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A case report and a review of the literature

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Early diagnosis of Meigs syndrome in children. A case report and a review of the literature

Meigs syndrome is a rare disease defined by the coexistence of benign ovarian neoplasm, ascites and hydrothorax, which mainly affects women over the age of 30. This clinical condition refers only to cases in which the ovarian neoformation is a fibroid, a thecoma, a granulosa cell tumor or a Brenner tumor with disappearance of symptoms and effusions after removal of the neoplasm. Meigs syndrome is most frequently characterized by the presence of an ovarian fibroid, which in childhood is very rare and not commonly associated with the disease. In this article we report the case of an 11-year-old girl who came to our observation for a high fever for five days accompanied by cough and abdominal pain; imaging methods revealed bilateral hydrothorax, ascites, and a voluminous expansive right ovarian formation. On histological examination, the mass showed a cellular fibroid and the diagnosis of Meigs syndrome was made. Furthermore, we present a review of the literature aimed at detecting the state of knowledge on this disease in pediatric age, giving particular emphasis to the condition for which, in the presence of pleural effusion and ascites, an ovarian neoformation is not necessarily malignant.

KEY WORDS: CT, Meigs syndrome, Pediatric, Pelvic mass, Ultrasounds

Introduction

Meigs syndrome is a rare entity of unknown etiology characterized by the following clinical triad: benign ovarian neoplasm, ascites and mono / bilateral hydrothorax. It occurs in 1-3% of adult patients, mainly in women over 30, especially postmenopausal around the age of 50, and is much less common in girls [1-4]. Essential conditions for diagnosis are: 1) ovarian neoformation consisting of fibroid, thecoma, granulosa cell tumor or Brenner's tumor; 2) resolution of the clinical picture, of the pleural effusion and of the free fluid in the peritoneal cavity, after surgical removal of the neoplasm [1-3,5-6]. In most adult patients, Meigs syndrome occurs with ovarian fibroma, which is a benign tumor of the stroma and sexual cords, belonging to the group of pure stromal tumors, according to the classification of the World Health Organization (WHO) [1,4-5,7-8]. Ovarian fibroma is very rare in pediatric age, accounting for less than 2% of ovarian neoplasms, and is infrequently associated with Meigs syndrome [2-3,7]. In this article we describe the case of an 11-year-old girl who presented with bilateral hydrothorax, ascites and a cellular fibroid of the right ovary. We also report a review of the literature highlighting the unique features of Meigs syndrome in pediatric age. The studies highlight the importance of a correct preoperative diagnosis since the removal of the ovarian neoformation alone represents the definitive treatment of the disease.

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Case Report

In December 2020, an 11-year-old girl arrived at the emergency room of our hospital for five days of high fever accompanied by cough and abdominal pain. The anamnesis revealed the onset of menarche at the age of 10 and regular menstrual cycles. The physical examination found a reduction of the vesicular murmur in the mid-basal range of the right lung and a globular abdomen with a palpable mass in the hypogastrium associated with a modest amount of free fluid in the cavity. Blood tests showed increased inflammation indices (ESR 83 mm, CRP 242 mg / L) and lactate dehydrogenase (517 U / L); there were high levels of CA125 (1504 U / mL), while CA19.9, alphaphetoprotein, human chorionic gonadotropin and carcinoembryonic antigen were negative. Thoraco-abdominal ultrasound showed anechoic bilateral pleural effusion, major on the right and with atelectasis of the lung parenchyma; furthermore, in the right adnexal region a voluminous, well-defined oval neoformation was noticeable, showing mainly solid echostructure with stripy shadows and some small cystic spaces, and poor color Doppler vascularization; the uterus and left ovary were normal and there was abundant ascites (Fig. 1). Thorax-abdomen-pelvis computed tomography (CT) was therefore urgently performed with intravenous (i.v.) administration of contrast medium (contrast medium) for in-depth diagnostics. CT confirmed bilateral hydrothorax, free fluid in the peritoneum and highlighted the abdominal-pelvic solid mass originating from the right ovary, with a longitudinal extension of about 17 cm; the oval-shaped neoformation showed late, tenuous, and slightly inhomogeneous enhancement due to the presence of some small necrotic area, and appeared well delimited by the adjacent anatomical structures; no other pathological findings in the thoraco-abdominal area were appreciated (Fig. 2). It was decided not to perform magnetic resonance imaging (MRI) because the little patient had respiratory compromise, she was uncooperative and needed prolonged sedation. US-guided thoracentesis and paracentesis were performed, resulting in the cytological examination of the fluid taken negative for atypical cells, and ultrasound-guided biopsy of the abdominal-pelvic mass with a trucut needle (16 Gauge), which deposited for fibroblastic stromal neoplasia. Therefore, on the basis of the clinical, laboratory, instrumental and histological findings, a provisional diagnosis of Meigs syndrome was formulat-

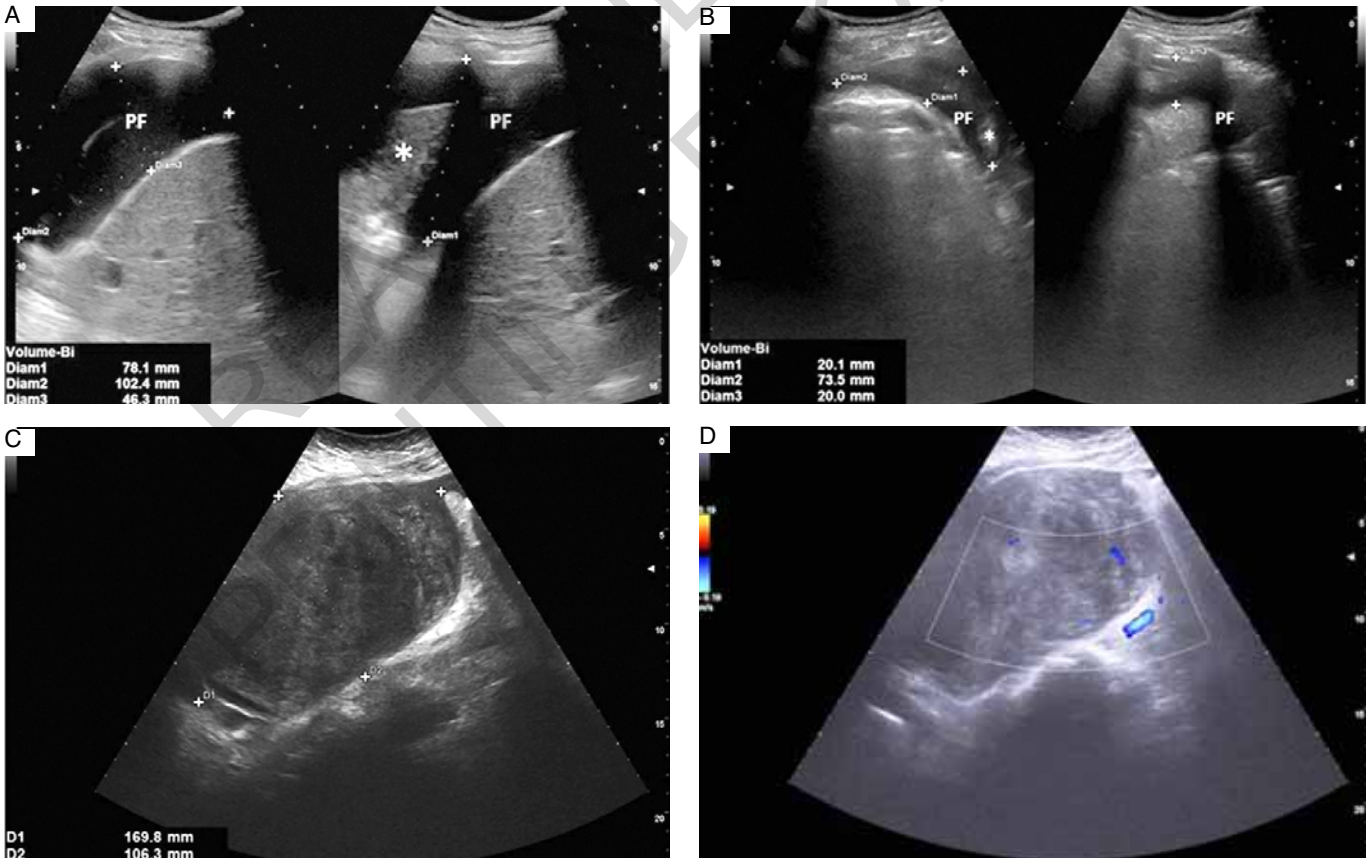


Fig. 1: (A) Thoracic abdominal ultrasound. The intercostal oblique scans of right and left (B) lung with the patient in sitting position, detect areas of atelectasis, very small on the left side (* in a and b), surrounded by anechoic pleural fluid (PF in A and B), more conspicuous on the right side. (C, D) The longitudinal oblique scans of the pelvis highlight a large inhomogeneous hypoechoic mass apparently right adnexal, with stripy shadows, (D) some small cystic areas and few vascular signals.

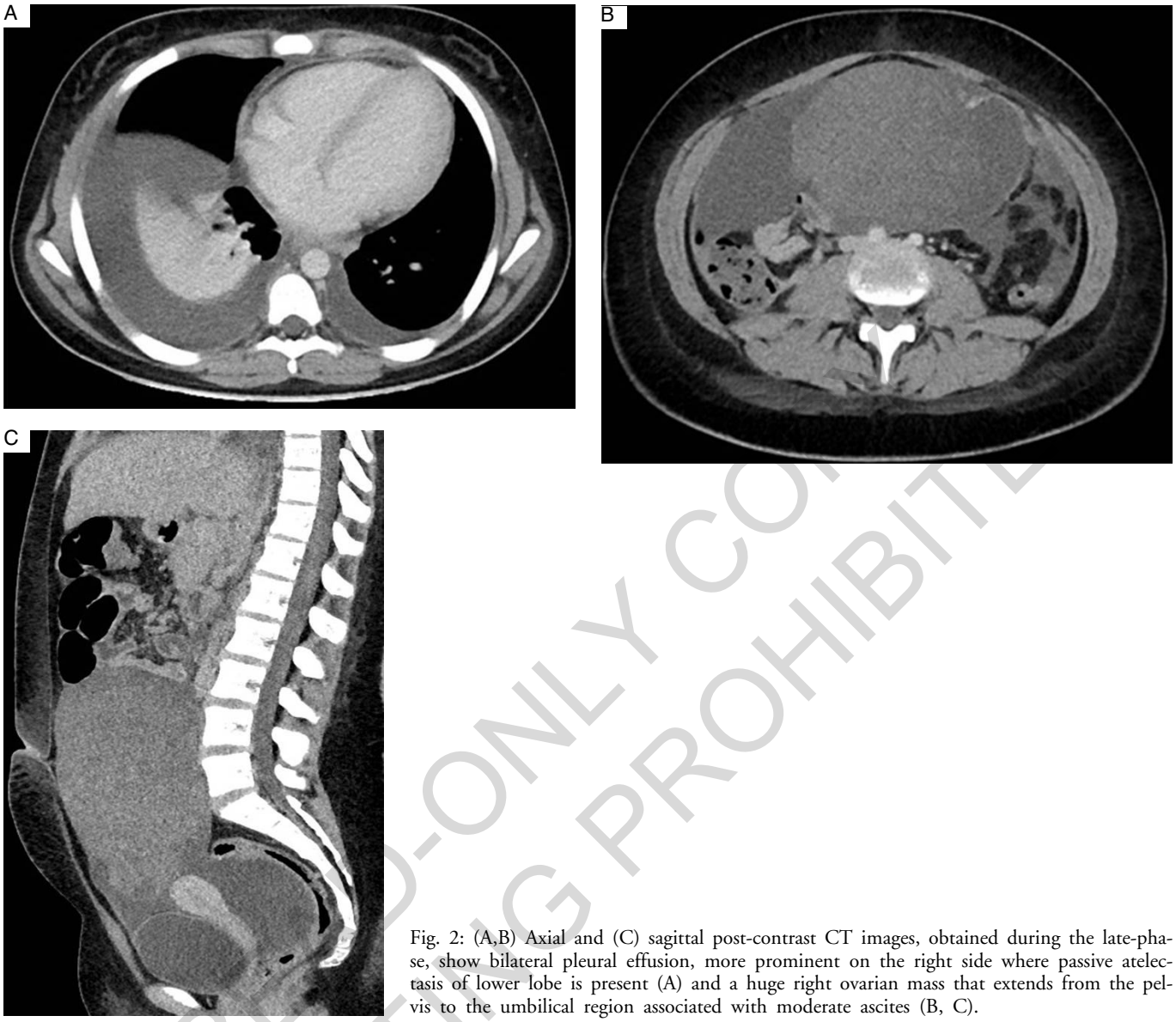
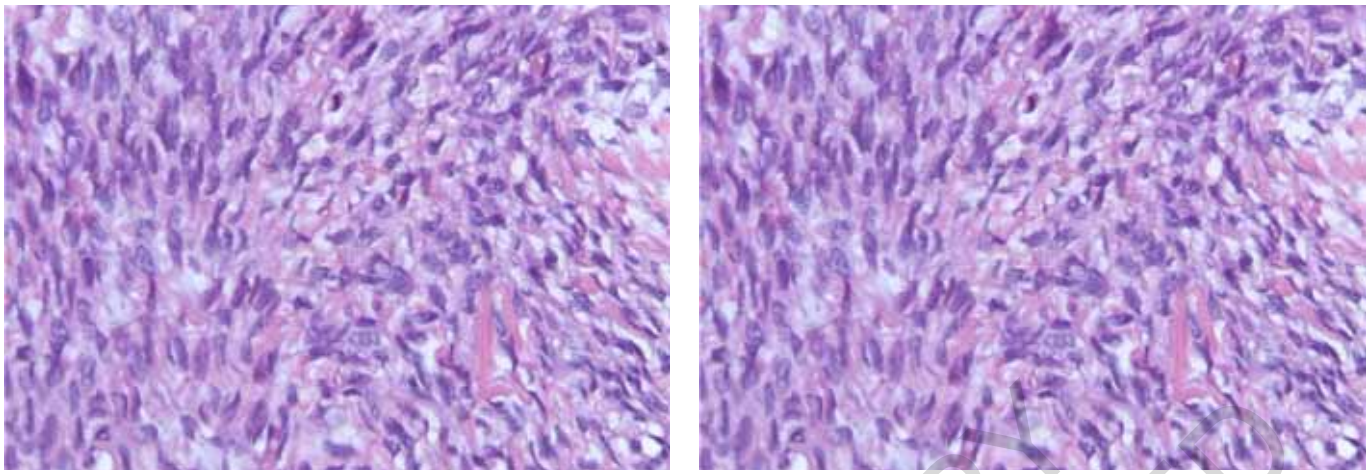


Fig. 2: (A,B) Axial and (C) sagittal post-contrast CT images, obtained during the late-phase, show bilateral pleural effusion, more prominent on the right side where passive atelectasis of lower lobe is present (A) and a huge right ovarian mass that extends from the pelvis to the umbilical region associated with moderate ascites (B, C).

ed and the child underwent surgery. After positioning to the right of the thoracic drainage, a large transverse sub-umbilical incision was made with abundant outflow of serum-haematic fluid, widely aspirated (about 850 ml), and a voluminous mass of right ovarian relevance was highlighted which presented numerous adhesions with intestinal loops contiguous and with the body of the uterus; the left ovary and the uterus were normal. The mass was completely removed and with it the homolateral tuba; Multiple biopsy samples were performed on the peritoneum and omentum and extensive intra-abdominal washing with collection of about 20 ml of liquid for cytological evaluation.Grossly the mass was solid, hard, with smooth, lumpy surface, measuring 16x12x10 cm, with white-tan cut surface and hemorrhagic cystic change (Fig. 3). Histological examination showed non capsulated, cellular neoplasm, with storiform

Fig. 3: Macroscopic appearance of the mass.



A) B)

Fig. 4: Microscopic histological examination. (A) Fascicles of bland spindle cells with storiform pattern. EE x100. (B) Cellular areas with mitotic figures. EE x 400.

pattern, composed of intersecting fascicles of cells with bland, spindled to ovoid nuclei and scant cytoplasm within variabily collagenized stroma; mitoses were observed, <4x10 high power fields (HPF).
Moreover, cystic changes, hemorrhage, intercellular edema, hyalinized stroma and infarct-type necrosis were found.
Immunohistochemically, the cells were: smooth muscle actin (SMA)+, CD56+, CD99-/+, CD10-/+, Calretinin+/, Inhibin-, WT1-, MelanA-, Desmin-, Caldesmon-, CD34, CK7-, epithelial membrane antigen (EMA)-, S100-, P53. The proliferating index Ki67 was low (2%). The final diagnosis was cellular fibroma, a pure stromal tumor with generally favourable outcome (Fig. 4). The neoplasm reached the outer surface, but was limited to the ovary and the peritoneal and omental biopsies as well as the cytological examination of peritoneal fluid were negative for tumor cells. The little patient was discharged on the 10th postoperative day, with the disappearance of the pleural effusion and ascites and laboratory tests were normal, with the exception of the levels of CA125, which however were reduced (800 U / ml). In the 6-month follow-up, chest x-ray and abdomen-pelvis MRI were negative and the girl completely healed with normalization of CA125.

Discussion

The disease known as Meigs' syndrome is so named as a result of the description by Dr. Joe V. Meigs and Dr. John W. Cass in 1937, when they reported seven cases of adult women who had ascites and hydrothorax associated with benign ovarian fibroma, with complete resolution of the pleural and peritoneal fluid after the removal of the tumor [9]. In 1954, Meigs reviewed 84 cases, not involving pediatric patients, and defined the syndrome may include also other types of benign ovarian neoplasm such as thecomas, granulosa cell tumors, and Brenner tumors [10]. Since Meigs' first report, the disease has been found mostly in postmenopausal women and very few cases have been described in the pediatric age group. Ovarian fibroma accounts for only 0.7-1.9 % of ovarian neoplasms in children, and from literature analysis it emerges that we have reported the fourth pediatric case of ovarian fibroma accompanied by ascites and hydrothorax [2-3,7,11-12]. The pathogenesis of the production of pleural and peritoneal effusions in Meigs' syndrome is not well established. Hypothesis include the secretion of liquid from the tumor as the source of the ascites, and/or the release of vasoactive substances by the neoplasm, such as vascular endothelial growth factor (VEGF) that raise local capillary permeability, leading to fluid in the abdomen. Hydrothorax is probably secondary to the passage of peritoneal effusion into the pleural cavity through congenital defects of the diaphragm or diaphragmatic lymphatics [2,6,12-13]. The typical clinical manifestations of Meigs' syndrome in children include bloating and abdominal pain due to ascites and tumor mass, usually large, with or without respiratory symptoms. In addition, increased serum CA125 levels are frequently present, as occurred in all three reported pediatric cases and in our little girl patient [3,11-12]. The precise mechanism that causes elevation of serum CA125 in Meigs' syndrome remains unclear, however, it is believed that it is secondary to mesothelial expression rather than direct production from tumor; biochemical factors, mechanical irritation caused by a voluminous neoplasm, or an increase in intra-abdominal pressure due to the ascites, probably determine damage to the peritoneal basement membrane which would react through the production and release of CA125 into the circulation [5,14-15]. CA125 is the typical marker of adult patients with advanced epithelial ovarian cancer, ascites and pleur-

al effusion, and its elevation in serum originate, at least in part, from the tumor cells. Anyway the elevation of CA125 level in our little girl patient, in the absence of radiological features suspicious for cancer (eg, lesion with irregular infiltrating borders, marked internal heterogeneity and highly vascularized solid areas) and in the presence of positive biopsy for fibroblastic stromal tumor, indicated a benign condition [2-3,12-15]. Imaging plays a pivotal role in the diagnosis of Meigs' syndrome. Ultrasound is undoubtedly the first choice radiological investigation in children with abdominal pain and palpable mass; it is a fast, non-invasive technique, which does not expose to ionizing radiation, and allows accurate exploration of the abdomen and pelvis, especially thanks to the reduced thickness of the subcutaneous adipose tissue, typical of the pediatric age [16-19]. Ultrasound accurately distinguishes the solid and cystic components of a neoformation, especially if with the use of high-frequency linear transducers, and demonstrates intratumoral vascularization by color-Doppler [16,18-19]. In the clinical case in question, the expansive formation presented ultrasound features suggestive of ovarian fibroma such as: predominantly solid structure, oval morphology, large dimensions, slightly irregular internal echogenicity with some small cystic spaces, low vascularity on color-Doppler, and precence of stripy acoustic shadows appearing vertically within the lesion, probably due to interlacing bundles of spindle cells with strips of hyaline-appearing collagen [2,5,20]. Concomitant conspicuous ascites and oblique intercostal thoracic scans performed with the patient in a sitting position, showed the accumulation of fluid in both pleural cavities associated with pulmonary atelectasis. Thoracic ultrasound is the gold standard for the diagnosis of pleural effusion, and in children this method, which does not use ionizing radiation, is even more valuable. It's more sensitive than chest x-ray in identifying the presence of even minimal amounts of liquid (<25 mL compared to about 200 mL needed to be visible on the X-ray), and allows you to define the characteristics of the effusion (simple anechoic, or complex corpuscular echogen with or without fibrin shoots), as happened in our case [21-22]. In addition, ultrasound-guided interventional procedures (thoracentesis, paracentesis, tru-cut biopsy) are fast, safe and effective. They represented an essential part of the diagnostic process, as the search for neoplastic cells in the pleural and ascitic fluid was negative and a stromal tumor of the ovary was identified by histological examination of biopsy samples of the abdominal-pelvic mass [21-24]. The CT performed in an emergency regime, as a second level instrumental investigation, showed a solid right ovarian neoformation, which consistently with what is reported in the literature, had the characteristics of a benign lesion, compatible with those of the fibroid; in fact, in the absence of metastatic disease, the expansive formation appeared well circumscribed and slightly inhomogeneous, with minimal and delayed post-contrast enhancement [2,12,25]. Imaging therefore ruled out a highly aggressive malignant tumor, such as primary ovarian rhabdomyosarcoma, which is usually advanced at the time of diagnosis and can manifest itself with bilateral pleural effusion, ascites, and elevated CA125 and lactate levels. dehydrogenase [26-27]. The histopathological examination on the surgical piece confirmed the presence of an ovarian fibroid, and specifically identified the cellular subtype, as the neoplasm appeared densely cellulated and showed the typical storiform pattern constituted by the proliferation of spindle elements, arranged in intersecting bundles, embedded in collagenized stroma. Degenerative aspects were also observed, namely cysts without epithelial lining, intercellular edema, stromal hyalinization and areas of necrosis and hemorrhage. However, there was no evidence of nuclear atypia and 4 mitotic figures per 10 HPF were detected, unlike fibrosarcoma, also it appertaining to the group of pure stromal tumors of the ovary, which usually presents moderate-to-severe nuclear atypia, high mitotic rate, and more aggressive clinical course [8,11,28]. From the literature it emerges that, although cellular fibroids have a benign clinical behavior, they must be considered neoplasms with a low potential for malignancy, which can recur, if they present adhesions with other structures, if not completely excised or complicated by rupture. In our case it was necessary to perform the right salpingo-oophorectomy which allowed the total removal of the mass, sparing the contralateral ovary and preserving fertility [3,5,11]. The prognosis of patients with Meigs syndrome is very good, surgery being the decisive and conclusive treatment. However, long-term follow-up is required for the risk, albeit minimal, of ovarian cancer recurrence [2-3,11].

Conclusion

The interest aroused by the clinical case described led us to consult the scientific studies in the literature for greater knowledge of Meigs syndrome in pediatric age, rarely found in clinical practice. It is very important to immediately identify this disease since the ovarian neoformation despite being associated with ascites and hydrothorax does not represent an advanced stage malignant neoplasm and the prognosis is very favorable, as the surgical intervention is curative.

Riassunto

La sindrome di Meigs è una rara malattia definita dalla coesistenza di neoplasia ovarica benigna, ascite ed idrotorace, che colpisce prevalentemente le donne di età superiore ai 30 anni. Tale condizione clinica è riferita solo ai casi in cui la neoformazione ovarica è un fibroma, un tecoma, un tumore a cellule della granulosa o un tumore

di Brenner con scomparsa della sintomatologia e dei versamenti dopo asportazione della neoplasia. La sindrome di Meigs è più frequentemente *ovarian cellular fibroma* caratterizzata dalla presenza di un fibroma ovarico, che in età pediatrica è molto raro e non comunemente associato alla malattia. In questo articolo riportiamo il caso di una bambina di 11 anni che giungeva alla nostra osservazione per febbre elevata da cinque giorni accompagnata da tosse e dolore addominale; le metodiche di imaging riscontravano idrotorace bilaterale, ascite ed una voluminosa formazione espansiva ovarica destra.
All'esame istologico la massa risultava un fibroma cellulare e veniva posta diagnosi di sindrome di Meigs. Inoltre, presentiamo una revisione della letteratura finalizzata a rilevare lo stato delle conoscenze su questa malattia in età pediatrica, dando particolare risalto alla condizione per la quale, in presenza di versamento pleurico ed ascite, una neoformazione ovarica non necessariamente è maligna

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