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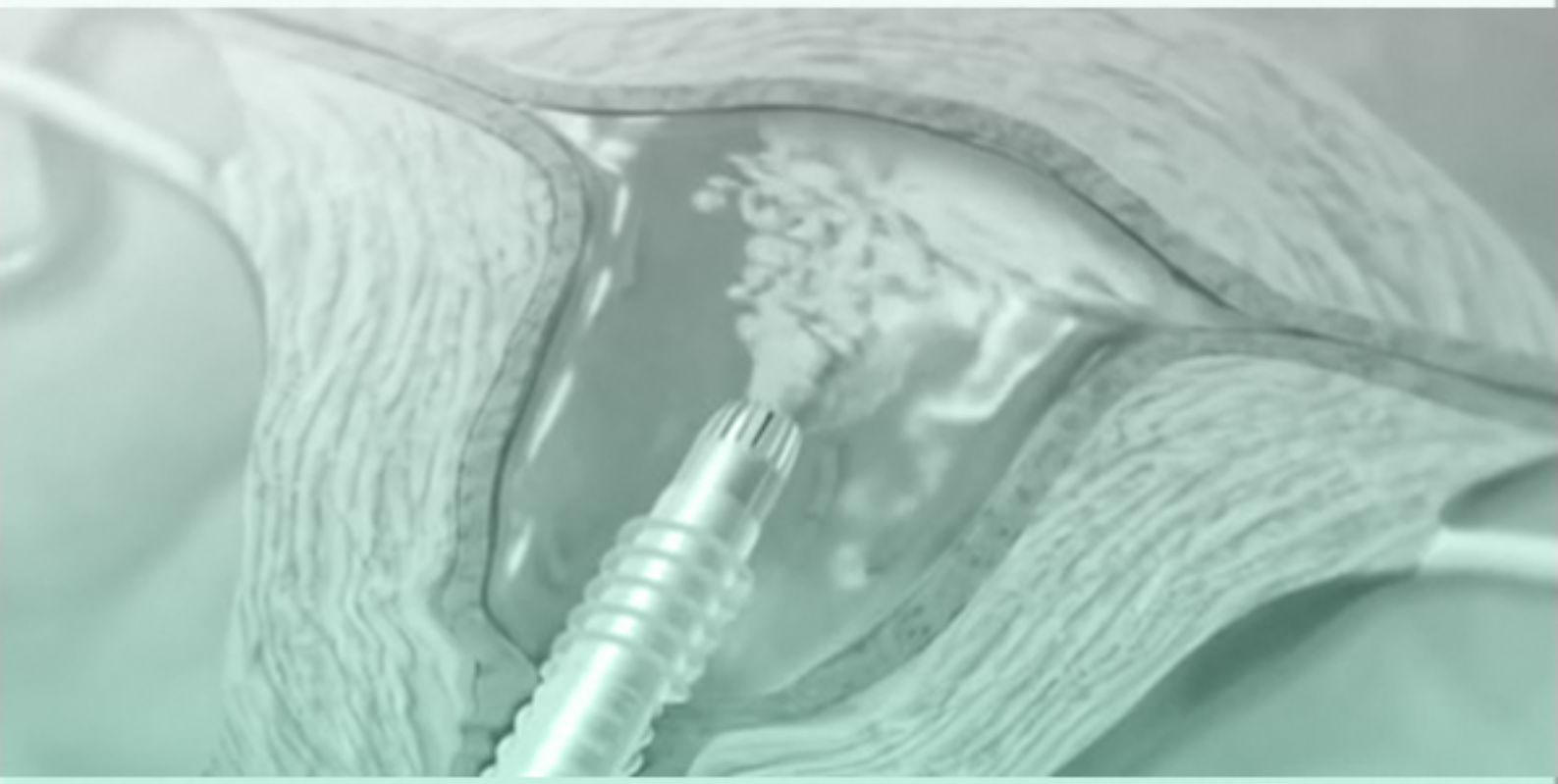

GYNECOLOGY AND OBSTERICS RESEARCH

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Case Report

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Elevation of Alpha-Fetoprotein in Sertoli-Leydig Cell Tumor: A Case Report

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ABSTRACT

Sertoli-Leydig cell tumors represent about 0.2 to 0.5% of all primary ovarian tumors. One of the main features of this type of tumor is the high production of androgens, which promotes hirsutism and virilization. This case reports a 28-year-old patient with severe abdominal pain whose physical examination showed a right adnexal mass, confirmed by pelvic US, without clinical evidence of virilization, who presented elevated alpha-fetoprotein (636 ng/mL), negative hCG-β and was negative to other tumor markers. Exploratory laparotomy was performed with right salpingo-oophorectomy. Histologically, it was identified a tumor with heterogeneous areas, retiform, tubular, microcystic, anastomosing cords and trabeculae with Leydig cells and areas of hepatoid differentiation. The tumor was positive for inhibin, cytokeratin AE1/AE3 and calretinin. One week after surgery, alpha-feto protein levels dropped to 150 ng/ml and to 0.89 ng/ml five months later. This is a case of Sertoli-Leydig cell tumor with elevated alpha fetoprotein no evidence of virilization and the histological pattern showing focal areas of hepatoid differentiation.

KEYWORDS: Sertoli-Leydig cell tumor; Alpha-fetoprotein; Hepatoid differentiation areas.

ABBREVIATIONS: CBC: Cell Blood Count; hCG-β: Chorionic-beta Gonadotropin; AST: Aspartate aminotransferase; ALT: Alanine aminotransferase; HCC: Hepatocellular carcinoma; FIGO: International Federation of Gynecology and Obstetrics.

INTRODUCTION

Sertoli-Leydig cell tumors are considered a rare disease, representing about 0.2 to 0.5% of all primary ovarian tumors.[1] They frequently occur in patients younger than 25 years-old. One of the main features of these tumors is the high production of steroid hormones (androgens), which promotes virilization, hirsutism, deepening voice, clitoromegaly, oligomenorrhea and temporary baldness in the patients.

Microscopically, it is characterized by a pattern similar to the stromal cell and sex cords tumors.[2] However, these tumors generally do not produce alpha-fetoprotein; as, until 1998, only 20 cases have been described.[3] We report the case of a patient with Sertoli-Leydig cell tumor with a high production of alpha-feto protein without any clinical feature added.

CASE

A 28-year old patient presented with a history of abdominal pain. Physical examination

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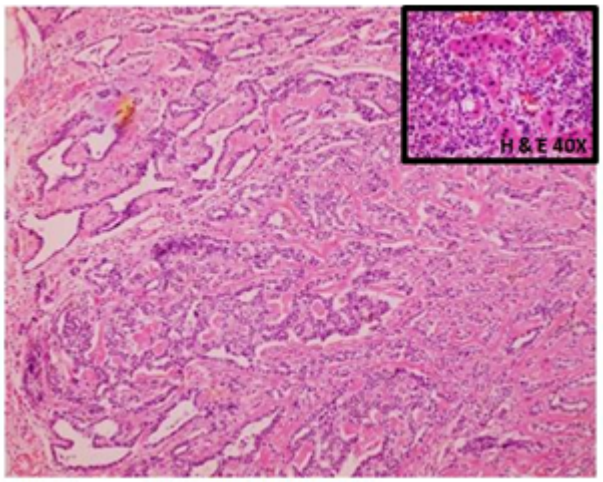
revealed a right adnexal mass, subsequently confirmed by pelvic ultrasound. At diagnosis, alpha-fetoprotein level was 636 ng/mL, the dehydrogenase level was 157 IU/L, the Chorionic-beta Gonadotropin (hCG-β) was 0.00 mIU/mL, the CA-125 antigen level was 12.20 IU/mL and CA-19.9 antigen was 0.80 IU/mL. The Cell Blood Count (CBC) revealed hemoglobin of 15.3 g/dL, 212,000 platelets/mcL, 7,400 leukocytes/mm,[3] and glucose level was 101 mg/dL. No features of virilization or hirsutism were detected. The patient underwent an exploratory laparotomy and a right salpingo-oophorectomy.

The tumor presented an irregular pattern of ovoid shape; measuring 13 cm long, with a gray-violet smooth outer surface, with congestive vessels. The cross-sectional surface was solid, cystic and whitish, with necrotic focal areas (Figure 1).

Macroscopic piece of ovoid shape, smooth, 13 cm in diameter at its major axis, purplish gray color. When cut, it is observed a white cystic solid surface with focal necrosis.

Figure 1: Right Ovary.

Histologically, it was a tumor with a heterogeneous pattern with retiform, tubular, and microcystic areas in cords and trabeculae, anastomosed with a few Leydig cells. Hepatoid areas of differentiation were focally identified (Figure 2).

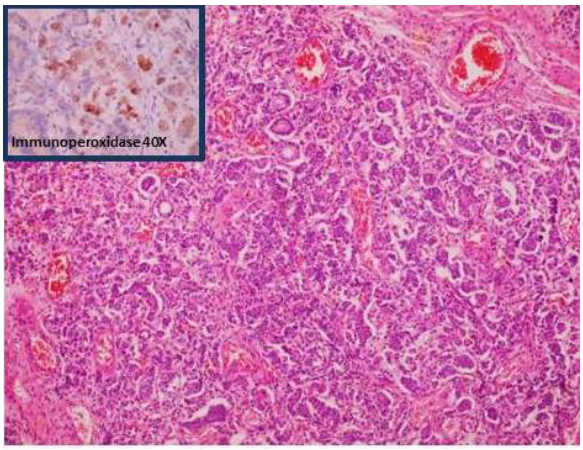


There is a retiform pattern on top and the tubular pattern with endometriod areas. In the small square (H&E 40X) some areas with focal haematoid differentiation can be identified.

Figure 2: Photomicrograph H&E 10X.

The immunohistochemistry staining was positive for inhibin, cytokeratin AE1/AE3 and calretinin. The epithelial membrane antigen was negative.

Microscopically, a composition of cells with scarce cytoplasm, large nuclei with granular chromatin and reinforcement of the membrane was described, and the cells were arranged in tubular structures of vesicular formation (Figure 3).



This photomicrograph with hematoxylin and eosin staining (10X) shows a tubular pattern on top and anastomosing cords with immature Sertoli cells. The small square with immunoperoxidase staining (40X) shows inhibin positive.

Figure 3: Photomicrograph H&E 10X.

One week after surgery, AFP dropped to 150 ng/ml, hCG-β levels continued at 0.0 mIU/mL, the Aspartate aminotransferase (AST) level was 19.0 IU/mL, the Alanine aminotransferase (ALT) level was 36.0 IU/L, and the lactic dehydrogenase level was 157.0 IU/L.

Finally, five months after surgery, measured level of alpha-fetoprotein was 0.89 ng/mL. The patient had been under surveillance for six months without evidence of recurrent disease.

DISCUSSION

We report the case of a patient with a Sertoli-Leydig cell tumor in the right ovary and its association with an overproduction of alpha-fetoprotein. A main characteristic in these patients is virilization, which has been found in about 70% of the previously reported cases. Sertoli-Leydig cells are classified as hormone (testosterone)-producing cells.[4] In our case, the levels of steroid hormones were not asked because of the lack of clinical evidence of testosterone production by the neoplasm.

Twenty-five cases of patients with Sertoli-Leydig cell tumors with elevation of the alpha-fetoprotein levels have been described since 1980; six of these ones have been reported in post menopausal women.[5] As expected, our 28-year old patient falls in the prevalent age range.

The reason why these tumors produce AFP is not clear, but it is suggested that the presence of hepatic tissue in the tu-

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mor is responsible for its synthesis.[6] Although the elevation of AFP has been associated with liver carcinoma, it is not specific to this condition, and its presence does not necessarily indicate malignancy.[7] This statement is confirmed by Gard GB, et al. who suggest that AFP is secreted in an endocrine fashion and the cyst fluid is an ultra filtrate of blood rather than a pooled secretion from an exocrine tumor.[3]

Alpha-fetoprotein (AFP) is a member of a multigene family comprising genes encoding albumin, alpha-protein bound to albumin and vitamin.[8] It is basically produced primarily by the fetal liver so it is considered a fetal specific glycoprotein. Normally, AFP levels decline rapidly after birth, reaching undetectable levels (less than 10 ng/mL) within several months after birth.[9] Its biological role is unknown; however, because it is synthesized during the G1and S phases of the cell cycle, it is thought to affect cell growth. AFP is able to bind other steroids and endogenous and exogenous substances such as fatty acids, bilirubin, and various pharmaceutical agents suggesting that it may play a role as conveyor.[8]

Histological examination revealed a moderately-differentiated Sertoli-Leydig cell tumor with areas containing a retiform pattern.[1] This type of pattern is characterized by the presence of tubular structures of Sertoli cells arranged in a dense or hyaline stroma-like the rete testis stroma. These structures build buds or polypoid structures with hyaline or edematous stroma, resulting in an aspect of a borderline serous tumor.[10]

Normal values of AFP in serum range from 0 to 0.89 ng/ml), five months after surgery AFP levels dropped to 0.89 ng/ml. These data confirm previous reports where the AFP has been used as a marker of malignancy in adults.[11] However, this is also an important marker of surgical prognosis because clinical studies have shown a close relationship between the level of serum AFP and Hepatocellular carcinoma (HCC) incidence, recurrence and metastasis. Accordingly serum AFP level has been used as the main index of prediction for HCC prognosis after laparotomy with higher preoperative AFP levels correlating with poorer prognosis.[12]

Considering initial surgery in ovarian cancer has the purpose to diagnose and stage disease and to provide therapeutic benefit with cytoreduction, in this case, a unilateral salpingo-oophorectomy was performed, the histology report showed an immunohistochemistry staining inhibin and vimentin positive and EMA negative. These was a predicted result because literature confirms that positive immunohistochemical staining for Sertoli-Leydig cell tumors are inhibin, calretinin, AE1/3CD 99 and vimentin, and negative markers are EMA and chromogranin.[4]

The clinical and pathological features of 207 ovarian Sertoli-Leydig cell tumors reviewed in 1985, Young, et al.[13] found at operation that 97.5% of the tumors were Stage I, 1.5% were Stage II, and 1% were Stage III. Both ovaries were involved in 1.5% of the cases. In this case, the tumor extirpated in our patient was in Stage IA according to the International Federation of Gynecology and Obstetrics (FIGO) staging system, and due to her age (28 years old), the fertility-sparing surgery is the treatment of choice.[14] These patients with early stage disease (stage I and II) have a very good prognosis with 5 year overall survival of 99% so they usually do not require any postoperative treatment. On the other hand, patients with stage IC disease or a higher stage, associated with poor prognostic factors, have a higher chance of relapse, and may benefit with neoadjuvant treatment.[15]

The incidence of malignancy in these tumors is10-30% and recurrence occurs in a period of 46 months in average. The 10-year survival in Sertoli-Leydig cell tumors is near 90%[16] but it depends on prognostics factors such as stage, intermediate and poor differentiation, presence or not of heterologous tissue, retiform structure, tumor spread beyond the ovary, etc., situations in which the patient may benefit from neoadjuvant chemotherapy, but the treatment must be according to each particular case.

The fact that the AFP is elevated does not rule out a sex cord tumor, although the probability is very low and the patient's age is necessary to diagnose a germ cell tumor as the first option. An accurate diagnosis is critical because treatment can be modified depending on the histological report, whether she requires adjuvant management or not.

In this case, the patient is in stage IA, accomplishes the criteria for surgical treatment so she has a favourable prognosis. However, her close surveillance and monitoring continues every 6months.

Finally, due to Sertoli-Leydig tumors are a rare disease, and even less frequent when combined with a raised alpha-fetoprotein at diagnosis, it is important to consider AFP as a reliable tumor marker not only at diagnosis, but after surgery and during follow-up so it must be documented as a baseline level in all patients with Sertoli-Leydig cell tumors. Despite these tumors produce high quantities of steroid hormones (androgens), which promotes virilization, hirsutism, etc., in this case, no virilization signs were found, which suggests not all of these tumors are virilizing.

As most patients are young women in early stages, they can benefit from fertility-sparing surgery as the treatment of choice. An accurate histological diagnosis and staging is necessary before systematic treatment because subsequent treatment and prognosis will depend on it. Fortunately, prognosis with 5-year overall survival is very good in most healthy women in this range of age.

CONFLICTS OF INTEREST

The author(s) declare(s) that there is no conflict of interests regarding the publication of this paper.

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DISCLOSURES

In our setting, for these cases neither acknowledgments nor consent statements are included, because it is not required in our institution.

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Case Report

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Giant Condyloma of the Uterus: Migrating Disease?

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ABSTRACT

Genital Human papillomavirus (HPV) infection is the most common sexually transmitted infection. Although most infections are asymptomatic, a proportion of these infections will result in clinical symptoms. Giant condyloma is an uncommon clinical manifestation of a low-risk HPV infection. In this case report we describe a unique presentation of a giant condyloma in the uterine cavity of a 59-year old women with a long history of abnormal cervical smears who presented with postmenopausal bleeding. HPV type 11 was detected.

KEY WORDS: Human papillomavirus (HPV); Giant condyloma; Uterus.

ABBREVIATIONS: HPV: Human papillomavirus; HIV: Human Immunodeficiency Virus; PAP: Papanicolaou; CIN: Cervical Intraepithelial Neoplasia; LLETZ: Large Loop Excision of the Transformation Zone.

INTRODUCTION

Genital Human papillomavirus (HPV) infection is the most common sexually transmitted infection. Although most infections are asymptomatic, a proportion of these infections will result in development of genital abnormalities. Persistent infection with high-risk HPV types is considered necessary for the development of cervical cancer whereas infection with low-risk types is associated with the development of genital warts or condylomata acuminata. Exuberant growth of a condyloma acuminatum is termed 'giant condyloma'. Giant condylomas usually present in young patients and growth has been associated with impaired immunity (such as infection with the Human Immunodeficiency Virus (HIV)) or pregnancy. Most common sites involved are the vulva, anus, perineum or perianal skin, penis or, more exceptional, at the cervical site. Giant condyloma might result to significant clinical concern as these tumors might mimic malignant tumors. Here, we report, to our knowledge for the first time, a unique presentation of a giant condyloma that had been 'migrated' from the cervical site into the uterine cavity.

CASE PRESENTATION

A 59-year-old woman was referred to the gynaecologist because of postmenopausal bleeding and a high-grade abnormality in her cervical Papanicolaou (PAP) test. The medical history included Insulin-dependent diabetes mellitus type 2, hypertension, hypercholesterolemia, heterozygous alpha thalassemia and obesity (Body Mass Index 41.7). The obstetrical and gynaecological history revealed two vaginal deliveries and one abortion. Since 1993, multiple cervical smears with alternating low grade abnormalities (n=3) and normal PAP tests (n=4) were diagnosed. During this period multiple cervical biopsies (n=8) had been performed showing viral changes with low-grade Cervical Intraepithelial Neoplasia (CIN 1). The gynaecologist took a cervical biopsy that showed a condylomatous aspect of the squamous epithelium with

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viral changes consistent with condyloma acuminatum. However, an endometrial biopsy that was taken at the same time showed an atypical squamous proliferation with severe dysplasia and viral changes (Figure 1). Although contamination from a primary cervical lesion was strongly suspected, immunohistochemical staining for p16 and high-risk Human papillomavirus (HPV) testing by PCR were both negative, which is unusual in high-grade HPV related genital lesions.[1] Because of the discrepancy between the low-grade abnormality found in the cervical biopsy and the high-grade abnormalities found in both the cervical PAP test and the endometrial biopsy specimen, a Large Loop Excision of the Transformation Zone (LLETZ) was decided. Again, histopathological evaluation was consistent with condyloma acuminatum. Subsequently, the patient underwent a cervical conisation and additional endometrial curettage, both with the same outcome: condyloma acuminatum in the cervical cone and a high-grade dysplastic squamous lesion in the endometrium. Low-risk HPV testing by PCR turned out to be positive and additional typing showed positivity for HPV type 11. The possibility of a giant condyloma was considered. Given the high-grade dysplastic squamous morphology in the endometrial biopsies, which is an unusual feature in low-risk HPV infections, and the differential diagnosis of an underlying squamous cell carcinoma at the endometrium, a total laparoscopic hysterectomy with bilateral salpingo-oophorectomy had been performed.

Gross inspection showed exophytic lesions in the cavum uteri (Figure 2). Consistent with the previous findings, microscopic evaluation of the lesions showed viral changes with high-grade dysplasia at the fundus uteri site and low-grade dysplasia at the cervical site. There were no signs of stromal invasion. A line of flat squamous epithelium with normal maturation and without viral changes interconnected the two lesions. Given the presence of HPV type 11 and resuming all histopathological findings, a low-risk HPV positive giant condyloma with high-grade dysplasia was diagnosed. After surgery, the patient recovered well and during a follow up period of 3 years no signs of residual HPV related anogenital disease were present.

DISCUSSION

Giant condyloma of the anogenital region was first described by Buschke in 1896 and is also known as a Buschke-Löwenstein tumor.[2-4] This uncommon lesion is caused by HPV.

HPV is the most prevalent sexually transmitted infection and its genotypes can be divided into different groups according to their ability to induce malignancy. Infection with low-risk types can result in genital warts or respiratory papillomatosis whereas infection with high-risk types can lead to malignant transformation of the epithelium in the anogenital or head and neck regions. Mostly, HPV infections are asymptomatic. It is unclear whether HPV infections can silently affect the reproductive function as it appears that HPV can be associated with apoptosis of sperm and embryonic cells and alterations in semen quality.[5]

Giant condyloma presents clinically as an exuberant exophytic growth of a condyloma acuminatum that typically appears after an infection with the low-risk HPV types 6 or 11 with the anus, penis, perineum, vulva, and to a lesser extent the cervix being the most common affected sites.[3,4,6,7] Although invasive squamous cell carcinoma have been reported in about half of the cases it is unclear whether these invasive cases represent true malignant transformation or misclassified cases.[6] Because of similarities in exophytic growth patterns the differential diagnosis between giant condyloma, warty, papillary, and verrucous squamous cell carcinoma can be difficult.[8,9] In contrast to giant condyloma, warty and papillary squamous cell carcinoma usually show high-grade neoplastic epithelium with areas of typical

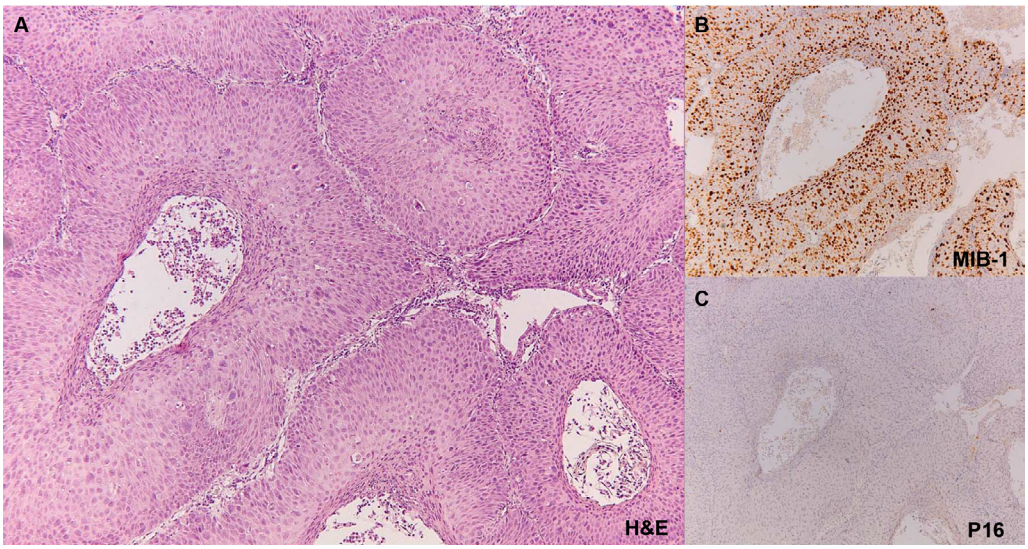

Figure 1: Histologic findings of the endometrial biopsy specimen revealed an atypical squamous proliferation with a papillomatous architecture lined by high-grade neoplastic epithelium (A, H&E objective 10x) with increased proliferation activity over full thickness of the epithelium of the epithelium (B, MIB-1 objective 10 x) that was negative for p16 immunohistochemical staining (C, p16 objective 10x).

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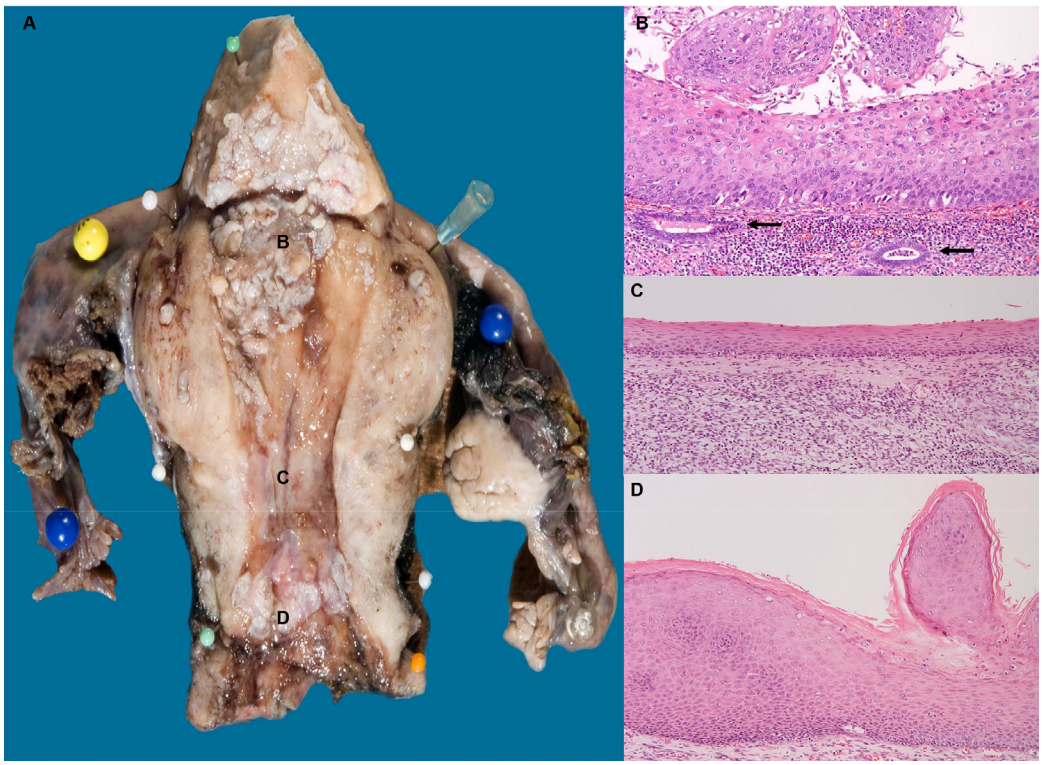

Figure 2: Gross specimen of the uterus showed exophytic proliferations at both the fundus and the cervical/isthmus site of the corpus uteri (A). At the fundus site a verrucous high-grade lesion over laid the normal endometrial mucosa (B, H&E objective 10x, arrows indicate underlying endometrial glands). At the cervical/isthmus site (status after prior cervical excisions by LLETZ and cone), a verrucous low-grade lesion with viral changes (D, H&E objective 10x) was present. The verrucous lesions at the fundus uteri and the cervix were connected by flat squamous epithelium without dysplasia and without viral changes (C, H&E objective 10x).

infiltrative stromal invasion. As these later tumours are positive for high-risk HPV, p16 immunostaining and/or HPV typing can be helpful to differentiate these tumours from giant condyloma. Verrucous carcinomas are not HPV related.[8]

To our knowledge this is the first report about a giant condyloma that had been 'migrated' into the uterine cavity. Although the finding of a squamous proliferation in material derived from the uterine cavity is probably more likely to be the result of extended growth or contamination from a cervical neoplasia, true endometrial involvement by squamous epithelium should be considered as well. Despite the unusual finding of high-grade morphology, lack of stromal invasion in our case supports the benign nature of infections with low-risk HPV types.

CONFLICTS OF INTEREST

There are no potential conflicts of interest to disclose.

CONSENT

We have obtained informed consent of the patient.

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Case Report

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Metastatic Cervical Carcinoma with High-Risk Human Papillomavirus (HPV) Positive and P16/Ki-67 Positive in a 28 Year-Old Female That Did Not Meet the Current Screening Guidelines

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ABSTRACT

A case presentation about an individual treated at Oklahoma State University Medical Center with high-grade metastatic squamous cell carcinoma of the cervix that was high-risk HPV and p16/Ki-67 positive. The clinical presentation, laboratory data, imaging, and subsequent therapy are reported as well as highlights of screening guidelines for cervical pathology

KEYWORDS: Cervical squamous cell carcinoma; Human papillomavirus; P16; Ki-67; Cervical screening guidelines.

INTRODUCTION

The clinical guidelines for frequency of cervical cytology testing were updated in March 2012 and have since been adopted by American Congress of Obstetricians and Gynecologists (ACOG), United States Preventive Services Task Force (USPSTF), American Cancer Society (ACS), and American Society for Colposcopy and Cervical Pathology (ASCCP). Physicians are obligated to interpret and implement these updated guidelines into their own clinical practice. Patient education, along with increased public awareness of the importance of cervical cancer screening, has resulted in a higher percentage of women being screened for cervical cancer. In 2013, the Centers for Disease Control and Prevention reported that while more women are being screened, this group includes women younger than 21 years of age, which conflicts with screening recommendations.[1] The report also revealed an increased in the percentage of women 22-30 years of age that have not been screened.[1] Another potentially concerning aspect of the updated guidelines is the recommendation for co-testing HPV screening every five years for women aged 30 or older. These findings raise the issues of reconsidering screening for high-risk HPV in a younger age group and decreasing the screening interval from three years to one or two years in women with high-risk HPV and negative cytology.

CASE PRESENTATION

A 28 year-old G3 P3003 Caucasian female presented with complaints of headaches, numbness on her left side, right shoulder pain, left hip and left knee pain. She also noted decreased energy and activity, as well as weight loss, in the past month. The patient denied any past medical history. Her Pap smear which was a satisfactory sample in 2011 was negative; however, patient did not have one performed in 2014. She did not have a history of sexually transmitted diseases or a family history of cancer. The patient did have increased risk for cervical cancer because of early onset of sexual activity, multiple sexual partners, early age at first parity, increased parity, and cigarette smoking. Upon presentation, basic labs were performed

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and abnormalities are as noted: white blood cell count of 28.2, hemoglobin of 9.0, platelets of 112,000, sodium of 121, calcium 14.0 and alkaline phosphatase was 389. Significant findings on imaging studies included erosive changes at the distal clavicle and acromion on chest x-ray, which was new from an exam 30 days prior. A head CT showed lytic lesions of the skull with overlying soft tissue swelling and dural thickening.

With the initial findings, the patient was admitted to the intensive care unit under her Family Medicine team for further care. The primary source was then found on CT of the abdomen and pelvis: a nodular mass within the uterus near the cervix measuring approximately 3.2 cm x 3 cm x 4 cm. Cervical exam performed by the gynecology service exhibited an approximately 5 cm cervical mass that was firm, irregular shape, friable and adhered to the anterior vaginal wall. Tissue sample showed high grade squamous cell carcinoma that was HPV p16 positive and Ki-67 positive. Gynecology/Oncology was consulted and their recommendations were initiated. Metastasis was noted in the skull, dura, bony spine, clavicle, scapula, ribs, pelvis, femur, adrenal glands, liver, lung, and esophagus. She was given Vitamin D, dexamethasone, controlled-release morphine, along with one dose of pamidronate. Other pathologic changes required supportive therapy, such as packed red blood cells and platelets. While the patient initially insisted she would eat more, megestrol acetate was administered to assist with appetite stimulation. The patient consistently had low blood sugar readings, and dextrose 5% with half-normal saline was required prior to steroid administration. For the concern for infection, the patient was treated with ampicillin/sulbactam. The patient was transferred to another facility for higher level of care to receive palliative radiation therapy due to an erosive lesion at T4-T5 vertebrae with significant compressive features on her spinal cord at the same level. She received two radiation treatments inpatient and was then released to continue outpatient therapy. The patient later died, within 3 weeks of initial diagnosis.

DISCUSSION

This case brings forward an important discussion about screening for cervical cancer and highlights the necessity of regular screening in this population. Current recommendations from the ACS, the USPSTF, and ACOG suggest that this patient have cytology performed every three years and that HPV co-testing should be performed in women once they become 30 years of age.[2] The current guidelines take into account increased risk of unnecessary procedures such as colposcopy, and likelihood that women under 30 years of age have the potential to clear the infection. However, in 2015, the Society of Gynecologic Oncology and the ASCCP suggested screening women for HPV starting at the age 25.[3] Also this year, the FDA approved the Cobas HPV test for the age of 25 or older. While the interim guidelines were given and testing is available, these recommendations are not consistent across all organizations and are not widely known; therefore they are not likely being used by all physicians. The patient presented had negative cytology on her last Pap smear but failed to have routine examination and did not meet criteria for HPV testing. Had guidelines recommended co-testing in a younger population, closer screening may have been warranted and early discover may have been possible.

One of the markers not currently being utilized to help screen for cervical cancer is p16/Ki-67. Protein p16 is overexpressed in cervical and/or HPV associated cancers. At the time of diagnosis of metastatic cancer, this patient was positive for HPV p16 and Ki-67. A study that looked at the dual stained cytology of p16/Ki-67 showed these markers have superior sensitivity with noninferior specificity with that of Pap cytology when screening for CIN2.[4] However, this testing currently is not FDA approved for routine screening.

CONCLUSION

It is unclear if this patient's outcome would have been different if routine screening had been performed according to the guidelines at that time. It falls upon the physician to stay current on screening recommendations to improve the chances of earlier detection of cervical cancer. Early recognition of this particular cancer is critical to institute the proper therapy and improve prognosis. In the future, the testing and guidelines may evolve to include testing for HPV at an age younger than 30 or other innovations that include screening with a precursor p16/Ki-67.

CONFLICTS OF INTEREST

Authors have no conflicts to declare.

CONSENT

No consent is required for our article publication.

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Research

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The Three Delays of Maternal Mortality in a Public-Sector Tertiary Teaching Hospital: Is There a Paradigm Shift?

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ABSTRACT

Objective: To describe the three delays of maternal mortality in a public-sector tertiary teaching hospital in one year.
Study Design: Retrospective, observational study.
Place and Duration of Study: Minia Maternity & Children's University Hospital, Department of Obstetrics and Gynaecology, Unit A, El Minya city, Egypt, from January 2014 to December 2014.
Methodology: 8915 of deliveries during the study period were reviewed and all causes of maternal deaths were analysed. Data regarding age, parity, sociodemographic characteristics, booking status, referral source, cause of death and the three delays was collected on structured proformas, analysed by the statistical software, SPSS version 16, and presented in the form of frequencies and percentages.
Results: The projected maternal mortality ratio was 89.7/100,000 live births. The mean age of women was 23±7.2 years and median parity was 4 (ranging from 0-11). 4 cases (50%) of the women had received no formal education and 5(62.5%) belonged to a lower socioeconomic class. Two cases (25%) of the women received no antenatal care while four cases (50%) received less than four antenatal visits during the whole pregnancy and classified as poor antenatal care attendee.
Direct causes were responsible for 62.5% of maternal deaths, 37.5% of deaths were due to indirect causes.
The third delay was found to be the most frequent (79%) followed by the first delay (71%) while the least one was the second delay (40%).
Conclusion: There is a paradigm shift of delays toward the third delay rather than the first or second delays which might be related to chronically under-resourced health facilities which are still unable to cope effectively with serious obstetric complications. Better understanding of the third delay co-factors could lead to significant improvement in the quality of care in our communities.

KEYWORDS: Maternal mortality; Three; Delays; Developing countries; Socio-demographic characteristic.

ABBREVIATIONS: MMR: Maternal Mortality Ratio; MDG: Millennium Development Goal; WHO: World Health Organisation.

INTRODUCTION

The Maternal Mortality Ratio (MMR) is considered as a sensitive indicator to many

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parameters like adequacy and quality of Healthcare of women, access to care, as well as the Women's status.[1] In the developing countries, one woman dies in 16 compared to 1 to 2800 in the high income countries[2] and most of such deaths due to pregnancy complications are preventable.[3]

The lag to achieve the targeted MMRs of the Millennium Development Goal (MDG)5, mostly is not due to absence of effective and evidence based interventions for such problems but due to difficulty to access timely to existing, emergency obstetric interventions which could avert 88%-98% of the maternal deaths as World Health Organisation (WHO) estimated in the Mother-Baby Package: Implementing Safe Motherhood in 1994.

According to the official reports of the Egyptian ministry of health, Egypt has maternal mortality ratio 52.5/100.000 in 2013 which means that Egypt is on the right track to achieve the target figure of the MDG5 by 2015. Extensive analysis of the causes of maternal mortality has resulted in five main causes are haemorrhage, obstructed labour, preeclampsia and eclampsia (pregnancy induced hypertension), sepsis and complications of unsafe abortion.[4]

However, these causes may not result directly in maternal deaths, but through other factors like delay in receiving timely and appropriate care in the event of a pregnancy complication. Such delays have been put forward as a major determinant in maternal mortality.

In 1994, Thaddeus and Maine proposed these delays into three types: three different levels:

1. Delay in decision to seek care,
2. Delay in reaching the appropriate facility and
3. Delay in receiving adequate care in the facility.[5]

There are many factors that can contribute to each delay.

In developing countries, poor economic condition usually contributes to low educational status; poor infra-structures in the health facilities, and may also reflected on the qualification and skills of the health professionals in such countries. This means contribution to the three delays together as major determinants in maternal mortality.

This study describe analysis of the maternal mortality in a public-sector tertiary teaching hospital in one year in relation to the three delays characteristics and does the contribution of each delay has different pattern than the other.

METHODOLOGY

This retrospective, observational study was undertaken in the Department of Obstetrics and Gynaecology, Minia Maternity & Children University Hospital, Egypt where the cases of maternal mortality within the hospital were studied from January 2014 to December 2014. The health facility is the only public-sector tertiary teaching University Hospital in El Minya governorate, Egypt that serves as a referral centre for all the health facilities of nine general hospitals in nine big cities and its suburbs as well as the adjoining areas of rural territories distributed along 160 kilometres.

Majority of the women admitted to the reception sector were emergency cases referred by various public or private hospitals, in a critical condition. All women who suffered a maternal death during the year of 2014 were included in the study. We used a structured proforma to collect the relevant information including means of both interviewing the relatives of the deceased women, doctors attended with the cases as well as from the patients' case files. Data was collected regarding age, parity, socio-demographic characteristics, booking status, referral source, cause of death and the analysis of the three delays according to Thaddeus and Maine.[5] Information regarding the first and second delay was obtained from interviews with patients' attendants while information regarding the third delay was taken from the case files and after the interviewing the health team who involved in the care provided. The delay in referral from various health facilities and multiple referrals were included in the second delay.

Booking was defined as those patients who were registered at any health facility which distributed alongside the governorate.

The data was analysed by computer software, SPSS version 16, and results presented as frequencies and percentages.

RESULTS

During the study period, there were 8915 deliveries, 9347 live births and 8 maternal deaths giving a maternal mortality ratio of 89.7 per 100,000 live births. Six women (75%) were booked in different health facilities. All women (100%) were referred, five cases (62.5%) from private hospitals, two (25%) from public hospitals, one case (12.5%) from maternity home. The mean age of women was 23±7.2 years and median parity was 4 (ranging from 0-11). The mean haemoglobin concentration was 7.2±2.8 gm/dl. At time of admission, the median time interval between admission and death was 28 hours. Five women died within 24 hours of admission, two were dead on arrival and one died within two hours.

Four cases (50%) of the women had received no formal education and 5(62.5%) belonged to a lower socioeconomic class. Two cases (25%) of the women received no antenatal care whatsoever throughout the index pregnancy and classified as non-attendee while four cases (50%) received less than four antenatal visits during the whole pregnancy and classified as poor antenatal care attendee.

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Direct causes were responsible for 62.5% of maternal deaths, the two most frequent being haemorrhage and hypertensive disorders.

Three cases (37.3%) of deaths were due to indirect causes, one case thromboembolism, one cardiac case and one case had breast cancer (Table 1).

Direct (5) (62.5%)	Indirect (3) (37.2%)	Accidental
Haemorrhage 3(37.5%)	Thromboembolism 1(12.5%)	No recorded cases
Hypertensive disorders 1(12.5%)	Cardiac disease 1(12.5%)	
Puerperal sepsis 1(12.5%)	Breast cancer 1(12.5%)	

Table 1: Causes of maternal deaths. Values are expressed as n(%).

Analysis of the reasons for the three delays of MM can be shown in Table 2. The third delay was found to be the most frequent (79%) followed by the first delay (71%) while the least one was the second delay (40%).

DISCUSSION

The projected maternal mortality ratio during the study period (89.7/100,000 live births) was markedly lower compared to that previously reported during the past eight years from the same Unit for the years 2007-2013 (in 2007 was 183.8, in 2008 was 165.9, in 2009 was 166.3, in 2010 was 117.6, in 2011 was 162.4, in 2012 was 90.7 and in 2013 was 94.3937 per 100,000 live births).

The plausible reasons for this discrepancy could be due to improving in the referral system between the general hospitals in the governorate and the tertiary one after initiation of the referral awareness program over the past two years period from 2012-2013, improved communication tools between the health physicians in the area, initiation of standard protocols, application of the auditing standards, improved reporting of the incidents and increased staff serving in the hospital since 2012.

The recorded MMR in the tertiary units were variable; a previous study from Karachi in Pakistan reported hospital-based MMR as varying from 17 deaths in a private tertiary hospital to 2,736 deaths in a public-sector tertiary hospital.[6]

In agreement with a systematic review, conducted by WHO, demonstrating haemorrhage and hypertensive disorders as the major contributors to maternal deaths in developing countries,[7] Haemorrhage was the leading causes of direct maternal deaths in this study.

Also we had three cases of indirect cause of MM were thromboembolism, cardiac, and breast cancer seems to be an important cause of indirect maternal deaths and needs further investigation.

During the study period the causes of death among the women who were brought dead did not mentioned as the cases were not initially admitted into the hospital as they not registered in the hospital files where the diagnosis of death were made in the reception room, however the interview with the relatives and persons who attended with the cases revealed the following causes, haemorrhage in two patients and ruptured uterus, pre-eclamp-

	First delay	Second delay	Third delay
1st case of Haemorrhage	Lack of awareness Fear of being ill-treated in the health facility	Long distance Late referral Multiple referrals Transport	Delay in getting blood Delay in surgery Substandard care
2nd case of Haemorrhage	Lack of awareness	Long distance Late referral	Failure of communications non-availability of blood in general hospitals
3rd case of Haemorrhage	Lack of awareness	Long distance Late referral Multiple referrals	Delay in getting blood Delay in surgery
Hypertensive disorders (preeclampsia and eclampsia)	Lack of awareness No available person to take care of the Children.	Long distance Late referral Multiple referrals	Delay in surgery Substandard care
Puerperal sepsis	Lack of awareness	Late referral	Failure of communications
Thromboembolism	Lack of awareness	Long distance Multiple referrals	Lack of agreed protocol Substandard care
Cardiac disease	Lack of finances	Long distance Late referral Transport	Failure of communications Lack of agreed protocol Substandard care
Breast cancer	Lack of finances Lack of companion in going to the health facility	Long distance Multiple referrals	Failure of communications Substandard care

Table 2: Relations between the cause of death and the three delays. Values are given as n(%).

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sia, induced abortion and puerperal sepsis in one woman each.

There is a positive relation between the literacy levels and the maternal morbidity and mortality and irrespective of sociocultural and demographic aspects, Poverty has also been strongly linked to the use of maternal health services, with the poor using fewer services than the rich.[8] The formal maternal education have been found a significant predictor of accessing the maternity service and their decision to deliver in a health institution.[9] In our study 50% of cases had received no formal education. In another study, the researchers reported odds ratio of 0.30 (0.21-0.44) for maternal mortality for more than eight years of schooling compared with no schooling.[10]

Our results showed that 5 cases (62.5%) belonged to a lower socioeconomic class which confirms the results of a study that confirmed that the most of maternal deaths occur in poor countries and poor women have the least access to skilled birthAttendants.[11] Another study from Nigeria concluded that 80% of mothers, who died in relation to pregnancy, belonged to the lower socio-economic class.[12]

The reported very high maternal mortality from public and tertiary hospitals (including ours) could be explained on the basis the large number of unbooked cases, referred in a critical condition, failure of communications between the health professionals in different hospitals, lack of agreed protocols and non-availability of blood in general hospitals.

In an agreement with a study which concluded that 88% maternal mortality among the unbooked patients compared to 11% among the booked,[13] the majority of women in this study did not have proper antenatal care during the index pregnancy where 2 cases (255) had no ANC and 4 cases (50%) had less than 4 antenatal visits and classified as poor attendee.

A study from Nigeria reported frequency of delay to be associated with 78% of maternal deaths. They found the first delay to be the most frequent (57%).[14] In our study, all cases had multiple delays and The third delay was found to be the most frequent (79%) followed by the first delay (71%) while the least one was the second delay (40%). Similar results were obtained from a facility based audit in Tigray, Ethiopia, 88% of the maternal deaths could be attributed to medical failures.[15]

Another hospital-based case control study of maternal mortality in Southern Nigeria, revealed that the most striking difference between the [maternal mortality and control] groups was in the third delay.[16]

Also, in a district-based audit in Indonesia, 60% of maternal deaths were attributed to third delay.[17]

The findings of these studies are supported by the WHO Health Report in 2005, which concluded that accessing good obstetric care could prevent 50-70% of global maternal deaths and substantially reduce the number of women living with sequelae of obstetric complications.[18]

The most common reason for the first delay was lack of awareness about the seriousness of the disease followed by financial problems, Fear of being ill-treated in the health facility or Lack of companion in going to the health facility. The second delay was mostly due to long distance (a high number of patients came from El Edwa or Malway cities where it can take upto three to four hours to reach the tertiary unit) followed by late referral from the different health facilities as well as time lag between the health facilities.

Also multiple referrals were also a significant factor in some patients who were referred to our hospital after having been to a number of different hospitals either private or general after being also delayed at home.

In our study, the most frequent reason for the third delay was the substandard care in the form of lack of agreed protocols in different settings, poor communications inside and between hospitals followed by difficulty in getting blood, which is usually attributed to donors not being available. This were followed by delay in surgical intervention, the usual reasons for which are delay in investigations and diagnosis.

This study is the first study from a large tertiary care hospital of Egypt which serves about eight million populations and has a rate of delivery from 12.000-15.000 per year, which has documented the reasons for the three delays of maternal mortality. Further studies are urgently required based on the whole governorate. The results of which could provide the policy makers and healthcare authorities with a useful data to plan appropriate interventions for reduction of maternal mortality.

However, this study was limited by a short period of time of one year and non-availability of control group that could have helped in statistically comparing the socio-demographic characteristics and the frequency of delays between mothers who died and those who lived.

CONCLUSION

Although there is a significant improvement in the MMR during the study period, still high MMR in this study suggests poor access of women to quality healthcare services. Although, the ‘‘three delays rarely operate in isolation, they indeed are likely to be interactive and multiplicative. However, there is a paradigm shift of delays toward the third delay rather than the first or second delays, which might be related to chronically under-resourced health facilities which are still unable to cope effectively with serious obstetric complications. Better understanding of the third delay co-factors could lead to significant improvement in the quality of care in our communities.

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COMPETING INTERESTS

The authors declare that they have no competing interests.

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Case Report

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Association of Pseudo-Meigs' Syndrome with Struma Ovarii and High CA125 Mimicking Ovarian Malignancy

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ABSTRACT

Pseudo-Meigs' syndrome (PMS) is a rare condition in which a non-fibroma ovarian tumor, pleural effusion, and ascites coexist, and in which removal of the tumor resolves the condition. We present here a patient with struma ovarii-associated PMS, and with high serum CA-125 levels, bearing a resemblance to a malignant ovarian tumor. Arriving at an accurate diagnosis prior to surgery and before to receiving the final pathology report is very difficult to achieve. However, this association must be considered when pleural effusion is found, in addition to a heterogeneous pelvic mass with a rise in CA-125 is evident.

KEYWORDS: Pseudo-Meigs' syndrome; Struma ovarii; Elevated CA-125; Ovarian malignancy.

ABBREVIATIONS: PMS: Pseudo-Meigs' syndrome; CT: Computed Tomography; TTF1: Thyroid transcription factor; EMA: Epithelial Membrane Antigen; VEGF: Vascular Endothelial Growth Factor; FGF: Fibroblast Growth Factor.

INTRODUCTION

Struma ovarii is a rare ovarian neoplasm composed predominantly of normal thyroid tissue and categorized as a variety of mature teratomas, representing only 2.7% of germ cell ovarian tumors.[1,2] It is generally benign, although it can present malignant transformation in 5-7% of cases, and is even more unusual as a metastatic disease.[2] The majority of cases are asymptomatic, but can be associated with a certain amount of ascitic fluid in up to 15-20% of the former, with reports of association with the hydrothorax, and development of the clinical features currently recognized as pseudo-Meigs' syndrome (PMS).[3] Among 20 cases reported as pseudo-Meigs' syndrome in a review of the literature from 1994-2014, only eight were related with struma ovarii (Table 1). The importance of this syndrome in benign pathology renders its recognition difficult.

Here, we present the case of a patient with struma ovarii associated with ascites, pleural effusion, and elevated CA125, simulating a malignant neoplasm of the ovary.

CLINICAL CASE

This was a 48-year-old Mexican mestizo post-menopausal patient with no previous

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Author	Year	Patient age (years)	Tumoral size (cm)	Ca125 (U/ml)	Ascitis (ml)	Type of surgery
Mui, et al.[4]	2008	56	6×5×4	5,218	5,000	Staging surgery
Mitrou, et al.[5]	2007	55	22×23×10	3,803	8,000	Staging surgery
Yücesoy, et al.[6]	2010	40	15×20	Not referred	Not referred	Hysterectomy + Right oophorectomy
Loizzi, et al.[3]	2005	65	7×7	161	Not referred	Right salpingo-oophorectomy
Paladini, et al.[7]	2008	42	11×7.3×8	2,548	8,000	Right salpingo-oophorectomy
Huh, et al.[8]	2002	66	5×4×4	402	20,000	Staging surgery
Rim, et al.[2]	2005	50	4×4	868.6	3,000	Staging surgery
Morán, et al.[9]	2006	46	25	1,808	500	Staging surgery
Present Report	2015	48	10x10	301	1,800	Staging surgery

Table 1: Cases reported of stuma ovarii and Pseudo-Meigs' syndrome.

clinical history of importance, with complaint of abdominal distension. The patient reported her illness as having initiated 4 months previously, with an increase in abdominal perimeter, not painful, in addition to precordial pain as well as respiratory distress for 2 weeks. She presented at a community hospital for evaluation, where a chest x-ray was performed, revealing a right pleural effusion of more than 50%; cytology of the pleural effusion was performed with a report of reactive mesothelium without evidence of neoplastic cells. An abdominal Computed Tomography (CT) Scan (Figure 1) was performed, identifying a right ovarian tumor 10×13×7.67 cm above the median line of the hypogastrium, with mixed density and small calcifications. The patient was referred to our Institute for treatment. A Ca125 of 301 U/ml was reported. On physical examination, the patient presented without data of respiratory difficulty; her vital signs were normal, with soft abdomen, not painful, not under tension ascites, with a poorly defined palpable mass in the hypogastrium and approximately 7 cm in size. On gynecological examination: vulva and vagina without lesions; uterine cervix of normal appearance without lesions; on rectovaginal examination, uterus approximately 8 cm, and the aforementioned mass was palpated with inability for determining the origin. Rectovaginal septum and parametria were not involved.

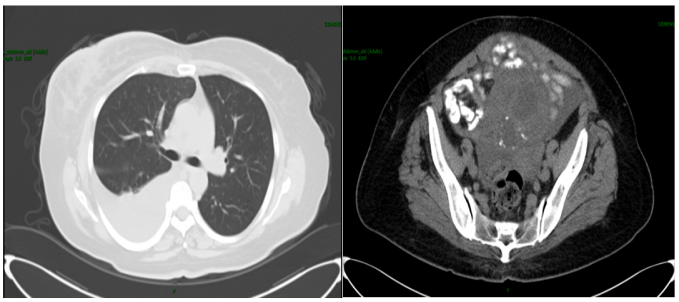

Figure 1: Thoracic CT scan with pleural effusion. Abdominal CT scan identifying a right ovarian tumor 10×13×7.67 cm above the median line of the hypogastrium, with mixed density and small calcifications.

An exploratory laparotomy was performed with the following findings (Figure 2): right adnexal mass of 10×10 cm, multilobular, with apparent capsular rupture, the presence of 1,800 ml of ascitic fluid, abdominal cavity and peritoneal surfaces without implants, as well as absence of tumor in contralateral adnexa and serosa of uterus, retroperitoneal lymph nodes were palpable and soft, considered to be inflammatory. The frozen section study of the tumor was reported as malignant but it could not be classified, and a complete cytoreduction and staging procedure was performed without complications. The patient evolved satisfactorily and was discharged from the hospital 3 days later.

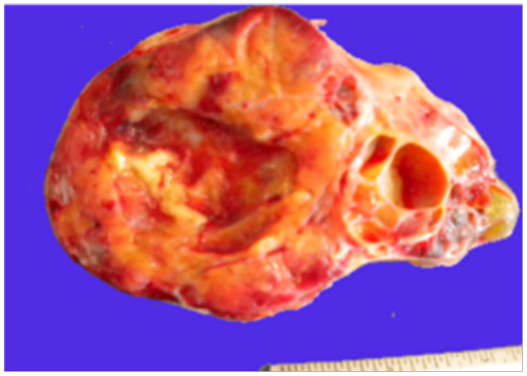

Figure 2: Macroscopic finding. Right adnexal mass of 10×10 cm, multilobular, with apparent capsular rupture.

The final pathology report disclosed the following:

- Right ovary with monodermic pure teratoma (struma ovarii) with follicular hyperplasia.
- Tumor size, 10×7 cm without capsule involvement.
- Fifteen right pelvic lymph nodes, seven left pelvic lymph nodes, and seven para-aortic lymph nodes negative for metastatic disease.
- Biopsies of peritoneum and omentum negative for metastatic disease.

The following complementary immunohistochemical studies (Figure 3) were carried out: Thyroid transcription factor (TTF1): positive; Thyroglobulin: positive; Inhibin: negative; Epithelial Membrane Antigen (EMA): negative, and Calcitonin,

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negative, supporting the previously mentioned diagnosis.

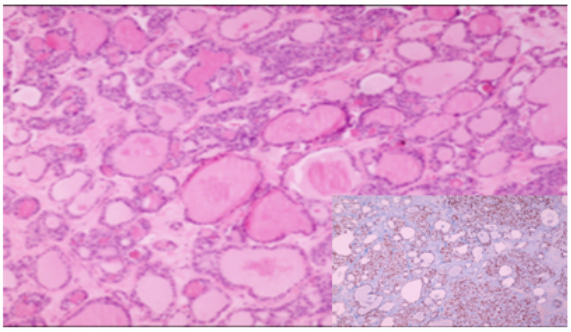

Figure 3: H&E and immunohistochemical stain. TTF1 positive.

The patient has remained under surveillance, and CA125 and thyroid profile studies have been conducted and reported as normal at her last clinical follow-up visit.

COMMENTARY

Struma ovarii is a rare variety of mature monodermal teratoma of the ovary that is composed entirely or primordially (>50%) of mature thyroid tissue.[1,2,5,6] It was originally described by Von Kalden in 1895.[3] At the beginning of the 20th Century, Pick identified struma ovarii as a germ cell neoplasm of the ovary comprising thyroid tissue.[10] In 1933, Plaut demonstrated that thyroid tissue of the struma ovarii is morphologically, biochemically, and pharmacologically identical to that of the thyroid gland.[8,10] Its frequency in ovarian neoplasms is less than 1%.[2,7] Peak incidence occurs between and 5th and 6th decades of life, and only 5% of these tumors comprise hyperthyroidism.[3,5,6,8,10] This is the most common type of monodermic teratoma, with a frequency of 3% among all ovarian teratomas.[10]

Macroscopically, struma is identified as a brown or brownish-green semi-solid mass that, on average, measures 10 cm.[5,10] Microscopically, the tumor is composed of thyroid tissue of normal appearance arranged in thyroid follicles of various sizes associated with mature cystic teratoma.[10]

Struma ovarii generally is a benign neoplasm; however, it has been reported that 5-37% can undergo a malignant transformation and is presents metastasis in less than 10% of cases.[2-4] It generally presents clinically as an asymptomatic mass that is diagnosed histologically after tumor resection; however, in 20% of instances, it can initially present with ascites.[2-4] The association of struma ovarii with ascites and pleural effusion is even rarer.[3]

Meigs' syndrome is the association of fibromas, ascites, and pleural effusion that resolve after surgical resection of the ovarian tumor.[3,4,11,12] Spiegelberg was the first to present the description of the syndrome in 1866; two decades later, Trait reported that the presence of an ovarian tumor with ascites and pleural effusion is not always associated with malignancy.[12]

In 1903, Demons described resolution of symptoms with ovarian tumor resection, and in 1937, Meigs and Cass described, in seven patients, the classical triad of pleural effusion, ascites, and ovarian tumor; in 1954, these authors described the syndrome, which consists of fibromas (fibromas, thecomas, or granulosa cell tumors) with ascites and hydrothorax, characterizing later resolution on removing the benign tumor.[3,8,12-14] Later, Rhoads and Terrell assigned the term Meigs' syndrome to this association.[13]

Meigs' syndrome is rare, presenting fibromas with pleural effusion in 10-15% of cases and with ascites and pleural effusion in 1%.[2,15] Other tumor types distinct from the fibroma, such as teratomas or uterine leiomyomas, are associated with Meigs' criteria, the preferred term being Pseudo-Meigs' syndrome (PMS).[1,3,16] The distinction between Meigs' syndrome and PMS is mainly academic, because the therapeutic strategy is identical in the two scenarios.[17]

Patients can present respiratory difficulty caused by massive ascites and by pleural effusion and, in extreme cases, may experience hypoxia, hypercapnia, and respiratory acidosis.[15] The pressure of lymphatic tissue by the tumor can result in the escape of fluid through the lymphatic vessels that are localized together within the epithelial layer covering the tumor, in combination with filtration of intratumor fluid, mechanical irritation of the tumor, and peritoneal inflammation as a result of ascites.[8,15] Other proposed mechanisms comprise active secretion of fluid by the tumor or the peritoneum, venous or lymphatic obstruction, decrease in serum proteins, or the presence of toxins or inflammatory products.[3]

The formation of pleural effusion in Meigs' syndrome and in PMS can be the result of the mechanical transference of ascites fluid through diaphragmatic openings or lymphatic vessels.[2,8,15] This theory is supported by the rapid occurrence of pleural effusion after thoracocentesis and its identical biochemical composition in peritoneal as well as in pleural fluid.[13] It has recently been suggested that Vascular Endothelial Growth Factor (VEGF), Fibroblast Growth Factor (FGF), and Interleukin 6 (IL-6) are related with the production of ascites and hydrothorax, in that these possess properties of vascular permeability.[15] The elevation of Ca125 in the serum of postmenopausal women suggests that, in 80% of cases, the presence of ovarian cancer.[1,5,7,12,18,19]

PMS associated with struma ovarii and accompanied by a rise in Ca125 is very rare: only eight cases have been reported in the medical literature to date (Table 1).[2-4,7,8,11,12,18,19] The possible causes of the increase of Ca125 in Meigs' syndrome include irritation of the mesothelial cells by the ovarian tumor, ascites, or pleural effusion, which leads to the antigen being released onto the surface of the serous membranes or the peritoneum.[7,16,18,19]

To date, no correlation has been found among volume

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of ascites fluid volume, tumor size, or the value of Ca125 in Meigs' syndrome.[5] What has been observed is that in Meigs' syndrome, Ca125 values are much lower that those typically found in ascites originating from malignant tumors.[3]

Authors have previously reported that if an ovarian solid mass is similar to thyroid tissue, in terms of its being both hyperechoic on Ultrasound (US) and hyperdense on unenhanced CT scan, struma ovarii should be considered in the differential diagnosis. The latter was confirmed in this patient, whose abdominal CT revealed a right ovarian tumor comprising mixed density and small calcifications.[20]

The surgeon should always consider atypical mature teratomas, cystadenofibromas, and even a malignant epithelial tumor as part of the differential diagnosis when pondering this entity.[21]

CONCLUSION

This case is uncommon due to the presentation of pleural effusion, ascites, high Ca125, and a complex pelvic mass, suggesting a malignant ovarian neoplasm and subsequently revealing struma ovarii in the histological report; thus, it is very difficult to perform an accurate diagnosis prior to surgery and before receiving the final pathology report. However, it is necessary to bear this possibility in mind in order to perform the appropriate tumor cytoreduction procedure.

CONFLICTS OF INTEREST

The author(s) declare that there is no conflict of interests regarding the publication of this paper.

CONSENT

The patient described in the case report has given their informed consent for the case report to be published.

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