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RECOMMENDATION OF THE PERITONEUM NEOPLASMS SERVICE OF ``*HOSPITAL SANTA RITA DA SANTA CASA DE MISERICORDIA*`` AT PORTO ALEGRE – CECAL APPENDIX MUCOCELE – LAPAROSCOPIC OR LAPAROTOMICAL APPROACH?

Fabio Ferreira Bueno
Resident Doctor of the Medical Residency Program at ``Universidade Federal de Ciências da Saúde`` at Porto Alegre (UFCSPA) – ``Irmandade da Santa Casa de Misericórdia`` at Porto Alegre (ISCMPA). Porto Alegre
http://lattes.cnpq.br/0090016821962697
Orcid: 0009-0008-3782-523X

Rafael Seitenfus
Preceptor of the Medical Residency Program at ``Universidade Federal de Ciências da Saúde`` at Porto Alegre (UFCSPA) – ``Irmandade da Santa Casa de Misericórdia`` at Porto Alegre (ISCMPA); Chief of the Peritoneal Neoplasms Service at: Hospital Santa Rita, at ``Santa Casa de Misericórdia`` at Porto Alegre; Post-graduation Program in Pathology at ``Universidade Federal de Ciências da Saúde`` de Porto Alegre`` (UFCSPA) – Graduation Program of Pathology, ``Universidade Federal de Ciências da Saúde`` at Porto Alegre (UFCSPA), Porto Alegre
http://lattes.cnpq.br/8217830088933648
Orcid: 0000-0001-8481-2759

Carlos Humberto Cereser Junior
Preceptor of the Medical Residency Program at ``Universidade Federal de Ciências da Saúde`` at Porto Alegre (UFCSPA) –``Irmandade da Santa Casa de Misericórdia`` at Porto Alegre (ISCMPA); Integrante do Serviço de Neoplasias do Peritônio do Hospital Santa Rita, at ``Santa Casa de Misericórdia`` at Porto Alegre, Porto Alegre
http://lattes.cnpq.br/3065720881566430

Tiago Auatt Paes Remonti
Supervisor do Programa de Residência Médica da ``Universidade Federal de Ciências da Saúde`` at: Porto Alegre (UFCSPA) – ``Irmandade da Santa Casa de Misericórdia`` at Porto Alegre (ISCMPA); Chief of the Oncological Surgery Service at: ``Santa Casa de Misericórdia`` at Porto Alegre, Porto Alegre
http://lattes.cnpq.br/7181868564070555
Orcid: 0000-0002-6136-7821

Guilherme Watte
Post-graduation Program in Pathology at ``Universidade Federal de Ciências da Saúde`` at Porto Alegre (UFCSPA) – Graduation Program of Pathology, ``Universidade Federal de Ciências da Saúde`` at Porto Alegre (UFCSPA), Porto Alegre, Porto Alegre
http://lattes.cnpq.br/2368890912230733
Orcid: 0000-0002-6948-3982

Jaime Andres Moreno Cando
Resident Doctor of the Medical Residency Program at ``Universidade Federal de Ciências da Saúde`` at Porto Alegre (UFCSPA) – ``Irmandade da Santa Casa de Misericórdia`` at Porto Alegre (ISCMPA), Porto Alegre

William Pfaffenzeller
Resident Doctor of the Medical Residency Program at: ``Universidade Federal de Ciências da Saúde`` at Porto Alegre (UFCSPA) - ``Irmandade da Santa Casa de Misericórdia`` at Porto Alegre ISCMPA), Porto Alegre
http://lattes.cnpq.br/7540070806133808

Ana Carolina Bathelt Fleig
Affiliation: Member of the Peritoneal Neoplasms service at: Hospital Santa Rita, of ``Santa Casa de Misericórdia`` at Porto Alegre (ISCMPA), Porto Alegre
http://lattes.cnpq.br/0271849988143561

Rodrigo Firmino Schirmbeck Moraes
Affiliation: Resident Doctor of the Medical Residency Program at ``Universidade Federal de Ciências da Saúde`` at Porto Alegre (UFCSPA) – ``Irmandade da Santa Casa de Misericórdia`` at Porto Alegre (ISCMPA), Porto Alegre
http://lattes.cnpq.br/5449281528269258
Orcid: 0009-0008-1705-5717

Ellen Cristina Moreira Lima
Affiliation: Resident Doctor of the Medical Residency Program at ``Universidade Federal de Ciências da Saúde`` at Porto Alegre (UFCSPA) – ``Irmandade da Santa Casa de Misericórdia`` at Porto Alegre (ISCMPA), Porto Alegre
http://lattes.cnpq.br/7288934867977074

Samuel da Silva Rosario
Affiliation: Resident Doctor of the Medical Residency Program at ``Universidade Federal de Ciências da Saúde`` at Porto Alegre (UFCSPA) – ``Irmandade da Santa Casa de Misericórdia`` at Porto Alegre (ISCMPA), Porto Alegre
http://lattes.cnpq.br/0259561657778109

Jonathan Adrian Abarca Cuenca
Affiliation: Resident Doctor of the Medical Residency Program at: ``Universidade Federal de Ciências da Saúde`` at Porto Alegre (UFCSPA) – ``Irmandade da Santa Casa de Misericórdia`` at Porto Alegre (ISCMPA), Porto Alegre
Orcid: 0000-0003-2274-8055

ABSTRACT: Introduction: Cecal appendix mucocele is complete or segmental dilatation of the cecal appendix full filled by mucus ou mucin. There isn't a radiologic characteristic that can define or suggest histologic alterations associated, different of another neoplasms. They range from cystadenoma, transient mucus accumulation for fecalith, benign or malign neoplasm. In up to 20% of cases there is association of this rare condition with an appendicular Mucinous Neoplasm, whose mucin leakage in to peritoneal cavity may progress for Peritoneal Pseudomyxoma (PSP) - catastrophic situation. There isn't consensus in the literature whether laparoscopic approach would be safe on this scenario.
Objective: systematically review the literature in order to determine oncological safety regarding the access route for treating cecal appendix mucocele: laparoscopic or laparotomic.
Methods and Results: the key words "appendix mucocele", "laparoscopic", "laparoscopy", "pathology" was searched on the PubMed and LILCAS, including review articles, reviews and series of cases since January/1900 until November/2023, relate of case was excluded. The results were tabled and the articles were discussed in routine multidisciplinary meetings. Total of 36 articles were included: 17 case series, 10 histopathological reviews and 9 literature reviews.
Discussion: In 1997 Sugarbaker described the case of a female of 37 years who underwent a laparoscopic appendectomy for mucocele of appendix whose associated histology was mucinous neoplasia. In 9 months, the patient developed peritoneal pseudomyxoma being submitted to a cytorredutive surgery and HIPEC. He attributed to laparoscopic manipulation of the lesion the rapid spread and progression for PSP. He concluded that the presence of appendix mucocele

contraindicates laparoscopic approach. Since then, numerous articles have been published describing laparoscopic approach to mucocele/clinical changes of the appendix as feasible and oncologically safe. All series of cases analysed were retrospective, few cases, post operative diagnosis, limited and inadequate follow up - considering peritoneal pseudomyxoma is a long-time developing disease. There is also biologic plausibility as LACC TRIAL suggested. At trial, group submitted to laparoscopic approach had worse oncologic outcomes when compared to another group - laparotomic ones – for radical hysterectomy for cervical cancer. Pneumoperitoneum, biologic behavior under CO2 tension, tumoral manipulation could explain the worst outcomes. Characteristics specific to the surgical technique of laparoscopic appendectomy imply manipulation of the cecal appendix – and of the lesion in turn – which can increase tumor exfoliation or fragmentation – as well as not guaranteeing adequate surgical margin in the cecum; It is also known that laparoscopic surgery increases the chance of mucocele rupture. There are no studies that describe the biological behavior of these cells when exposed to pneumoperitoneum, CO2 and increased intra-abdominal pressure. Therefore, it is not possible to consider laparoscopic appendectomy oncologically safe, despite being technically feasible.

Conclusion: In light of the best existing evidence gathered in this review, it is not possible to consider laparoscopic appendectomy oncologically safe. We recommend that cecal appendix mucoceles be approached by laparotomy.

Keywords: Cecal Appendix Mucocele; Laparoscopy; Laparotomy.

INTRODUCTION

Cecal appendix mucocele is a cystic formation, segmental or complete dilation of the vermiform appendix filled with mucus or mucin [1]. The radiological aspects of these changes do not correlate with histology, unlike other neoplasms. [2,3]. They range from appendix cystadenoma, accumulation of transient intraluminal secretion due to fecality, adenomas, benign neoplasia and malignant neoplasm. In the literature there was relative confusion in the classification and terminology of lesions of the cecal appendix [4–7] *(Table 1[8])*. In 2016, Peritoneal Surface Oncology Group International (PSOGI) standardized the classification of mucinous neoplasms of the cecal appendix [9].

Appendiceal mucocele is a rare pathological entity, with a prevalence of between 0.07% and 0.63%4 of appendectomies, and only surgical treatment. [1]. It is generally an occasional finding during imaging examinations, but the clinical presentation may be pain in the right iliac fossa mimicking acute appendicitis, recurrent pain in the same topography such as chronic appendicitis or even a tumor in the right iliac fossa. [10]. In up to 20% of cases of appendiceal mucocele, there may be an associated malignant neoplasm [3,11]. In some situations, intraluminal cellular and mucinous content may leak into the abdominal cavity - during surgical manipulation, for example -, evolving into a serious and lethal clinical condition called Pseudomyxoma Peritoneal. (PMP)[12].

For some time now, it has been a source of debate about the feasibility of performing laparoscopic appendectomy in this condition13,[14], however, there are no non-inferiority or oncological safety studies involving the laparoscopic approach in this type of situation. As it is a rare phenomenon, there are no well-designed studies capable of determining the oncological safety of the

Comparisons Among Classification Schemes for Appendiceal Mucinous Neoplasms and Pseudomyxoma Peritonei

	Source, y					
	Carr and Sobin,[11] 2010	Misdraji et al,[15] 2003	Pai and Longacre,[17] 2009	Ronnett et al,[1] 1995	Bradley et al,[12] 2006	AJCC and WHO[10,11] 2010
Tumor confined to appendix						
Limited to mucosa						
Low-grade cytology	Adenoma	Low-grade appendiceal mucinous neoplasm	Adenoma	NA	NA	Adenoma
High-grade cytology	Adenoma	Noninvasive mucinous cystadenocarcinoma	Adenoma	NA	NA	Adenoma
Positive surgical margin	Adenoma	Low-grade appendiceal mucinous neoplasm	Uncertain malignant potential	NA	NA	Adenoma
Neoplastic epithelium in appendix wall	Uncertain malignant potential	Low-grade appendiceal mucinous neoplasm	Uncertain malignant potential	NA	NA	Invasive Mucinous Adenocarcinoma
Tumor beyond appendix						
Low-grade epithelium in peritoneal mucin	Invasive mucinous adenocarcinoma	Low-grade appendiceal mucinous neoplasm	High-risk for recurrence	Disseminated peritoneal adenomucinosis	Low-grade mucinous carcinoma peritonei	Low-grade mucinous adenocarcinoma
High-grade epithelium in peritoneal mucin	Invasive mucinous adenocarcinoma	Invasive mucinous adenocarcinoma	Invasive mucinous adenocarcinoma	Peritoneal mucinous carcinomatosis	High-grade mucinous carcinoma peritonei	High-grade mucinous adenocarcinoma

Abbreviations: AJCC, American Joint Committee on Cancer; NA, not applicable; WHO, World Health Organization.

Table 01: [8]

Author, Year	Number of patients	Notes	Follow-up	Neoplasia
M. Senturk, 2021[3]	14 patients: 03 female, 11 males, Age: 39 years old.	No description of approach.	Not described.	01 Mucinous adenocarcinoma cyst
T. Kim, 2018[11]	96 patients: 52 female, 43 males, Age: 61 years.	58 Laparoscopies, 38 Laparotomies: 02 perforations per group, when perforation there was conversion.	36 months	Laparoscopy: 34,5% LAMN, 1.7% mucinous adenocarcinoma Laparotomy: 31,6% LAMN, 10.5% mucinous adenocarcinoma
K.J. Park, 2015[16]	24 patients: 14 female, 10 male, Age: 60 years.	24 Laparoscopies	26 months, 50% of patients	24 cystadenomas
M. Rabie, 2015[4]	09 patients: 06 female, 03 male, Age: 62 years.	03 Laparoscopies 06 Laparotomies	06 months	02 Mucinous cystadenocarcinoma with PMP, 01 Carcinoid tumor associated with mucinous hyperplasia, 01 LAMN
E. Tarcoveanu, 2015[17]	07 patients: 01 female, 06 male, Age: 68 years.	03 Laparoscopies 04 Laparotomies	48 months	01 LAMN
M. Singh, 2014[18]	08 patients: 06 female, 02 male, Age: 46 years.	08 Laparoscopies	24 months, only 5 patients.	Not described.
A. Lozano, 2010[2]	31 pacientes: 17 female, 14 males, Ag: 62 years.	25 Laparotomies, 05 laparoscopies; 05 PMP cases, with no correlation described.	Not described.	10 adenocarcinoma cyst
L. Stocchi, 2003[15]	135 patients: 74 female, 61 males, Age: 56 years.	135 Laparotomies	Up to 72 months.	47 cystadenocarcinoma
Acronym:	**PMP – Pseudomyxoma Peritoneal**	**Age: Middle age**		**LAMN: Low Grade Mucinous Neoplasia**

Table 02: Prepared by the author

laparoscopic approach.

Therefore, establishing safe oncological management regarding the access route (laparoscopic or laparotomic) for cystic lesions of the cecal appendix is urgent, considering that the access route could influence the chances of developing peritoneal carcinomatosis or Pseudomyxoma Peritoneal[13].

GOAL

Review the literature systematically in order to establish safe oncological management regarding the access route – laparoscopic or laparotomic – for cystic lesions of the cecal appendix.

METHODS AND RESULTS

The terms "mucocele of appendix", "laparoscopic", "laparoscopy", "pathology" was searched on the Pubmed and LILCAS platforms and studies published between January 1900 and November 2023 were included, case reports were excluded.

The resulting articles were tabulated, as were their results (Table 2), and discussed in multidisciplinary meetings at the Peritoneal Neoplasms Service of Hospital Santa Rita, Santa Casa de Misericórdia de Porto Alegre.

A total of 36 articles were included, 17 case series, 10 histopathological reviews and 9 literature reviews.

DISCUSSION

In the current PSOGI classification9, there is everything from pathology with non-malignant histology with potential for malignant complications (Low-Grade Mucus-Producing Appendix Neoplasm (LAMN) complicated with Pseudomyxoma Peritonealis after extravasation of mucin into the cavity – pathological or iatrogenic) to pathology malignant (Appendix Carcinoma (MACA) with potential for hematogenous, lymph node and peritoneal dissemination (Table 01).

PSOGI Classification of Non-Carcinoid Neoplasms of the Appendix
Adenomas;
Polyps;
Low Grade Appendicular Mucinous Neoplasia;
High Grade Appendicular Mucinous Neoplasia;
Mucinous Adenocarcinoma: well differentiated, moderately differentiated and poorly undifferentiated;
Poorly Differentiated Mucinous Adenocarcinoma with Signet Ring Cells;
Mucinous Carcinoma with Signet Ring Cells;
Adenocarcinoma (Colon Adenocarcinoma).

Table 01 – Prepared by the Author

In 1997, Sugarbaker[13] describes the case of a 37-year-old patient who presented with Pseudomyxoma peritonei nine months after a laparoscopic appendectomy due to mucocele of the appendix associated with mucinous adenocarcinoma of the cecal appendix. In the article, he attributes the dissemination of neoplastic cells in the peritoneum and rapid progression to Pseudomyxoma peritonealis to the laparoscopic method. It concludes that the presence of a mucocele in the cecal appendix contraindicates the procedure via laparoscopy, with conversion to laparotomy for appendectomy being mandatory.

Since then, numerous articles have been published describing laparoscopic approach to mucocele/cystic changes of the appendix as feasible and oncologically safe.

In 2018, Tae Kyu Kim[11] reviewed 96 cases of mucocele operated between 2007-2016 in 06 hospitals in South Korea – 58 cases operated by laparoscopy and 38 cases operated by laparotomy; perforation with extravasation of secretion into the cavity occurred in 04 cases (two in each group). There was conversion of the procedure in cases of perforation during laparoscopic surgery; around 36% of cases operated via laparoscopy had an associated diagnosis of malignancy, while in the laparotomy group this number was 42%. Among the cases that suffered perforation, only

one had a diagnosis of associated malignancy. The average follow-up time was 36 months. Filip Eugene Tarcoveanu [17] in 2015 found 07 cases of mucocele in 1007 appendectomies – 03 cases treated by laparoscopy and 04 by laparotomy; has a single case of Low-Grade Mucinous Neoplasia and a follow-up of 48 months. In 2021, Mustafa Senturk [3] reviewed specimens from 4850 appendectomies performed between 2012-2018 and found 14 cases of appendiceal mucocele, 78.6% cystadenoma, 14.3% simple mucocele (or retention cyst) and 7.1% cystadenocarcinoma, without description of surgical method or case follow-up time.

All are retrospective case series, with a significantly small number of patients, heterogeneous in the population, different post-operative histopathological diagnoses, sometimes without prior radiological suspicion of neoplasia and mainly with limited or inadequate post-operative oncological follow-up (Table). Furthermore, the most feared complication of appendix mucocele is Pseudomyxoma peritonei, which is a pathology that develops insidiously and can take decades for the formation of symptomatic mucinous ascites.[3,12,19].

The minimally invasive approach (laparoscopic or robotic) has numerous advantages when compared to the traditional approach. However, these benefits are not necessarily reflected in oncological safety. For example, the study "Minimally Invasive versus Abdominal Radical Hysterectomy for Cervical Cancer – LACC TRIAL "[20] showed worse oncological outcomes in patients undergoing minimally invasive radical hysterectomy when compared to patients undergoing the procedure via laparotomy – including higher rates of peritoneal carcinomatosis.

Possible factors attributed [20] these results in the study were the use of the uterine manipulator in contact with the cervical tumor used routinely (increasing tumor fragmentation, even if microscopic), intracavitary colpotomy associated with pneumoperitoneum as a carrier of cells through the cavity and the effect of CO2 and increased intra-abdominal pressure on tumor cell growth[21,22].

Characteristics specific to the surgical technique of laparoscopic appendectomy imply manipulation of the cecal appendix – and of the lesion in turn – which can increase tumor exfoliation or fragmentation – as well as not guaranteeing adequate surgical margin in the cecum; It is also known that laparoscopic surgery increases the chance of mucosis rupture[11,17].

Besides, there are no studies that describe the biological behavior of these cells when exposed to pneumoperitoneum, CO2 and increased intra-abdominal pressure. Mucin-producing neoplastic cells originating from the appendix, whether malignant or not, have a special characteristic of implantation and predilection for the peritoneum, as well as cellular entrapment/incarceration in surgical wounds and tumor development in these sites. [7–9,23]. Therefore, both manipulation of the cecal appendix or surgical specimen within the abdominal cavity and abdominal wall with cells of uncertain malignant potential, associated with the presence of CO2 and pneumoperitoneum, may increase the risk of cell dissemination or implantation. [22,24].

Considering 1) impossibility of predicting the histology associated with appendiceal mucocele (up to a quarter have associated malignancy)[3,11], 2) catastrophic abdominal complication if peritoneal dissemination of malignancy [25], 3) lack of knowledge of cellular behavior exposure to CO2 and pneumoperitoneum, 4) biological plausibility of increased cellular aggressiveness seen in other tumors [20,24] 5) Existing scarce and low-quality evidence makes it impossible

to consider laparoscopic appendectomy oncologically safe, despite being technically feasible.

Among the possible limitations of this review, we can mention precisely the literature found to be scarce, limited to case series with retrospective analyses, even in the context of a recent change in classification, without it even being possible to adapt one classification to another. Even so, cecal appendix mucocele is rare, often asymptomatic and discovered in the context of emergency/acute abdomen and with insidious and slow progression, making it difficult to design and execute studies with better methodology.

CONCLUSION

Mucocele of the cecal appendix is an infrequent pathology, with a varied spectrum of clinical presentation and with potential for catastrophic complications (Pseudomyxoma peritonei). Sometimes, appropriate management upon presentation of the initial lesion determines the patient's oncological prognosis. In light of the best existing evidence gathered in this review, it is not possible to consider laparoscopic appendectomy oncologically safe, although technically it is feasible. Therefore, it is recommended that cecal appendix mucoceles be approached using a laparotomic approach.

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