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REVIEW

Benign multicystic mesothelioma and peritoneal inclusion cysts: are they the same clinical and histopathological entities? A systematic review to find an evidence-based management

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Abstract

Purpose Peritoneal mesothelial cysts (PMC) are a clinical dilemma because of their true pathogenic nature. Many definitions have been associated with PMC, including "benign multicystic mesothelioma", "cystic mesothelioma", "multilocular peritoneal inclusion cysts", ''inflammatory cysts of the peritoneum" or "postoperative peritoneal cyst".

Methods We herein performed a systematic review of the literature focusing on clinical and histopathological aspects of PMC, diagnosis, and therapies. Moreover, we described our experience with a case of PMC in a young female.

Results Since there is often a history of prior surgery or inflammatory disease, most authors consider PMC of reactive origin. However, in some cases they occur without any documentable signs of disease or injury. A variety of clinical findings can complicate the preoperative assessment and a multitude of histological pictures may potentially lead to a misdiagnosis. The absence of a uniform treatment strategy and lack of long-term follow-up often hinder the accurate definition leading to unnecessary or unnecessarily aggressive therapy.

Conclusions PMC are more common than had previously been thought. Most authors consider them non-neoplastic; thus the designation of "peritoneal inclusion cyst" is preferable. The term "mesothelioma" should be used only in cases of histological evidences of atypia. The high rates of recurrence suggest that the goal of treatment should not be necessarily complete eradication, but symptomatic relief through individualized treatment. This is a topic of particular importance, especially in young female where recurrence rates could be lower than those reported in adults and where an improperly aggressive treatment could have repercussions on fertility.

Keywords Peritoneal mesothelial cysts · Peritoneal inclusion cyst · Benign multicystic mesothelioma · Inflammatory cysts of the peritoneum · Postoperative peritoneal cyst · Young female

Introduction

Peritoneal mesothelial cysts (PMC) are rare lesions, resulting from uncommon mesothelial proliferations that may primarily involve not only the pelvis, but also the upper abdomen, and retroperitoneum [1–7]. Since the first description in 1979 by Mennemeyer and Smith [8] approximately 200 cases have been reported in the literature [9]. Currently, it has not been definitively established whether these ones were due to a reactive response to injury or a neoplasia. For this reason, various terms were applied to designate them, including "benign multicystic mesothelioma", "cystic mesothelioma", "multilocular peritoneal inclusion cysts", ''inflammatory cysts of the peritoneum" or "postoperative peritoneal cyst". Moreover, it created much disagreement regarding the most appropriate treatment

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[1, 10, 11], because these ones often tend to recur and their biological behavior still remains unclear [12]. Only a few cases have been reported in adolescent and young females in the past 30 years. They could show some particular features distinguishing them from those ones described in adult population [11].

These evidences prompt to clarify the nature of these lesions and to provide a well-defined denomination establishing the most appropriate management. This review describes the state of the art on PMC, according to recent literature findings. Our attention has been focused on the clinical presentation, diagnosis, natural history and treatment with particular attention on young females (age range 10–20 years). Particularly, the aim of this paper was to clarify the best management for PMC since there is no standard of care in the literature and different approaches have been proposed. Indeed, this review tries to suggest when it is advisable to manage a conservative treatment, analyzing clinical and histopathological aspects, symptoms, main complications and surgical outcomes. Finally, we described our experience with a case of PMC, involving the pouch of Douglas in a 19-year-old female.

Methods

In this systematic review, we performed a PubMed search comprising the terms: "benign multicystic mesothelioma" and "peritoneal inclusion cyst". A total of 338 articles were found through this search, with publication dates from 1960 to 2017. A total of 181 papers were excluded for the following reasons: the abstract was not available, the study was not published in English, the subject was not related to the topic of our review or not provided any noteworthy information. Thus, a total of 157 references were selected. We sequentially reviewed all available articles on PMC describing clinical presentation, pathogenesis, macroscopic and histopathological aspects, natural history, diagnosis and treatment. Moreover, our attention has been focused on the young female group. Therefore, we selected all reported cases aged 10–20 years and analyzed the following aspects: clinical features, symptoms, associated diseases, previous surgery, macroscopic features, localization, cancer markers, intervention and follow-up. Finally, we described our experience with a case of PMC, involving the pouch of Douglas in a 19-year-old female.

Results

Our research highlighted that no uniform data about PMC exist. The controversial pathogenesis and consequently, the lack of consistent definitions, led to a lack of agreement on the therapeutic approach. Moreover, the shorter follow-up times made it difficult drawing any firm conclusions from published reports.

Current literature on PMC is mostly based on case reports or series of cases analyzing small subject groups. Cases described in the literature are updated and reported in Table 1. Clinical features, pathogenesis, macroscopic and histopathological aspects, natural history, diagnosis and treatment of PMC were described. Moreover, we found a total of 21 cases of PMC in young females (aged 10–20 years) that we analyzed. Data were summarized in Table 2. Of the reported cases, 7 patients were nulliparous [11, 13–15] and 1 [16], parous. Data regarding parity were not recorded in the other cases. The mean age at diagnosis was 16.7 years (range 11–20 years). The most typical localization was the pelvis; indeed almost all of the examined cases showed a pelvic localization of the lesions. In six cases the lesions were specifically localized at the level of the Douglas [11, 16, 17], in five cases they involved also the abdomen, including colon, omentum or appendix [14, 16, 18–20]. Pelvic pain was the most common presenting symptom, recorded in ten cases [11, 21–24]; other reported symptoms were abdominal pain or distension, constipation, amenorrhea, dysuria, recurrent urinary symptoms, fever and anorexia [1, 11, 13–15, 17–20]. In four cases the presenting symptom was acute abdominal pain [13–15, 20], in two of these [14, 20], this symptom was associated with fever, simulating the occurrence of acute appendicitis or a bowel inflammatory disease. Only one case [16] of reported series was completely asymptomatic. Only one had a medical history positive for PID [15]. One patient reported ulcerative colitis [21], two had congenital genitourinary anomaly [11, 24] and in another case, although medical history was negative for any noteworthy diseases, an unconfirmed suspicion of bowel inflammatory disease was done during the intervention [14].

Ten patients underwent previous surgery. Appendectomy (three cases) [11, 21] and oophorectomy (four cases) [11, 21–23] were the most reported prior surgery; others included pancreatectomy, splenectomy, colectomy, cystectomy and renal transplant [21, 22, 24]. The main macroscopic aspects observed during the interventions were multiloculated thin-walled cyst (six cases) [11, 14, 17, 18, 20, 24] or multiple cysts [14, 15, 21], sometimes with a grapelike appearance [15, 19] or cystic mass [1, 22, 23], occasionally free-floating [23, 24] or connected to the peritoneum by a pedicle [11]. In one case, ascites were also reported [19]. As regards the preoperative evaluation of tumor markers in our selected series, unfortunately, most studies did not pay attention to such aspect, except for one case [17] in which an increase of serum Ca 19.9 was observed. The treatment strategy adopted in most of the examined cases was the surgical removal by laparoscopy or laparotomy [11, 14, 15, 17, 19–22], while in three cases cyst drainage [18, 24] was performed. In two of

Table 1 Case reports and case series of peritoneal mesothelial cysts (PMC) in the literature

First author, year	PMC; setting	References
Khurram, 2017	3 cases in male patients (age: 61–72 years); St. John Hospital and Medical Center, Detroit, USA	[68]
Stallone, 2017	1 case in a 65-year-old male; Department of Medical and Surgical Sciences, Nephrology, University of Foggia, Italy	[70]
Mehta, 2017	1 case in a 22-year-old female; Department of Radiology, Staten Island University Hospital, Northwell Health New York City	[162]
Campbell, 2017	1 case in a 49-year-old woman; Department of Surgery, Caboolture Hospital, Caboolture, Queensland, Australia	[50]
D'Antonio, 2016	1 case in 58-year-old female; Department of Pathologic Anatomy, AOU San Giovanni di Dio e Ruggi D'Aragona, Salerno, Italy	[62]
Macedo, 2016	1 case in a 25-year-old male; Department of Surgery, Providence Hospital and Medical Centers, Michigan State University College of Human Medicine, USA	[92]
Mishra, 2016	1 case in a 40-year-old female; Department of Obstetrics and Gynaecology, V.M.M.C. and Safdarjung Hospital, Delhi, India	[105]
Tuncer, 2016	1 case in a 2-year-old male; Department of Pediatric Surgery, Yüksekova State Hospital, Hakkari, Turkey	[69]
Shin, 2016	1 case in a 52-year-old male; Department of Internal Medicine, Dankook University College of Medicine, Cheonan, Korea	[63]
Cotter, 2016	1 case in a 49-year-old male; Department of Internal Medicine, Mayo Clinic College of Medicine, Rochester, Minnesota	[102]
Bray Madoué, 2016	1 case in a 22-year-old female; Surgical Service, Renaissance Hospital of N'Djamena, N'Djamena, Chad	[116]
Santangelo, 2016	1 case in a 73 year-old male; Department of General and Specialist Surgery, Second University of Naples, Napoli, Italy	[48]
Lee, 2016	1 case in 47-year-old female; Departments of Radiology (R.L., A.T., A.G.G.) and Pathology (B.K.), Westchester Medical Center, Valhalla, NY	[161]
Occhionorelli, 2016	1 case in a 41-year-old man; Department of Morphology, Surgery and Experimental Medicine, University of Ferrara, Ferrara, Italy	[120]
Durell, 2016	1 case in a 10-year-old female; Department of Paediatric Surgery, Leicester Royal Infirmary, Leicester, United Kingdom	[79]
Jerraya, 2016	1 case in a 84-year-old maale; Department "B" of General Surgery, University of Medicine of Tunis, hôpital Charles Nicolle, Tunis, Tunisia	[136]
Ianieri, 2016	1 case in a 40-year-old female; SS. Annunziata Hospital, Obstetrics and Gynecology Unit, Gabriele D'Annunzio University, Chieti, Italy	[10]
Mazziotti, 2016	3 cases in female patients (age: 35–49); Department of Biomedical Sciences and Morphological and Functional Imaging, University of Messina, Italy	[27]
Iacoponi, 2015	1 case in a 35-year-old female; Gynecologic Oncology Unit, Quiron University Hospital, Calle Diego de Velasquez 1, Madrid, Spain	[65]
Firatligil, 2015	3 cases in female patients (age: 35–42 years); Obstetrics and Gynecology, Gulhane Military Medical Academy, Ankara, Turkey	[64]
Hinsch, 2015	1 case in a 12-year-old male; Department of Pathology, Health Care Center, Lukaskrankenhaus Neuss, Neuss, Germany	[80]
Tamhankar, 2015	1 case in a 23-year-old female; Department of Obstetrics and Gynaecology, Jessop Wing, Sheffield Teaching Hospitals NHS Foundation Trust, UK	[90]
Fernandez Eire, 2015	1 case in a 11-year-old male; Department of Pediatric Surgery, Complejo Hospitalario de Vigo, Vigo, Spain	[81]
Somasundaram, 2015	1 case in a 40-year-old male; Department of General Surgery, Seth GS Medical College and KEM Hospital, India	[51]
Yeom, 2015	1 case in a 27-year-old female; Department of Surgery, Eulji General Hospital, Eulji University School of Medicine, Seoul, Korea	[122]
Singh, 2015	1 case in a female (age non reported); Department of Obstetrics and Gynaecology, Government Medical College and Hospital, Chandigarh, India	[32]
Marien, 2014	1 case in a 38-year-old female; Department of Urology, NYU Langone Medical Center, New York, New York, USA	[97]
Murro, 2014	1 case in a 26-year-old male; Department of Pathology, Rush University Medical Center, Chicago	[207]
Al-Safi, 2014	1 case in a 25-year-old female; Department of Obstetrics and Gynecology, University of Colorado Anschutz Medical Campus, Aurora, Colorado	[209]

Table 1 (continued)

First author, year	PMC; setting	References
Momeni, 2014	1 case in a 47-year-old female; Department of Obstetrics, Gynecology and Reproductive Medicine, New York, USA	[9]
Witek, 2014	1 case in 50-year-old female; The Commonwealth Medical College †Geisinger-Community Medical Center, Scranton, PA	[203]
Jouvin, 2014	1 case in a 43 year-old male; Service de chirurgie digestive et cancérologique, hôpital Lariboisière, Assistance Publique-Hôpitaux de Paris, France	[52]
Goldfisher, 2014	2 cases in female patients (age 16 and 17 years); Department of Radiology, SUNY Downstate Medical Center, NY, USA	[24]
Hitzerd, 2014	1 case in a 27-year-old female; Utrecht University, Utrecht, The Netherlands	[91]
Yokoyama, 2014	2 cases in female patients; Health Science Clinic of Osaka Medical College, Akutagawa-machi, Takatsuki, Osaka, Japan	[185]
Trehan, 2014	1 case in a 51-year-old female; Lincoln College, University of Oxford, Oxford	[202]
Gupta, 2013	1 case in a middle age female (age not reported); Department of Surgery, Kasturba Medical College, Mangalore, India	[107]
Hong, 2013	1 case in a 28-year-old female; Department of Obstetrics and Gynecology, Soonchunhyang University Cheonan Hospital, Cheonan, Korea	[119]
Wang, 2013	1 case in a 56-year-old Caucasian male; Department of Surgery, the First Affiliated Hospital, Sun Yat-sen University, China	[71]
Elbouhaddouti, 2013	1 case in a 71 year-old female; Department of Surgery, School of Medicine and Pharmacy of Fez, Morocco	[98]
Singh, 2013	1 case a 34-year-old female; Department of Medical Oncology, Christian Medical College, Tamil Nadu, India	[32]
Canbay, 2013	1 case in a 57-year-old female; Department of General Surgery, Kishiwada Tokushukai Hospital, Kishiwada City, Japan	[108]
Bakhshi, 2013	1 case in a 32-year-old female; Department of Surgery, Grant Medical College and Sir JJ Group of Hospitals, Mumbai, India	[2]
Veldhuis, 2013	40 cases in male patients and 188 cases in female patients; Department of Radiology, University Medical Center Utrecht, The Netherlands	[132]
Khuri, 2012	1 case in a19-year-old male; Department of General Surgery, Rambam Health Care Center, Haifa, Israel	[205]
Stojsic, 2012	1 case in a 11-year-old male; Institute of Pathology, Faculty of Medicine, University of Belgrade, Serbia	[208]
Aber, 2012	1 case in a 77-year-old male; Urology Department, Royal Free Hampstead NHS Trust, London, UK	[72]
Takemoto, 2012	1 case in a 23-year-old female; Department of Obstetrics and Gynecology, Omuta City Hospital, Japan	[125]
Dellaportas, 2012	3 cases in female patients (age: 32–34 years); 2nd Department of Surgery, Aretaieion University Hospital, Athens, Greece	[109]
Tentes, 2012	1 case in a 16-years-old female; Surgical Department, Didimotichon General Hospital, Diagnostiko Center of Pathology, Didimotichon, Greece	[19]
Husain, 2012	2 cases in female patients (age: 56 and 58 years); Lombardi Comprehensive Cancer Center, Georgetown University Hospital, Washington, D.C., USA	[127]
Dellaportas, 2012	1 case in a 82-year-old female; 2nd Department of Surgery, University of Athens, Aretaieion Hospital, Athens, Greece	[126]
Lee, 2012	83 cases in female patients; Department of Obstetrics and Gynecology, The Catholic University of Medicine, Korea	[181]
Dzieniecka, 2011	1 case in a 46-year-old female; Department of Clinical Pathomorphology, Research Institute of the Polish Mother's Memorial Hospital, Łódź, Poland	[26]
Sizzi, 2011	1 case in a 36-year-old female; Department of Obstetrics and Gynecology, Universita' di Cagliari, Cagliari, Italy	[201]
Shakya, 2011	1 case in a 4-year old female; Department of Surgery, B. P. Koirala Institute of Health Sciences, Dharan 56701, Nepal	[82]
Akbayir, 2011	3 cases in female patients (age: 32–38 years); Oncology Unit, Istanbul Bakirkoy Maternity and Children Diseases Hospital, Istanbul, Turkey	[89]
Snyder, 2011	1 case in a 65-year-old female; Pinnacle Health Community Campus, Harrisburg, PA	[33]
Kurisu, 2011	2 cases in female patients (age: third and fourth decades of life); Department of Pathology, Osaka Medical College, Osaka, Japan	[28]

Table 1 (continued)

First author, year	PMC; setting	References
Testa, 2011	1 case in a 70-year-old female; Department of Obstetrics and Gynecology, Catholic University of the Sacred Heart, Rome, Italy	[128]
Cavallaro, 2011	1 case in a 45-year-old; Department of Surgery, University of Catania, Catania, Italy	[112]
Saxena, 2011	1 case in a 7-year-old female; Department of Pediatric- and Adolescent Surgery, Medical University of Graz, Auenbruggerplatz 34, A-8036 Graz, Austria	[83]
Ho-Fung, 2011	1 case in a 18-year-old female; Department of Radiology, The Children's Hospital of Philadelphia, Philadelphia, USA	[18]
Lehwald, 2010	1 case in a 86-year-old female and 2 cases in male patients (age: 45 and 59 years); Department of General, Visceral and Pediatric Surgery; Germany	[93]
O'Connor, 2010	1 case in a 19-year-old female; Department of Surgery, St Vincent's University Hospital, Elm Park, Dublin 4, Ireland	[20]
Pitta, 2010	1 case in a 72-year-old female; Department of Radiology, General Hospital "Agios Pavlos", Thessaloniki, Greece	[3]
Hollington, 2010	1 case in a 37-year-old female; Department of Surgery, Flinders Medical Centre Adelaide, South Australia	[4]
Pinto, 2010	1 case in a 20-year-old female; Department of Gynaecology, Obstetrics, and Neonatology, University Medical School of Bari, Bari, Italy	[17]
Kemp, 2010	1 case in a 61-year-old female; Department of Pathology, Northwestern Memorial Hospital, Feinberg School of Medicine, Northwestern University, Chicago, USA	[192]
Limone, 2010	1 case in a 61-year-old female; Department of Obstetrics and Gynaecology, IRCCS Burlo Garofolo, Trieste, Italy	[200]
Lim, 2010	29 cases in female patients; Department of Radiology, Seoul National University College of Medicine, Republic of Korea	[191]
McCaffrey, 2009	1 case in a 59-year-old female; Department of General Surgery, Tameside General Hospital, Manchester, UK	[115]
Uzüm, 2009	1 case in a 48-year-old female; Mikro-Pat Pathology Laboratory, General Surgery Division, Gazi University, School of Medicine, Ankara, Turkey	[99]
Koo, 2009	1 case in a 27-year-old female; Department of Radiology, Pennsylvania Hospital, University of Pennsylvania Health System, USA	[133]
Terry, 2009	1 case in a 11-month-old male; Department of Surgery, Memorial Health University Medical Center, Mercer University School of Medicine, Savannah Campus, USA	[84]
Bernstein, 2009	3 cases in female patients (age: 35–53 years); Department of Obstetrics and Gynecology, Yale University, New Haven, Connecticut	[35]
Amesse, 2009	4 cases in female patients (age: 11–16 years); Department of Obstetrics and Gynecology, Wright State University Boonshoft School of Medicine, Dayton, USA	[11]
Dillman, 2009	1 case in a 16-year-old female; Department of Radiology, C.S. Mott Children's Hospital, University of Michigan Health System, Ann Arbor, USA	[134]
Asghar, 2008	1 case in a 40-year-old female; Department of Gyneacology, Unit-1, Sir Ganga Ram Hospital, Lahore	[110]
Cuartas, 2008	1 case in a 44-year-old female; Department of Musculoskeletal Oncology, University of Miami Miller School of Medicine, Miami, FL, USA	[94]
Assaly, 2008	3 case in female patients (age: 45–63 years); Department of Pathology, Geneva University Hospital, Geneva, Switzerland	[178]
de Keizer, 2008	1 case in 38-year-old male; Department of Nuclear Medicine, University Medical Center Utrecht, Utrecht, The Netherlands	[95]
Vallerie, 2008	1 case in a 29-year-old female; Department of Obstetrics and Gynecology, Columbia University College of Physicians and Surgeons, New York, USA	[210]
Saad, 2007	1 case in a 23-year-old female; Department of Surgery, Cologne-Merheim Medical Center, University of Witten-Herdecke, Cologne, Germany	[199]
Rougemont, 2007	2 cases in neonates; Department of Pathology, CHU Sainte-Justine, Montréal, Canada	[37]
Coskun, 2006	1 case in a 25-year-old female; Department of Obstetrics and Gynecology, Kahramanmaras Sutcu Imam University, Faculty of Medicine, Kahramanmaras, Turkey	[111]
Safioleas, 2006	1 case in a 62-year-old female; Department of Propedeutic Surgery, School of Medicine, Athens University, Laiko Hospital, Athens, Greece	[66]
Ng, 2006	2 cases in male patients (age: 60 and 72 years); Departments of Surgery and Pathology Yan Chai Hospital Hong Kong, China	[135]

Table 1 (continued)

First author, year	PMC; setting	References
Jerbi, 2006	1 case in a 35-year-old female; Gynaecologic and Obstetric Department, Farhat Hached Hospital, Sousse, Tunisia	[138]
Søreide, 2006	2 cases in female patients (age: 67 and 76) and 1 case in a 46-year-old male; Department of Surgery, Stavanger University Hospital, Stavanger, Norway	[49]
Bansal, 2006	1 case in a 58-year-old female; Department of Histopathology, Arrowe Park Hospital, UK	[96]
Advincula, 2006	1 case in a 36-year-old female; Department of Obstetrics and Gynecology, University of Michigan Medical Center, USA	[117]
Tangjitgamol, 2005	2 case in female patients (age: 42 and 56); Department of Gynecologic Medical Oncology, The University of Texas M. D. Anderson Cancer Center, Houston, USA	[38]
Urbańczyk, 2005	5 cases in female patients (age: 22–53 years) and 1 case in a 47-years-old male; Department of Clinical and Experimental Pathomorphology, Kraków	[54]
Samson, 2005	1 case in a 79-year-old male; Department of General Surgery North Shore Hospital, Takapuna, Auckland	[179]
Nayak, 2005	1 case in a 26-year-old female; Department of Pathology, Govt. Medical College, Nagpur	[88]
Kagalwala, 2005	1 case in a 57-year-old female; Department of Radiology, University of Massachusetts Memorial Medical Center, Worcester, USA	[174]
Durak, 2005	1 case in a 32-year-old male; Department of Surgery, Izmir Ataturk Teaching Hospital, Turkey	[6]
Varma, 2004	1 case in a 51-year-old female; Academic Department of Obstetrics and Gynaecology, Birmingham Women's Hospital, Birmingham, UK	[7]
Muscarella, 2004	1 case in a 53-year-old female; Department of Surgery, The Ohio State University, Columbus, Ohio, USA	[5]
Guerriero, 2004	13 cases in female patients; Department of Obstetrics and Gynecology, University of Cagliari, Ospedale San Giovanni di Dio, Italy	[163]
Curgunlu, 2003	1 case in a 25-year-old female; Department of Internal Medicine, Cerrahpasa Medical Faculty, Istanbul University, Istanbul, Turkey	[36]
Abdullahi, 2003	1 case in a 18-year-old female; South Tyneside General Hospital, South Shields, UK	[55]
Sawh, 2003	13 cases in female patients (age: 18–54) and 4 cases in male patients (age: 44–77); Division of Pathology and Laboratory Medicine, The University of Texas M.D. Houston, USA	[16]
Sethna, 2003	4 cases in female patients and 1 case in a male patient; The Washington Cancer Institute, Washington Hospital Center, Washington, USA	[104]
Hove Kanstrup, 2002	3 cases in female patients (age: 26–40 years); Institute of Pathology and Department of Gynecology and Obstetrics, Aalborg Hospital, Denmark	[137]
Flemming, 2002	1 case in a 51-year-old female; Institut fuer Pathologie, Medizinische Hochschule Hannover, Germany	[53]
Cavallaro, 2002	1 case in a 28-year-old male; Institute of Surgical Semiotics. Catholic University of the Sacred Heart, Rome, Italy	[121]
Adolph, 2002	1 case in a 36-year-old female; Endocopic Surgery, Center for Women's Care and Reproductive Surgery, Atlanta, GA, USA	[100]
Vara-Thorbeck, 2002	1 case in a 43-year-old; Department of General Surgery, Hospital Universitario, Colonia Santa Inés S/N, Málaga, Spain	[56]
González-Moreno, 2002	1 case in a a 36-year-old female; The Washington Cancer Institute, Washington Hospital Center, Washington, District of Columbia, USA	[47]
van Ruth, 2002	1 case in a 34-year-old male; Department of Surgical Oncology, The Netherlands Cancer Institute/Antoni van Leeuwenhoek Hospital, Amsterdam, The Netherlands	[73]
Häfner, 2002	1 case in a 28-year-old male; Department of Gastroenterology and Hepatology, University of Vienna, Vienna, Austria	[74]
Petrou, 2001	1 case in a 60-year-old female; Division of Surgery, Department of Anatomical Pathology, Liverpool Hospital, Liverpool, New South Wales, Australia	[106]
Omeroglu, 2001	1 case in a 31-year-old female; Department of Pathology, Loyola University Medical Center, USA	[140]
Holtzman, 2001	1 case in a 58-year-old male; Department of Neurosurgery, College of Physicians and Surgeons, Columbia University, NY, USA	[182]
Kanasugi, 2001	1 case in a 31-year-old female; Department of Obstetrics and Gynecology, Iwate Medical University School of Medicine, Morioka, Iwate, Japan	[129]
Jeong, 2001	7 cases in female patients; Department of Radiology, Seoul National University College of Medicine, Seoul, Korea	[158]
Guzzo, 2001	1 cases in female; Department of Surgery, Gundersen Lutheran Medical Center, La Crosse, Wisconsin, USA	[57]

Table 1 (continued)

First author, year	PMC; setting	References
Talib, 2000	2 cases in female patients (age: 53 and 64); Department of Gynaecology, Benenden Hospital, Kent, UK	[58]
Brustmann, 2000	1 case in a 21-year-old female; Department of Pathology, Landeskrankenhaus, Vienna, Austria	[130]
Nozawa, 2000	8 cases in female patients; Department of Obstetrics and Gynecology, Keio University School of Medicine, Tokyo, Japan	[39]
Inman, 2000	1 case in a 13-year-old male; Department of Surgery, Derriford Hospital, Plymouth, UK	[193]
Rosen, 1999	1 case in a 23-year-old female; Department of Obstetrics and Gynaecology, Royal Surrey County Hospital, Guildford	[59]
Lane, 1999	1 case in a 27-year-old male; Departments of Surgery and Cellular Pathology, The Maidstone Hospital, Kent, UK	[75]
Ozgen, 1998	1 case in a 43-year-old male; Department of Radiology, School of Medicine, Hacettepe University, Ankara, Turkey	[76]
Letterie, 1998	1 case in a 19-year-old female; Department of Obstetrics and Gynecology, Virginia Mason Medical Center, Seattle, Washington, USA	[23]
Birch, 1998	1 case in a 43-year-old female; Department of Surgery, McMaster University, St. Joseph's Hospital, Hamilton, Ont.	[198]
Van der Klooster, 1997	1 case in a 57-year-old female; Department of Internal Medicine, St Clara Ziekenhuis, Rotterdam, The Netherlands	[194]
Kim, 1997	15 cases in female patients; Department of Diagnostic Radiology, Keimyung University, School of Medicine, Chung Ku, Taegu, Korea	[166]
Yaegashi, 1996	1 case in a 19-year-old female; Department of Obstetrics and Gynecology, Tohoku University School of Medicine, Sendai, Japan	[15]
Takenouchi, 1995	1 case in a 32-year-old male, Department of Surgery, Anjo Kosei Hospital, Aichi, Japan	[77]
Letterie, 1995	1 case in a 17-year-old female; Department of Obstetrics and Gynecology, Virginia Mason Medical Center, Seattle, Washington, USA	[22]
Ricci, 1995	1 case in a 44-year-old male; First Department of General Surgery, University of Verona, Italy	[197]
Sohaey, 1995	6 cases in female patients (age: 24–46 years); Department of Radiology, University of Utah Hospital, Salt Lake City, USA	[164]
McCullagh, 1994	1 case in a 2-year-old female; Children's Hospital Lewisham, London, England	[85]
Bhandarkar, 1993	1 case in a 47-year-old male; Department of Surgery, Manchester Royal Infirmary	[78]
Hasan, 1993	1 case in a 79-year-old female; Department of Clinical Radiology, Ninewells Hospital and Medical School, Dundee	[177]
Kampschöer, 1992	1 case in a 45-year-old female; Department of Obstetrics and Gynecology, De Wever Ziekenhuis, Heerlen, The Netherlands	[113]
Hanukoglu, 1992	1 case in a11-year-old male; Department of Pediatrics, Edith E. Wolfson Medical Center, Holon, Israel	[86]
Pelosi, 1992	1 case in a 46-year-old male; Institute of Surgical Pathology, Hospital Civile Maggiore, Verona, Italy	[34]
Pollack, 1991	1 case in a 15-year-old female; Division of Emergency Medicine, University of Mississippi Medical Center	[14]
Hidvégi, 1991	1 case in a 25-year-old female; 2nd Department of Pathology, Semmelweis University, Medical School, Budapest, Hungary	[173]
Baddoura, 1990	1 case in a 70-year-old male; Department of Pathology, Emory University School of Medicine, Atlanta, Georgia	[180]
Chen, 1990	1 case in a 36-year-old female; Department of Internal Medicine, Taipei County Pan Chiao Hospital, Taiwan, ROC	[103]
Suh, 1989	1 case in a 53-year-old female; Department of Pathology, College of Medicine, Hailym University, Seoul, Korea	[114]
O'Neil, 1989	3 cases in female patients (age: 34–53 years); 2 cases in male patients (age: 26 years); Department of Radiology and Department of Pathology, University of Florida, Gainesville	[176]
Ross, 1989	25 cases in female patients (age: 17–61 years); Department of Pathology, Harvard Medical School, Boston	[1]
Iversen, 1988	1 case in a 27-year-old female; Institute of Pathology, University of Oslo, National Hospital (Rikshospitalet), Norway	[45]
Raafat, 1988	1 case in a 14-year-old male; Department of Histopathology, Children's Hospital, Birmingham, UK	[87]
Hoffer, 1988	4 cases in female patients (age: 13 to 24 years); Department of Radiology, Children's Hospital, Harvard Medical School, Boston, USA	[21]

Table 1 (continued)

First author, year	PMC; setting	References
Weiss, 1988	31 cases in female patients and 6 cases in male patients; Department of Soft Tissue Pathology, Armed Forces Institute of Pathology, Washington	[25]
McFadden, 1986	5 cases in female patients (age: 15–51 years); Department of Pathology, University of British Columbia, and Vancouver General Hospital, Canada	[13]
Schneider, 1983	4 cases in female patients (age: 24–43 years); Departments of Pathology and Obstetrics and Gynecology, Medical College of Virginia	[101]
Katsube, 1982	5 cases in female patients (age: 23–44 years); Departments of Pathology, University of Colorado School of Medicine	[118]
Moore, 1980	1 case in a 73-year-old male; Departments of Surgery and Pathology, University of Virginia, Charlottesville, Virginia	[123]

the reported cases [22, 23], hormonal therapy with tamoxifen [23] or leuprolide acetate plus estrogen progestin [24] was carried out. Patients had a history of recurrence of PMC and they previously had undergone surgical procedures in the management of the disease. In another reported case [19], complete cytoreductive surgery (resection of the pelvic peritoneum en bloc with the internal female genitalia, and low anterior resection), greater and lesser omentectomy in combination with hyperthermic intraoperative intraperitoneal chemotherapy was performed. The mean follow-up period was 33.9 months (range 2–253 months). One patient was lost to follow-up [11] and in eight cases, recurrence rates were not reported [14–16, 18, 21]. Recurrences in only three cases occurred [1, 24]. In two of these cases the previous treatment was cyst drainage [24].

Discussion

History and pathogenesis

PMC were first described by Plaut in 1928 who incidentally observed 'loose cysts of the pelvis' during an operation for uterine leiomyoma [25, 26]. However, their mesothelial nature was confirmed later in 1979 by Menemeyer and Smith [8]. In 1989 Ross et al. [1] reported the clinical and pathological features of 25 cases of PMC, most of them derived from Dr. Scully's consultation files. A history of abdominal surgery, pelvic inflammatory disease and/or endometriosis, was found in most of their cases, supporting a reactive nature opposing to the view, still supported by others, that PMC are well-differentiated cystic mesotheliomas [25]. To date the pathogenesis of PMC still remains controversial. According to some authors [1, 12] PMC are the result of particular proliferative reactions within the peritoneal tissue secondary to intra-abdominal inflammation and subsequent cyst formation [27, 28]. The normal peritoneum is able to easily transport the fluid produced by the ovaries, but when its integrity is compromised, as a result of injury, its absorption ability is impaired. In addition, postsurgical adhesions can trap ovarian fluid forming complex cystic masses. According to this theory, functional, active ovaries and adhesions are thus essential for the development of PMC [24].

In several reports, 30–87% of patients with PMC had a history of previous abdominal surgery [1, 21, 29, 30]. The time between the most recent surgery and detection of the PMC ranged from 6 months to 20 years [13].

Although PMC is often accompanied by endometriosis, histologic findings of the lesion have not been well documented [28, 31].

In one case the lesion consisted of multiple cysts having thin walls lined with single-layered cuboidal mesothelial, and inside the cystic walls, small foci of endometriosis were found. In another case the mesothelial lesion was next to the endometriotic cysts, in the pelvic cavity [28].

These histologic findings further support the hypothesis that endometriosis plays a role in the pathogenesis of PMC and that cystic lesions are the results of a reactive rather than a neoplastic process [31].

In contrast, the lack of previous surgery or inflammation observed in some cases, as well as the developmental behavior and the high recurrence rate, led other authors to theorize a neoplastic origin for these lesions. For this reason, it has been suggested that PMC may be placed on a spectrum between an adenomatoid tumor and a malignant mesothelioma [12, 25, 32, 33].

It is well known that there are some precipitating factors such as foreign fibers or dust, inflammatory mediators and mechanical injuries that may promote hyperplastic and neoplastic changes in mesothelial cells. Proliferation and metaplasia of underlying connective tissue cells, surface attachment and differentiation of mononuclear cells have all been postulated as mechanisms of mesothelial proliferation in pathological conditions [34].

Moreover, a possible genetic or familial predisposition for PMC has been proposed [35–38]. Specifically, a case report by Bernstein et al. [35] described the occurrence of PMC in two sisters. In addition, a third sister had also findings

Table 2 Case reports and case series of peritoneal mesothelial cysts (PMC) in young females

Author's	Age	Parity	Symptomps	Associated desease	Previous surgery	Features	Localization	Markers	Intervention	Follow-up
McFadden and Clement [13]	15	0	Acute abdominal pain	No	NO	Thin-walled cysts	Pelvis	NR	NR	NED at 36 months
Hoffer et al. [21]	19	NR	Pelvic pain	No	Pancreatectomy, splenectomy	NR	Pelvis	NR	Surgical removal	NR
	20	NR	Pelvic pain	Ulcerative colitis	Colectomy	Multiple cysts	Pelvis	NR	Surgical removal	NR
	13	NR	Pelvic pain	No	Appendectomy, Oophorectomy	Single cyst	Pelvis	NR	Surgical removal	NR
Ross et al. [1]	17	NR	Constipation	No	NR	Cystic mass 19 cm	Pelvis		Cystectomy	NED at 83 months
	18	NR	Abdominal pain	No	No	NR	Pelvis		Cystectomy	recurrences until 253 months
Pollack and Jorden [14]	15	0	Acute Abdominal pain, fever, dysuria, anorexia	Bowel inflammatory desease?	No	Multiple loculated pockets of ascitic-type and a cystic mass	Omentum	NR	Surgical removal	NR
Letterie and Yon [22]	17	NR	Pelvic pain	No	Cystectomy, left salpingo-oophorectomy (previous PMC)	Cystic mass	Pelvis	NR	Leuprolide acetate + E/P; total hysterectomy and right salpingo-Oophorectomy	NR
Yaegashi and Yajima [15]	19	0	Acute abdominal pain	PID	NO	Thin-walled, smooth-surfaced, translucent locules, arranged in grape-like clusters	Pelvis	NR	LPT removing	NR
Letterie and Yon [23]	19	NR	Pelvic pain	No	Unilateral ooforectomy	Cystic fluctuant mass	Pelvis	NR	Tamoxifene	No increment
Sawh et al. [16]	18	Parous	Asymptomatic (incidental finding)	No	No	6 cm cyst 3 cm cyst	Cul de sac Colon	NR	NR	NR
Pinto et al. [17]	20	NR	Amenorrhea	No	No	Thin- walled translucent cyst 0.5 cm free-floating	Cul de sac	Ca 19.9 +	LPS removing	NED at 24 months

Table 2 (continued)

Author's	Age	Parity	Symptomps	Associated desease	Previous surgery	Features	Localization	Markers	Intervention	Follow-up
Amesse et al. [11]	11	0	Pelvic pain	No	Appendectomy	Multiloculated cysts connected to peritoneum by a pedicle.	Cul de sac	NR	LPS removing	NED AT 37 months
	13	0	Pelvic pain	No	Ooforectomy	Multiloculated cyst connected to peritoneum by a pedicle	Cul de sac.	NR	LPS removing	NED at 26 months
	16	0	Pelvic pain, fever	No	Appendectomy	Complex fluid-filled cystic lesion connected to peritoneum by a pedicle	Cul de sac	NR	LPS removing	Lo
	15	0	Recurrent urinary symptoms	Horseshoe kidney benign teratoma	No	Smooth and shiny cyst connected to peritoneum by a pedicle	Cul de sac	NR	LPS removing	NED at 8 months
O'Connor et al. [20]	19	NR	Acute abdominal pain, fever	No	No	Multiloculated, thin-walled cyst	Right iliac fossa, appendix	NR	LPS removing	NED at 3 months
Ho-Fung et al. [18]	18	NR	Chronic abdominal pain, dysuria	No	No	Multiloculated lesion	Pelvis abdomen	NR	Ultrasound-guided drainage	NR
Tentes et al. [19]	16	NR	Abdominal pain, distension	No	No	multiple grape-like clusters and ascites	Pelvis, Abdomen	NR	cytoreductive surgery, intra-operative chemo-therapy	NED at 1 year
Goldfisher et al. [24]	16	NR	Pelvic pain	Genitourinary anomalies	Renal transplant	Cystic mass	Pelvis	NR	Percutaneous drainage	Recurrence after 2 months
	17	NR	Pelvic pain	No	Partial colectomy	Multiloculated cystic mass	Pelvis	NR	Surgical drainage	Recurrence

0 nulliparous, *PID* pelvic inflammatory disease, *E/P* estrogen and progestin, *Lo* lost to follow-up, *NR* not reported, *NED* no evidence of disease

consistent with PMC. However, the discrete histological diagnosis was never confirmed. Another case report, published by Curgunlu et al. [36], describes a man with familial Mediterranean fever who also developed PMC.

Finally, the evidence that the great majority of patients are women of reproductive age has suggested a hormonal dependency and, as such, a potential role for hormonal manipulation as medical management and an alternative to surgery [39].

Some important epidemiological differences between peritoneal and pleural mesothelial proliferations have been reported in literature. Indeed, while peritoneal mesotheliomas are more frequent in women, peritoneal mesotheliomas more often occurs in men. Likewise, prognosis seems better in females [40, 41].

Asbestos exposure is strongly related with an increased risk of malignant pleural mesothelioma. On the contrary, the link between asbestos exposure and peritoneal mesotheliomas is less strong, and it is estimated that approximately 20–40% of all cases occur spontaneously without any evidence of previous asbestos exposure [40, 42].

The median age at diagnosis is earlier in peritoneal mesotheliomas, and the latency period between asbestos exposure and development of peritoneal mesotheliomas is shorter (20 years) compared with pleural mesotheliomas (30–40 years). The mechanism whereby asbestos fibers reach the peritoneum is unknown but they have been found in the omentum and in the mesentery of the gastrointestinal tract. It has been supposed that irritation of the peritoneum is able to induce a chronic inflammatory process with disruption of the mitotic process and chromosomal instability [40, 43, 44].

Although PMC are usually qualified as benign, their natural history has not been definitively established. There are several case reports of these cysts recurring despite successful operative removal with some patients requiring multiple operations to reduce the cystic load and relieve symptoms. Local recurrence is reported to be as high as 50%, even when all visible lesions have been removed [1]. Local relapse may occur decades after diagnosis and primary surgery [45]. Other concerns are reports of malignant transformation observed in some patients with a primary PMC [46–48]. The absence of a uniform treatment approach, lack of long-term follow-up in most patients, and the rarity of this entity seriously hinder an accurate assessment of the disease process [49].

Clinical features

PMC typically arise from the peritoneum of the pelvic region; exceptionally, they can develop on the serosal surfaces of the pelvic viscera including kidney, bladder, lymph nodes, liver and spleen [50–62]. Occasionally, PMC can also be accompanied by ascites [63–65].

They mostly occur in women of reproductive age [66], although cases involving men [67–78] and children [79–87] are documented. The average age at diagnosis is approximately 32 years [1].

A diagnosis of PMC during pregnancy has been reported [88–91]. In most cases, these cysts have been found incidentally at the time of full term Cesarean sections in asymptomatic patients with uneventful pregnancies. Indeed, the most typical presentation of PMC is characterized by the absence of specific symptoms and there could be an incidental finding at surgery for other abdomino-pelvic complaints [92–96]. In other cases, common presenting symptoms are vague lower abdominal pain or discomfort [97–101] and fullness [102, 103]. Other described features include abdominal distension [104], pelvic pain [105, 106], palpable mass [107–114], weight loss, nausea, vomiting [115], constipation or signs of bowel obstruction [116] and urinary retention or dysuria [117, 118]. Sometimes the presenting symptom can be acute abdominal pain [119] simulating the occurrence of acute appendicitis [20, 120–123]. Knowledge of PMC is important because especially in symptomatic patients undergoing evaluation for abdomino-pelvic complaints, PMC may be mistaken for borderline or malignant cystic tumors or tumor with degenerative cystic changes that prompt unnecessary or unnecessarily aggressive therapy [124–132].

Macroscopic aspects

Macroscopically, PMC can be unilocular or multilocular. They may be adherent to surrounding structures, including the ovaries, fallopian tubes, large bowel, appendix, omentum and uterus with a strong predilection for the pelvic peritoneum [133–135]. The cysts can also be free floating in the peritoneal cavity. The cystic formations can be of different sizes ranging from few millimeters to 20 cm [136]. Unilocular cysts can be single or multiple; they are usually small, thin-walled, translucent, attached or lie free in the peritoneal cavity. Multilocular cysts, typically consists of multiple grapelike clusters of mesothelium-lined cysts, confluent or discontinuous, studding the peritoneal surface. Unlike the smaller unilocular cysts, in multilocular cysts the septa and the walls may contain considerable amounts of fibrous tissue. The intracystic fluid varies from clear to blood tinged and may occasionally be mucinous or gelatinous [1, 9, 12, 137, 138].

Histopathologic characteristics

On microscopic examination PMC are typically lined by a single layer of flat to cuboidal mesothelial cells with generally bland nuclear features. The septa typically consist of a

loose, fibrovascular connective tissue with a sparse inflammatory infiltrate accompanied by fibrin, granulation tissue, and recent and old hemorrhages in the cyst walls. However, many unusual morphological features may pose problems for differential diagnosis with malignant lesions. The lining cells may exhibit unusual reactive histological findings such as atypia with hyperchromatic enlarged nuclei that may have a hobnail appearance and exhibit complex architectural arrangements including intraluminal small papillae, gland-like structures or nests and cribriform patterns or they may resemble squamous metaplasia, mimicking a malignant primitive peritoneal mesothelioma [13, 16, 139, 140]. Furthermore, patterns resembling adenomatoid tumors may be encountered. Occasional vacuolated mesothelial cells in the stroma may simulate signet-ring cells [1]. Mesothelial cells are typically immunoreactive for calretinin, cytokeratin 5/6, CA125, Vimentin and Wilms' tumor antigen and, in some cases, they are positive for estrogen (ER), progesterone receptors (PR), or both [21, 32, 34]. A multitude of definitions has been associated with PMC [1, 10, 12], creating misunderstandings between clinicians and pathologists. Since most authors agree to consider these lesions non-neoplastic [1, 12, 21], the designation of "peritoneal inclusion cyst" rather than "benign cystic mesothelioma" is preferable. However, no specific histopathological features predicting the risk of recurrences have been identified. The term "mesothelioma" should be used only in the presence of atypia, suggestive of malignancy such as proliferative mesothelial components, moderate to severe atypia or numerous mitoses. Improper use of this term could result in very aggressive and unjustified therapeutic attitudes.

New markers in mesothelial proliferations

The distinction of a benign mesothelial reaction from a malignant proliferation is crucial for patient care and prognosis, but it often results exceedingly difficult on biopsy. Indeed, while morphology is diagnostic in many instances, a significant proportion of cases show equivocal aspects, making it necessary to resort to ancillary tests.

Immunohistochemistry (IHC) has been instrumental in allowing the pathologist to distinguish malignant proliferations from other processes. Loss of specific genes expression is useful in supporting the diagnosis of malignant mesotheliomas (MM) in a subset of patients with atypical biopsy findings, but lack without traditional definitive morphologic features of MM (invasion or tumefactive growth). [141–143]. A variety of immunostains have been investigated, including p53 nuclear positivity, desmin, membranous staining for epithelial membrane antigen (EMA), GLUT-1 and IMP3 positivity; however, the lack of specificity has not made them suitable for extensive use in clinical practice [143–146]. Recently, loss of BRCA1-associated protein-1 (BAP1) expression and/or homozygous deletion of cyclin-dependent kinase inhibitor 2A (CDKN2A) were identified in some MM, but not in reactive mesothelial proliferations [147, 148]. BAP1 is a tumor suppressor gene that encodes a protein involved in the regulation of important target genes implied in transcription, cell cycle control, DNA damage repair, and cellular differentiation through its deubiquitinase activity. The inactivating mutations in the BAP1 gene have been identified in 23–63.6% of MM [149–153].

CDKN2A gene encodes p16INK4a, a protein that acts through inhibition of CDK4 and CDK6 as a negative regulator of cell cycle progression leading to uncontrolled tumor cell proliferation. The loss of p16 tumor suppressor results from homozygous deletion of the 9p21 region, and it is detectable by fluorescence in situ hybridization (FISH). Homozygous deletion of CDKN2A is highly specific for malignancy, but only demonstrable in 22–88% of MM [154, 155]. Although neither loss of BAP1 expression nor homozygous deletion of CDKN2A is entirely sensitive for MM, the combination of both tests has been shown to increase the sensitivity for MM to 58–92% with 100% specificity [156].

Diagnosis

Since cystic lesions in the pelvic cavity are common in post-pubertal women, their detection prompts a long list of differential diagnoses, including ovarian cancer [157]. However, in premenopausal women with peritoneal adhesions due to previous surgery, endometriosis or PID, PMC should be included in the differential diagnosis. This is even more important considering that these cysts are suggested to be more common than had been thought [158]. To improve the preoperative assessment of pelvic masses, assessing the risk of malignancy, several parameters are used such as gray-scale sonographic parameters, color Doppler ultrasonography, gynecological examination, tumor markers, and patient characteristics, and most of these parameters have been combined in diagnostic models [159, 160]. Transabdominal and/or transvaginal (TV) ultrasound (US) are the first-line imaging techniques in detection of pelvic masses. At US, PMC typically appear as multiseptate, anechoic cystic structures lacking internal vascularity at color Doppler evaluation, and they have an intimate anatomical association with the uterus and ovaries [161–163].

Peritoneal adhesions may extend to the surface of the ovary and distort the ovarian contour but do not penetrate the ovarian parenchyma. As fluid accumulates from these adhesions, the ovary appears entrapped within the cystic lesion. This appearance has been described as a "spider's web" where a morphologically normal ipsilateral ovary is identified within a "web" of adhesions. The position of the ovary is variable and it can be centrally or eccentrically

placed [164–166]. In the presence of typical imaging features, the diagnosis of PMC is relatively straightforward, particularly when accompanied by an appropriate clinical history. In many cases, however, the lesion may show a non-classic appearance; thus PMC could be misdiagnosed. The differential diagnosis includes benign and malignant conditions such as ovarian cystadenoma or cystadenocarcinoma, endometriosis, cystic teratoma, Brenner tumors, mesenteric-omental cysts, pseudomyxoma peritonei, lymphangioma, cystic adenomatoid tumor, malignant mesothelioma and other serous tumors of the peritoneum [132, 166–173]. Computed tomography (CT) and magnetic resonance imaging (MRI) may be complementary in preoperative diagnosis [137, 174]. MRI is the most useful second-line technique in problematic cases thanks to its high soft-tissue resolution and multidimensional imaging capabilities [175]. CT can be useful in differentiating ovarian malignancy from PMC by enhancing solid components within the lesion. The presence of calcification, peritoneal deposits and ascites are further features that should raise the suspicion of a malignancy [165, 176, 177]. However, a tissue sample is required for definitive histologic diagnosis. Negative cytology on fine-needle aspiration can decrease suspicion for malignancy, but results are usually inconclusive because the aspirate commonly shows reactive mesothelial cells that are non-specific [178–180]. Therefore, especially in any suspicion of malignancy, a biopsy is recommended [12]. Laparoscopy remains the best diagnostic tool because it can perform biopsies and establish a definitive diagnosis [181]. Evaluation of complex pelvic masses usually includes a serum assessment of tumor markers. In most reported cases of the literature a significant increase in serum tumor markers has not been observed. However, PMC have occasionally been associated with an increased CA 19.9 serum concentration [17, 182, 183]. Some tumor cells express this antigen and it has a role in adhesion between tumor and endothelial cells. It was suggested that metaplastic changes in mesothelial cells were responsible for secretion of this marker [17]. A few cases of PMC were associated with a raised serum CA125 level, which makes the distinction with serous epithelial tumors, including papillary serous carcinoma and borderline serous tumors, extremely difficult. However, ovarian malignancies often showed a markedly elevated CA-125 level. Moreover, an elevated CA-125 level may be seen in peritoneal inclusion cysts with associated endometriosis [12]. It has also been reported that PMC have the worst behavior when CA125 levels are high [184].

Treatment

Current literature is mostly based on case reports and small series and a uniform treatment approach and long-term follow-up data are lacking. The treatment options for PMC, range from observation to complete resection [15]. Although the treatment of choice has not been firmly established, conservative management is preferable to surgery in asymptomatic patients [158, 185]. There are several reasons for conservative management. First, most authors consider PMC pathologically reactive, not neoplastic lesions and even in the presence of squamous metaplasia, they have no malignant potential [1, 12, 13, 24, 29]. Second, PMC can adhere to the surface of the ovary not involving the ovarian parenchyma, and most cases occur in patients of reproductive age; consequently, fertility preservation techniques are advisable [1, 165, 186]. Moreover, PMC tend to easily rupture, frequently just after the abdomen is opened, and resection is difficult because tissue planes are poorly defined [187]. Third, after surgical resection, the recurrence rate is 30–50% [1, 45]. Moreover, most patients are asymptomatic and had previously undergone several laparotomies; thus additional surgical intervention is undesirable [1, 16, 25]. Conservative treatment includes observation with serial imaging in asymptomatic patients, with more aggressive treatment if the disease develops. Hormonal treatment with oral contraceptives, gonadotropin-releasing hormone agonist and the anti-estrogenic agent, tamoxifen, can be administered to suppress the formation of ovarian fluid [22, 23, 39, 158, 188]. Minimally invasive/radiological treatment involves image-guided drainage. PMC are generally accessible to US-guided drainage or aspiration via a transabdominal route. Previous reports have suggested that aspiration is a safe and effective nonsurgical treatment for PMC; simple aspiration is, however, associated with a high recurrence rate; therefore, sclerotherapy following drainage can improve treatment success [158, 189–191]. Image-guided aspiration provides fluid for cytological evaluation and can lead to the resolution of symptoms with minimal intervention and few complications. However, in doubtful cases and especially when there is any suspicion of malignancy, conservative management has not been recommended and a tissue sample is required for making the histologic diagnosis [49, 181, 192–194]. Considering the high rate of recurrence, some authors have proposed surgery with complete removal. Indeed, complete surgical excision is considered the treatment of choice for relief of symptoms and for prevention of recurrence [181, 195]. The choice of a surgical approach can depend on gross appearance, organ involvement, and differential diagnosis at the time of surgery [12, 181]. While laparoscopy is the approach of choice for investigation of masses or pain in women, open surgery is safer when a malignant process is suspected owing to the possibility of cyst rupture and seeding [20, 196–203]. Finally, given the rare reported case of malignant transformation, some authors have advocated aggressive surgery (extended peritonectomy) followed by hyperthermic intraperitoneal chemotherapy (HIPEC). They have been performed in cases of recurrence or even in first-line

treatment, as the optimal treatment to prevent transition to a truly aggressive tumor [18, 19, 204–206]. However, since PMC mainly affect women of reproductive age, these therapeutic strategies often result very aggressive, with important repercussions on fertility. For these reasons, in the choice of the most appropriate treatment, careful consideration should be given on above discussed aspects and, especially in the light of the knowledge of the biological behavior of such lesions, it would be advisable, when possible, to offer the woman a more conservative treatment.

PMC in young female

Although PMC represent a well-established entity in the adult population, they remain a poorly characterized phenomenon in the pediatric population. In the young age group, this condition is fairly rare and difficult to diagnose because the clinical presentation might mimic numerous diseases [11]. After Mennemeyer and Smith's definition of this pathology, there are few reports of PMC occurring in adolescent female individually cited in case reports. The 21 cases of adolescent female (age range 11–20 years) included in this investigation represent the largest case collection of PMC analyzed in the young female adolescent population, although unfortunately, some features were partially reported by several authors.

Typical reported localization was the pelvis, while the cul de sac was the only anatomical location in five reports [11, 16, 17]. Pelvic pain was the most common presenting symptom, in accordance with the collective data from the literature deriving from adult population [1, 9, 12]. In four cases the presenting symptom was acute abdominal pain [13–15, 20]; in two of these [14, 20], it was associated with fever. Such acute presentations, occasionally simulating appendicitis, have also been described in adult females [1]. For all the patients with acute presentations, PMC were the major intraoperative finding. In the McFadden et al. report [13], a ruptured PMC was considered the source of hemoperitoneum and multiple cysts were adherent to the ovarian surfaces. Only in one case of our reported series [16], the condition was asymptomatic and lesions were occasionally discovered at surgery for a ruptured left tubal ectopic gestation. Among all the examined patients, medical history was negative for endometriosis and only one patient reported a history of PID [15]: a patient reported a previous diagnosis of ulcerative colitis [21], while in another case, although medical history was negative for any noteworthy diseases, an unconfirmed suspicion of bowel inflammatory disease was done during the intervention [14]. These data are in apparent contrast with the previous reports of adult females, where PMC usually occurred in a background of PID, endometriosis and/or bowel inflammatory diseases [1, 6]. No other relevant associated diseases were identified, with the exception of two cases: one patient reported congenital genitourinary anomaly [24], and another had a horseshoe kidney [11]. Other cases of PMC associated with various congenital renal abnormalities have been reported in literature, and all occurred in young patients [207, 208]. In this series, ten patients underwent previous surgery [11, 21–23]; a history of previous abdominal surgery correlates with similar reports of adult women, but in about 30% of the analyzed cases, patients gave a negative history of prior surgery or associated inflammatory diseases. This finding may be related to the small sample size; alternatively, this atypical occurrence could characterize some variants with particular features and different pathogenesis, which may distinguish them from those ones reported in adult patients with a positive history for the above discussed factors.

The main macroscopic aspects observed were similar to those described in adult population group: multiloculated thin-walled cyst (six cases) [11, 14, 17, 18, 20, 24] or multiple cysts [14, 15, 21], sometimes with a grapelike appearance [15, 19] or cystic mass [1, 22, 23] occasionally free-floating [23, 24] or connected to the peritoneum [11]. The presence of a well-formed peduncle was previously identified, though this has been rarely described. It is possible that peduncles are common components of PMC, but it has been widely overlooked [11]. As regards the preoperative evaluation of tumor markers in our selected series, unfortunately, most studies had not paid attention to such aspect, except for one case [17], so it was not possible to analyze this aspect. The treatment strategy adopted in most of the examined cases was surgical removal by laparoscopy or laparotomy [11, 14, 15, 17, 19–22], and in three cases cyst drainage [18, 24] was performed.

In Letterie et al. report [22], the reduction of tumor size secondary to the hypoestrogenism induced by the GnRH agonist suggests a sensitivity to manipulation of the hormonal milieu. Indeed, the immediate increase in size with the addition of add-back therapy of estrogen and progestin further confirmed these findings. Another report by Letterie et al. [23] described the role of the antiestrogen tamoxifen in the management of recurrent PMC after radical surgery. The initial reduction in tumor size was followed by a stabilization in size and disappearance of symptoms. The use of tamoxifen in these circumstances may offer conservative management for long-term therapy in cases of recurrences.

Finally, Tentes et al. reported [19] a demolitive treatment strategy, and despite the histopathological definition of PMC, they performed a complete cytoreductive surgery (resection of the pelvic peritoneum en bloc with the internal female genitalia, and low anterior resection) with greater and lesser omentectomy in combination with hyperthermic intraoperative intraperitoneal chemotherapy. Unfortunately, further histopathological features, useful to better characterize such case, have not been reported. Such aggressive

therapy is based on the assumption of s neoplastic origin, in which microscopic residual disease can disseminate thought the peritoneal cavity [204–206].

Despite a full spectrum of management options, because of a lack of knowledge of pathogenesis and long-term outcomes, there is no clear standard of treatment. In addition, there are no guidelines for following patients and no standard definition of recurrent versus persistent disease in temporal relation to medical or surgical management. Nevertheless, data from our collection suggest that local recurrences of PMC could follow a less aggressive course in young female group. It may be less likely than in adult females, in whom recurrences approach is nearly 50% [1, 11, 12]. Thus, in these cases, and especially when PMC have been discovered incidentally with no concerning history and in the absence of pelvic pain or compressive symptoms, a conservative management may be advisable, following the patient over time using transvaginal and/or transabdominal ultrasound [209]. This is a topic of particular importance, especially in young patients, where the choice of demolitive strategy may be extremely aggressive and irrational, with important repercussions on fertility [209, 210]. However, it is still unknown whether the cysts, over time, can spontaneously develop to potentially compress nearby structures. Therefore, treatment strategies must be carefully evaluated and individualized for each case, until larger studies will be conducted and definitive management guidelines established.

Case presentation

We herein described our experience with a case of PMC in a young female. A 19-year-old woman presented to our Department [omissis for blind review] for chronic pelvic pain. The patient was admitted to our hospital for a preliminary assessment that included: medical history, physical examination, complete blood biochemical assessment, including tumor biomarker (CA 125; CA 19.9; CA 15-3; carcinoembryonic antigen (CEA); Alpha fetoprotein (AFP); human chorionic gonadotropin (hCG)) and pelvic ultrasound (US). As standard protocol, the patient was informed and signed a consent allowing data collection for research purposes. This case report is in accordance with the Helsinki Declaration, conforms to the Consensus-based Clinical Case Reporting Guideline Development (http://www.equator-network.org/) the Committee on Publication Ethics (COPE) guidelines (http://publicationethics.org/) and was approved by the Institutional Review Board (IRB) of the university hospital in which it was performed. She had no relevant family history for main pathologies and cancers. She did not smoke or drink alcohol. She had no previous surgical history; she only reported an idiopathic thrombocytopenia during childhood that spontaneously resolved. Gastrointestinal and genitourinary symptoms, as well as sexual activity, were denied. Menstrual cycles were reported as regular. On physical examination, vital signs were normal; abdomen was treatable in all quadrants, with achiness to deep palpation of the left lower quadrant. Laboratory data were within normal ranges. Particularly, all cancer marker values were in the range of normality although there was a minimal increase in serum levels of CA 125 and CA 19.9, which, however, were a little below the threshold considered as significant. Pelvic US evaluation revealed a normal retroverted uterus, with a mild bilateral increment in ovarian volume, which also showed a micropolycystic appearance. A wide, well-organized multilocular anechoic mass of 57 mm × 36 mm × 32 mm was detected, floating in a free fluid effusion at the level of the pouch of Douglas. A total abdomen magnetic resonance imaging (MRI) was performed giving no more details concerning the pelvic mass, but just showing a collection of free fluid, partially septate, at the level of the pouch of Douglas. No other noteworthy lesions were documented and no bulky lymph-nodes were observed in the pelvic and retroperitoneal areas. The patient was evaluated through pelvic US 1 month later. Surprisingly, the free fluid effusion, previously noted, had disappeared and only a pelvic mass of unvaried size was detected. This was described as multilocular mass with regular walls, internal septa and low-level fluid content without any feature of blood supply at color and spectral Doppler. Given the ultrasound findings and the persistence of pelvic pain it was decided to perform a laparoscopic investigation. At laparoscopy, the uterus and the adnexa appeared regular for volume and morphology. We observed a single, thin-walled, cystic mass, with multiple septa inside rising from the bottom of the pouch of Douglas; it was of opaque appearance and was connected to peritoneum by a short peduncle. Cysts freely filled the pouch of Douglas because no adherence between cyst walls and peritoneal surface was seen. No other lesions in the upper and inferior abdomen or evidence of ascites were found. Because of its delicate constitution, a rupture occurred during resection and a yellowish liquid came out. The deflated cyst was detached from its peduncle and removed (Fig. 1). Microbiological examination of the contents of the cyst did not detect signs of bacteria proliferation, mycetes or other microorganisms. At the histological examination, the cyst was lined by a single, flattened layer of mesothelial cells, with bland ovoid to flattened nuclei and with a wall of fibrous connective tissue. No mitosis or metaplasia was observed and the cyst did not exhibit reactive features such as chronic or acute inflammatory components and degenerative cytological changes. Immunohistochemically, it showed a diffuse nuclear and cytoplasmic expression for calretinin and nuclear expression of WT-1 confirmed the mesothelial origin of the cyst (Fig. 2). The definitive diagnosis of PMC was made. The patient had an uneventful recovery. She was then enrolled to follow-up including trimestral cancer marker dosage and pelvic US for the first year. No evidence

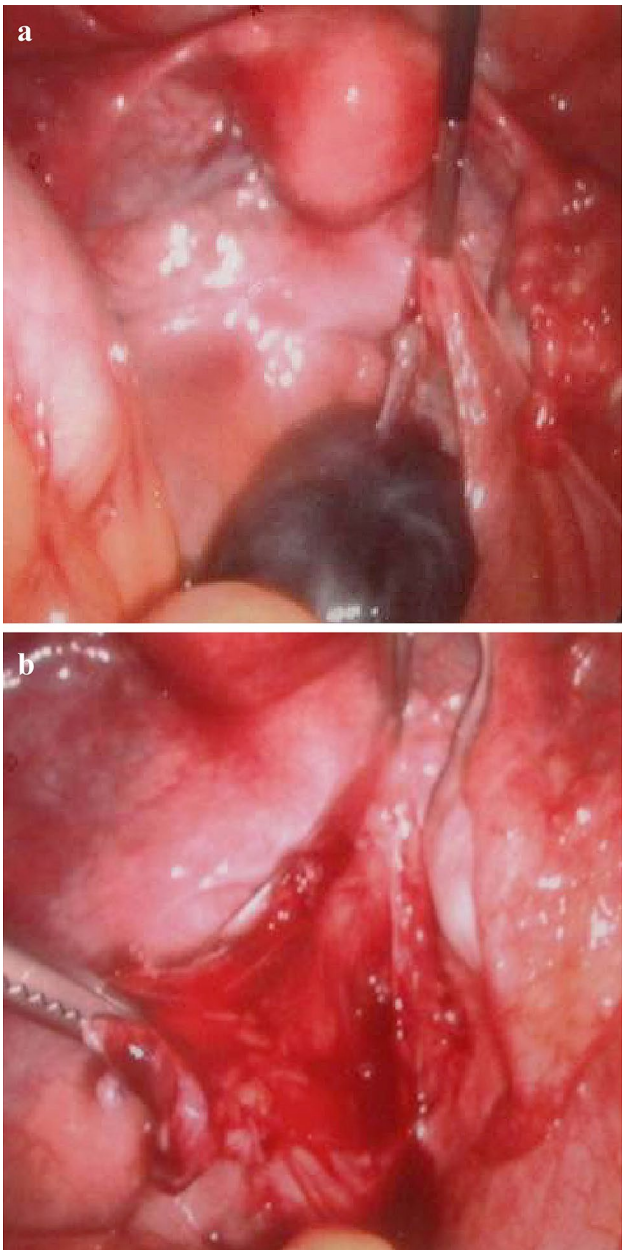

Fig. 1 Laparoscopic view of a single, opaque, thin-walled cystic mass with inner multiple septa, freely filled the pouch of Douglas without any adherence and connected to the peritoneum by a short peduncle (**a**); deflated cyst after accidental rupture rising from the bottom of the pouch of Douglas (**b**)

of pelvic mass at US and no positivity for cancer marker were reported after 3 months from the intervention.

Conclusions

To date, PMC have represented a clinical dilemma because their true pathogenic nature still remains controversial. This systematic review demonstrates the variety of information available regarding the etiology, clinical features, method of diagnosis and treatment of PMC. Lack of consistent definitions, uniform treatment approaches and mostly short follow-up times make it difficult to draw any firm conclusions from published reports. However, when the typical histological aspects are identified, most authors agree to consider these lesions as non-neoplastic, eschewing the term "cystic mesothelioma" and using the more appropriate term "peritoneal inclusion cyst". This is even more important, considering that PMC are suggested to be more common than had previously been thought. Actually, there are no standard algorithms by which the patients are evaluated, treated, or followed up but it is apparent that PMC have a low mortality and the potential for high morbidity. Thus the goal of treatment should not be necessarily complete eradication, but symptomatic relief through individualized approach. This is a topic of particular importance, especially in young patients, where recurrence risk could be lower than those reported in adults and knowledge of the clinical context and typical features can avoid unnecessary, or unnecessarily aggressive, therapy.

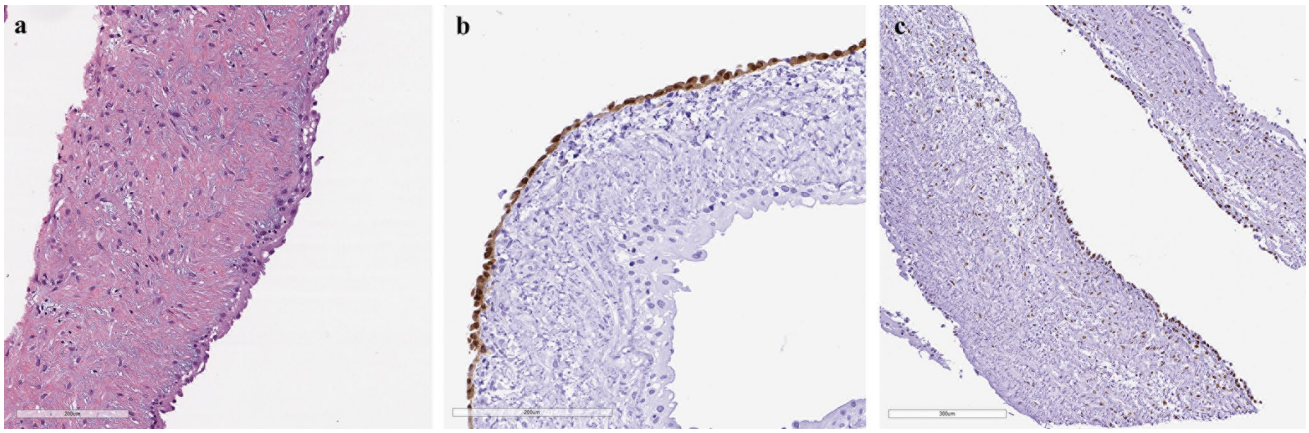

Fig. 2 Peritoneal inclusion cyst: cystic spaces are lined by a single layer of flat mesothelial cells and are separated by thin fibrous septa [haematoxylin and eosin] (**a**); immunohistochemical view of Mesothelial cells with diffuse nuclear and cytoplasmic expressions for calretinin (**b**) and nuclear expression of WT-1 (**c**)

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Compliance with ethical standards

Research involving animals This article does not contain any studies with animals performed by any of the Authors.

Conflict of interest The authors have no proprietary, financial, professional or other personal interest of any nature in any product, service or company mentioned in this study.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from the subject included in the study.

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