Understanding Glandular Cell Carcinoma of the Appendix: Pathology, Diagnosis, and Management Strategies

Rathin Joshi[1], Abiy Tereda[2], Saheli Kansara[3], Kirtan Patel[4]

[1]GMERS Himmatnagar, Gujarat, India
Email: rathinjoshi2002[at]gmail.com

[2]Georgetown American University, U.S.
Email: abiykifle[at]hotmail.com

[3]GMERS Himmatnagar, Gujarat, India
Email: stkansara212[at]gmail.com

[4]MERS Himmatnagar, Gujarat, India
Email: patelkir10p[at]gmail.com

Abstract: ***Appendiceal adenocarcinoma, a rare malignancy originating from glandular cells, poses significant challenges in diagnosis and treatment due to its rarity and complex presentation. This review provides an indepth exploration of the pathology, diagnostic challenges, and management strategies for this malignancy. Despite its location within the gastrointestinal tract, the appendix's exact function remains elusive, though research suggests roles in microbiota regulation, endocrine cell production, and immune modulation. Epidemiologically, adenocarcinoma of the appendix is exceptionally rare, with a slight increase in prevalence observed recently, predominantly affecting individuals in their fifth to seventh decades, with gender-specific patterns evident in subtypes. Histologically, it manifests through glandular formations, cytological abnormalities, tissue infiltration, and mucin secretion, defining distinct subtypes with varying clinical implications. Surgical excision remains the cornerstone of treatment, supplemented by chemotherapy and emerging targeted therapies. The review also delves into the molecular mechanisms, including genetic mutations, that underlie the development of glandular cell carcinoma of the appendix.***

Keywords: Appendiceal adenocarcinoma, glandular cell carcinoma, appendix cancer, pathology, management strategies

1. Introduction

Glandular cell carcinoma of the appendix presents a formidable challenge in diagnosis and treatment due to its rarity and unique clinical characteristics. Despite its infrequent occurrence, this malignancy demands careful consideration given its potential implications for patient outcomes. In this extensive review, we embark on a detailed exploration of appendiceal glandular cell carcinoma, examining its pathological manifestations, diagnostic methodologies, and therapeutic interventions.

- **Epidemiology and Occurrence**: While glandular cell carcinoma constitutes only a small fraction of appendiceal tumors, its scarcity does not diminish its clinical importance. Understanding its prevalence, age-related distribution, and associated risk factors is paramount for early detection and optimal management.
- **Pathological Characteristics**: We delve into the histopathological features of glandular cell carcinoma, emphasizing critical aspects such as mucin production, architectural patterns, and immunohistochemical markers. Comprehensive insights into tumor grading and staging are indispensable for accurate classification and prognostic assessment.
- **Diagnostic Complexity**: Diagnosing glandular cell carcinoma poses significant challenges due to its nonspecific symptoms and lack of distinctive radiological findings. We explore the role of various diagnostic modalities, including imaging, endoscopy, and histopathology, in achieving timely and precise diagnoses.
- **Genetic and Molecular Insights**: Recent advancements have illuminated the genetic alterations underlying appendiceal glandular cell carcinoma. We discuss somatic mutations, chromosomal abnormalities, and potential therapeutic targets identified through molecular profiling.
- **Multidisciplinary Management Approach**: Effective management necessitates collaboration among surgical, oncological, and pathological specialists. Surgical resection, chemotherapy, and emerging targeted therapies constitute the cornerstone of treatment. We underscore evidence-based strategies and ongoing clinical trials shaping contemporary management protocols.

This review endeavors to heighten clinical awareness, streamline diagnostic protocols, and enhance patient care by unraveling the complexities surrounding glandular cell carcinoma of the appendix. Given the rarity of glandular cell carcinoma of the appendix, this review aims to enhance clinical awareness and improve patient outcomes through a comprehensive examination of the current understanding and treatment strategies for this malignancy.

Join us on this journey as we navigate through the intricacies of this rare yet impactful malignancy.

Anatomy and Physiology of the Appendix

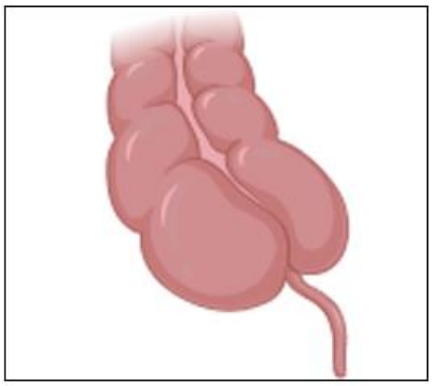
The Appendix is a blind-ending, vermiform (Worm-like) structure that typically originates inferior to the ileocecal valve from the posteromedial wall of the cecum. It has an average length of 6-9cm in adults and is suspended from the terminal ileum by the mesoappendix, which contains blood vessels and Lymphoid tissue.

The appendicular wall consists of Four layers like Most structures in the Gastrointestinal Tract include Mucosa (Epithelium and Muscularis Mucosa), submucosa. muscularis propia, and serosa. A normal collapsed appendix on computed tomography (CT) is ≤ 6 mm but it can measure up to 10 mm if it's distended by air or contrast material

It is mostly found in the right lower quadrant (RLQ).In half of the individuals its Retrocecal while it can also be pelvic, right upper quadrant, and in 1 % of individuals it can be found in the Left Upper Quadrant

Despite the mysterious nature of the appendix, its yet to be identified what the exact functions are. Some of the suspected functions include:

- **Beneficial gut flora**: some studies showed that the Appendix is responsible for the Cultivation of beneficial gut bacteria which are useful for repopulation of the digestive system after an illness wipes the normal population.
- **Endocrine cell production**: Earlier in fetal development, the Appendix plays an important role by producing molecules that are essential in regulating homeostasis.
- **Immune system**: The appendix may expose white blood cells (Leukocytes) to antigens in the gastrointestinal tract by modulating immune reactions in the gut [1][2]



Epidemiology

Glandular carcinoma of the appendix is very rare, in the United States it affects approximately 0.12 per 1.000.000 people annually. It is diagnosed in the fifth to seventh decade of life. some studies showed that there is a very slight female predominance for mucinous adenocarcinoma and signet ring cell adenocarcinoma subtypes while the nonmucinous adenocarcinoma is predominant in male

Even though the number of diagnosed cases of appendix cancer increased over the last decades, the prevalence of Glandular carcinoma is 1 to 2 people out of every 1 million individuals

Data collected from patients who underwent appendectomy between 2010 to 2018 in two municipal hospitals in the Bronx, New York, USA by the National Surgical Quality improvement program (NSQIP) showed a 1.7% incidence of appendiceal neoplasms locally and a 0.53% incidence in a national population sample. Both local and national populations demonstrated an increased incidence of appendiceal carcinoma with age, particularly after 40 years old. The incidence of appendiceal tumors increased with each decade interval up to the age of 80, peaking at 2.1% in patients between 70 and 79 years [3]

Pathology

Histological features of glandular carcinoma of the appendix.

Glandular carcinoma of the appendix also known as Adenocarcinoma of the appendix is a very rare malignancy arising from the glandular cells lining the appendix. It displays gland-like structures, and abnormal cellular features, invades surrounding tissues, and may produce mucin.

a) **Gland Formation**:

- Glandular carcinoma of the appendix displays structures that resemble normal glandular tissue found in the appendix.
- These glandular formations consist of tumor cells arranged in a gland-like pattern.

b) Cytological Atypia:

- Cytological atypia refers to abnormal cellular characteristics observed under a microscope.
- In glandular carcinoma, the tumor cells exhibit irregular nuclear features, such as varying nuclear size, shape, and prominent nucleoli.
- These atypical cells deviate from the typical appearance of healthy glandular cells.

c) Invasion into Surrounding Tissues:

- Glandular carcinoma often invades neighboring tissues beyond the appendix.
- Invasion occurs in structures like the muscularis propria (the muscle layer of the intestinal wall) or the subserosa (the layer beneath the serosa, which covers the outer surface of the appendix).
- This invasive behavior contributes to the tumor's potential to spread locally.

d) Mucin Production:

- Some cases of glandular carcinoma exhibit abundant mucin production.
- Mucin is a gel-like substance produced by certain epithelial cells.
- Within the tumor, mucin can accumulate, forming pools or lakes of mucin.
- This mucinous component contributes to the tumor's histological appearance. [4][5]

Subtypes

a) Colonic-Type Adenocarcinoma:

- Resembles colorectal adenocarcinoma.
- Often happens in the tip of the appendix.
- Histologically like adenocarcinomas arising in the colon.
- May invade surrounding tissues.
- Exhibit varying degrees of differentiation.

b) Mucinous Neoplasms:
- Characterized by abundant mucin production.
- Tumor cells are embedded in pools of extracellular mucin.
- Subtypes include low-grade and high-grade mucinous neoplasms.

c) Goblet Cell Carcinoma (GCC):
- Rare subtype of appendiceal adenocarcinoma.
- GCC cells exhibit goblet cell differentiation, producing mucin and displaying neuroendocrine characteristics.
- Looks and acts like neuroendocrine and colonic-type adenocarcinomas but are more aggressive than Neuroendocrine tumors.

- **Signet Ring cell Adenocarcinoma**
  is a very rare and aggressive form of appendicular cancer, that resembles signet rings under a microscope

- **Neuroendocrine/Carcinoid Tumor**
  usually occurs near the tip of the appendix.

- **Appendiceal Mucoceles**
- Mucoceles are small sacs filled with mucous within the appendix, those sacs can be either cancerous (Malignant) or Non-cancerous(benign)

- **Paraganglioma**
  Those are rare tumors that usually have a benign (non-cancerous) nature and arise from specialized cells called paraganglia and are infrequently encountered in the appendix.

Molecular mechanisms underlying tumor development and progression

The Molecular mechanisms underlying Glandular carcinoma of the appendix include: [6]

a) **RAS–RAF–MEK–ERK Signaling Pathway**:
- This pathway drives cancer cell proliferation.
- Key players include RAS family proteins (KRAS, HRAS, NRAS), which link extracellular signals to intracellular responses.
- Aberrations in this pathway, including mutations, contribute to appendiceal cancers.

b) **TP53 and RB1 Genes**:
- TP53 (p53) ensures cell fate when genetic material is altered.
- RB1 arrests cells in G-phases to prevent proliferation.
- Mutations in these genes disrupt cell cycle control, promoting tumor growth.

c) **WNT Signaling Pathway**:
- Normally regulates tissue development and repair during embryogenesis.
- Dysregulation in adults is associated with various cancers, including colorectal and breast cancer.
- Mutations in WNT pathway genes (APC, AXIN1, RHOA, TCF7L2) occur in some appendiceal cancers.

2. RAS–RAF–MEK–ERK Signaling Pathway

2.1 RAS Gene Family

Among the three members constituting the RAS gene family, in the context of appendiceal cancers, the predominant mutations manifest in the KRAS gene, eliciting an activating influence. Encapsulated within the KRAS gene lies the blueprint for the membrane-associated GTPase protein KRAS, which orchestrates critical roles in cellular division and proliferation. Dormant in mature individuals, the KRAS gene undergoes reactivation through missense mutations, predominantly single-amino-acid substitutions. These mutations engender an aberrant KRAS protein, thereby instigating unbridled cellular proliferation.

The reinstatement of KRAS gene functionality due to mutational events is a recurring theme across various tumor manifestations notably those afflicting the gastrointestinal tract Within appendiceal tumors, KRAS gene mutations are prevalent, identified in over 50% of cases. They are discernible in epithelial tumors, encompassing sessile serrated lesions with or without dysplasia, low-grade appendiceal mucinous neoplasms (LAMN), high-grade appendiceal mucinous neoplasms (HAMN), mucinous adenocarcinomas of the appendix [, non-mucinous adenocarcinomas of the appendix, and appendiceal goblet cell adenocarcinoma, yet conspicuously absent in neuroendocrine tumors of the appendix. Among the array of single-amino-acid substitution (missense) mutations characterizing KRAS protein perturbations in appendiceal cancers are Gly12Asp/Val/Ser/Arg/Cys and Gly13Asp/Arg/Cys. It is noteworthy that mutations in the other two family members, HRAS and NRAS, occur with substantially lower frequency [7][8][9].

2.2 RAF Gene Family

The family of RAF genes, abbreviated for rapidly accelerated fibrosarcoma, encompasses three distinct mammalian genetic elements known as Raf-1/c-Raf, B-Raf, and A-Raf, all utilizing MEK1/2 kinases as their substrates [19]. During the prenatal period, members of the RAF family exhibit heightened activity, crucially supporting the embryonic and fetal growth and development processes. However, postnatally, as the rapid growth phases diminish, their activity undergoes a significant reduction, often only being reactivated through mutational events, particularly evident in various tumorigenic contexts.

Within appendiceal cancers, the most frequently altered gene within the RAF family is BRAF (rapidly accelerated fibrosarcoma B), located on chromosome 7q34. This gene encodes the serine/threonine kinase BRAF (consisting of 766 amino acids; with a molecular weight of 84,437 Da) and commonly harbors the missense mutation Val600Glu, which contributes to its activation. This mutation is associated with cardiofaciocutaneous, Noonan, and Costello syndromes, as well as several types of cancer, including non-Hodgkin's lymphoma, colorectal cancer, thyroid carcinoma, non-small-cell lung carcinoma, hairy cell leukemia, and lung adenocarcinoma [12].

In appendiceal tumors, the prevalent mutation in the BRAF gene is V600E, detected in less than 5% of cases of sessile serrated lesions without dysplasia [12], low-grade appendiceal mucinous neoplasms [13], appendiceal goblet cell adenocarcinomas, well-differentiated neuroendocrine tumors of the appendix [14], and mucinous adenocarcinomas of the appendix. Additionally, a pseudogene of BRAF is present on the X chromosome.

2.3 TP53 Signaling Pathway

The gene known as TP53, situated on locus 17p13.1, encodes the tumor suppressor protein P53, also referred to as TP53 or protein 53, with a molecular structure consisting of 393 amino acids and weighing 43,653 Da. Renowned as the guardian of the genome due to its indispensable role in cellular function maintenance, P53 holds a pivotal position within the TP53 signaling pathway. It serves crucial functions in safeguarding DNA integrity, orchestrating DNA repair mechanisms during cell division, differentiation, and senescence, regulating metabolic processes, and curtailing tumor initiation and progression. Operating as a transcription factor localized within the nucleus of all cells, P53 directly interfaces with genetic material, becoming activated in response to cellular stress signals such as oncogene activation, DNA damage, and replication stress. Its activation leads to the transcriptional regulation of stress-specific genes and influences cellular fate determination, intricately intertwining with cancer signaling pathways, notably its interplay with HIF1A. [15][16] The expression of the HIF1A gene is induced under conditions of reduced intracellular oxygen pressure, with the HIF1A protein triggering TP53 activation, thereby impeding tumorigenesis. TP53 undergoes degradation within proteasomes through ubiquitin-dependent/independent mechanisms mediated by MDM2, the Human Homolog of Mouse Double Minute 2. Mutations within the TP53 gene, resulting in aberrant protein synthesis, are observed across various malignancies, including Li Fraumeni syndrome, predisposing individuals to early-onset tumors.

In the context of appendiceal tumors, TP53 mutations are infrequent in low-grade appendiceal mucinous neoplasms, serving as markers for progression to high-grade tumors. Conversely, they occur more frequently in high-grade appendiceal mucinous neoplasms and appendiceal adenocarcinomas, including mucinous adenocarcinomas, signet ring cell adenocarcinomas, and appendiceal goblet cell adenocarcinomas. TP53 inactivation via mutations significantly contributes to the aggressive nature of these tumors. Additionally, TP53 mutations are identified in well-differentiated neuroendocrine tumors of the appendix.[17][18]

3. Wnt/β-Catenin Signaling Pathway

3.1 APC Gene

The APC gene (located at 5q22.2) enciphers the APC–Adenomatosis Polyposis Coli Tumor Suppressor protein (comprising 2843 amino acids; with a molecular weight of 311,646 Da), possessing regulatory influence over the WNT signaling pathway. The WNT signaling pathway actively participates in tissue morphogenesis and repair, functioning physiologically during embryonic and fetal stages. In adulthood, this pathway is impeded via β-catenin inactivation, facilitated by the assembly of a complex involving GSK3–Glycogen Synthase Kinase-3, APC–Adenomatosis Polyposis Coli, AXIN–Axis Inhibitor, and CKIa–Casein Kinase Ia [20]. Mutations that deactivate genes encoding components of this complex hinder its formation, consequently allowing for the activation of the canonical (β-catenin-dependent) WNT signaling pathway. By antagonizing the WNT signaling pathway, the APC protein assumes a critical role in curbing cell proliferation and survival (by averting apoptosis), as well as impeding tumor progression and regulating cellular processes such as migration, adhesion, differentiation, and chromosome segregation [21]. Mutations within the APC gene impair its function and are commonly associated with digestive tract cancers, including gastric, colorectal, and some appendiceal malignancies such as low-grade appendiceal mucinous neoplasms, appendiceal adenocarcinomas, mucinous adenocarcinomas of the appendix, and appendiceal goblet cell adenocarcinoma [22].

3.2 AXIN1 Gene

The AXIN1 gene (located at 16p13.3) encodes the AXIN1–Axis Inhibitor 1 or Axis Inhibition Protein 1 protein (comprising 862 amino acids; with a molecular weight of 95,635 Da), which, in conjunction with APC, GSK3, and CKIa, integrates into the complex structure to deactivate β-catenin and thereby obstruct the WNT signaling pathway, thereby restraining cell proliferation and survival by inhibiting apoptosis. Inactivating mutations in the AXIN1 gene have been documented in hepatocellular carcinoma, hepatoblastomas, ovarian endometrioid adenocarcinomas, medulloblastomas, prostate cancers, and colorectal cancers [23]. In the realm of appendiceal malignancies, a missense mutation (Arg484Cys) has been reported in a case of low-grade appendiceal mucinous neoplasm, although its significance remains unknown.

3.3 TCF7L2 Gene

The TCF7L2 gene (located at 10q25.2-q25.3) encodes the transcription factor TCF7L2–Transcription Factor 7-Like 2 (T-Cell Specific, HMG-Box) (comprising 619 amino acids; with a molecular weight of 67,919 Da) within intestinal cells. It encompasses a high-mobility group (HMG) and plays a pivotal role in transmitting mitogenic signals necessary for cell proliferation and those vital for cell survival by thwarting apoptosis. TCF7L2 serves as a crucial hub in the WNT signaling pathway, receiving signals from β-catenin and positively regulating the MYC/c-MYC proto-oncogene and the BIRC5–Baculoviral IAP Repeat Containing five proteins. Additionally, TCF7L2 protein impedes the action of cell cycle inhibitors CDKN2C/CDKN2D. Conversely, TCF7L2 also exhibits an anti-tumor function by suppressing cell motility and invasiveness and directly inhibiting the activity of pro-metastatic RUNX2–Runt-related transcription factor 2. Loss of TCF7L2 function exacerbates tumor aggressiveness [[24]. Furthermore, TCF7L2 protein is implicated in blood glucose regulation, with defects in its function associated with an elevated risk of developing type 2 diabetes or nonspecific syndromic intellectual disability Polymorphisms within this gene have been identified in colorectal cancer and a subset of

appendiceal malignancies, although their specific types remain unspecified [25].

Microsatellite Instability in Appendix Tumors

Microsatellite instability (MSI) is a phenomenon observed in various types of appendiceal tumors, alongside the presence of genetic mutations. MSI refers to the instability of small repetitive segments of one, two, or three nucleotides scattered within non-coding regions between or within genes. This instability arises from dysfunctions in DNA mismatch repair (MMR) mechanisms, leading to the accumulation of mutations within nucleotide repeats, particularly in coding regions of genes associated with cancer, such as TGFβRII, PTEN, and BAX [25].

The DNA mismatch repair (MMR) system is instrumental in preserving genomic integrity, orchestrated by several key proteins including MLH1, MLH3, MSH2, MSH6, MSH3, PMS2, PMS1, and Exo1. These proteins work together to identify DNA errors from various sources. MMR proteins like MSH2/MSH6 and MSH2/MSH3 heterodimers detect and bind to mismatches in the DNA sequence. Subsequently, the MLH1/PMS2 complex is recruited to the error site, initiating the repair process by introducing nicks in the DNA strand [26].

Disruption of primary partners (MLH1 and MSH2) leads to the loss of the entire heterodimer, while the loss of secondary partners (PMS2 and MSH6) does not affect the heterodimer. Mutations or alterations in MMR proteins can result in microsatellite instability (MSI), marked by the accumulation of errors in microsatellite regions of DNA [27].

MSI can stem from various sources including point mutations in MMR genes like MLH1 and MSH2, errors during DNA replication where DNA polymerase slips and introduces errors in repetitive DNA sequences, and insertions or deletions of bases in microsatellite regions [28].

Beyond genetic causes, other aberrations contribute to the MSI phenotype. For instance, hypermethylation of the MLH1 promoter can silence MLH1 gene expression, leading to MSI. Epigenetic inactivation of MSH2 or MLH1, downregulation of MMR genes by microRNAs, and slipped strand mating errors (SSMs) are among the factors linked with MSI .MSI is strongly associated with Lynch syndrome (LS), an inherited genetic disorder resulting from germline mutations in MMR genes. LS commonly affects colorectal and endometrial cancer but can also impact various other cancer types including ovarian, gastric, hepatobiliary tract, upper urinary tract, pancreatic, brain, and skin cancer [29][30].

Both familial and sporadic colorectal cancer (CRC) can manifest MSI. Familial cases, constituting around 2–3% of all CRC cases, are linked to inherited mutations in DNA mismatch repair genes such as MLH1, MSH2, MSH6, or PMS2. Sporadic cases, on the other hand, are more prevalent and often arise from epigenetic silencing of the MLH1 gene through promoter hypermethylation, often accompanied by generalized methylation of CpG islands, known as the CpG island methylator phenotype (CIMP) [31][32].

MSI has been detected in various human cancers, predominantly gastrointestinal and endometrial cancers. It is also reported in certain types of appendiceal cancers, including appendiceal adenocarcinomas and both mucinous and non-mucinous adenocarcinomas of the appendix In cancer, MSI is associated with a more favorable disease course and prognosis compared to microsatellite stability, although the response to 5-fluorouracil (5-FU)-based chemotherapy may be poorer [33][34]

Clinical Presentation:

Signs and symptoms of glandular carcinoma of the appendix [35]

- Right lower quadrant pain
- Changes in Bowel habits like constipation or diarrhea
- Nausea and vomiting potentially stemming from appendix blockage or associated complications.
- Unexplained reduction in appetite and loss of weight
- Observable lump or enlargement in the abdominal area upon examination
- Expansion or swelling of the abdomen.
- Signs akin to appendicitis, encompass abrupt stomach discomfort, elevated temperature, and emesis.
- Existence of ascites
- Generalized weakness and Fatigue.

Diagnosis:

Imaging Techniques for Diagnosis of Glandular Carcinoma in the Appendix:

a) Computerized Tomography (CT) Imaging

Widely adopted for diagnostic purposes, CT scans offer detailed cross-sectional views of the appendix and adjacent structures. These scans aid in identifying any visible tumors present in or around the appendix, particularly beneficial in detecting glandular carcinoma. CT imaging assists in determining tumor size, extent, and potential spread to neighboring tissues or lymph nodes.

b) Magnetic Resonance Imaging (MRI)

Employing strong magnetic fields and radio waves, MRI generates intricate images of soft tissues, crucial in identifying visible tumors within the appendix and characterizing their features. MRI proves especially valuable for assessing disease extent and detecting any spread beyond the appendix in cases of glandular carcinoma.

c) Colonoscopy

Endoscopic instruments equipped with illumination and cameras facilitate direct visualization of the gastrointestinal tract. Among these, colonoscopy stands out as a prevalent procedure. During a colonoscopy, a flexible tube (colonoscope) is inserted via the rectum, allowing examination of the colon. While primarily utilized for colorectal assessment, colonoscopy can reveal tumors originating from the appendix extending into the colon, aiding in the diagnosis of glandular carcinoma of the appendix.[35]

Staging

Tumor Progression (T Stage)

Aligned with the AJCC 8th edition guidelines, the categorization of T stages remains uniform for various forms of appendiceal adenocarcinomas, except for the omission of pTis (HAMNs) terminology. Tis, T1, and T2 delineate carcinoma in situ and tumors infiltrating the submucosa and muscularis propria, respectively. LAMNs confined within the muscularis propria are labeled as Tis. T1 or T2 designations do not apply to LAMNs, and the T stage holds minimal influence on the risk of recurrent disease post-appendectomy. In rare instances, both LAMNs and HAMNs might be associated with apparent peritoneal disease due to sealed perforation or undiscovered invasive adenocarcinoma.

Advancing to T3 occurs when the tumor penetrates (with acellular mucin or mucinous epithelium) through the muscularis propria into the subserosa or mesoappendix. If the tumor infiltrates the visceral peritoneum (with acellular mucin or mucinous epithelium), involving the appendix or mesoappendix serosa, it earns a classification of T4a. Tumors directly invading or adhering to neighboring organs or structures (excluding luminal or mural spread) are classified as T4b. In scenarios devoid of nodal involvement, T1/T2 corresponds to stage group I, while T3/T4 corresponds to stage group II**.**

Regional Lymph Nodes (N Stage)

Regional lymph node metastasis, primarily along the ileocolic chain, is prevalent in poorly differentiated mucinous and non-mucinous appendiceal adenocarcinomas. Conversely, low- and high-grade mucinous neoplasms and well-differentiated mucinous adenocarcinomas often present with peritoneal disease sans regional nodal involvement. Positive lymph nodes in LAMNs/HAMNs are exceedingly rare and mandate comprehensive pathological specimen assessment for unsampled or undetected invasive adenocarcinoma.

Like the preceding AJCC 8th edition, regional lymph node involvement (tumor in lymph nodes measuring ≥ 0.2 mm) is categorized as N1a with one positive lymph node, N1b with two or three positive nodes, and N2 with four or more positive nodes. Node positivity corresponds to stage group III.

In instances where all regional lymph nodes test negative but discrete tumor deposits are present in the subserosa or within the lymph drainage area of the primary carcinoma without identifiable lymph node tissue or vascular or neural structure, the N stage is denoted as N1c. Tumor deposits do not impact the T category for LAMNs or HAMNs, and the count of tumor deposits is not added to the tally of positive regional nodes. Although tumor deposits signify adverse prognostic factors in colon adenocarcinomas, their prognostic relevance in appendiceal cancer remains uncertain. The count of tumor deposits is being documented separately for further studies.

Distant Metastasis (M) and Histological Tumor Grade (G)

Intraperitoneal acellular mucin, devoid of identifiable tumor cells in disseminated peritoneal mucinous deposits, is delineated as M1a, while intraperitoneal metastasis exclusively, encompassing peritoneal mucinous deposits containing tumor cells, is categorized as M1b. Metastasis to sites beyond the peritoneum is demarcated as M1c. Tumor grade emerges as the pivotal predictive factor for overall survival in patients with disseminated appendiceal mucinous neoplasms. LAMNs are graded as G1 (well-differentiated), whereas HAMNs are graded as G2 (moderately differentiated). Appendiceal mucinous adenocarcinomas, characterized by infiltrative invasion associated with extracellular mucin comprising > 50% of the tumor and desmoplastic stroma, are classified as either G2 (moderately differentiated) or G3 (poorly differentiated). If cancer constitutes < 50% of signet ring cells, the designation is mucinous adenocarcinoma with signet ring cells or poorly differentiated mucinous adenocarcinoma. Signet ring cell mucinous adenocarcinoma, characterized by infiltrative invasion associated with intracellular mucin comprising > 50% of the tumor, is classified as G3 (poorly differentiated) and carries the bleakest prognosis among all appendiceal cancer histology.

In patients with M1b disease, a histological grade is pivotal for stage grouping, categorized as IVA (G1) or IVB (G2, G3, or GX). Patients with M1a disease, regardless of grade, are also assigned to stage group IVA. Metastatic tumor grade guides stage group assignment in cases of grade discordance with the primary tumor.

Treatment

An integrated approach encompassing surgical intervention, systemic therapies, and multidisciplinary collaboration is indispensable in effectively managing glandular carcinoma of the appendix. Ongoing research endeavors are aimed at refining outcomes and tailoring treatments to align with individual tumor characteristics:

Surgical Management

Surgery remains the mainstay of treatment for glandular carcinoma of the appendix. The extent of surgical intervention depends on factors such as the tumor size, location, histological subtype, and presence of metastasis. Appendectomy, either open or laparoscopic, is often performed for localized tumors without evidence of metastasis. However, for more advanced cases or those with peritoneal spread, more extensive procedures such as right hemicolectomy or cytoreductive surgery (CRS) with hyperthermic intraperitoneal chemotherapy (HIPEC) may be warranted. CRS and HIPEC aim to remove visible tumor nodules and administer heated chemotherapy directly into the abdominal cavity to eliminate microscopic residual disease.

Chemotherapy

The role of chemotherapy in the management of glandular carcinoma of the appendix is not yet standardized due to its rarity and the lack of large clinical trials. However, chemotherapy regimens commonly used for colorectal cancer, such as fluoropyrimidines (e.g., 5-fluorouracil, capecitabine), oxaliplatin, and irinotecan, may be considered for patients with advanced or metastatic disease. In cases of appendiceal mucinous neoplasms with pseudomyxoma peritonei (PMP), systemic chemotherapy combined with CRS and HIPEC has shown promising outcomes inselect patients.[35]

In conclusion, glandular cell carcinoma of the appendix, though rare, requires a multidisciplinary approach for effective management. Ongoing research is essential for understanding its molecular mechanisms and improving therapeutic outcomes. This review highlights the importance of early recognition and a comprehensive treatment strategy to enhance patient prognosis.

Conflict of Interests: The authors declare no conflict of interest.

References

[1] Fenwick, A.K., Hartery, A. (2021) Appendicitis and beyond a pictorial review of various appendiceal abnormalities. Emerg Radial 28, 651–664).

[2] Chauhan, S., Anand, S. (2018) Intracecal appendix: an extremely rare anatomical variation. A case report and review of the literature. Surg Radiol Anat 40, 111–114

[3] Skendelas, J.P., Alemany, V.S., Au, V., Rao, D., McNeils, J., &Kim, P.K. (2021). Appendiceal adenocarcinoma found by surgery for acute appendicitis is associated with older age.BMC Surgery,21,228

[4] Wang, Y., Ran, D., Li, Y., Zhu, C., Zhang, R., Jiang.B., & Wang, S. (2023). Histopathological features of glandular atrophy of lamina propria of the gastric mucosa during its occurrence and development Gastroenterology,23,395

[5] Rindi, G., Inzani, F. (2022). Goblet Cell Carcinoid. In: La Rosa, S., Uccella, S. (eds) Endocrine Pathology. Encyclopedia of Pathology. Springer, Cham. https://doi.org/10.1007/978-3-030-62345-6_5263

[6] Chicago Consensus Working Group.(2020) The Chicago Consensus on Peritoneal Surface Malignancies: Management of Appendiceal Neoplasms. Ann Surg Oncol 27, 1753–1760.https://doi.org/10.1245/s10434-020-08316-w

[7] Patel, S.; Alam, A.; Pant, R.; Chattopadhyay, S. (2019) Wnt signaling and Its significance within the tumor microenvironment: Novel therapeutic insights. Front. Immunol. 10, 2872.

[8] Gremer, L.; Merbitz-Zahradnik, T.; Dvorsky, R.; Cirstea, I.C.; Kratz, C.P.; Zenker, M.; Wittinghofer, A.; Ahmadian, M.R. (2011), Germline KRAS mutations cause aberrant biochemical and physical properties leading to developmental disorders. Hum. Mutat. 32, 33–43.

[9] Davison, J.M.; Choudry, H.A.; Pingpank, J.F.; Ahrendt, S.A.; Holtzman, M.P.; Zureikat, A.H.; Zeh, H.J.; Ramalingam, L.; Zhu, B.; Nikiforova, M.; et al. (2014) Clinicopathologic and molecular analysis of disseminated appendiceal mucinous neoplasms: Identification of factors predicting survival and proposed criteria for a three-tiered assessment of tumor grade. Mod. Pathol. 27, 1521–1539.

[10] Noguchi, R.; Yano, H.; Gohda, Y.; Suda, R.; Igari, T.; Ohta, Y.; Yamashita, N.; Yamaguchi, K.; Terakado, Y.; Ikenoue, T.; et al. (2015) Molecular profiles of high-grade and low-grade pseudomyxoma peritonei. Cancer Med., 4, 1809–1816.

[11] Matallanas, D.; Birtwistle, M.; Romano, D.; Zebisch, A.; Rauch, J.; von Kriegsheim, A.; Kolch, W. Raf family kinases: (2011) Old dogs have learned new tricks. Genes Cancer, 2, 232–260

[12] Pai, R.K.; Hartman, D.J.; Gonzalo, D.H.; Lai, K.K.; Downs-Kelly, E.; Goldblum, J.R.; Liu, X.; Patil, D.T.; Bennett, A.E.; Plesec, T.P.; et al. (2014) Serrated lesions of the appendix frequently harbor KRAS mutations and not BRAF mutations indicating a distinctly different serrated neoplastic pathway in the appendix. Hum. Pathol., 45, 227–235.

[13] Munari, G.; Businello, G.; Mattiolo, P.; Pennelli, G.; Sbaraglia, M.; Borga, C.; Pucciarelli, S.; Spolverato, G.; Mescoli, C.; Galuppini, F.; et al. (2021) Molecular profiling of appendiceal serrated lesions, polyps, and mucinous neoplasms: A single-center experience. J. Cancer Res. Clin. Oncol. 147, 1897–1904.

[14] Ottaiano, A.; Santorsola, M.; Perri, F.; Pace, U.; Marra, B.; Correra, M.; Sabbatino, F.; Cascella, M.; Petrillo, N.; Ianniello, M.; et al. (2022) Clinical and molecular characteristics of rare malignant tumors of colon and rectum. Biology 11, 267

[15] Liu, X.; Mody, K.; de Abreu, F.B.; Pipas, J.M.; Peterson, J.D.; Gallagher, T.L.; Suria Winata, A.A.; Ripple, G.H.; Hourdequin, K.C.; Smith, K.D.; et al. (2014) Molecular profiling of appendiceal epithelial tumors using massively parallel sequencing to identify somatic mutations. Clin. Chem. 60, 1004–1011.

[16] Singhi, A.D.; Davison, J.M.; Choudry, H.A.; Pingpank, J.F.; Ahrendt, S.A.; Holtzman, M.P.; Zureikat, A.H.; Zeh, H.J.; Ramalingam, L.; Mantha, G.; et al. (2014) GNAS is frequently mutated in both low-grade and high-grade disseminated appendiceal mucinous neoplasms but does not affect survival. Hum. Pathol, 45, 1737–1743.

[17] Mikaeel, R.R.; Young, J.P.; Tapia Rico, G.; Hewett, P.J.; Hardingham, J.E.; Uylaki, W.; Horsnell, M.; Price, T.J. (2021), Immunohistochemistry features and molecular pathology of appendiceal neoplasms. Crit. Rev. Clin. Lab. Sci. 58, 369–384.

[18] Ottaiano, A.; Santorsola, M.; Perri, F.; Pace, U.; Marra, B.; Correra, M.; Sabbatino, F.; Cascella, M.; Petrillo, N.; Ianniello, M.; et al. (2022)Clinical and molecular characteristics of rare malignant tumors of colon and rectum. Biology,11, 267

[19] Patel, S.; Alam, A.; Pant, R.;(2019) Chattopadhyay, S. Wnt signaling and Its significance within the tumor microenvironment: Novel therapeutic insights. Front. Immunol10, 2872

[20] Zhang, Y.; Ng, P.K.-S.; Kucherlapati, M.; Chen, F.; Liu, Y.; Tsang, Y.H.; De Velasco, G.; Jeong, K.J.; Akbani, R.; Hadjipanayis, A.; et al. (2017) A pan-cancer proteogenomic atlas of PI3K/AKT/mTOR pathway alterations. Cancer Cell.31, 820–832

[21] Pengelly, R.J.; Rowaiye, B.; Pickard, K.; Moran, B.; Dayal, S.; Tapper, W.; Mirnezami, A.; Cecil, T.; Mohamed, F.; Carr, N.; et al. (2018) Analysis of mutation and loss of heterozygosity by whole-exome sequencing yields insights into Pseudomyxoma peritonei. J. Mol. Diagn. 20, 635–642.

[22] Picco, G.; Petti, C.; Centonze, A.; Torchiaro, E.; Crisafulli, G.; Novara, L.; Acquaviva, A.; Bardelli, A.; Medico, E. (2017) Loss of AXIN1 drives acquired resistance to WNT pathway blockade in colorectal

cancer cells carrying RSPO3 fusions. EMBO Mol. Med., 9, 293–303

[23] Wenzel, J.; Rose, K.; Haghighi, E.B.; Lamprecht, C.; Rauen, G.; Freihen, V.; Kesselring, R.; Boerries, M.; Hecht, A (2020). Loss of the nuclear Wnt pathway effector TCF7L2 promotes migration and invasion of human colorectal cancer cells. Oncogene 39, 3893–3909.

[24] Iacopetta, B.; Grieu, F.;(2010) Amanuel, B. Microsatellite instability in colorectal cancer. Asia Pac. J. Clin. Oncol., 6, 260–269.

[25] Amato, M.; Franco, R.; Facchini, G.; Addeo, R.; Ciardiello, F.; Berretta, M.; Vita, G.; Sgambato, A.; Pignata, S.; Caraglia, M.; et al (2022). Microsatellite Instability: From the Implementation of the Detection to a Prognostic and Predictive Role in Cancers. Int. J. Mol. Sci. 23, 8726.

[26] Bonneville, R.; Krook, M.A.; Chen, H.Z.; Smith, A.; Samorodnitsky, E.; Wing, M.R.; Reeser, J.W.; Roychowdhury, S. (2020) Detection of Microsatellite Instability Biomarkers via Next-Generation Sequencing. Methods Mol. Biol. 2055, 119–132.

[27] Li, K.; Luo, H.; Huang, L.; Luo, H.; Zhu, X. (2020) Microsatellite instability: A review of what the oncologist should know. Cancer Cell Int., 20, 16.

[28] Dominguez-Valentin, M.; Sampson, J.R.; Seppälä, T.T.; Ten Broeke, S.W.; Plazzer, J.P.; Nakken, S.; Engel, C.; Aretz, S.; Jenkins, M.A.; Sunde, L.; et al. (2020) Cancer risks by gene, age, and gender in 6350 carriers of pathogenic mismatch repair variants: Findings from the Prospective Lynch Syndrome Database. Genet. Med. 22, 1569.

[29] Bucksch, K.; Zachariae, S.; Aretz, S.; Büttner, R.; Holinski-Feder, E.; Holzapfel, S.; Hüneburg, R.; Kloor, M.; von Knebel Doeberitz, M.; Morak, M.; et al. (2020) Cancer risks in Lynch syndrome, Lynch-like syndrome, and familial colorectal cancer type X: A prospective cohort study. BMC Cancer., 20, 460.

[30] Morales-Miranda, A.; Rosado, I.D.; Núñez, C.C.; Montero, F.C. (2018) Appendiceal carcinoma associated with microsatellite instability. Mol. Clin. Oncol., 8, 694–698.

[31] Taggart, M.W.; Galbincea, J.; Mansfield, P.F.; Fournier, K.F.; Royal, R.E.; Overman, M.J.; Rashid, A.; Abraham, S.C. (2013) High-level microsatellite instability in appendiceal carcinomas. Am. J. Surg. Pathol. 37, 1192–1200.

[32] Misdraji, J.; Burgart, L.J.; Lauwers, G.Y. (2004) Defective mismatch repair in the pathogenesis of low-grade appendiceal mucinous neoplasms and adenocarcinomas. Mod. Pathol.17, 1447–1454.

[33] Komm, M.; Kronawitter-Fesl, M.; Kremer, M.; Lutz, L.; Holinski-Feder, E.; Kopp, R. (2011) Primary mucinous adenocarcinoma of the vermiform appendix with high-grade microsatellite instability. J. Cancer 2, 302–306.

[34] Andjelkovic, B., Stojanovic, B., Stojanovic, M.D., Milosevic, B., Cvetkovic, A., Spasic, M. Jakovljevic, S., Cvetkovic, D., Stojanovic, B.S., Milosev, D., & et al. (2023). Appendiceal Signet Ring Cell Carcinoma: An Atypical cause of Acute Appendicitis-A Case study and Review of Current knowledge. Diagnostics.13(14) 2359.DOI:10.3390/diagnostics13(14)2359

[35] Hanna, N., Hanna, A.N. & Hanna, D.N. (2024) AJCC Cancer Staging System Version 9: Appendiceal Adenocarcinoma. *Ann Surg Oncol* 31, 2177–2180. https://doi.org/10.1245/s10434-024-14892-y

Author Profile

Rathin Joshi is an M.B.B.S. doctor at GMERS Himmatnagar.

Abiy Tereda is both an M.B.B.S. and M.D. doctor at Georgetown American University.

Saheli Kansara is an M.B.B.S. doctor at GMERS Himmatnagar.

Kirtan Patel is an M.B.B.S. doctor at GMERS Himmatnagar.