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The Granulosa Juvenile Cell Tumors of Ovary (About 4 Cases)

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Abstract: The juvenile granulosa tumors of the ovary are rare tumors, secreting estrogen, diagnosed by precocious puberty or a mass syndrome. Diagnosis is based on pelvic imaging: ultrasound and MRI, and hormonal balance sheet: estradiol, inhibin and Anti-Mullerian hormone. Their prognosis is quite favorable related to their diagnosis released at an early stage. We performed a retrospective descriptive study in the Visceral Pediatric Surgery Department "A" of children Rabat hospital, over a period of 18 years, during which 4 cases of juvenile granulosa tumors were listed. Our study focused on the analysis of the epidemiological profile, circumstances of discovery, clinical symptomatology, Para clinical characteristics and treatment started: The age of our patients was between 3 months and 14 years, precocious puberty and increased abdominal girth were the two main telltale signs. Pelvic ultrasonography was performed for all patients, the tumor was cystic in 2 cases and solido-cystic in 2 cases, an abdominal CT was performed in 3 patients and an MRI performed in one case, confirmed the ovarian origin of the abdominal pelvic mass. The hormonal balance achieved in two patients, revealed very low levels of gonad tropic hormones unlike the rate of estradiol which is very high income. Histological study micro follicular arrangement was predominant; the atypia was evident, with a positivity of all tumors vimentin, inhibin and CD99. The treatment was essentially surgical; all of our patients underwent unilateral oophorectomy by laparotomy. The evolution was marked by a case of postoperative recurrence, which underwent chemotherapy, adjuvant first, then palliative.
Keywords: granulosa juvenile cell tomor, Ovarian Tumor- premature pseudopuberty, stromal tumor and sex cord.

INTRODUCTION

The so-called juvenile granulosa tumors are malignant tumors belonging to the group of sex cord tumors and stroma; they are rare and represent less than 5% of ovarian tumors in children and adolescents, with a maximum of frequency between 0 and 10 years old. They have the distinction of being in most cases secreting and hyperoestrogenic, and are considered tumors with low potential for malignancy.

MATERIALS & METHODS

This is a study concerning a fourth case of tumors with granulosa of the ovary, followed at the pediatric visceral surgery department A of the Rabat Children's Hospital over a period of 20 years, stretching from January 1998 to October 2018.

Patients were referred to us for primary surgery after having consulted for different reasons for consultation. Our study looked at the analysis of the epidemiological profile, circumstances of discovery, clinical semiology, paraclinical specificities and treatment.

RESULTS

Case no 1

14-year-old girl, last in a family of four, with no notable pathological history, having a menarche at the age of 13 with an irregular menstrual cycle. She consults for abdomino-pelvic mass whose onset of symptomatology dates back to 15 days before admission, by the appearance of abdominal pain localized especially in the right iliac fossa, paroxysmal, moderate intensity, without particular irradiation, associated with an increased abdominal volume and unencrypted weight loss.

The clinical examination found a child in fairly good general condition with abdominal palpation a huge abdominal-pelvic mass measuring 22 × 21 cm in diameter, more lateralized right, firm consistency, fixed relative to the deep plane, mobile relative at the superficial level, without collateral venous circulation, with a non-depleted umbilicus, as well as sensitivity at the level of the right iliac fossa.

An abdominal and pelvic ultrasound performed revealed a voluminous abdomino-pelvic mass,

occupying most of the abdomen, with echo-shaped heterogeneous tissue structure, double-component (fleshy and cystic), measuring 20 × 13.5 × 20.3 cm in diameter, more lateralized on the right, most probably related to an ovarian mass, associated with an intraperitoneal effusion of average abundance, without deep lymphadenopathies.

Magnetic resonance imaging showed a large abdominal-pelvic mass lateralised on the right, polylobed contours and heterogeneous signal, containing a cystic component in T1 hyposignal tissue and T2 hyposignal tissue, enhancing strongly after injection of gadolinium. It measures 213 × 120 × 190 mm. Topographically, it arrives, in front, in contact with the anterior abdominal wall with loss of the border of separation in places, behind, it is in contact with the large vessels that are permeable, digestive structures, the anterior surface of the kidney right and both psoas especially right, bottom and right, it achieves an attraction of the uterus, it is related to the iliac vessels that remain permeable, laterally, it is related to the digestive structures.

A biological assessment was not carried out for lack of means. An exploratory laparotomy was indicated. A median incision straddling the umbilicus was performed. On exploration, whitish peritoneal nodules were found. A right appendectomy was performed carrying the tumor, with a delayed histopathological study.

The anatomo-pathological study of the operative specimen returned to favor a juvenile granulosa tumor (Figure 1), with:

- Macroscopically: a tumor measuring 26 × 25.5 × 15 cm, weighing 3 kg, with a smooth, bumpy surface, without rupture, having a semi-cystic semi-solid appearance when the part is opened, with the end of a gelatinous material. Foci of moral necrosis and reworkings bleeding were observed.
- At the microscopic level, we find a tumor proliferation made of medium size cells with round or oval nuclei, discreetly anisokaryotic, containing a small nucleolus. Chromatin is vesicular. The cytoplasm is poorly limited, eosinophilic. Cytonuclear atypias were not observed. The cells are essentially arranged in follicles bordered by several cellular bases and containing in their light a mucoid material. Rare cellular foci arranged in diffuse layers producing a sarcomatoid appearance are observed. The stroma is loose, vascularized with some foci of ischemic necrosis.

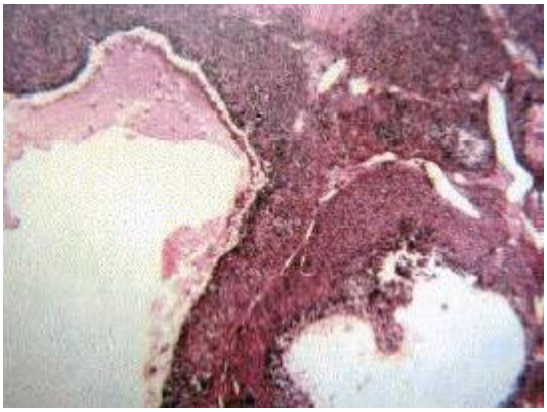

Fig-1: Histological section of the tumor: Macrofolicular aspect (x50)

The patient benefited postoperatively, at first, a clinical and radiological periodic monitoring through chest radiography and abdominopelvic ultrasound.

During her evolution, the patient accused, five months after the gesture surgical, pains of the right side. An abdominal ultrasound and an abdominal CT were performed, having objectified an injury process in susutin, hypoechogene heterogeneous 5.9 × 3.9 × 3.8 cm in diameter, in favor of locoregional recurrence, as well as heterogeneous heterogeneous hypoechoic retroperitoneal and iliac right adenopathies, the largest one measure 4.5 × 3.9 cm.

Chemotherapy was indicated, based on Vogaset, Ifosfamide and cisplatinium, three cures. The patient also had low back pain radiating to the lower limbs, which was a type of electric shock. A medullary MRI showed a sacral anterior epidural mass displacing the dural sac and engulfing the roots, measuring 33.17 mm × 10.27 mm, as well as a compressive retroperitoneal lymphadenopathy, measuring 122.65 mm × 70.49 mm × 131.83 mm.

The evolution was marked by a minimal reduction in tumor size, however, the pains were accentuated, and a secondary hepatic localization was objectified. The patient was put under a palliative treatment based on analgesics belonging to the third palliated, corticosteroid therapy and chemotherapy containing Endoxan.

Case no 2

A 3-year-old and 4-month-old, the last of four siblings, with no particular personal history; having as family history, a notion of familial diabetes (in a paternal uncle and paternal grandparents); Admitted for abundant, intermittent macroscopic hematuria, terminal type, appeared 2 weeks before admission, accompanied by pollakiuria and urinary burns. What motivated the parents to consult, or an abdomino-pelvic ultrasound was made, returned to a homogeneous ovarian cyst of fluid nature, with a uterus increased in size relative to the age of the patient. Intraperitoneal effusion of average abundance was also found.

Examination of the patient, on admission, found a conscious patient, in fairly good general condition, a size at 100 cm (corresponding to -1.5 standard derivations), a weight at 12 kg (corresponding to -2, 5 standard derivation).

The abdominal examination was normal, while the gynecological examination, we find pubic hair, with slight vulvar hypertrophy. The breast examination found a gynecomastia, corresponding to a stage 3 of Tanner. The biological assessment is normal, with the hormone balance low FSH and LH, testosterone slightly decreased. Estradiol, beta hCG and hydroxy-progesterone and alpha fetoprotein returned normal.

An abdomino-pelvic ultrasound was performed, having objectified a uterus pubescent, with the presence in the left lateral uterine, of a cystic lesional process, containing echogenic images within it, mobile, measuring 62 × 40 mm in diameter, probably related to a left ovarian process. The right ovary was not seen.

An abdominopelvic CT was performed, which demonstrated the presence of a left hypodense, well-defined left lateral uterine mass, which measures 45 mm × 55 mm in diameter, thin-walled, regular, with neither septum nor calcification, not enhanced after injection of the contrast medium, but without endovaginal extension.

- On the left, it comes into contact with the iliac vessels that remain permeable.
- At the top, she pushes the digestive structures.
- Down and back, it comes into contact with the rectum, which remains separated after a separation border.
- CT also showed an enlarged uterus, pushed right, without visualization of intraperitoneal effusion or inguinal lymphadenopathy.

Mammary ultrasound was also performed and revealed a homogeneous mammary glandular tissue, without visible nodular or cystic lesions, without visualization of axillary adenopathies. The bone age of the patient was consistent with chronological age.

On exploration, a tumor process was found at the expense of the left ovary. A left annexectomy was performed, taking away the tumor (Figure 2). A delayed anatomo-pathological study of the operative specimen was made in favor of a cystic tumor of the ovarian granulosa cells. The postoperative course was simple. The follow-up of the patient was without particularities. The patient did not require chemotherapy.

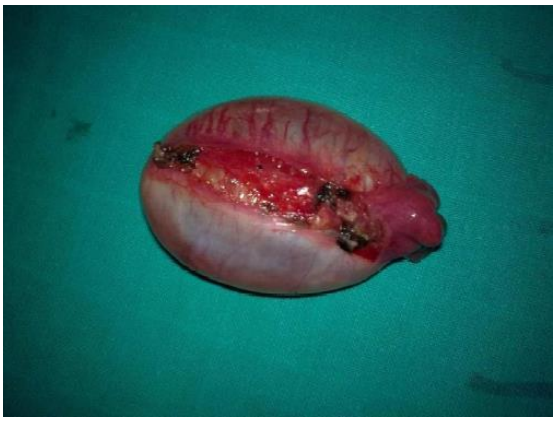

Fig-2: Image showing the resected mass of the second case

Case no 3

Infant of 3 months and 24 days, single girl, without particular pathological antecedents, admitted after the observation of the mother of a right swelling of the external genital organs with an abdominal bloating without other associated signs, the whole evolves in a context of apyrexia and conservation of the general state. The clinical examination found an infant in good general condition, with abdominal distension with umbilicus unfolded on abdominal examination, and diffuse dullness on palpation.

The gynecological examination objectified a soft straight swelling extending from the large lip to the pubis. No vulvar bleeding or pubic hair. Breast examination does not show gynecomastia. The ganglionic areas are free.

The abdominopelvic ultrasound was performed, having objectified the presence of a voluminous right ovarian mass, heterogeneous tissue measuring 43x15mm, with intraperitoneal effusion of great abundance taking off the spleen and the liver. The uterus was puberty type, and the right inguinal mass corresponds to a venous aneurysm.

The CT performed (Figure 3), returned to a right ovarian mass measuring 39x40x40 mm, tissue, discreetly heterogeneous without calcification or fat zone in sound sound. She takes venous contrast. CT also showed the presence of large ascites with perineal development through the vagino-peritoneal canal. The uterus is normal. The left ovary is normal, and there is no visible bone involvement.

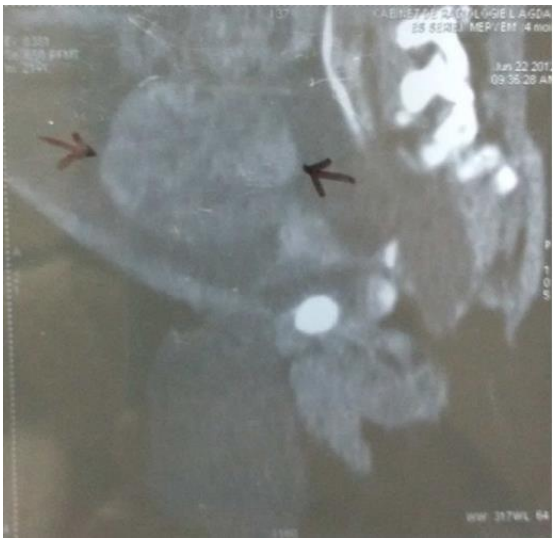

Fig-3: Abdominopelvic CT showing right ovarian mass of the third case

The bone age returned in favor of a 2 year old child

FSH and LH are decreased. Estradiol very high at 387pg / ml. Alpha fetoprotein is very high at 134.4ug / ml. The dosage of Testosterone and beta-HCG returned normal.

At the exploration we found a mass at the expense of the ovary well limited without adhesion, an externalization of the mass then a right annexectomy was carried out (Figure 4).

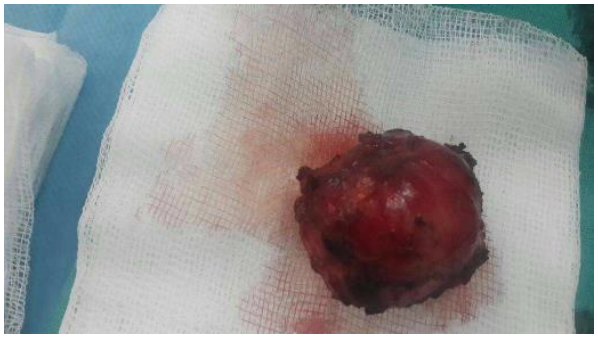

Fig-4: Image showing the resected mass of the third case

A pathological anatomical study delayed from the operative part was made which came back in favor of a juvenile granulosa tumor with luteinization phenomenon.

The postoperative course was simple. The follow-up of the patient was without particularities with normalization of the hormonal and echographic balance after 6 months. The patient did not need chemotherapy (Figure 17).

Case no 4

Infant 8 months, last of a sibling of 3, no particular pathological history, admitted for vulvar bleeding for a few days before admission with gynecomastia.

The clinical examination shows an infant in good general condition. At the gynecological examination, we find a black blood at the level of the vulva with a vaginal prolapse of 0.5cm.

Breast examination found a bilateral tanner stage 2 gynecomastia. The rectal examination found a pelvic mass 0.2 cm from the anal margin, hard rectal, upper limit not precise.

The abdomino-pelvic ultrasound realized, objectified at the latero-level right of the uterus a rounded multi-septate formation, measuring 44x32 mm associated with thickening of the endometrium probably evoking a germ tumor (granulosa tumor) (Figure 5).

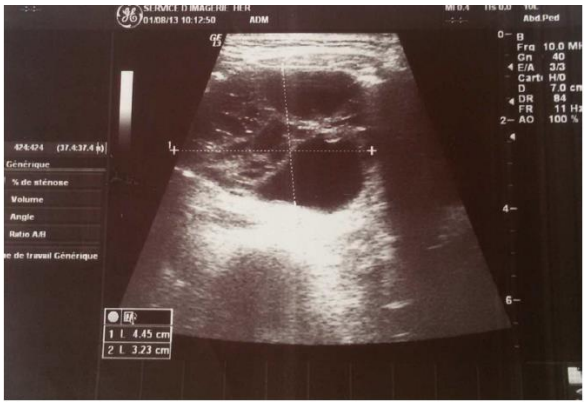

Fig-5: Ultrasound image of a multiseptate ovarian mass

The abdominopelvic CT was performed, which demonstrated the presence of a fluid density formation at the abdominopelvic level discretely lateralized on the right side with septa enhanced after injection of PDC measuring 60x40x43, without endocystic bud or calcification.

Topographically

- Forward: the cyst comes into contact with the anterior abdominal wall without infiltrating it
- Back: it comes into contact with the wall of the psoas muscle especially straight and in front of lumbosacral vertebrae with greasy lip of separation.
- Laterally and upwards: it is in contact with the digestive loops that are repressed but not invaded.
- In conclusion the CT with ultrasound complement in favor of an ovarian tumor of the granulosa tumor type.

The hormonal assessment was not carried out for lack of means. Alpha fetoprotein level is high. On exploration, a mass at the expense of the right ovary was found mostly fleshy with a cystic part, an ovariectomy taking away the mass was performed.

An anatomo-pathological study delayed from the operative specimen was returned to a juvenile granulosa tumor. The postoperative course was simple. The patient did not require chemotherapy. The follow-up of the patient was without particularities.

DISCUSSION

Juvenile granulosa tumors constitute a particular pathological entity that accounts for 5% of ovarian tumors in children and adolescents [1]. The juvenile form of tumors of granulosa is diagnosed in patients under 20 years in 80% of cases, and less than 10 years in 50% of cases, hence its name [2]. Several associations of juvenile granulosa tumors with more general pathologies have been reported; such as Olliers endochondromatosis, Maffucci syndrome, dysplastic abnormalities [3]. Cellular and molecular alterations are involved in the development of JTG: role of growth factors and oncogenes, proliferation of granulosa cells induced by FSH and Gαs, abnormality of expression of genes of gonadal determination [4]. The tumors of the juvenile granulosa are manifested by: a tumor syndrome: painful abdominal distension related to the size of the tumor [5]. Sometimes, the pain is acute, resulting from ovarian torsion, their haemorrhagic nature.

Exceptionally tumors of granulosa may be in the form of a rupture table with hemoperitoneum and this because of their haemorrhagic nature [1-5]; an endocrine syndrome related to the secretory functions of these tumors: pseudopuberty precocious isosexual in the girl in case of estrogenic secretion; hirsutism, clitoral hypertrophy in the case of androgenic secretion [6].

Ultrasound is the most commonly used complementary examination for the exploration of ovarian tumors, it allows to confirm the data of the clinical examination, to attach the pelvic mass to its ovarian origin, to determine its semiological characteristics and to evaluate the degree of abdomino-pelvic extension of the tumor.

Ultrasonography may reveal a large echoic mass, or a cystic mass with septa, producing a multilocular appearance, but the unilocular appearance is also found, or it may appear as a pure solid homogeneous or heterogeneous [5].

CT has a detection rate sometimes lower than that of ultrasound, in the presumptive diagnosis of ovarian tumors. It could be justified in view of a large

pelvic tumor size which poses the problem of its primitive siege and its relationship with neighboring anatomical structures [7].

The information provided by the MRI does not appear to be superior to a pelvic ultrasound performed under excellent technical conditions by an experienced sonographer [7]. Estradiol is dosed in cases of pseudo-precocious puberty; it can be used as a tumor marker, as for inhibin, it currently represents a good marker specific for tumors of granulosa [5].

The tumor is usually unilateral (97%) and measures on average 12.5 cm. Its surface is smooth, solid, cystic, or association of the two forms. It is characterized by dense plaques of non-incisored, hyperchromatic and often mitotic cells. Rare immature follicles secreting mucus are observed. Luteinization is common. The vimentin marker is positive in about 80% of cases [1-8].

The ideal treatment of these tumors is surgical: annexectomy. Chemotherapy is proposed in case of recurrence in addition to a surgical revision, and must use at least one anthracycline [9, 10]. Radiation therapy has not been shown to be effective [9, 10].

Tumors of juvenile granulosa are generally of very good prognosis: 92% survival at 5 years [9, 10]. The factors of poor prognosis are: large size, ascites and capsular rupture [10]. The risk of recurrence predominates in the first two years, but recurrences of up to five years have been observed, requiring regular monitoring by abdominal and pelvic ultrasound (and chest x-ray) for 5 years [11]. This appears to be different for adult-type granulosa tumors that present a much greater risk of late recurrence, with a recent series accounting for 39% of recurrences occurring between 5 and 10 years after diagnosis. After 5 years, an annual regular gynecological follow-up with pelvic ultrasound is recommended throughout the woman's period of genital activity to monitor the absence of developing pathology on the remaining contralateral ovary [11].

CONCLUSION

The juvenile tumor of the granulosa is a rare tumor, but the diagnosis should be mentioned before any ovarian tumor of the child, especially when associated with signs of early puberty.

Para-clinical diagnosis is based on ultrasound and the dosage of estradiolemia very frequently elevated. The histological diagnosis is not always obvious, several readings of veterinary pathologists are sometimes necessary.

The prognosis of tumors of a granulosa remains good at the child in the majority of cases. The main prognostic factor is the stage of extension local. The early diagnosis of signs of early puberty is an important prognostic factor.

The treatment of choice in children is conservative surgery and must therefore intervene before any abdominal, pelvic or lymphatic extension.

Biological monitoring is based on the regular evaluation of the dosages of estradiol, plasma inhibin and AMH. Relapses are reported mainly in the first three postoperative years;but they can occur in the long term.

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