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Review

Various facets of low-grade appendiceal mucinous neoplasms (LAMNs)

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Abstract

Low-grade appendiceal mucinous neoplasms are rare tumors of the appendix that affect women and men equally from the fifth decade of life. They are characterized by the replacement of normal appendiceal mucosal tissue with villous proliferations of mucinous epithelium. The tumor cells secrete mucin, which accumulates in intracytoplasmic vacuoles. Tumor growth occurs by pushing mechanisms without invasion, invasion defining adenocarcinomas. In the early stages, these tumors have low risk of recurrence and are not life-threatening, appendectomy being sufficient for cure. Sometimes, the accumulation of mucin produces ruptures of the appendiceal wall, which may seed tumor content outside the appendix, complicating diagnosis and prognosis, presenting a high risk of recurrence and, in the case of pseudomyxoma peritonei, becoming disabling and life-threatening. For these, treatment becomes more complex, with decreased survival rate.

Keywords

low-grade appendiceal mucinous neoplasms (LAMNs); appendix; pseudomyxoma peritonei; signaling pathways; metastasis

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Introduction

Low-grade appendiceal mucinous neoplasms (LAMNs) are rare epithelial neoplasms of the cecal appendix, accounting for less than 1% of gastrointestinal tract neoplasms and approximately 0.3% of appendiceal neoplasms [1, 2, 3]. These are heterogeneous diseases of unknown etiology, occurring in the sixth or seventh decade of life and have a female to male ratio of ~1. One study, published by Akay et al. [4] indicates a lower age for males than females and the overall average. Thus, they present cases of low-grade appendiceal mucinous neoplasms with mean ages of 48.6 years (55.4 years for women and 41.4 years for men), indicating that this type of tumor may occur earlier than initially thought. Low-grade appendiceal mucinous neoplasms (LAMNs) are characterized by well-differentiated tumors with proliferation of the appendiceal mucosal epithelium, extracellular mucinous secretion and pushing tumor margins. Being frequently asymptomatic and without causing discomfort, low-grade appendiceal mucinous neoplasms are difficult to diagnose before appendectomy for appendicitis [5]. However, in some cases, there may be abdominal pain and distention, or a palpable mass may be identified on abdominal or pelvic examination, but these are not mandatory. In almost half of the cases, calcifications of the appendiceal wall may occur. Low-grade appendiceal mucinous neoplasms are considered to have variable malignant potential and are generally perceived as semi-malignant tumors. They lack classical invasiveness, often being confined to the appendiceal wall, sometimes perforating it, seeding the peritoneal cavity with neoplastic mucinous cells, acquiring malignant potential and causing pseudomyxoma peritonei [6, 7, 8].

Anatomopathological features

Low-grade appendiceal mucinous neoplasms are a unique subtype of appendiceal tumors, which, under the microscope, take several forms, all of which have low atypia, resemble low-grade colonic dysplasia, and often lack lymphoid tissue. The typical form of low-grade appendiceal mucinous neoplasm is characterized by the replacement of normal mucosal tissue with villous filiform mucinous epithelial proliferations (Figure 1). The tumor cells begin to secrete excess mucin, which becomes accumulated in the cytoplasm as vacuoles, the increased volume and number of vacuoles compressing the nuclei. Other forms of low-grade appendiceal mucinous neoplasms present mucosa with a wavy or scalloped appearance, columnar epithelial cells having nuclear pseudo-stratification and growing on fibrotic submucosal tissue, whereas other forms present the mucinous epithelium as a flattened or attenuated monolayer [6, 7, 9, 10, 11]. Frequently, the appendix wall may have varying degrees of hyalinization, calcification and fibrosis, with epithelial proliferation increasing within this tissue, partially or completely invading the appendix wall structures. Invasion of the appendiceal wall is destructive, confluent, cribriform and with desmoplasia, indicating infiltrative growth and leading to the diagnosis of appendiceal mucinous adenocarcinoma. Fibrosis of the appendix wall structures makes it difficult to identify its layers and, consequently, to assess the

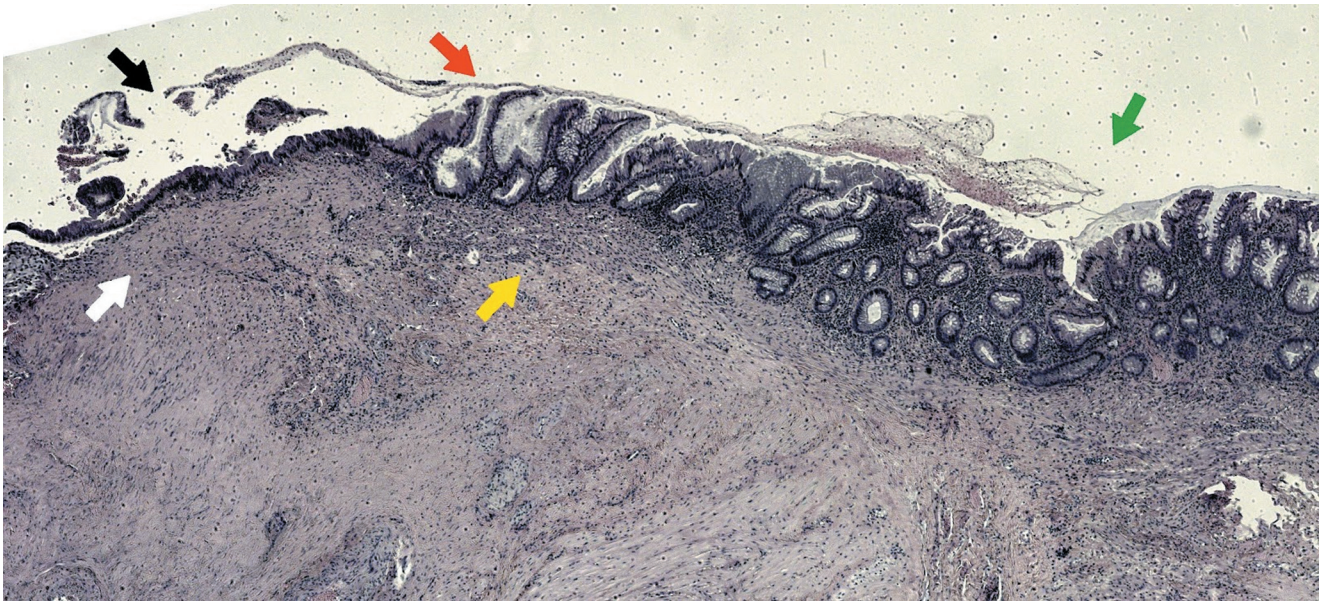

Figure 1. Transition between normal-appearing appendiceal epithelium (right, indicated by green arrow) and transformed epithelium with lesions characteristic of low-grade appendiceal mucinous neoplasm (left), represented by reactive epithelium (red arrow), which has a muscular layer underneath (yellow arrow), and dysplastic epithelium (black arrow), underneath which the muscular layer of the mucosa is missing (white arrow), HE, 100×.

status of the invasion. When serosa is affected, portions of the hyaline wall are replaced by bands of low-grade mucinous epithelial cells that abundantly produce extracellular mucin. In some cases, mucin causes dissection of the appendix wall, resembling diverticula, and further ruptures of the appendix, with intraperitoneal seeding of mucinous tumor cells [6, 12].

Genetic features

In low-grade appendiceal mucinous neoplasms, mutations have been identified in many genes that are part of the RAS–RAF–MEK–ERK, PI3K–PKB/AKT, JAK–STAT, angiogenesis (including NOTCH) WNT and TGFB–TGFBR–SMAD signaling pathways (Figure 2). A smaller number of mutations are present in genes involved in DNA metabolism/expression, in genes encoding for enzymes and in genes with various cellular activities. In the RAS–RAF–MEK–ERK signaling pathway, genes mutated in low-grade appendiceal mucinous neoplasms are *KRAS*, *NRAS*, *BRAF*, mainly targeting the *KRAS* (Kirsten ras oncogene homolog) gene. It is part of the RAS gene family, which encodes GTPases that transduce signals between the cell membrane and the Golgi apparatus and are involved in proliferation, cell adhesion and migration, evading apoptosis, and stimulating angiogenesis. In some cases, mutations of the *KRAS* gene are present together with inactivating mutations of the *TP53* (Tumor Protein 53) gene. Another member of this gene family, *NRAS* (Neuroblastoma RAS Viral Oncogene Homolog), appears mutated in some cases of low-grade appendiceal mucinous neoplasms. Of the RAF

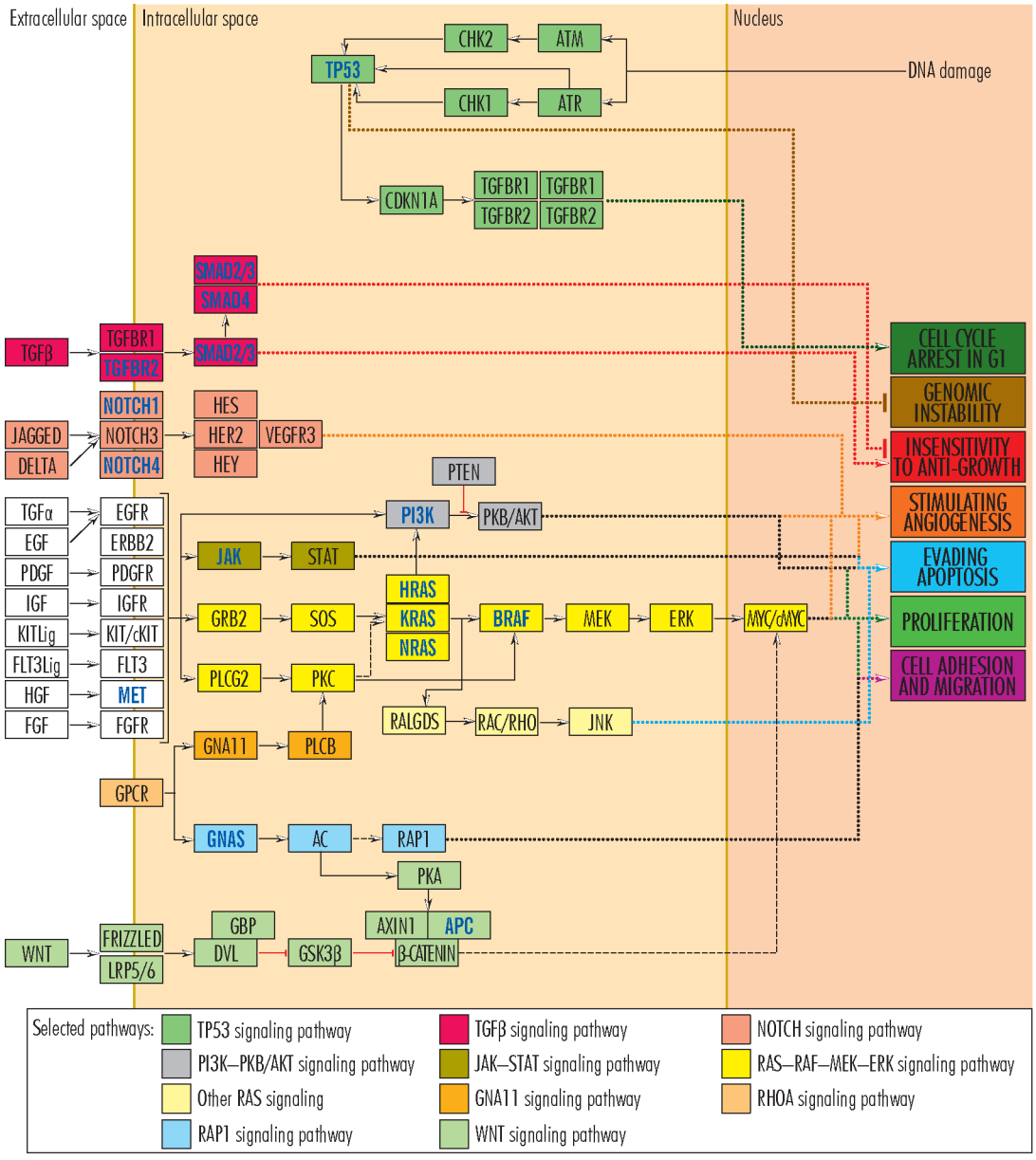

Figure 2. Altered signaling pathways in low-grade appendiceal mucinous neoplasms. Genes affected by mutations are written in bold, blue characters.

gene family, the *BRAF* (Rapidly accelerated fibrosarcoma B) gene is mutated, the most common defect affecting codon 600 (V600E), sometimes occurring simultaneously with mutations in the *TP53* gene. Of the genes involved in the PI3K–PKB/AKT signaling pathway, most mutations occur in the *PIK3CA* (Phosphatidylinositol-4,5-Bisphosphate 3-Kinase Catalytic Subunit Alpha), and *AKT1* (AKT Serine/Threonine Kinase 1) genes. The PI3K–PKB/AKT pathway constitutes an alternative pathway to RAS–RAF–MEK–ERK by which tumors proliferate, evade apoptosis, and stimulate angiogenesis. In most cases, mutations in the *PIK3CA* gene rarely occur simultaneously with those in *KRAS*. The JAK–STAT signaling pathway contributes to evading apoptosis and stimulating angiogenesis and, in low-grade appendiceal mucinous neoplasms, the most mutated gene is *JAK3* (Janus Kinase 3 protein). Stimulation of angiogenesis is enhanced by mutations in *GNAS* (G Protein Subunit Alpha S or Secretogranin VI) gene, which modulates the function of a number of hormones and molecules and is also involved in activating cAMP and stimulating several signaling pathways, and *CBP/CREBBP* (Cyclic adenosine monophosphate Response Element Binding Protein or CREB-binding protein) gene, which is a cofactor in the transcription of many genes, including *MYB*, *JUN*, *FOS*, *E1A* and *E6* oncogenes, as well as the tumor suppressor genes *TP53*, *E2F* (E2F Transcription Factor), *RB* (Retinoblastoma-Associated Protein), *SMAD*s (Mothers Against DPP Homologues), *RUNX*s (Runt-Related Transcription Factors) and *BRCA1* (Breast And Ovarian Cancer Susceptibility Protein 1). The most common mutations in the *GNAS* gene are p.R201H, c.602G>A and p.R201C, c.602 C>T. These defects are likely to play an important role in the mucin abundance that characterizes low-grade appendiceal mucinous neoplasms. The four members of the *NOTCH* gene family encode the type I transmembrane receptors NOTCH1 through NOTCH4 (Translocation-Associated Notch Protein TAN-1–4), which play an important role in the transduction of the pro-angiogenic signal via the NOTCH–HER/ERBB2–HES/HEY–VEGFR3 pathway. Inactivating mutations in the *APC* (Adenomatosis Polyposis Coli Tumor Suppressor) gene, which acts as an antagonist of the WNT signaling pathway, contribute to MYC/cMYC (V-Myc Avian Myelocytomatosis Viral Oncogene Homolog) activation and cell proliferation, tumor invasion and metastasis, evasion of apoptosis, and angiogenesis, all very important events in tumorigenesis. Insensitivity to anti-growth signals via the TGFB–TGFBR–SMAD signaling pathway sustains tumor growth. Of the genes involved in this signaling pathway, *TGFBR2* (Transforming Growth Factor Beta Receptor 2), *SMAD2* (SMAD-Mothers Against Decapentaplegic Homologue 2), *SMAD3* (SMAD-Mothers Against Decapentaplegic Homologue 3) and *SMAD4* (SMAD-Mothers Against Decapentaplegic Homologue 4) are mutated in a few cases of low-grade appendiceal mucinous neoplasms. Mutations in other genes, such as those involved in DNA metabolism/expression (*FANCA*, *RAD51C*), in those encoding for enzymes (*ARID1A*, *DIS3*, *FH*, *SMARCA4*) and in genes with various cellular activities (*FAT4*, *MED12*, *RNF43*, *STK11*, *TSC1*), are rare, but these may be important events in the tumor process [6, 13, 14, 15, 16, 17].

Staging and prognosis of low-grade appendiceal mucinous neoplasms

According to the Union for International Cancer Control (UICC) staging system, low-grade appendiceal mucinous neoplasms comprise stages pTis, pT3 and pT4, while pT1 and pT2 are missing. Thus, tumors extending only to the muscularis propria, without affecting the mesoappendix or serosa, are considered pTis, although this diagnosis requires correlation with the intraoperative findings and an evaluation by the operator (Table 1; Figure 3). Low-grade appendiceal mucinous neoplasms staged pTis are at no risk of recurrence and have an excellent prognosis. Tumors with acellular mucin or mucinous epithelium extending into the subserosa (without serosa involvement) or mesoappendix are considered pT3. To observe the extent of the tumor and

Table 1. Staging and prognosis of low-grade appendiceal mucinous neoplasms

pT stage	Features	Prognostic
pTis	Lesion affecting only the appendiceal wall, with the possibility of acellular mucin or mucinous epithelium disrupting muscularis propria. Histological examination of the entire appendix is required.	In general, there is no risk of recurrence.
pT3	Appendiceal subserosal or mesoappendix involvement without extension to the serosa. Histological examination of the entire appendix is required.	As the risk for recurrence is not known, follow-up is required for 10 years until the risk of recurrence is updated.
pT4a	Peritoneal involvement and invasion of the serosa or mesoappendix with cellular or acellular mucin	In acellular mucin, the risk of peritoneal recurrences is low. In the case of cellular mucin, the risk of peritoneal recurrences is high. Cytoreductive surgery with or without HIPEC, and follow-up within 10 years is required.
pT4b	Involvement of the peritoneum and direct invasion of adjacent organs or structures	

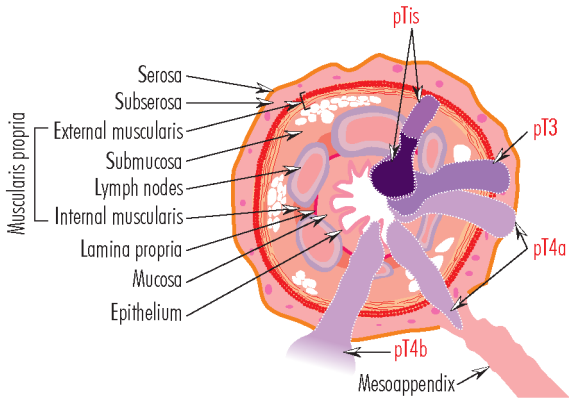

Figure 3. Illustration of structures affected by low-grade appendiceal mucinous neoplasms in different stages. With black text the normal components of the appendix wall are shown in cross-section and with red text the low-grade appendiceal mucinous neoplasms.

whether or not it affects the subserosa, histological examination of the entire appendix is required. Low-grade appendiceal mucinous neoplasms staged pT3 have an unknown risk of peritoneal recurrence, requiring long-term follow-up for 10 years or until the recurrence status changes. By invasion of at least the appendiceal serosa or by perforation of the appendix with invasion of adjacent organs, tumors are classified as pT4. In this sense, when mucinous epithelium invades the appendiceal serosa or mesoappendix, or when the appendiceal tumor seeds the peritoneal cavity and acellular/cellular mucin invades the visceral peritoneum, the tumors are staged as pT4a. The presence of mucin does not include luminal or mural spread in the cecum, but mucinous deposits on the serosa are associated with neovascularization, being traversed by small capillaries with red cells. The presence of neovascularization indicates activation of signaling pathways that promote angiogenesis. On the other hand, when cell seeding from the tumor into the peritoneal cavity leads to direct invasion of adjacent organs and structures, tumors are staged as pT4b. Peritoneal dissemination limited to acellular mucin only indicates stage M1a. When metastases are confined to the peritoneum only, regardless of their nature, the tumor stage is M1b, and when they develop outside the peritoneum, the tumor stage is M1c. The risk of peritoneal recurrence is reduced when the mucin is acellular, but becomes increased in the presence of cellular mucin, and long-term follow-up for 10 years with periodic imaging is highly required [16, 18].

Metastasis and complications of low-grade appendiceal mucinous neoplasms

Low-grade appendiceal mucinous neoplasms are recognized as indolent tumors, characterized by “push” patterns of growth instead of invasiveness, and which rarely metastasize or produce complications. Metastases derived from low-grade appendiceal mucinous neoplasms occur preferentially in the peritoneal cavity and ultimately lead to pseudomyxoma peritonei [1, 19, 20, 11, 4, 21], a life-threatening condition. Rarely, low-grade appendiceal mucinous neoplasms can metastasize to the fallopian tube mucosa [22], pulmonary pleura [23, 24] and inguinal nodes [25] (Figure 4). Although located at a great distance, pleuropulmonary metastases may arise from low-grade appendiceal mucinous neoplasms alone [23] or from their collisions with appendiceal neuroendocrine tu-

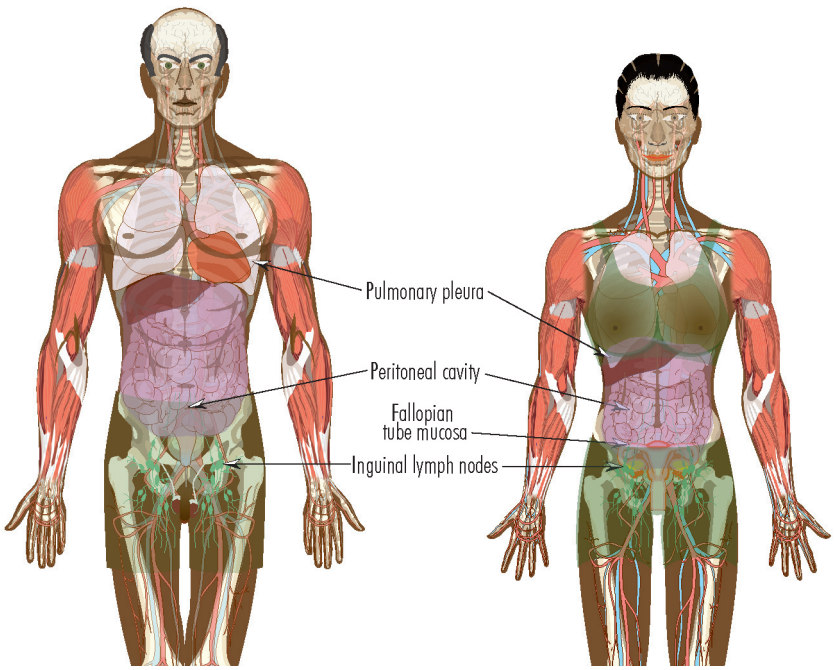

Figure 3. Metastatic sites of low-grade appendiceal mucinous neoplasms.

mors [24]. In some cases, low-grade appendiceal mucinous neoplasms may occur in association with other tumor times, such as urothelial carcinoma [26] and mucinous neoplasm of the renal pelvis [27], with no known causal relationship between them.

Among the most common complications of low-grade appendiceal mucinous neoplasms are ileocecal intussusception with bowel obstruction [28, 29], small bowel obstruction [30], ureteral obstruction [2], volvulus [31], ovarian lesions [32], rupture [33], abscesses [34], fistula [35, 36], and pseudomyxoma peritonei [2, 33]. Abscesses originating in low-grade appendiceal mucinous neoplasms can occur in internal organs in close proximity to the appendix, including the fallopian tube and ovary [37] and the iliopsoas muscle, the latter being very difficult to treat or untreatable. Appendiceal fistula defines spontaneous rupture of inflamed appendix internally, into urinary bladder, ileum, caecum, duodenum, ascending colon, Meckel's diverticulum and uterus, and externally, into right buttock, right flank, iliac fossa, groin or umbilicus [38]. Sometimes external fistulas may open from an internal abscess in contact with the tip of the neoplastic appendix. Fistula formation can lead to favorable prognosis. When the evacuation of appendix contents occurs in the peritoneal cavity and tumor cells seed the peritoneum, pseudomyxoma peritonei may result. Its frequency is 1-2 per million and it is a debilitating, disabling condition with increased risk of death [39, 40].

Treatment options

According to the Chicago Consensus Working Group [41], the first invasive investigation is surgical exploration to identify peritoneal spread. In low-grade appendiceal mucinous neoplasms, appendectomy is recommended, with verification of the invasiveness of the margins of the tumor lesion. When the margins are negative, the therapeutic course follows two strategies, depending on the perforation of the appendiceal wall. Thus, when the appendiceal wall is not perforated and the mucin or neoplastic cells have not been seeded extra-appendiceal, appendectomy is curative, without the need for post-operative monitoring. However, when mucin or mucinous cells are present extra-appendiceal, consideration of intraperitoneal chemotherapeutic treatment with subsequent monitoring is recommended. When the margins of the appendiceal tumor lesion are positive, cecectomy or ileocecectomy is recommended, with subsequent monitoring. For pseudomyxoma peritonei, cytoreductive surgery and hyperthermic intraperitoneal chemotherapy are indicated, with or without perioperative systemic chemotherapy [41, 42, 43, 44]. For low-grade appendiceal mucinous neoplasms, one-year survival is over 90% and five-year survival is over 80%, decreasing considerably for complicated cases, including pseudomyxoma peritoneum [45].

Discussions

Low-grade appendiceal mucinous neoplasms are epithelial tumors that result from uncontrolled proliferation of mucinous cells in the lining of the appendix. Mucin becomes accumulated as vacuoles in the cell cytoplasm. As the vacuoles increase in volume, they marginalize the cell nucleus, in some cases compressing it. At the same time, the wall of the appendix becomes fibrotic and hyalinized, gradually giving way to mucinous cells. It is important to note that the margins of low-grade appendiceal mucinous neoplasms advance by pushing, without invading the surrounding area. Sometimes, the pressure that the mucin exerts on the appendiceal wall is felt as pain and leads to the diagnosis of appendicitis, and the tumor progression is stopped by appendectomy. These are the happiest cases and are usually free of recurrences, with patients resuming their pre-operative lives. At other times, the pain is absent and the progression continues, with mucin accumulation and cell proliferation continuing and pressing on the wall of the appendix, which becomes very swollen and may rupture. Through the fissure, the contents of the appendix are released, consisting of acellular mucin or mucin with tumor cells, which reaches the peritoneal cavity and seeds various organs, most commonly the peritoneum or, in the case of women, the internal genitalia. There are cases when the ruptured appendix is trapped by internal organs (cecum, internal genitalia, bladder, iliopsoas muscle) or the abdominal wall and perforates them, producing abscesses or fistulas through which its contents are released. When the appendix is not attached to any internal organ, its contents are discharged into the abdominopelvic cavity. In the absence of pain, other symptoms do not alarm patients, and the diagnosis cannot easily be made. It is only when the fistula perforates the abdominal wall or when the accumulation of mucin in the abdomen causes it to become distended that patients receive a strong alarm signal and present themselves to the doctor. Through imaging investigations, surgery and pathological, genetic and immunohistochemical analyses, the correct diagnosis is made and patients are given a chance of a cure. While for some cases a single surgical intervention, followed or not by chemotherapy, is sufficient for cure, other cases are marked by recurrences, requiring repeated evacuation of mucinous accumulations, which, over time, can become disabling, difficult to operate and with an increased risk of death.

Conclusions

Low-grade appendiceal mucinous neoplasms are diseases with semi-malignant features which, when confined to the appendiceal mucosa, have a very good prognosis, but as they become more extensive and extend beyond the appendix, they become more difficult to treat and have a higher risk of recurrence and death. As rare neoplasms, no standardized methods of diagnosis, treatment or monitoring have been developed for low-grade appendiceal mucinous neoplasms, making their management difficult, especially for advanced cases.

Future perspectives

For low-grade appendiceal mucinous neoplasms, future perspectives are directed towards difficult cases, including pseudomyxoma peritonei, and are geared towards improving diagnosis, increasing treatment efficacy and reducing the risk of recurrence and mortality. To improve diagnosis, a battery of specific markers for these diseases needs to be identified and included in a set of analyses performed annually. To increase the effectiveness of treatment, knowledge of the disease and its response to therapy needs to be improved. In addition, it is necessary to test innovative therapies or to find therapeutic strategies that combine several types of treatment and that take into account the genetic characteristics of this type of tumor in order to reduce their resistance and the risk of recurrence as much as possible.

Conflicts of interest

The author declares that he has no conflicts of interest.

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