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Giant ovarian tumors: diagnosis, management, and treatment

Tumores ováricos gigantes: diagnóstico, manejo y tratamiento

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SUMMARY

The large size of some tumors has been described with fascination over time. These include gynecological ones, of which cases of enormous growth are described, especially before the advent of ultrasound. The terminology used to describe these large tumors contains a variety of confusing qualifiers, including "immense", "extensive", "voluminous", "massive", "large", "very large", "giant", and " gigantic gigantic". Likewise, their measurements are usually used to refer to "giants", but the limits for their definition are not mentioned. In the English literature, there has been agreement for 54 years on defining uterine or ovarian tumors weighing more than 25 lb. as "giants", because, in 1971, the uterine or ovarian tumors, between 1946-1970, weighing 25 lb. or more, were reviewed. The most common clinical signs are rapidly expanding abdominal distension and a palpable mass. The primary imaging modality is ultrasound. The management approach is determined by tumor size, available equipment, and the surgeon's skill level and must be discussed with the gynecology team. The treatment of choice is surgery. This article aims to provide updated information on the diagnosis, management, and treatment of giant ovarian tumors, serving as a comprehensive guide.

Keywords: *Giant, ovarian, ovary, tumors, cysts, cystadenomas.*

RESUMEN

A lo largo del tiempo, se ha descrito con fascinación el gran tamaño de algunos tumores. Entre ellos se encuentran los tumores ginecológicos, de los que se han descrito casos de crecimiento enorme, especialmente antes de la introducción de la ecografía. La terminología de estos tumores grandes presenta calificativos muy variados y confusos, como «inmenso», «extenso», «voluminoso», «masivo», «grande», «muy grande», «gigante», «gigantesco», etc. Del mismo modo, se suelen utilizar sus medidas para referirse a ellos como «gigantes», pero no se mencionan los límites de dicha definición. En la literatura inglesa, durante 54 años se ha acordado definir como «gigantes» los tumores uterinos u

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ováricos que pesan más de 25 libras, ya que en 1971 se revisaron los que pesaron 25 libras o más entre 1946 y 1970. Los signos clínicos más comunes son la distensión abdominal de rápida expansión y una masa palpable. La modalidad de imagen principal es la ecografía. El enfoque terapéutico se determina en función del tamaño del tumor, del equipo disponible y del nivel de habilidad del cirujano y debe discutirse con el equipo de ginecología. El tratamiento de elección es la cirugía. El objetivo de este artículo es proporcionar información actualizada sobre el diagnóstico, el manejo y el tratamiento de los tumores ováricos gigantes, así como servir de guía.

Palabras clave: *Gigante, ovario, ovarios, tumores, quistes, cistoadenomas.*

INTRODUCTION

The large size of some tumors has been described with fascination over time. These include gynecological cases in which marked growth is defined, particularly before the advent of ultrasound (US) (1). The terminology used to describe these large tumors contains a variety of confusing qualifiers, including "immense", "extensive", "voluminous", "massive", "large", "very large", "giant", and "gigantic gigantic" (1-3). The term "giant" is often used to refer to these large gynecological tumors. Additionally, to describe them as "giants", measurements exceeding 10 cm (4-6), 15 cm (7,8), and 20 cm (9) are typically used; however, the limits for their definition are sometimes not specified (1,4,5,9-14). Others define "large" ovarian cysts as those >5 cm (7), those measuring between 10 and 20 cm (9), or those reaching above the umbilicus (15). In the English literature, there has been agreement for 54 years on defining uterine or ovarian tumors weighing more than 25 lb. as "giants" (1,2,16,17), because, in 1971, Beacham et al. (18) reviewed the uterine or ovarian tumors, weighing 25 lb. or more, between 1946 and 1970. These authors noted the following: 1. They defined as "giants" only gynecologic tumors weighing 25 lb. or more, and 2. the parameter used for their definition was weight, not measurements (18). We will use to define "giant", ovarian tumors (GOT) weighing 25 lb. or more because: 1. Weight is unique, 2. It is accepted in the English literature.

In clinical practice, it is rare and difficult to manage a case of GOT, for which this article is intended to provide information on the diagnosis of GOT, their management and treatment, and to serve as a guide.

METHODS

We conducted a narrative review of the literature on GOT. The PubMed database was searched for literature published from May 01, 2024, to November 30, 2024, using the following keywords: "giant" AND "ovarian" AND "tumor", "giant ovarian tumor" AND "diagnosis", "giant ovarian tumor" AND "management", "giant ovarian tumor" AND "treatment". We also included studies from other sources that we considered historical or relevant to the topic. We excluded studies that did not focus on giant ovarian tumors.

REPORTED CASES

Before 1929, nine GOT had been reported, weighing between 200 and 300 pounds, 87 weighing greater than 100, and 203 weighing between 50 and 100 (17). GOT is rare in the present day, due to early diagnosis and treatment (5,9,15,17). The most remarkable description of GOT is that of Spohn in 1962 (19), who reported a weight of 148.6 kg (328 lb). Other GOTs are reported in Table 1 (16,17,19-33). The GOT Study Group previously reported a case series of GOT 4 (3).

DIAGNOSIS

Definition

A cyst is a fluid-filled sac that is greater than 5 cm, and so a 'cyst' that is less than 5 cm should not be classified as a cyst; it is a normal physiological process unless the child has not yet achieved menarche. In prepubertal girls, follicular activity may be observed, but the follicles are typically less than 10 mm in diameter (34). In 1971, Beacham et al. (18) defined "giants" as only gynecologic tumors weighing 25 lb. or more. The used parameter was weight, not measurements.

Table 1. Characteristics of reported giant ovarian tumors weighing >40 kg.

Author, Year	Age (years) Female period	Tumor weight (kg)	Surgery	Histopathology type of tumor	Outcome
Sphon, 1962 (19)	-	148.7	-	-	-
O'Hanlan, 1994 (17)	35 Mature	137.5	Laparotomy, resection of the intact mass	Benign, mucinous cystadenoma with teratoma components	Fair
Alobaid, 2019 (20)	53 Post-menopausal	108	Laparotomy, bilateral salpingo-oophorectomy	Benign, bilateral mu-cinous cystadenoma	Fair
Yanazume et al., 2007 (21)	30 Young	100	Laparotomy, unilateral adnectomy?	Malignant, mucinous cystadenocarcinoma	Died, disseminated intravascular coagulation
Ueda et al., 2008 (22)	34 Mature	86.5	Laparotomy, large volume aspiration, left salpingo-oophorectomy	Benign, serous cystadenoma	Fair
Eames et al., 1954 (23)	-	83.5	-	-	-
Symmons, 1963 (24)	-	79.4	-	-	-
Tait et al., 1997 (16)	-	70.8	-	-	-
Zamora et al., 1992 (25)	22 Young	70	Laparotomy, unilateral salpingo-oophorectomy	Benign ovarian cyst of 6 years' duration	Fair
Fu et al., 2022 (26)	64 Post-menopausal	62	Intratumorally fluid drainage, laparotomy, tumor removal, unilateral oophoro-salpingectomy?	Benign, mucinous cystadenoma	Fair
Hackethal et al., 2008 (27)	60 Post-menopausal	60	-	Benign, mucinous cystadenoma	Fair
Fobe et al., 2011 (28)	24 Young	59	Laparotomy, right salpingo-oophorectomy	Benign, mucosal serosal cystadenoma with borderline potential	Fair
Madhu et al., 2013 (29)	55 Post-menopausal	56.95	Laparotomy, left salpingo-oophorectomy, total hysterectomy, abdominal reconstruction	Benign, mucinous cystadenoma	Fair
Stukan, 2009 (30)	52 Post-menopausal	54	Laparotomy, aspiration, left salpingo-oophorectomy	Benign, fibroma	Slow recupe-ration by mucus in the bronchial tree was discharged on post-surgery day 40
Einenkel, 2006 (31)	57 Post-menopausal	49	--	Benign, mucinous cystadenoma	-
Khoiwal et al., 2022 (32)	24 Young	41.1	Laparotomy, aspiration, total hysterectomy, bilateral adnexec-tomy, total omentectomy, bilateral pelvic lymph node dissection, appendicectomy, peritonectomy, removal of pouch of Douglas tumor deposits	Malignant, mucinous cystadenocarcinoma with left parietal peritoneum and pouch of Douglas involvement	Fair
de Lima et al., 2014 (33)	57 Post-sal	40	Bilateral salpingo-ophorectomy, total hysterectomy, omentectomy	Malignant, mucinous cystadenocarcinoma	Fair

Etiology

The etiology is fetal gonadotrophins, maternal estrogen, or placental human chorionic gonadotropin. Endocrine conditions such as precocious puberty, hypothyroidism, and aromatase deficiency can be associated with ovarian growth (34).

Histopathology

Ovarian tumors are common and can generally be classified into four main types: epithelial tumors, germ cell tumors, sex cord-stromal tumors, and metastatic tumors. Most are epithelial tumors. The serous histotype is the most common (9,15,28,29,33,35). Mucinous tumors comprise benign mucinous cystadenomas (75 %-85 %), borderline lesions (10 %), and malignant lesions (15 %). They can reach a large size and typically present as large multicystic masses containing mucus and fluid, occurring in women in their 20s to 50s (4,5,15,29). The vast majority of ovarian cysts will regress spontaneously, but this can take several months (34). Mucinous cystadenomas have the potential to grow into large masses and rarely remain undiagnosed until malignant transformation. They are incidentally found on routine physical examination and sonograms (5).

Clinical signs

Cysts may grow to a considerable size (13). Most common clinical signs are rapidly expanding abdominal distension and a palpable mass; these findings may be accompanied by nonspecific abdominal pain, vomiting, constipation, ovarian torsion, and rupture (4,14).

Presentation age

Giant ovarian tumors can occur at any age, although their frequency tends to decline throughout childhood (12,28,34). In prepubertal girls, follicular activity may be present; however, the follicles are usually less than 10 mm in diameter (34). With the onset of puberty, follicular activity increases again, which is associated with an increased risk of ovarian enlargement or tumor development (12,34). They are more common during the reproductive years and in females with menarche, due to endogenous hormone production (4,14,28,29). In premenopausal women, they are persistent, and most are benign and functional (13). They are rare among postmenopausal women (26).

Uni or bilateral

A giant ovarian tumor is characteristically unilateral, with only 5 %-10 % presenting bilaterally (15,29,31). Approximately 7 % of all ovarian tumors presenting as primary origin are metastases, and almost half of them are bilateral (9,34).

Differential diagnoses

When a patient presents with a large abdominal mass, the differential diagnosis should encompass a broad spectrum of conditions, ranging from normal physiological states such as intrauterine pregnancy to pathological entities including fibromyomatosis, pelvic endometriosis, urinary retention, abdominal cysts, abdominal pregnancy, intestinal tumors, hydronephrotic kidney, retroperitoneal tumors, marked obesity, localized ascites, urachal cyst, mesenteric cyst, abdominal cocoon, and echinococcosis, among others (13,33). Moreover, if ovarian cystic cavities exhibit internal nodules or solid components, these findings are highly suggestive of malignancy (9,28).

Tumor markers

Tumor markers are valuable tools in the differential diagnosis of malignant ovarian cysts; however, elevated levels have also been reported in patients with benign tumors (33). Immunohistochemistry is often required to resolve uncertainties regarding the tumor's cellular origin (9). Among the most relevant markers, carcinoembryonic antigen (CEA), CA-125, and CA19-9 are frequently elevated in GOT. Notably, CEA tends to be higher in GOT compared to non-mucinous ovarian carcinomas (9,36).

Although CA19-9 is primarily associated with gastrointestinal tract malignancies, it may also be elevated in ovarian mucinous neoplasms (36).

Image methods

Abdominal imaging studies are useful for excluding major alternative pathologies (33). Ultrasonography (US) is the primary modality for evaluating ovarian and adnexal masses, with an accuracy of approximately 90 % (4,34). In pediatric patients, most large ovarian masses, whether complex or straightforward, can be safely monitored with serial pelvic ultrasound, as most will either decrease in size or resolve spontaneously (13). Transvaginal US with color Doppler mode should be performed to determine the side of origin and evidence of malignancy by resistive index. Transabdominal or transvaginal studies will only visualize a small portion of the mass; thus, no firm exclusion of malignancy can be stated (17). The diagnosis may be overlooked due to pronounced obesity (28). Unfortunately, imaging studies such as US, computed tomography (CT), and magnetic resonance (MRI) do not always determine the origin, thus limiting their diagnostic usefulness (13). CT is more sensitive yet less specific than US in detecting ovarian tumors. It allows assessment of abdominal and retroperitoneal structures (8,13).

MANAGEMENT

GOT present diagnostic and management challenges (4,17,33). Moreover, concomitance with overweight and obesity can be an additional diagnostic pitfall (33). Early diagnosis contributes to a good prognosis (28). The management approach is determined by tumor size, available equipment, and the surgeon's skill level. Most are functional in nature and resolve without treatment. Management of all adolescents with an ovarian cyst should ideally be discussed with the gynecology team (34). In general, the management goal for the younger population is conservative, focusing on observation, symptom resolution, complication prevention, and, when necessary, proper treatment of malignant tumors while preserving ovarian structure and function (4,6).

Needle aspiration

Needle aspiration for cytology often yields inaccurate results and, due to its associated complications (bowel perforation, cyst rupture, and the risk of peritoneal dissemination of malignant cells), is not recommended (13).

Giant ovarian tumors during pregnancy and puerperium

The coexistence of ovarian cysts during pregnancy is not uncommon, particularly when reliable diagnostic imaging techniques are available (37). Ovarian growths of varying sizes are observed in approximately 0.2 %–2 % of pregnancies, most often identified in the third trimester. At the same time, their occurrence in the puerperium is exceedingly rare (6). GOT occurring during pregnancy may present with a variety of manifestations, most commonly non-specific pressure symptoms such as back or abdominal pain, constipation, abdominal distension, and urinary complaints. Because these symptoms are often attributed to the usual discomforts of pregnancy, they may be overlooked by both patients and physicians. In some cases, a GOT can even mimic ascites. Although ultrasonography remains the primary diagnostic tool for detecting coexisting ovarian cysts in pregnancy and generally provides high accuracy, the possibility of misdiagnosis cannot be excluded (37). Although antepartum removal of GOT has been recommended to ensure a good pregnancy outcome, expectant management and timed intervention can be adopted for pregnancy with GOT. GOT increase maternal morbidity due to abdominal pain, torsion, rupture, and secondary infection. It may cause wrong calculation of gestational age, malpresentation, obstructed labor, and restriction of fetal growth (FGR). No specific protocol has been developed to date; hence, case management varies from case to case. The management stay includes tumor size, type, origin, gestational age, presenting symptoms, and medical condition. Management is primarily surgical. The risk of spontaneous abortion in the first trimester, preterm labor, and RFG in the third trimester should always be kept in mind (10).

The second trimester is generally considered the optimal period for surgical removal of giant ovarian tumors (GOT) during pregnancy (10,11). Numerous case reports have described watchful expectancy as the preferred management strategy when GOTs present in the third trimester, with cyst removal performed at the time of elective cesarean section. Importantly, vaginal delivery remains feasible in pregnancies complicated by GOT (10).

GOT are exceedingly rare during the gravid puerperium. Both patients and physicians may overlook symptoms, as they are often subtle or nonspecific. Early detection of ovarian cysts before they reach a significant size can be facilitated by complications such as torsion or through systematic ultrasound screening. Imaging plays a crucial role in establishing the diagnosis. In most cases, these cysts remain asymptomatic and regress spontaneously. Ultrasound features that increase the suspicion of malignancy are loss of any normal ovarian tissue surrounding the cyst and the existence of solid areas or papillary projections within the cyst. However, borderline tumors can be challenging to differentiate from benign tumors based on ultrasound image characteristics. A GOT can pose a diagnostic dilemma when compared with another cyst-filled abdominal mass. The management approach depends on cyst size, available equipment, and the surgeon's experience. Surgical management can be performed in the postpartum period with satisfaction. Ovariectomy may slightly reduce fertility and decrease the age of onset of menopause. Most cysts in the gravid-puerperium period are functional and therefore benign (6). Surgery can be done laparoscopically, but it is not recommended when the cyst is suspected of malignancy because of the risk of spreading cancer cells (6,37). An immediate complication to be feared is vacuum shock, which requires a thorough preventive vascular filling (6).

Cryopreservation of ovarian tissue

Cryopreservation of ovarian tissue from the unaffected ovary may be an option for preserving fertility (12).

TREATMENT

Surgical treatment

The treatment of choice is surgery and must be carried out by a gynecologist with the appropriate surgical skills to reduce the need for an unnecessary laparotomy, removal of healthy ovarian tissue, or oophorectomy (3,29,34). It can be accomplished by in-bloc removal of the tumor (Figure 1) with or without controlled drainage of the tumor fluid. Removal of the tumor *in bloc* is thought to reduce the risk of spillage of potentially malignant cells. Intraoperative drainage of cystic fluid prevents splanchnic shock. The supine position should be avoided as resultant vena cava compression can reduce the cardiac output with sudden loss of pulse and cardiac arrest. The lateral decubitus position is the preferred surgical position. Resection of the mass, intact, with intense intraoperative and postoperative monitoring, will provide the safest and optimal setting (7,28,29). In 2024, the GOT Study Group reported four cases of GOT that were successfully managed with bloc laparotomy, accompanied by intensive intraoperative and postoperative monitoring, and notably without complications (3).

Indications for surgery include a symptomatic or rapidly growing tumor and a situation in which its malignant potential cannot be excluded (13). Whatever type of surgery is performed, all attempts should be made to save the ovary and perform a cystectomy rather than an oophorectomy (34). The management approach is determined by the size, available equipment, and the surgeon's skill level (12). Successful management requires a comprehensive approach before, during, and after the operative procedure. There are three keys to optimal management: 1. a multisystem, team approach, 2. intact cyst removal for histology is the gold standard, and 3. a special incision and reconstructive technique (13,36). Surgical management of GOT must consider various factors, particularly in adolescents, where the operative strategy aims to cure the condition while preserving fertility (4,12). The cyst capsule should be respected to avoid potential tumoral dissemination (28). Hemodynamic instability induced by fluid depletion and aorto-cava decompression during removal of the tumor is also a concern. Some advocate progressive

preoperative drainage to avoid the development of severe clinical hypotension (6,12,17,28). Many experts advise against aspirating cyst contents due to potential complications, including infection, hemorrhage, cyst rupture, and an increased risk of peritoneal adhesion (12,31).

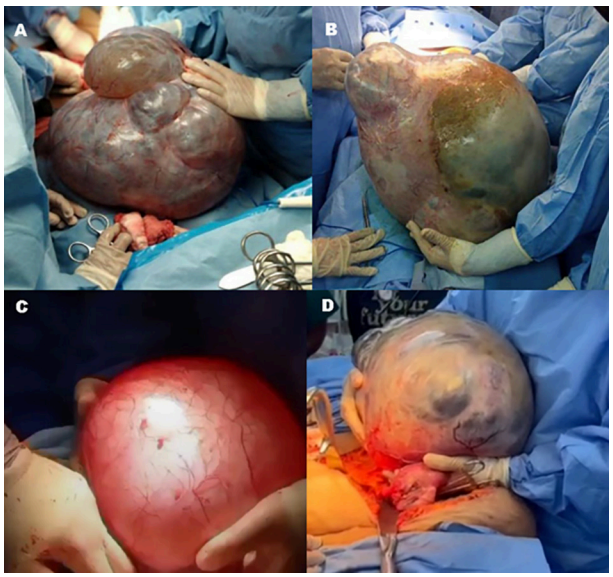

Figure 1. Four cases of Giant Ovarian Tumors during surgery. A: case 1. B: case 2. C: case 3. D: case 4 (3).

A. Laparotomy resection

Laparotomy resection may be preferred for the in-bloc GOT removal, adequate abdominal cavity irrigation, and avoidance of accidental mass rupture in the management of GOT (7). Some surgeons advocate a vertical incision with overlapping closure of the fascial layers. In contrast, others favor the low transverse incision, as it is associated with a lower risk of ventral hernia formation and permits the restoration of normal rectus abdominis muscle function (17,29). A major factor that makes the gynecologic surgeon decide to perform a laparotomy is definitely the tumor size (15). In addition, severe intra-abdominal adhesions are also the main limit to conducting conversion from laparoscopic to laparotomy surgery (8). Hence, laparotomy and total excision of GOT in these situations is the treatment of choice until or unless laparoscopic surgery is clubbed with pre-operative decompression of the cyst under US or contrast-enhanced CT-guided aspiration (15). Samples of peritoneal fluid for cytology must be collected as the first procedure. Decompression of the cystic component before mass excision is often necessary to avoid injury to the adjacent structures (12). Decompression using spillage-free techniques can be beneficial for achieving radical therapy with minimal tissue manipulation. It cannot be confirmed that laparotomy could replace laparoscopy in all instances (7).

B. Intraoperative or preoperative drainage

Many authors inserted trocars either percutaneously in the preoperative setting or through the cystic wall intraoperatively to decompress the tumor, facilitate its removal, and minimize vascular pressure changes (17,21,23,28). Intraoperative or preoperative drainage of complex masses can result in spillage of tumor cells into the abdominal cavity at the drain site with potential for subsequent seeding. It can also cause hemorrhage into the cystic compartments of the mass itself or into the abdominal cavity with sudden pulmonary edema (17). Preoperative or intraoperative drainage of a mass should be reserved for patients *in extremis* with cardiovascular or respiratory compromise due to compression (17,18). Given the possibility of a malignant component within a complex mass, all patients undergoing elective resection of complex masses should undergo every effort to remove the mass intact. Drainage of a simple cyst can be performed preoperatively or intraoperatively, if necessary, only after sonographic evidence of mural papillation or solid element is absent (17,24,36).

C. Other maneuvers

A multi-disciplinary team approach is necessary to maximize care for such complex patients (29). An arterial line should be inserted preoperatively for continuous blood pressure monitoring. The supine position should be avoided in patients with GOT, as the resultant vena cava compression can reduce the cardiac

output with sudden loss of pulse. The left lateral tilt position should be employed. Some patients have been intubated while sitting upright and awake via a nasal route (17). A Swan-Ganz catheter should be inserted in all patients who have evidence of cardiac or respiratory compromise, are elderly, or are about to undergo an operation in the supine position. Assessment of the ureters is necessary in patients with a suggestion of retroperitoneal location on ultrasound (17,23). Preoperative teaching on the use of an incentive spirometer and evaluation of pulmonary function should be performed, as respiratory dysfunction may occur after GOT removal due to sudden relaxation of the chronically distended, flaccid abdominal and diaphragmatic muscles (17,36). A nutritional evaluation, including consideration of hyperalimentation, should be undertaken preoperatively to optimize postoperative healing. Mechanical and antibiotic bowel preparation are recommended before surgery. Preoperative placement of a Cantor tube, or intraoperative insertion of a nasogastric tube maintained until bowel function resumes, has also been suggested. In addition, it is essential to ensure an adequate supply of red blood cells, preferably autologous or banked, packed cells if necessary, for transfusion support (17).

D. Laparoscopy

Laparoscopy can be used for both diagnostic and surgical purposes. It can be helpful in the differential diagnosis between ovarian tumors and other intra-abdominal cystic masses. In addition, the tumor can be inspected and, when there are signs of malignancy (abnormalities, adhesions to adjacent structures, etc.), the surgeon may change the procedure to an open laparotomy (3). Laparoscopic surgery, as opposed to laparotomy, will reduce post-operative pain, length of hospital stays, and the possibility of developing adhesions. Therefore, for some, it is the preferred surgical route (34). For the laparoscopic techniques applied to the management of GOT, pre-laparoscopic decompression is necessary to allow for room to establish pneumoperitoneum and manipulate the tumors, which is not possible in solid tumors. Despite drainage of these cystic tumors via a mini-laparotomy or percutaneous techniques, in GOT, especially those that reach the umbilicus, inadvertent perforation and spillage must be prevented. A comprehensive review of previous studies indicates that laparoscopic procedures have rarely been performed on ovarian masses exceeding 10 cm in diameter (7). Although numerous reports advocate for and describe the feasibility of laparoscopic removal of giant ovarian tumors (GOT), documented cases of successful laparoscopic excision remain exceedingly scarce (15).

Perioperative and postoperative complications

Surgical management of GOT is associated with significant risks, including severe hypotension, heart failure, respiratory failure, intestinal distension, and hypovolemic shock (4). The high incidence of serious perioperative and postoperative complications must be carefully weighed when considering tumor removal. Notably, the occurrence of these complications appears to be influenced less by tumor volume or weight and more by patient age and the amount of fluid contained within the tumor (22). Five potential problems have been associated with the resection of GOT: respiratory failure, intraoperative fluid shifts, inadequate exposure, orthostatic hypotension, and adynamic intestine (28). Owing to their large size, they can often compress the inferior vena cava, and sudden decompression during the removal can lead to hemodynamic instability with disastrous outcomes (9,17). Pulmonary complications occurred in many patients whose GOT was removed. Bronchopneumonia has been reported in these patients due to their inability to cough effectively and to take deep breaths. Loss of bladder tone because of chronic compression from the mass has been described, resolving with self-catheterization for two months (17).

Abdominoplasty

When indicated, abdominoplasty is performed when the patient has fully recovered (28).

CONCLUSIONS

GOT constitute a rare but clinically relevant condition. They can occur at any age and most often present as unilateral, benign epithelial lesions. The most common clinical manifestations include rapidly progressive abdominal distension and the presence of a palpable mass. Establishing an accurate diagnosis is challenging, as tumor markers show variable levels and imaging studies may not reliably determine the origin of the mass.

Surgical treatment remains the standard of care, with laparotomic in-bloc resection recommended as the approach. Management of very large GOTs often requires specialized surgical maneuvers and carries a considerable risk of complications, underscoring the importance of careful perioperative planning and monitoring.

Authorship

CB-P had conceptualization and methodology. CBP, BC, OH, and RR contributed to data curation, writing, original draft preparation, visualization, investigation, supervision, software development, validation, review, and editing, as well as final approval of the manuscript and agreement to be accountable for ensuring that subjects are appropriately investigated and resolved.

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Conflicts of interest

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